Pharmacology & Therapeutics 270 (2025) 108850

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Resetting the aging clock through epigenetic reprogramming: Insights from natural products☆

Xin Liu [a,b,c], Jing Feng [a,b,c], Madi Guo [a,b,c], Chen Chen [a,b,c], Tong Zhao [a,b,c], Xiuxiu Sun [a,b,c], Yong Zhang [a,b,c,*]

[a] State Key Laboratory of Frigid Zone Cardiovascular Diseases (SKLFZCD), Department of Pharmacology, College of Pharmacy, and Department of Cardiology, the Second Affiliated Hospital, Harbin Medical University, Harbin 150081, China
[b] State Key Laboratory -Province Key Laboratories of Biomedicine-Pharmaceutics of China, and Key Laboratory of Cardiovascular Research, Ministry of Education, College of Pharmacy, Harbin 150081, China
[c] Research Unit of Noninfectious Chronic Diseases in Frigid Zone (2019RU070), Chinese Academy of Medical Sciences, Harbin 150081, China

ARTICLE INFO

Article history:
Received 1 May 2024
Received in revised form 4 December 2024
Accepted 7 April 2025
Available online 10 April 2025

Editor: M. Curtis

Keywords:
Natural products
Aging
Epigenetic modifications
Aging clock
Longevity

ABSTRACT

Epigenetic modifications play a critical role in regulating gene expression under various physiological and pathological conditions. Epigenetic modifications reprogramming is a recognized hallmark of aging and a key component of the aging clock used to differentiate between chronological and biological age. The potential for prospective diagnosis and regulatory capabilities position epigenetic modifications as an emerging drug target to extend longevity and alleviate age-related organ dysfunctions. In the past few decades, numerous preclinical studies have demonstrated the therapeutic potential of natural products in various human diseases, including aging, with some advancing to clinical trials and clinical application. This review highlights the discovery and recent advancements in the aging clock, as well as the potential use of natural products as anti-aging therapeutics by correcting disordered epigenetic reprogramming. Specifically, the focus is on the imbalance of histone modifications, alterations in DNA methylation patterns, disrupted ATP-dependent chromatin remodeling, and changes in RNA modifications. By exploring these areas, new insights can be gained into aging prediction and anti-aging interventions.

Abbreviations: ACE2, angiotensin converting enzyme-2; AD, Alzheimer's disease; ADC, antibody-drug conjugate; ADM, adrenomedullin; AF, aflatoxin; AGE, aging clock model; AMD, age-related macular degeneration; ATF, activating transcription factor; ATG, autophagy related protein; BAF, BRG1-associated factor; BDNF, brain-derived natriuretic factor; B2M, beta-2 microglobulin; BNP, B-type natriuretic peptide; CBC, complete blood counts; CYR61, cysteine-rich protein 61; CDK, cyclin-dependent kinase; CHD, chromodomain helicase DNA binding; CNS, conserved noncoding sequence; CR, caloric restriction; CRCs, chromatin remodeling complexes; CRP, C-reactive protein; cTnI, cardiac troponin I; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; DNMTs, DNA methyltransferases; DOSI, dynamic quantitative organism state indicator; ECM, extracellular matrix; EGCG, epigallocatechin gallate; ERα, estrogen receptor alpha; Foxp, forkhead box protein; FP, zinc-finger protein; FOXO, forkhead box O; GAGs, glycosaminoglycans; GDF, growth differentiation factor; GSPs, grape seed proanthocyanidins; GSTP, glutathione S-transferase P; GTPs, green tea polyphenols; HATs, histone acetyltransferases; HDACs, histone deacetylases; HFD, high-fat diet; HP1α, heterochromatin protein 1α; HKDC, hexokinase domain-containing protein; hMSCs, human bone marrow mesenchymal stem cells; HMVEC, human microvascular endothelial cell; HSCs, hematopoietic stem cells; hTERT, human telomerase reverse transcriptase; HUVEC, human umbilical vein endothelial cell; iAGE, inflammatory aging; iCAS, Chinese Aging Score; IL, interleukin; INO80, inositol requiring 80; ISWI, imitation switch; KDM BA, Klemera-Doubal method for estimating biological age; KLF, krueppel-like factor; LINE, long interspersed element; lncRNA, long non-coding RNA; MBD, methyl-CpG-binding domain protein; MeCP, Methyl-CpG-binding protein; METTL, methyltransferase-like protein; MMP, matrix metalloproteinase; mtDNA, mitochondrial DNA; NAFLD, non-alcoholic fatty liver disease; ncRNAs, non-coding RNAs; NPs, nanoparticles; Nrf, NF-E2-related factor; NSCLC, non-small cell lung cancer; NSUN, NOP2/Sun domain family, member; NuRD, nucleosome remodeling and deacetylase; PAI-1, plasminogen activator inhibitor-1; PBMCs, peripheral blood mononuclear cells; PedBE, pediatric-buccal-epigenetic; PGs, proteoglycans; PPAR-α, peroxisome proliferator-activated receptor-alpha; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; SAHF, senescence-associated heterochromatin foci; SIRT, histone deacetylase sirtuin; SNF, sucrose nonfermenting; SWI, switching defective; TAC, transverse aortic constriction; TIMP, tissue inhibitor metalloproteinase; TL, telomere length; Treg, T regulatory cells; UPRmt, unfolded protein response; UPR^{ER}, the unfolded protein response of the endoplasmic reticulum; UPR^{mito}, unfolded protein response of the mitochondria; UTR, untranslated region; YBX, Y-box-binding protein; YTHDF, YTH domain-containing family protein.

☆ This article is part of a Special issue entitled: 'Natural Products P&T' published in Pharmacology and Therapeutics.

* Corresponding author at: State Key Laboratory of Frigid Zone Cardiovascular Diseases (SKLFZCD), Department of Pharmacology, College of Pharmacy, and Department of Cardiology, the Second Affiliated Hospital, Harbin Medical University, Harbin 150081, China.
E-mail address: zy@ems.hrbmu.edu.cn (Y. Zhang).

https://doi.org/10.1016/j.pharmthera.2025.108850
0163-7258/

Contents

1. Introduction

Aging is an intricate process characterized by decreased functional abilities and increased susceptibility of various diseases, including cardiovascular diseases, cancer, neurodegenerative disorders, immune system dysfunctions, endocrine and metabolic diseases, etc. (Abdelgawad et al., 2021; Park et al., 2023). Research has identified key aging hallmarks, such as genetic instability, telomere shortening, mitochondrial damage, epigenetic changes, abnormal cellular metabolism (Birch, Barnes, & Passos, 2018; Denomme et al., 2024; Milosic, Hengstschlager, & Osmanagic-Myers, 2023; Siddiqui, Sharma, Kesharwani, & Parihar, 2024), all of which play pivotal roles in the development of aging. These insights are fundamental for identifying aging biomarkers and developing age-related diseases interventions.

Natural products are bioactive compounds sourced from plants, animals, marine organisms, microorganisms, and other natural sources, known for their diverse chemical structures and pharmacological properties (Luo, Yin, Wang, & Kong, 2024; Zhang et al., 2020). These compounds have been extensively studied for their potential in various therapeutic applications, including anti-aging effects and modulation of epigenetic modifications. This review aims to provide a comprehensive overview of natural products that target epigenetic reprogramming to enhance longevity and alleviate age-related organ dysfunctions.

2. Aging clock and the determinant factors

Histologically, aging is characterized by evident tissue lesions and senescence, while clinically, it is observed through a decline in overall organ function. Although these tissue and organ lesions may initiate at different time points and operate somewhat independently, once a specific lesion emerges, it can potentially trigger or exacerbate degenerative changes in other organs following a cascade model. The onset of aging-related changes varies among different organs and tissues (Le Gall & Ardaillou, 2009; F. Yan, Li, Powell, & Wang, 2022). And the function and risk of age-related diseases exhibit non-linear changes throughout the human life cycle (X. Shen et al., 2024). Research has revealed that the decline in human motor function typically commences around the age of 35, while the visual field diminishes gradually from birth, leading to the development of presbyopia between 45 and 50. Reproductive function begins to decrease at around 50 years of age, significant hearing loss often begins around 65, and central nervous system function experiences a rapid decline from around 70 years of age (Warthin, 1928). These alterations serve as clinically significant indicators of an individual's physiological age.

The global population is experiencing rapid aging, but the disease-free survival period, known as healthspan, have not kept pace with this trend. In recent decades, pioneering studies have introduced indicators to estimate healthspan, offering a promising possibility to extend lifespan and healthspan. Andrews et al. introduced the concept of "biological age" as an indicator of human healthspan in 2017 (Andrews et al., 2017), indicating the age of organs, tissues, and cells based on physiological markers. A younger biological age compared to chronological age signifies better health outcomes, while an older biological age often correlates with poor physical health or potential chronic diseases. Advancements in biotechnologies have led to the discovery of biomarkers that differentiate between chronological and biological age, enabling the quantification of aging across different levels. The concept of aging clocks has been developed in response to this, which refers to mathematical models trained on omics data using one or a set of biomarkers to predict biological age (H. Zhu et al., 2023). Our review provides a systematic summary of aging biomarkers (Fig. 1) and their corresponding aging clocks (Table 1) at both the organ and molecular levels.

2.1. Aging clock in circulatory system

Aging across various body systems results in the emergence of diverse biomarkers associated with the aging clock. In the circulatory system, blood biomarkers and blood cells are commonly employed to establish biological or digital models for predicting the aging clock. Researchers developed a dynamic quantitative organism state indicator (DOSI) to quantify the healthspan of organism by utilizing Complete Blood Counts (CBC) and physical activity variables. This DOSI, identified as an aging clock, predicts the risk of age-related diseases and mortality as age increases (Pyrkov et al., 2021). Polina Mamoshina developed an AI deep learning-based hematological aging clock model (AI-based hematological AGE) utilizing hematological parameters, transcriptomic, and proteomic data from a large combined dataset of population blood samples. This model suggests the specificity of aging patterns and hematologic clocks in different populations, with the ability to predict all-cause mortality (Mamoshina et al., 2018). Similarity, by introducing an advanced single-cell lineage-tracing system, researchers observed that hematopoietic stem cells (HSCs) clone diversity decreases significantly with age, highlighting the complex relationship between HSC behavior, human hematopoietic complexity and aging (HSCs AGE) (Weng et al., 2024). Notably, blood biochemistry parameters such as albumin, glucose, urea, and hemoglobin were identified as crucial predictors for aging specific to the population (blood biochemistry AGE) (Mamoshina et al., 2018). Additionally, C-reactive protein (CRP) and interleukin-6 (IL-6) levels were sensitive predictors of physical quality, cognitive ability and mortality risk in the elderly population (Puzianowska-Kuznicka et al., 2016). Age is one of the independent risk factors for cardiovascular diseases, as it can induce structural remodeling and functional deterioration in the heart leading to ventricular diastolic dysfunction, seriously shorten lifespan (North & Sinclair, 2012). Our previous studies highlighted the strong correlation between non-coding RNAs (ncRNAs) in cardiomyocytes and human age, as well as age-related cardiac dysfunction, encompassing long non-coding RNA (lncRNA) SMAL and microRNA-203 (ncRNA AGE) (Liu et al., 2022; Zhao et al., 2024). B-type Natriuretic Peptide (BNP) is a circulating hormone predominantly synthesized by the myocardium in response to cardiac stress. A community-based cohort study demonstrated that

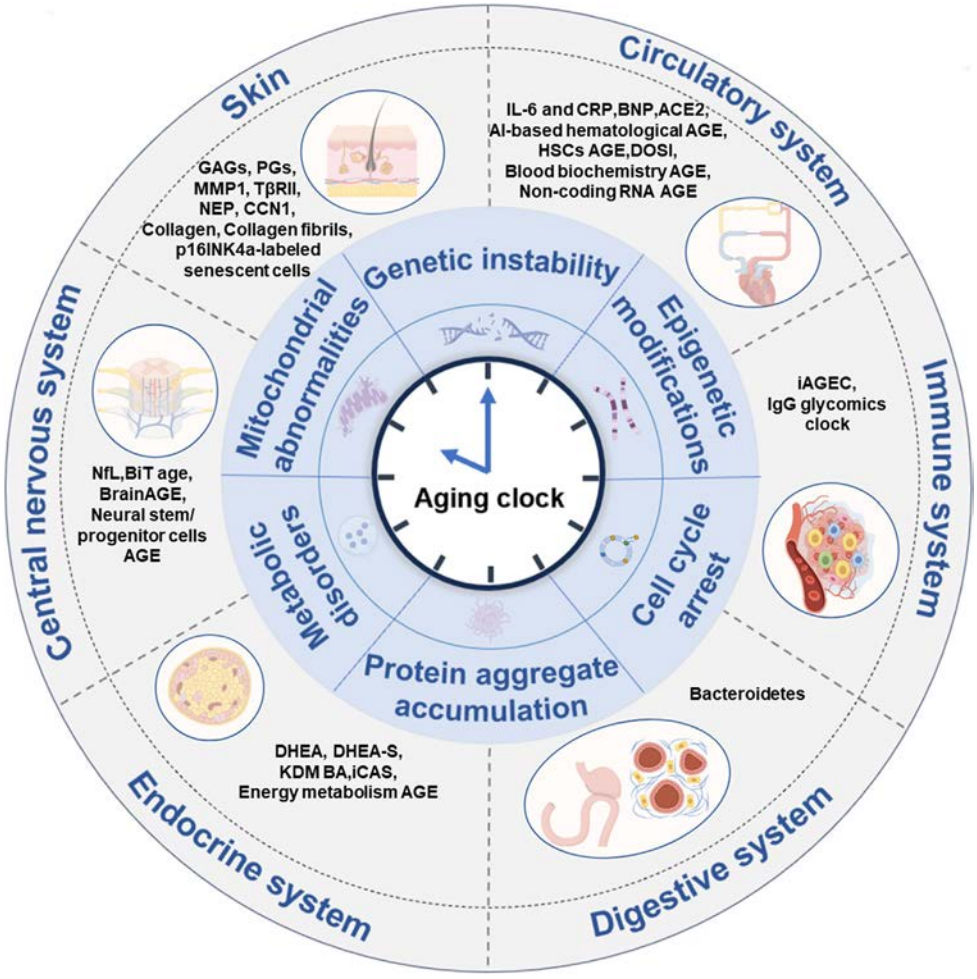


Fig. 1. Aging clocks and molecular biomarkers of aging. At the edge of the circle, aging clock prediction models representing various body systems are showcased as reviewed in this document. In the center, particular biomarkers at the molecular level are presented to predict overall lifespan and healthspan. (by Figdraw).

serum BNP levels increase with healthy aging and serve as an independent predictor of heart failure in elderly (Yoshida et al., 2019). Increased the expression of angiotensin converting enzyme-2 (ACE2) in alveolar epithelial cells of non-cancerous elderly lung tissue leads to increased susceptibility to SARS-CoV-2 (Schneider et al., 2021).

2.2. Aging clock in immune system

Aging is often accompanied by immune system disorders, with chronic inflammation being a characteristic of immunosenescence and one of the main risk factors for age-related diseases (Liu et al., 2023). Sayed et al. used circulatory immune protein data which containing 50 cytokines, chemokines and growth factors to develop a new inflammatory aging (iAGE) clock using deep learning to predict the incidence of multiple diseases. This innovative tool emphasizes the key role of iAGE in the aging clock, illustrating its effect to assess the aging process and related health outcomes (Sayed et al., 2021). Erin Macdonald-Dunlop and colleagues analyzed various omic aging clocks and discovered that IgG glycomics clock is capable of effectively tracking generalized aging and predicting biological age (Macdonald-Dunlop et al., 2022).

2.3. Aging clock in digestive system

Within the digestive system, the gut microbiota is a crucial role as a biomarker of aging and age-related diseases, containing a diverse range of health and longevity-related biomarkers (R. Li & Roy, 2023; B. Wang, Yao, Lv, Ling, & Li, 2017). One notable example is the depletion of Bacteroidetes, which is considered a key feature of healthy aging and serves as a predictive indicator of prolonged survival among the elderly (Wilmanski et al., 2021). However, according to Li et al., the predictive potential of microbiota for aging seems to vary across different races and genders. Their study highlighted that microbiota diversity showed minimal differences during aging in Chinese women (Li et al., 2023). Further research is essential to fully understand the role of microbiota in influencing lifespan and healthspan.

2.4. Aging clock in endocrine system

Hormones and metabolic products produced in the endocrine system have been identified as novel components of an aging clock. Research indicates that centenarians demonstrate greater insulin sensitivity and β-cell activity compared to younger individuals, underscoring the significance of energy metabolism in promoting healthy aging (energy metabolism AGE) (Paolisso, Barbieri, Bonafe, & Franceschi, 2000). The key steroid precursors of sex hormones, including dehydroepiandrosterone (DHEA) and its ester metabolite, dehydroepiandrosterone sulfate (DHEA-S), significantly decrease from around the age of 30 in males and have become prospective biomarkers of aging and predictive indicators of male lifespan (Enomoto et al., 2008; Labrie, 2010). John C. Earls et al. developed the computer-based Klemera-Doubal method for estimating biological age (KDM BA). This

Table 1
Reported aging clocks and their related components and methods utilized in different body systems.

Body system	Aging clock	Components and methods	Reference
Circulatory System	DOSI	Emphasizing the intertwined evolution of the genome and epigenome, shaping the characteristics of different mammalian species.	Pyrkov et al., 2021
	AI-based hematological AGE	Developing an AI deep learning-based hematological aging clock model (AI-based hematological AGE) utilizing hematological parameters, transcriptomic, and proteomic data from a large combined dataset of population blood samples.	Mamoshina et al., 2018
	HSCs AGE	Introducing an advanced single-cell lineage-tracing system, researchers observed that hematopoietic stem cells (HSCs) clone diversity decreases significantly with age.	Weng et al., 2024
	Blood biochemistry AGE	Blood biochemistry parameters such as albumin, glucose, urea, and hemoglobin were identified as crucial predictors for aging specific to the population.	Mamoshina et al., 2018
	IL-6 and CRP	CRP and IL6 levels were reliable indicators of physical, cognitive abilities as well as the risk of mortality in the overall elderly population.	Puzianowska-Kuznicka et al., 2016
	ncRNA AGE	Long non-coding RNA (lncRNA) SMAL and microRNA-203 in cardiomyocytes are strongly correlated with human age, as well as age-related cardiac dysfunction.	Liu, Bai, et al., 2022; Zhao, Sun, et al., 2024, Zhao, Tang, et al., 2024
	BNP	Serum BNP levels increase with healthy aging and serve as an independent predictor of heart failure in older adults.	Yoshida et al., 2019
	ACE2	High ACE2 expression in alveolar epithelial cells of non-cancerous elderly lung tissue increases susceptibility to SARS-CoV-2.	Schneider et al., 2021
Immune System	iAGEC	By analyzing circulating immune protein data from 50 cytokines, chemokines, and growth factors, multiple incidence rates were predicted, and a new inflammatory aging (iAGE) clock was developed using deep learning techniques.	Sayed et al., 2021
	IgG glycomics clock	IgG glycomics clock is capable of effectively tracking generalized aging and predicting biological age.	Macdonald-Dunlop et al., 2022
Digestive System	Bacteroidetes	The reduction of Bacteroidetes is regarded as a significant characteristic of healthy aging and acts as a predictive marker for increased longevity in older adults.	Wilmanski et al., 2021
Endocrine System	Energy metabolism AGE	Centenarians demonstrate greater insulin sensitivity and maintained β-cell function.	Paolisso et al., 2000
	DHEA, DHEA-S	Sex hormones DHEA and DHEA-S are significantly decline from around the age of 30 in males and have become prospective biomarkers of aging.	Enomoto et al., 2008; Labrie, 2010
	KDM BA	Developing the computer-based Klemera-Doubal method for estimating biological age (KDM BA) to analyze longitudinal data, for existing research identified metabolic well-being, inflammatory responses, and toxin buildup are prominent indicators of biological age.	Earls et al., 2019
	iCAS	Chinese Aging Score (iCAS) was created using multi-omics data to assess aging and evaluate physiological conditions related to chronic inflammation, hormone and metabolic dysfunction, and tissue degeneration.	Li, Xiong, et al., 2023
Central Nervous System	NfL	Plasma NfL shows promise as a tool for indicating the absence of detecting neurodegeneration with minimal false positives across various age-related thresholds.	Ashton et al., 2021
	Neural stem/progenitor cells AGE	Single-cell RNA-seq data revealed that in neural stem and progenitor cells, 96 to 359 genes were associated with chronological clocks, and 174 to 399 genes were linked to biological clocks.	Buckley et al., 2023
	BiT AGE	By applying temporal scaling and binarization to *C. elegans* transcriptomes, a set of 576 genes related to innate immunity, neural signaling, and transcriptional regulation was identified. This gene set effectively predicts biological age.	Meyer & Schumacher, 2021
	BrainAGE	The Brain Age Gap Estimation (BrainAGE) method is the foremost and widely utilized concept for individual brain age prediction and assessment using structural MRI data.	Kalc et al., 2024; Lu et al., 2023
Human Skin	Collagen and collagen fibrils	Inhibition of collagen synthesis and acceleration of collagen fibril fragmentation led to a net deficiency of collagen in aged skin structure, with protease-mediated degradation becoming dysregulated, contributing to ECM alterations.	Panwar et al., 2015; Quan & Fisher, 2015
	Elastic fibers GAGs PGs	Other ECM components, such as glycosaminoglycans (GAGs), alike experience age-associated changes, ultimately resulting in a decline in functional components.	Shin et al., 2019
	MMP1	Prominently in aged human skin, there is an upregulation of matrix metalloproteinase-1 (MMP-1) expression and reduced type I collagen synthesis by dermal fibroblasts.	Xia et al., 2013
	TβRII	The decline in dermal collagen production is linked to aging, with the downregulation of TβRII playing a significant role in this process.	T. He et al., 2014
	NEP	An increase in neutral endopeptidase 24.11 (NEP) expression leads to the degradation of various neuropeptides, consequently reducing their effectiveness as inflammatory regulators. This process contributes to the fibrodegeneration of elastin.	Morisaki et al., 2010
	CCN1	The cysteine-rich protein 61 (CCN1) is predominantly present in dermal fibroblasts, with elevated expression observed in both naturally aged and photoaged human skin in vivo.	Qin et al., 2013; Quan et al., 2006
	p16INK4a-labeled senescent cells	Fewer p16INK4a-positive cells suggest a longevity trend in middle-aged individuals.	Waaijer et al., 2012
	H4K16ac	In the aged basal epidermis, there are significantly decrased expression of H4K16ac and H4K20me1.	Dube et al., 2022
Epigenetic modifications	DNA methylation clock	First proposed the DNA methylation clock to identify age-related methylation patterns for predicting human age.	Norby & Jensen, 1989
	Epigenetic clock	First proposed epigenetic clock correlating constant shifts in DNA methylation levels with aging, reflected not only in physiological aging but also in declining health, the onset of chronic diseases, and increasing mortality rates.	Horvath, 2013
	DNAm PhenoAge	An extensive transcriptional analysis revealed an increase in epigenetic age compared to chronological age.	Levine et al., 2018
	GrimAge clock	The GrimAge clock utilizes seven plasma protein markers - ADM, B2M, cystatin C, GDF-15, leptin, PAI-1, and TIMP-1, in combination with DNA methylation data and smoking history, to estimate biological age.	A. T. Lu et al., 2019
	Pediatric-Buccal-Epigenetic (PedBE) clock	Creating the Pediatric-Buccal-Epigenetic (PedBE) clock using DNA methylation groups during child growth to measure the biological age of children.	McEwen et al., 2020

method integrates data from genetics, clinical trials, metabolomics, and proteomics to analyze human health indices from multiple perspectives, demonstrating that metabolic abnormalities, inflammatory stress, and toxin accumulation could serve as powerful indicators for predicting biological age (Earls et al., 2019). Recently, the Chinese Aging Score (iCAS) was created using multi-omics data to assess the correlation between aging and chronic inflammation, hormonal disorders, and tissue degeneration. Hormone replacement therapy may lower aging clock scores, emphasizing the role of hormones in healthspan (Li, Xiong, et al., 2023).

2.5. Aging clock in neuron system

The aging of the neuronal system is closely linked to the development of neurodegenerative diseases (Castellano et al., 2017; W. Xiong et al., 2023). Elevated levels of neurofilament light (NfL) in cerebrospinal fluid are important marker of neurodegenerative diseases and can also be measured in blood (Freedman, et al., 2024). The inclusion of NfL in the biological age algorithm further improves the prediction of increased dementia risk (J. W. Wu et al., 2021). In another study, it was proved that plasma NfL is a clinically valuable biomarker for distinguishing atypical parkinsonian syndromes and dementia in individuals with amyotrophic lateral sclerosis, atypical Parkinson's syndrome and cortical neurodegenerative diseases. Plasma NfL shows promise as a tool for indicating potential neurodegenerative diseases with high accuracy at age-related critical values, suggesting its potential role in the aging clock (Ashton et al., 2021). A single-cell RNA seq data from the adult mammalian brains have been used to create aging clocks based on physiological age or biological age. Finally, there are 96 to 359 genes in physiological clocks and 174 to 399 genes in biological clocks were identified in neuronal stem cells (neural stem/progenitor cells AGE). Among them, AC149090.1 and interferon alpha inducible protein 27 (Ifi27) were the key genes influencing the aging clock in these cell types (Buckley et al., 2023). The transcriptome data of different age groups of *Caenorhabditis elegans* have been used to identify a gene set containing 576 genes related to neuronal signaling, innate immune response and transcription factors. This geneset accurately predicts biological age and has been named the binarized transcriptomic aging (BiT AGE) clock (Meyer & Schumacher, 2021). In addition to biomarkers, computer modeling methods and machine learning simulation techniques provide a robust approach for predicting brain age, typically utilizing imaging indicators. The Brain Age Gap Estimation (BrainAGE) method is the foremost and widely utilized concept for individual brain age prediction and assessment using structural MRI data. Studies have explored BrainAGE findings in neuropsychiatric conditions and identified its potential utility as a biological age marker (Kalc et al., 2024; Lu et al., 2023).

2.6. Aging clock in human skin

As aging progresses, collagen fibers gradually lose their elasticity and undergo degradation, causing a decline in the structure and function of the skin (Quan & Fisher, 2015). The decrease in collagen production and the increase in collagen fiber breakage leads to a lack of net collagen in the aging skin structure, with protease-mediated degradation becoming dysregulated, contributing to extracellular matrix (ECM) alterations (Panwar et al., 2015). The reduction of collagen can disrupt the interaction between ECM and fibroblasts, inhibiting fibroblast function, and decreasing the collagen content in the dermis. ECM components such as elastic fibers, proteoglycans (PGs) and glycosaminoglycans (GAGs) can also undergo age-related changes, leading to a decrease in functional components (Shin et al., 2019). Prominently in aged human skin, the expression of matrix metalloproteinase-1 (MMP-1) is significantly upregulated in skin fibroblasts, and the production of type I collagen is significantly reduced (Xia et al., 2013). As age increases, the reduction in collagen content in the human skin leads to the downregulation of TβRII, ultimately resulting in skin thinning in elderly people (T. He, Quan, Shao, Voorhees, & Fisher, 2014). An increase in neutral endopeptidase 24.11 (NEP) expression leads to the degradation of various neuropeptides, consequently reducing their effectiveness as inflammatory regulators. This process contributes to the fibrodegeneration of elastin (Morisaki et al., 2010). The cysteine-rich protein 61 (CCN1) is mainly expressed in skin fibroblast cells (Qin, Fisher, & Quan, 2013; Quan et al., 2006). Of note, CCN1 levels are significantly elevated in both natural aging and photoaging human skin (Quan et al., 2006; Quan et al., 2010; Quan, Shin, Qin, & Fisher, 2009). It is plausible that the CCN1-induced age-associated dermal microenvironment (AADM) may promote the development of epithelial skin cancer in the elderly individuals (Quan & Fisher, 2015). Additionally, the number of p16INK4a-labeled senescent cells in skin can serve as a biological age marker, where fewer p16INK4a-positive cells suggest a longevity trend in middle-aged individuals (Waaijer et al., 2012). Certain epigenetic markers have been shown to exhibit abnormalities in the process of human skin aging. In the aging epidermis, the levels of H4K16ac and H4K20me1 are significantly reduced, and the total content of intercellular histones H3 and H4 is altered (Dube, Jahan, & Lim, 2022).

2.7. Molecular biomarkers in aging

In addition, there are also some specific biomarkers in molecular levels for predicting lifespan and healthspan. One of the most important biomarkers of aging is genetic instability. As one ages, the DNA carrying genetic information undergoes various changes that disrupt normal cellular function and tissue homeostasis. The double strand break biomarker γH2AX increases with age in human lymphocytes and is also upregulated in fibroblasts of patients with Werner syndrome (Sedelnikova et al., 2008). Additionally, telomere length (TL) is known to decrease gradually with human aging (Lopez-Otin, Blasco, Partridge, Serrano, & Kroemer, 2013). Epigenetic modifications play an crucial role in regulating genomic function when the DNA sequence remains unchanged, linking genotype and phenotype, and regulating the aging process under environmental stimuli (Unnikrishnan et al., 2019). During aging in multiple species, DNA methylation is present in global and local genome (Klutstein, Nejman, Greenfield, & Cedar, 2016; Yagi et al., 2020). Multiple epigenetic clocks have been proposed, including PhenoAge (Levine et al., 2018), DunedinPoAm and DunedinPACE (Belsky et al., 2020), GrimAge (McCrory et al., 2021) and DNAmAge (Murach et al., 2022) have been developed to predict physiological age and biological age based on DNA methylation analysis. Moreover, other epigenetic modifications, including chromatin remodeling, histone modifications, and RNA modifications have also been reported to show a strong correlation with aging (Adelman et al., 2019; Feser et al., 2010; Q. Li et al., 2017). Stagnation of the cell cycle in G1 or G2 phase, preventing proliferation of damaged cells is another important marker of cellular aging, which is influenced by the p16INK4a/RB and p53/p21CIP1 pathways (Beausejour et al., 2003; Gire & Dulic, 2015). Age related mitochondrial abnormalities, including increased reactive oxygen species (ROS), mutanted mitochondrial DNA (mtDNA), mitochondrial dynamics changes, decreased unfolded protein response (UPRmt), and decreased respiratory chain activity, are also markers of senescent cells (Calculli et al., 2021). Recent studies have suggested that low levels of ROS may activate signaling pathways that contribute to enhanced longevity. (Payne & Chinnery, 2015; Sanz & Stefanatos, 2008). The lifespan of *Caenorhabditis elegans* can be shortened by mitochondrial oxidative stress increased (Dilberger et al., 2019). Mutations in mtDNA can induce aging in multiple organs of mice, including the ovaries, liver and heart (Giorgi et al., 2018). Low-frequency mtDNA mutations, occurring at rates below 0.5 %, build up in human oocytes and are connected to reduced blastocyst formation efficiency (L. Yang et al., 2020). What's more, the gradual deterioration of proteostasis with aging heightens the likelihood of abnormal protein aggregates

accumulating. Molecular chaperones and cochaperones facilitate the proper folding and assembly of proteins, while also inhibiting the aggregation of misfolded proteins (Goloubinoff, Sassi, Fauvet, Barducci, & De Los Rios, 2018; L. Wang, Xu, Jiang, & You, 2020). The extent of chaperone networks was linked to the lifespan of species. For instance, the short-lived vertebrate (*Nothobranchius furzeri*) possesses fewer chaperones and is commonly used to model fragile protein homeostasis (Draceni & Pechmann, 2019). In addition, the unfolded protein response of the endoplasmic reticulum (UPRER) in the elderly *Caenorhabditis elegans* decreased, while the unfolded protein response of the mitochondria (UPRmito) increased and was associated with extended lifespan (Ben-Zvi, Miller, & Morimoto, 2009; X. Li et al., 2022). Cellular metabolism is closely involved in the aging process, and there are differences in metabolic products among different age groups. The MetaboAge database contains studies on human aging related metabolomics (Bucaciuc Mracica et al., 2020). In this database, 7 metabolites are closely related to age or have cross species aging protection effects, including NAD^+ (H. Zhang et al., 2016), α-ketoglutarate (Asadi Shahmirzadi et al., 2020), tryptophan (Salminen, 2022), methionine (Barcena, Lopez-Otin, & Kroemer, 2019), spermidine (Liu et al., 2022), triglycerides (Auro et al., 2014), cholesterol (Bucaciuc Mracica et al., 2020). In addition, when cellular glycolysis increases or glucose metabolism changes, it promotes extensive glycosylation of intracellular proteins. The buildup of advanced glycation end products (AGEs) contributes significantly to the development of various age-related diseases. (Neelamegham & Mahal, 2016; Zhao, Sun, Wang, & Shang, 2024) (Fournet, Bonte, & Desmouliere, 2018). The proposal of "glycan age" signifies that glycosylation level has become an important marker in aging (Yu & Wang, 2021). The Immunoglobulin G (IgG) N-glycome determines 23.3 % -58.0 % of age differences. Besides, hormones, blood factors and body fat are closely related to IgG glycome (W. Wang, 2023).

Despite the identification of numerous aging biomarkers linked to lifespan and healthspan, further validation of their real-world correlation is vital. In fact, due to the complexity of the biological and molecular mechanisms of aging, a single biomarker is difficult to provide a precise evaluation of healthy aging. Chao et al. combined multiple omics data, such as clinical trials, immune banks, targeted metabolomics, gut microbiota, physical fitness evaluations, and facial skin assessments, to estimate the physiological age of various organs (like the liver and kidneys) and systems (immune and metabolic). They also created a polygenic risk score (PRS) to evaluate the aging rates of these organs and systems (Nie et al., 2022). Using comprehensive indicators can help evaluate complex aging systems, but selecting the best combination is not an easy task. On the other hand, large-scale cohort population studies are necessary to substantiate the relationships between these markers and aging outcomes, paving the way for more scientifically robust findings in the field of aging research.

3. Epigenetic reprogramming in longevity and aging related diseases

Epigenetic changes, including DNA methylation, histone modifications, chromatin remodeling, and RNA modifications, are strongly linked to aging and age-related diseases. These modifications can disrupt gene regulation, leading to genomic instability and contributing to the aging process and related conditions (K. Wang et al., 2022).

A significant amount of research on epigenetic modifications in aging has provided insights into potential interventions to delay aging lately. Notable studies in this area should be highlighted. With the help of epigenetic regulatory factors, epigenetic modifications are usually reversible, offering a theoretical foundation for aging regulation and presenting a potential focus for anti-aging approaches. In 1967, DNA methylation across the genome has been linked to the spawning age of salmon (Berdyshev, Korotaev, Boiarskikh, & Vaniushin, 1967). Subsequent study has shown that DNA methylation is generally decreased in different tissues of mice and human fibroblasts with aging (Wilson & Jones, 1983). In 1987, Y Ishimi et al. first discovered that the occupancy rate of nucleosomes in human skin fibroblasts decreased with age. Further analysis of the chromatin structure of skin fibroblasts from donor individuals at different ages was conducted, and found that the chromatin structure became disordered during aging processes (Ishimi et al., 1987). In 2011, Bocklandt et al. proposed the DNA methylation clock identifies age-related changes at many genomic positions, and methylation at just three of these sites can effectively predict human age. (Norby & Jensen, 1989). In 2013, Hannum et al. first proposed the concept of epigenetic clock correlating constant alterations in DNA methylation levels with aging, reflected not only in physiological aging but also in declining health, the onset of chronic diseases, and increasing mortality rates (Horvath, 2013). In 2015, Marjolein J. Peters et al. showed associations between CpG-methylation sites in enhancer and insulator regions, impacting both aging and gene expression patterns by meta-analysis (Peters et al., 2015). In 2017, Qiu et al. found that RNA methylation enhances cellular senescence under oxidative stress (Q. Li et al., 2017). In 2018, Levine et al. developed the "DNAm PhenoAge" epigenetic clock, which assesses biological age instead of chronological age (Levine et al., 2018). In 2019, Lu et al. introduced the GrimAge clock, utilizing seven plasma protein markers based on DNA methylation and smoking history, including ADM, B2M, cystatin C, GDF-15, leptin, PAI-1, and TIMP-1, to predict biological age (Lu et al., 2019). Compared to adults, DNA methylation alterations in children are more variable. In 2020, Lisa et al. developed the Pediatric-Buccal-Epigenetic (PedBE) clock to assess the biological age of young individuals may help understand the the contextual factors that influence the development of DNA methylation groups during child growth, as well as its inverse relationship with child health and disease (McEwen et al., 2020). In 2023, Haghani et al., through the analysis of DNA methylation patterns from 348 mammalian species, Amin Haghani et al. identified 30 cytosine modules associated with traits such as lifespan, adult weight, age, sex, and mortality risk. The study emphasizes how the genome and epigenome coevolve to shape the traits of mammalian species. (Haghani et al., 2023).

The breakthrough in unraveling epigenetic modifications within the latest decades has underscored their promising potential as diagnostic biomarkers and therapeutic targets in aging (Fig. 2). As a result, among over 1100 references, a series of anti-aging drugs that regulate epigenetic modifications have been investigated. This review offers a detailed look at natural products that modulate epigenetic modifications for anti-aging purposes, offering valuable references for further drug discovery.

4. Epigenetic modifications and natural products

4.1. Imbalance of histone modifications

Chromatin's fundamental unit is the nucleosome, consisting of an octamer of four histone proteins (H2A, H2B, H3, and H4) wrapped around DNA strands (Roberts, Sanicola, Emmons, & Childs, 1987). Histone modifications are extensively studied epigenetics and are crucial for various physiological processes throughout life, but their patterns change with aging (Fyodorov, Zhou, Skoultchi, & Bai, 2018; Y. Wang, Yuan, & Xie, 2018). There are at least ten a range of histone modifications have been discovered with acetylation (ac), methylation (me), phosphorylation (phos), and ubiquitination (ub) being the most famous, in addition to *n*-acetylglucosamine glycosylation (O-GlcNAcylation), citrullination(cit), deimination (deim), proline isomerization and lactylation (lact) (Kouzarides, 2007; Torres & Fujimori, 2015). Histone methylation and acetylation often occur on specific lysine (K) residues across the four histones, including H2AK5/13, H2BK5/46/108, H3K4/9/14/23/27/36/56/64/79/122, and H4K5/8/12/20/31/79 (Chan & Maze, 2020; Z. Zhao & Shilatifard, 2019). Multiple modifications can be present on histone tails, like H2AK13me/ac/ar/bio, H3K9me/ac/cr, H3K14me/ac/pr/bu., H3K18me/ac/la/cr, H4K5me/ac/pr/bu./la, H4K8me/ac/pr/bio/cr, and

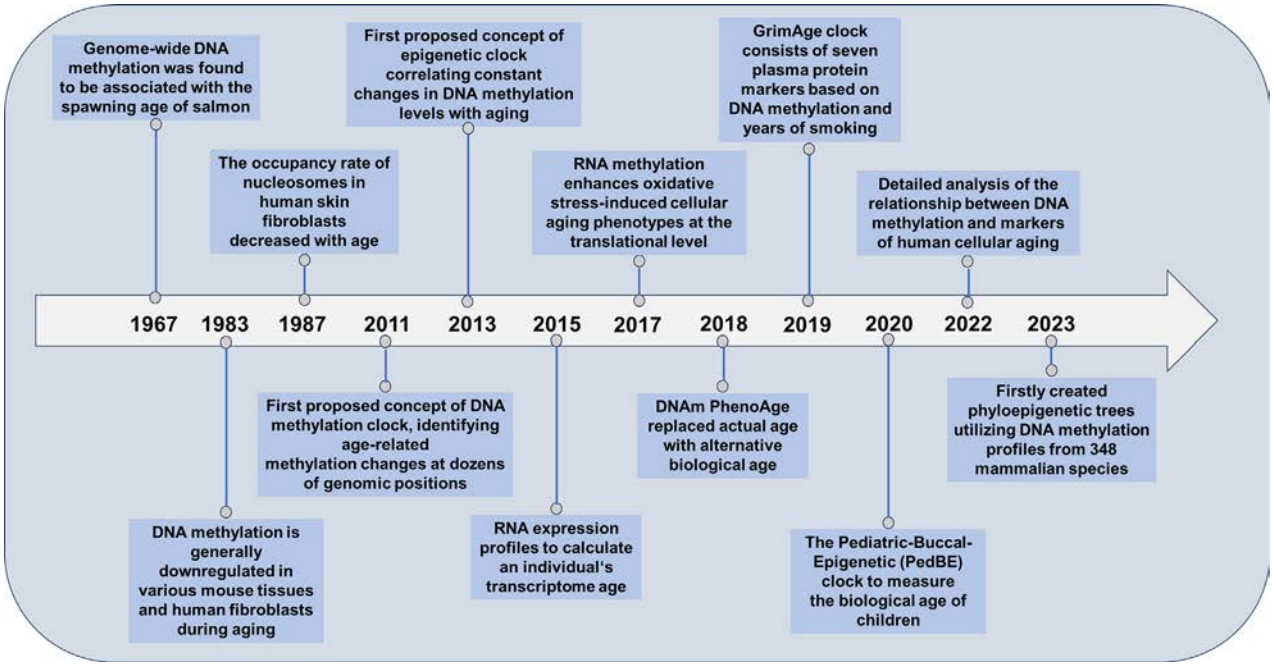


Fig. 2. The discovery and recent advancements in the aging clocks.

H4K12me/ac/pr/bu./bio. (Y. Yang, Zhang, & Wang, 2022). These modifications impact chromatin structure, gene expression, gene regulation, and cell fate determination.

4.1.1. Histone modifications targeted natural products for longevity

The correct inheritance of histone modification during DNA replication is one of the basic characteristics of differentiation and development (Wen et al., 2023). Thus, an imbalance in histone modifications can alter transcriptome-wide alterations associated with aging, thereby participating in affecting human aging processes and aging-related diseases (Y. Wang et al., 2018). Acetylation and methylation of lysine residues are well-known to be involved in regulating longevity processes. Previous studies have found that the level of H3K9ac decreased with age in rats (Kawakami, Nakamura, Ishigami, Goto, & Takahashi, 2009), while H3K56ac levels decreased during yeast aging process (Feser et al., 2010). Histone acetyltransferases (HATs) and histone deacetylases (HDACs) respectively regulate the addition and elimination of acetyl groups. Knocking out relevant HDACs such as histone deacetylase 3 (Hst3) and histone deacetylase 4 (Hst4) that remove H3K56ac, leads to a shortened yeast lifespan(Hachinohe, Hanaoka, & Masumoto, 2011). Additionally, numerous researches have focused on the alterations in histone methylation during aging. Histone methylation primarily occurs at the amino terminals, with lysine residues undergoing mono-, di-, or tri-methylation (Jambhekar, Dhall, & Shi, 2019). Substantial changes associated with aging have been observed in histone methylation marks such as H3K4me3, H3K9me3, H3K27me3, and H3K36me3, underscoring the significance of methylation in longevity (Larson et al., 2012). Histone ubiquitination is another type of modification associated with lifespan. The age-related ubiquitination level of H2A was initially observed in Drosophila and has since been demonstrated to be evolutionarily conserved in humans (Gao, Xu, Barnett, & Xu, 2011). Further investigation into potential ubiquitination sites in other histones and exploring their impact on longevity would be invaluable. Despite the correlation between histone modifications and aging has been supported by a wealth of studies, research on the therapeutic natural products in extending lifespan through regulating histone modifications is currently limited, with room for further investigation in this area.

4.1.2. Histone modifications targeted natural products for aging related organ dysfunction

As research into natural products intensifies, it has become evident that these compounds may help mitigate the progression of age-related organ dysfunctions by modulating histone modifications (Fig. 3).

Emodin is an anthraquinone compound derived from rhubarb, found in several medicinal plants, such as *Polygonum cuspidatum*, *Rheum palmatum*, Polygonum Multiflorum, *Cassia obtusifolia* and *Aloe vera* (Dong et al., 2016). Research has shown that emodin has a

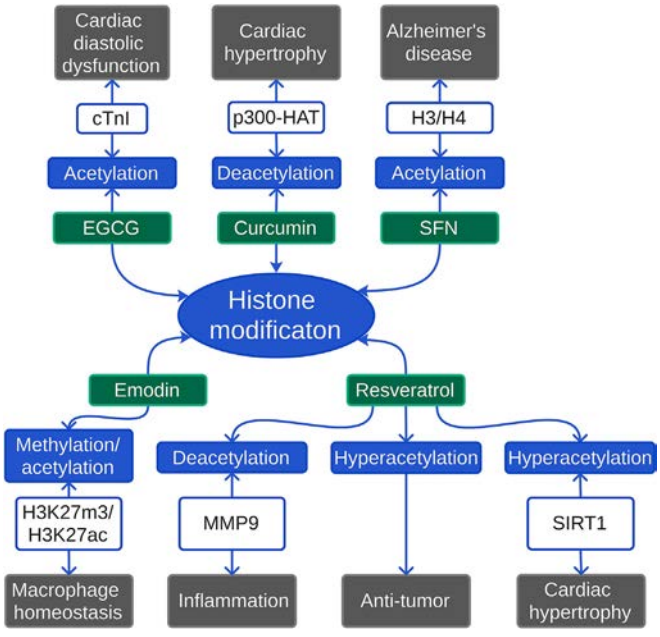


Fig. 3. Histone modifications targeted natural products for aging related organ dysfunctions, cTnI, P300-HAT, H3/H4, H3K27me3/H3K27ac, MMP9 and SIRT1 are involved in deacetylation, acetylation and hyperacetylation.

regulatory effect on the expression of histone modifying enzymes in macrophages under inflammatory stress. It can inhibit the removal of H3K27me3 marks, promote the addition of H3K27ac marks on M1 or M2 polarization key genes, and affect macrophage phagocytosis, migration, and nitric oxide production (Iwanowycz, Wang, Altomare, Hui, & Fan, 2016). In another study, emodin dose dependently inhibited HDAC activity in the heart and promoted histone acetylation in cardiac myocytes, providing a potential strategy for preventing cardiac dysfunction in preclinical animal models of heart failure (Godoy, Lucas, Bender, Romanick, & Ferguson, 2017). Our published study unveiled the anti-heart aging effects of emodin, which can be attributed to the promotion of mitophagy through the enhancement of Parkin protein stability (Wang et al., 2023), indicating the diverse regulatory roles of emodin on aging related organ dysfunction.

Resveratrol was first extracted from Veratrum grandiflorum by Takaoka in 1939 (Breuss, Atanasov, & Uhrin, 2019). It is a phenolic compound naturally found in grapes, blueberries, berries, and peanuts (Breuss et al., 2019). Resveratrol has strong antioxidant properties and has the ability to scavenge ROS and free radicals including hydroxyl and superoxide radicals. The effects of resveratrol in anti-aging have been well-documented in numerous model-based studies (Hongyan Zhu, Qiao, Sun, & Li, 2023; Hosoda et al., 2023; Santos et al., 2023). Resveratrol deacetylates the promoter region of matrix metalloproteinase 9 (MMP9), leading to a decrease in its expression and inhibiting the progression of inflammation (Gao & Ye, 2008). Consistent with this, as a pan-HDAC inhibitor, resveratrol also modifies the acetylation levels of histone in human hepatoblastoma cell (Gaetano et al., 2013). Another study has shown that resveratrol can inhibit histone deacetylase sirtuin 1 (SIRT1)-induced IL-6 activation, thereby protecting H9C2 cells from Ang II-induced cellular hypertrophy (Akhondzadeh et al., 2020). A few researches have highlighted the beneficial effects of resveratrol on clinical parameters of diabetes. For instance, taking grape extract rich in resveratrol every day for a year resulted in a decrease in pro-inflammatory cytokine levels and altered inflammation-linked microRNAs in the peripheral blood mononuclear cells in patients with type 2 diabetes and coronary artery disease complicated with hypertension (Tome-Carneiro et al., 2013). A separate study, administering resveratrol to obese subjects for 30 days suppressed glucagon levels after dinner (Knop et al., 2013). Additionally, type 2 diabetes patients took 250 mg resveratrol every day for three consecutive months, which significantly reduced systolic blood pressure and total cholesterol, although it had no effect on body weight or LDL/HDL cholesterol ratios compared to placebo (Bhatt, Thomas, & Nanjan, 2012). A 45-day resveratrol treatment (1 g/day) also significantly reduced fasting blood glucose and improved insulin resistance (Movahed et al., 2013). Prolonged resveratrol intake further led to reductions in fat mass, body weight as well as systolic blood pressure, triglyceride levels, HbA1c, and creatinine in type 2 diabetes patients (Hausenblas, Schoulda, & Smoliga, 2015; Tabrizi et al., 2020; H. Zhao et al., 2019).

Epigallocatechin Gallate (EGCG) is the most abundant and biologically active natural polyphenol in green tea. Increasing evidence suggests that EGCG inhibits apoptotic and inflammatory by combating oxidative stress in neurons (S. R. Kim, Seong, Kim, & Jung, 2022; Zuo et al., 2024). Cardiac troponin I (cTnI) is a key regulatory factor in diastolic function. Study has demonstrated that EGCG can delay hypoacetylation of cTnI proximal promoter region in aging mice, leading to increased cTnI expression as well as improved cardiac diastolic function (Pan et al., 2017). Short-term green tea treatment has also been shown to result in both methylated and nonmethylated forms of EGCG can be detected in prostate tissue. The methylation of EGCG may exert a preventive effect on prostate cancer by affecting the activity of catechol *O*-methyltransferase (Wang et al., 2010). In addition, administering green tea extract capsules containing 800 mg EGCG can regulate biomarkers associated with colorectal cancer, particularly genes related to WNT signaling, selenoproteins, inflammation and DNA methylation (Hu et al., 2016).

Curcumin is a natural product primarily extracted from the rhizome of turmeric that exerts anticancer, anti-inflammatory, antioxidant, and neuroprotective activities (Stachowiak, Mlynarczyk, & Dlugaszewska, 2024). Study has confirmed that curcumin can prevent ventricular hypertrophy in rat models of heart failure by inhibiting histone acetylation and hypertrophy-associated transcription factors, thereby downregulating gene expression related to cardiac hypertrophy, inflammation and fibrosis (H. L. Li et al., 2008). Clinical researches also indicated that curcumin may delay tumor formation and metastasis by inducing apoptosis, inducing apoptosis, interfering with the cell cycle and exhibiting anti-angiogenic effects (Carroll et al., 2011; Ghalaut et al., 2012; Z. Y. He et al., 2011; Sharma et al., 2001).

Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane, SFN), an aliphatic isothiocyanate, originating from its precursor glucoraphanin, predominantly found in brussels sprouts, broccoli, cauliflower and cabbage, has anti-inflammatory and antioxidant effects (Ruhee & Suzuki, 2024; Schepici, Bramanti, & Mazzon, 2020). It has also been shown to regulate histone acetylation. In human primary cortical neuron cells, sulforaphane increases H3 and H4 acetylation at the promoter regions of brain-derived natriuretic factor (BDNF), leading to enhanced BDNF expression and promoting brain health (Kim et al., 2017).

Nuclear factor erythroid factor 2 (Nrf2) is an essential trancription factor that enhances the body's ability to resist oxidative stress. Increasing studies also suggest that Nrf2 plays a crucial role in preventing and mitigating physiological aging and aging-associated diseases (K. Chen et al., 2021; George, Tharakan, Culberson, Reddy, & Reddy, 2022). Nrf2 served as a target for xanthohumol to improve drug-induced hepatic ferroptosis (Deng et al., 2024). Nevertheless, Nrf2 signaling pathway is regulated by epigenetic mechanisms under different pathological conditions. For instance, modifications of histones in the promoter region can influence the accumulation and activation of Nrf2 in the nucleus (Ray, Huang, & Tsuji, 2015), while histone acetylation affects the expression level of Nrf2-dependent genes (Correa, Mallard, Nilsson, & Sandberg, 2011). The aforementioned compounds, such as emodin, resveratrol, EGCG, curcumin and sulforaphane, which act as Nrf2 agonists, have been extensively studied and shown to be applicable in various inflammatory diseases and age-related organ dysfunction disorders (Franco et al., 2024; Y. He, Xi, Fang, Zhang, & Cai, 2023; Tang et al., 2024; Wang et al., 2024; X. Zhang et al., 2024). Notably, resveratrol and sulforaphane have strong Nrf2 activation effects, and their anti-aging effects may be more pronounced (Lin et al., 2023; Wang et al., 2024). However, the underlying epigenetic regulatory mechanisms warrant further investigation.

Peroxisome Proliferator-Activated Receptor Alpha (PPAR-α), also a member of the nuclear receptor transcription factor family, is mainly involved in regulating energy balance, lipid metabolism, energy balance, and inflammatory response (Bougarne et al., 2018). Previous researches have demonstrated that acute liver injury can be alleviated by pectinsaponins in a Nrf2 and PPARα dependent manner (Li et al., 2023). Recently, its close association with aging has also been widely studied. For example, Xiong Y et al. discovered that the endogenous agonists of PPAR-α, omega-3 polyunsaturated fatty acids, effectively suppressed age-related pathological changes and delayed the aging process (Y. Xiong et al., 2024). Another PPAR receptor agonist, MHY3200, has been shown to alleviate renal inflammation during aging though the ROS/Akt/FoxO1 signaling pathway (M. J. Kim et al., 2021). Many plant-derived natural compounds, including curcumin, flavonoids, and cannabinoids, have also been identified as direct or indirect agonists of PPAR-α, offering protective effects against neurodegenerative diseases (Sanjay Sharma & Lee, 2021). The involvement of PPAR-α in epigenetic regulation and the impact of histone modifications on PPAR-α gene expression have become key areas of research in recent years (Porcuna, Minguez-Martinez, & Ricote, 2021; Warren, Oka, Zablocki, & Sadoshima, 2017). However, whether these natural products also exhibit epigenetic factor-mediated synergistic regulation in PPAR-α activation remains unexplored.

Limited study has focused on the regulatory effects of natural products on histone modifications beyond methylation and acetylation. Extensive screening is crucial to identify potential therapeutics from the diverse array of natural products that serve as histone modifiers in the context of aging and age-associated diseases.

4.2. Alteration in DNA methylation patterns

4.2.1. Alteration of DNA methylation in longevity

DNA methylation is a form of epigenetic modification that can alter gene expression and genetic performance without altering DNA sequence. It involves the covalent attachment of a methyl group to the carbon at position 5 of cytosine within a CpG dinucleotide sequence. This process is facilitated by enzymes known as DNA methyltransferases (DNMTs), forming 5-methylcytosine (5mC) (Chialastri, Sarkar, Schauer, Lamba, & Dey, 2024; A. V. Lee, Nestler, & Chiappinelli, 2024; Schübeler, 2015). DNA methylation can regulate the changes in chromatin structure, DNA conformation and stability, and interactions between proteins and DNA, thereby regulating gene expression. The heritable transfer of this epigenetic mark is regulated by DNMTs. In mammals, there are three main DNMTs: DNMT1, DNMT2, DNMT3A/B/L (Mattei, Bailly, & Meissner, 2022; Moore, Le, & Fan, 2012; Schubeler, 2015). Approximately 1 % of the DNA bases in human cells are methylated. A recent advancement has allowed for accurate biological age estimation of any tissue across all life stages using aging biomarkers derived from DNA methylation data. These "epigenetic clocks" link the developmental and maintenance processes with biological aging, offering valuable insights into a unified theory of aging across the lifespan. (Horvath & Raj, 2018; Kenneth Day et al., 2013).

4.2.2. DNA methylation targeted natural products for longevity and aging related organ dysfunction

Curcumin is originated from turmeric, renowned for its medicinal properties, has been a staple in herbal medicine for addressing skin and gastrointestinal inflammation, as well as aiding in weight management and alleviating indigestion (Vollono et al., 2019). Research has shown that curcumin can reduce DNA hypermethylation level at several CpG sites (360, 341, 329, 316 and 307) within the PPAR-α promoter region in non-alcoholic fatty liver disease (NAFLD) rats (Y. Y. Li et al., 2018; Patsouris, Reddy, Muller, & Kersten, 2006). Moreover, it was confirmed that supplement curcumin has been demonstrated to improve dementia in rodents and adult mice, it improves synaptic plasticity, neuronal repair, and hippocampal neurogenesis (S. J. Kim et al., 2008). In addition, Tetrahydrocurcumin, a metabolic of curcumin, can prolong the lifespan of male mice (Kitani, Osawa, & Yokozawa, 2007), however, whether its mechanism is related to DNA methylation has not yet been elucidated.

Sulforaphane has been found to regulate DNA methylation (Schepici et al., 2020), reduce inflammation, thereby promoting cancer cell proliferation and alleviating inhibition of other age-related diseases (Cao et al., 2023; Kaufman-Szymczyk, Majewski, Lubecka-Pietruszewska, & Fabianowska-Majewska, 2015; Tomasello et al., 2020). Additionally, F. Zhao et al. have proved that sulforaphane can prevent Alzheimer's disease (AD)-associated neurodegeneration by blocking the transmission of pro-inflammatory signals mediated by DNA hypermethylation in the Nrf2 promoter region (F. Zhao, Zhang, & Chang, 2018).

Ascorbic acid, often abbreviated as AA, is a vital vitamin for humans, synthesized by all plants and the majority of animals (Padayatty & Levine, 2016). It is a potent reducing agent and has been suggested as potential remedy for aging-associated diseases (Boo, 2022). Study have shown that ascorbic acid can demethylate the CpG-rich conserved noncoding sequence 2 (CNS2) of the transcription factor forkhead box protein 3 (Foxp3) in T regulatory cells (Tregs), suggesting that ascorbic acid may counteract the pro-inflammatory state associated with aging by modulating immune cell functions (Sasidharan Nair, Song, & Oh, 2016).

The term "quercetum", derived from Latin, refers to the flavonoid quercetin means "oak forest" (Deepika & Maurya, 2022). Quercetum was found in various foods, including apples, berries, broccoli, pepper, coriander, grapes, cherries, red onions, citrus fruits and tea (Di Petrillo, Orrù, Fais, & Fantini, 2022), known for its therapeutic uses in the treatment of allergies, cancer, inflammation and cardiovascular diseases. Quercetin also plays a crucial role in the treatment of aging-related diseases (Cui et al., 2022; Hosseini, Razavi, Banach, & Hosseinzadeh, 2021). Quercetin can protect against mitochondrial dysfunction and alleviate obesity and insulin resistance. These pharmacological effects are due to the inhibition of DNA methylation in the promoter region of peroxisome proliferator activated receptor gamma coactivator 1-α (Pgc-1α), leading to a decrease in its expression (Devarshi, Jones, Taylor, Stefanska, & Henagan, 2017). In the bleomycin induced aging model of human foreskin fibroblasts, quercetin significantly inhibit the secretion of SASP related inflammatory factors to improve the adverse signs of skin aging (Csekes & Rackova, 2021).

Resveratrol modulates the function of SIRT1 and DNMT, restoring long interspersed element 1 (LINE-1) methylation levels under conditions of oxidative stress and inflammation conditions in ARPE-19 cells. These effects indicated resveratrol could be a promising strategy for age-related macular degeneration (AMD) treatment (Maugeri et al., 2018).

Catechins, natural polyphenolic compounds of flavonoid classified as flavan-3-ols (or flavanols). Rich concentrations of catechins are found in fresh tea leaves, broad beans, strawberries, rock-rose leaves, red wine, black grapes and apricots (Bernatoniene & Kopustinskiene, 2018). Treatment with catechins, especially EGCG, in MCF-7 cells inhibits methylation of the human telomerase reverse transcriptase (hTERT) promoter and H3K9ac activity. Therefore, EGCG can alter epigenetic mechanisms through its antioxidant properties, ultimately inducing cell death in MCF-7 and HL60 cells (Berletch et al., 2008). In addition, in another study, EGCG inhibited DNMT activity and reactivated methylation related genes in human colon cancer HT-29 cells, prostate cancer PC3 cells, and cancer KYSE-150 cells (Fang et al., 2003). Together, these results highlight the numerous beneficial properties of EGCG, particularly in relation to aging.

Grape seed proanthocyanidins (GSPs) contain a variety of polyphenolic compounds, including catechins, ellagic acid and resveratrol, which offer potential health benefits. The significant implications of GSPs for epigenetic modulation have been reported. Administration of GSPs in A431 and SCC13 cells inhibits overall DNA methylation, 5mC, and DNMT activity, thereby activating tumor suppressor genes in cancer cells (Vaid, Prasad, Singh, Jones, & Katiyar, 2012).

In conclusion, changes in DNA methylation patterns are closely linked to the onset and progression of various aging-associated diseases, including cancer (Nishiyama & Nakanishi, 2021), osteoporosis (Visconti et al., 2021), neurodegenerative diseases (Martinez-Iglesias et al., 2020), cardiovascular diseases (Westerman & Ordovas, 2020), obesity and diabetes (Chu, Bui, Vu Thi, & Nguyen Thi, 2023) and numerous natural products have been found to be involved in this process (Fig. 4). More and more research support the hypothesis that food and natural products can regulate disease progression by modulating DNA methylation. Investigating the role of natural products as regulators of DNA methylation epigenetic adaptations will provide valuable insights into the disease pathogenesis and openpotential avenues for developing new therapeutic options.

4.3. ATP-dependent chromatin-remodeling

ATP-dependent chromatin remodeling includes the repositioning of nucleosomes to regulate various DNA-templated processes, including replication, recombination, repair, and transcription. This process is mediated by ATP-donating and chromatin remodeling complexes (CRCs) (Hargreaves & Crabtree, 2011; Swer & Sharma, 2021). Currently, CRCs are classified into four families and these families exhibit shared

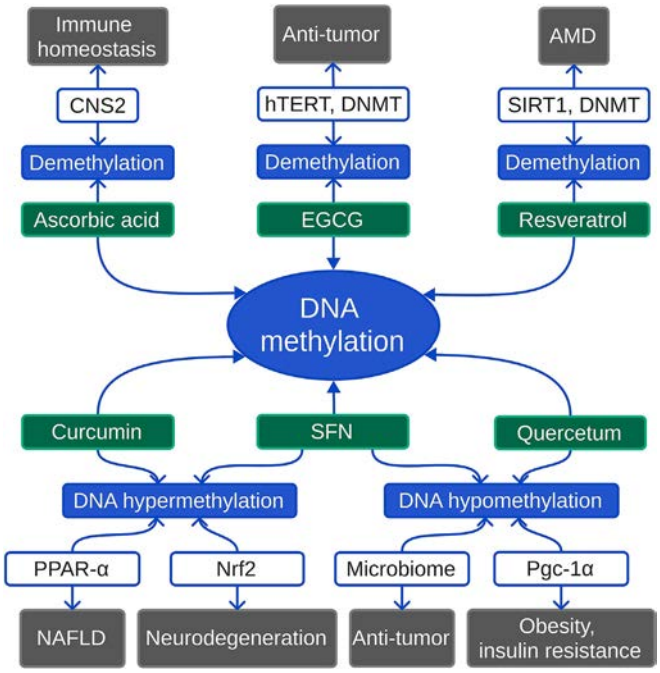


Fig. 4. DNA methylation targeted natural products for aging related organ dysfunctions, CNS2, hTERT, DNMT, SIRT1, PPAR-α, Nrf2, Microbiome and Pgc-1α are involved in demethylation, DNA hypermethylation and DNA hypomethylation.

characteristics, such as a strong affinity for nucleosomes, transcription factors, and chromatin. They also contain specialized protein subunits or domains that interact with histone modification marks and possess DNA-dependent ATPase activity (Clapier, Iwasa, Cairns, & Peterson, 2017; Otto et al., 2023). The effect of CRCs (chromatin-remodeling complexes) on gene expression is mainly governed by the ATPase subunit, which hydrolyzes ATP to enhance nucleosome mobility by breaking the interactions between nucleosomes and DNA (Blossey & Schiessel, 2018). This dynamic transition between euchromatin (open chromatin) and heterochromatin (closed chromatin), orchestrated by chromatin remodelers, allows for precise gene expression control during different developmental stages and cellular states. (Clapier & Cairns, 2009; Ram et al., 2011).

4.3.1. ATP-dependent chromatin-remodeling changes in longevity and aging related organ dysfunction

There is a significant connection between chromatin remodeling and the aging process. Numerous studies have shown that different forms of chromatin manipulation can either positively or negatively impact lifespan. For instance, the loss of function of the key Drosophila chromatin protein, heterochromatin protein 1α (HP1α), has been linked to a shortened lifespan, while overexpression of HP1α can extend lifespan (Feser & Tyler, 2011). Additionally, during cellular senescence, distinct regions of the genome experience notable changes, including the formation of senescence-associated heterochromatin foci (SAHF) and alterations in nucleosome spacing (Narita et al., 2003). These alterations in chromatin structure alterations, together with epigenetic modifications, result in a general loss of heterochromatin in senescent cells, impacting cell function and lifespan (W. Zhang, Qu, Liu, & Belmonte, 2020). A single short induction of Oct4, Klf4, Sox2, and c-Myc (OSKM) in early life protects musculoskeletal functions in mice and improves tissue structures in kidney, skin, spleen and lung in old age. Moreover, treated mice exhibit a 15 % increase in lifespan, with organ-specific changes in DNA methylation changes associated with rejuvenation by the treatment (Alle et al., 2022). The chromatin remodeling factor SWI/SNF activates transcription through presumed local chromatin remodeling in the promoter region of the forkhead box O (FOXO) transcription factor DAF-16 (DAF-16/FOXO), thereby promoting stress resistance and longevity in *Caenorhabditis elegans* (Riedel et al., 2013). Chromodomain helicase DNA binding protein 1 (CHD1) regulates the incorporation of H3.3 into adult brain chromatin to maintain metabolic homeostasis and support normal lifespan (Schoberleitner et al., 2021). Knockout of Brahma, a chromatin remodeling gene, reduces the reproductive capacity and lifespan in common bed bugs (Basnet & Kamble, 2018).

Metabolism and chromatin are intricately connected. As individuals age, alterations in mitochondrial-derived vesicles, such as enhanced lysosomal degradation of citrate carriers, can influence the cellular localization of acetyl-CoA. This dysregulation can lead to decreased lipid synthesis and epigenetic changes that affect chromatin plasticity, ultimately resulting in altered transcription and diminished osteogenic capacity in aged mesenchymal stem cells (Reid, Dai, & Locasale, 2017). Treatment with acetate has shown the ability to restore cytoplasmic acetyl-CoA levels, improve histone acetylation, and enhance chromatin plasticity, thereby reversing the impaired osteogenic ability of aged mesenchymal stem cells (Pouikli et al., 2021). Decreased acetyl-CoA levels due to mitochondrial stress can signal the nucleosome remodeling and deacetylase (NuRD) complex to mediate chromatin modifications, promoting longevity (Di Zhu et al., 2020). This complex is involved in regulating chromatin remodeling. Furthermore, mitochondrial stress can induce nuclear accumulation of NuRD components, and the increased expression of these parts can extend lifespan in nematodes(D. Zhu, Li, & Tian, 2022).

Alterations in chromatin remodeling play a role in the onset and advancement of various age-associated organ malfunctions, including cardiovascular diseases, and cancer. Disruptions in chromatin remodeling processes can lead to memory-related brain disorders (D. Jiang, Li, Guo, Tang, & Liu, 2023). Mutant mice lacking the chromatin remodeling-associated protein BRG1-associated factor 170 (BAF170) exhibit adaptive behavioral defects, and loss of BAF170 linked to learning and memory deficits (Tuoc et al., 2017). Similarly, humanized mice carrying a mutation in the chromodomain helicase binding protein 4 (CHD4) displays developmental defects such as biventricular cardiac noncompaction (Shi et al., 2023). Mutations in SWI/SNF subunits are frequently observed in various cancers, with ARID domain-containing protein 1 A (ARID1A) being one of the most commonly mutated subunits (J. N. Wu & Roberts, 2013). Inhibiting the mSWI/SNF complex with specific inhibitors has demonstrated efficacy in inhibiting tumor growth and boosting antitumor immune responses in both cell and animal studies (Zhou et al., 2023). Moreover, studies indicate that activating transcription factor 3 (ATF3) can induce senescence in HUVECs by modulating chromatin accessibility and regulating the expression of genes involved in aging-related genes (C. Zhang et al., 2021).

4.3.2. Potential anti-aging drugs from natural products targeting ATP-dependent chromatin-remodeling

Only a few natural products have been identified for their modulation effects on ATP-dependent chromatin-remodeling, further research is needed to confirm their potential roles in aging and age-related organ dysfunctions.

Green tea polyphenols (GTPs) contain active components such as catechins and EGCG. Exposure to GTPs has been shown to decrease the expression of methyl-CpG-binding domain protein 1 (MBD1), MBD4, Methyl-CpG-binding protein 2 (MeCP2), HDAC1–3, while increasing the levels of H3K9/18 ac. Additionally, treatment with GTPs has been found to reduce the accessibility of MBD2 to the binding sites of the transcription factor Sp1, resulting in enhanced transcriptional activation of the glutathione S-transferase P (GSTP1). These findings highlight the dual potential of GTPs to modulate DNA methylation and chromatin remodeling, making them promising candidates for prostate cancer chemoprevention (Pandey, Shukla, & Gupta, 2010). Moreover, EGCG affects chromatin structure by reducing the level of

HP1α and HP1γ in human microvascular endothelial cells (HMVECs) and HUVECs. (Ciesielski, Biesiekierska, & Balcerczyk, 2020).

Germacrone, derived from Rhizoma curcuma, exhibits anti-tumor effects in numerous human cancer cells. Blocking estrogen receptor alpha (ERα) recruitment to the estrogen response element on chromatin. This disrupts the binding of the SWI/SNF complex and RNA polymerase II, hindering estrogen-induced chromatin accessibility and suppressing ERα-mediated gene expression in MCF-7 cells at the transcriptional level.

In summary, ATP-dependent chromatin remodelers are emerging as potential therapeutic targets for age-related conditions (Swer & Sharma, 2021). It is crucial to comprehend how natural products regulate ATP chromatin remodeling to develop treatments that can mitigate the aging process.

4.4. RNA modification changes

4.4.1. RNA modification changes in longevity and aging related organ dysfunction

RNA modification is a crucial post-transcriptional regulatory mechanism that involves altering the chemical nature and structure of RNA by adding chemical groups to the RNA molecule. This process plays a significant role in regulating RNA stability, translocation, and translation (Roundtree, Evans, Pan, & He, 2017). More than 150 distinct RNA modifications have been discovered, among them, 5-methylcytosine (m^5C), pseudouridine (ψ), 5-hydroxymethylcytosine (hm^5C), N1-methyladenine (m^1A), N7-methylguanosine (m^7G), and N6,2′-*O*-dimethyladenine nucleoside (m^6A) are extensively investigated (L. Y. Zhao, Song, Liu, Song, & Yi, 2020). These dynamic RNA modifications have diverse biological functions and are instrumental in regulating many physiological and pathological processes, including embryonic development, tumorigenesis, neurodegenerative diseases, and ultimately impacting the overall lifespan of an organism (Roignant & Soller, 2017).

N6-methyladenine (m6A) is a prevalent RNA methylation modificatio. This modification can be "written" by writers (methyltransferases including METTL3/14, METTL16, WTAP, RBM15/15B, VIRMA, CBLL1 and others), "erased" by erasers (demethylases like FTO and ALKBH5), and "read" by readers (m6A-specific binding proteins such as YTHDF1/2/3, YTHDC1/2, IGH2BP1/2/3 and others) (L. Chen et al., 2023; Wang et al., 2023). Alterations in m6A modification levels in senescent cells affect the expression of key genes involved in inflammation, cell proliferation, and metabolism (Fan, Lv, Chen, Peng, & Zhang, 2023; Sun et al., 2022). Studies on human peripheral blood mononuclear cells (PBMCs) have shown lower m6A modification levels in PBMCs of the elderly, with the expression of m6A-modified transcripts was greater than that of unmodified transcripts (Min et al., 2018). Methyltransferase-like protein 3 (METTL3) downregulation in human bone marrow mesenchymal stem cells (hMSCs) leads to reduced m6A modification and accelerated aging after METTL3 gene knockout (Wu et al., 2020). Additionally, aside from m6A modification, m5C modification of RNA has emerged as an epitranscriptional mark linked to aging. NOP2/Sun domain family, member 2 (NSUN2-mediated m5C modification in the 3′-untranslated region (3′-UTR) of cyclin-dependent kinase inhibitor 2 A (CDKN2A) mRNA and stabilizes it, promoting cellular senescence (X. Zhang et al., 2012). Interestingly, other studies showed the opposite function of NSUN2 exhibits dual roles in cellular senescence, as it can promote CDK1 mRNA and the 5′-UTR of the CDK inhibitor 1B (CDKN1B) mRNA, facilitating the translation of CDK1 through m^5C modification while inhibiting CDKN1B translation through m5C modification, alleviating replicative senescence (Hao Tang et al., 2015; Xing et al., 2015). Despite no relevant natural products currently known to delay the aging process and extend lifespan through RNA modification. However, caloric restriction (CR) has demonstrated lifespan extension in rodents, and these effects of CR are at least partially attributed to alleviating age-related epigenetic changes associated with aging, including RNA m6A modifications (Hahn et al., 2017; Ma et al., 2020). Rat studies have shown that CR effectively counteracts the age-related downregulation of the RNA m6A reader protein Y-box-binding protein 1 (YBX1), a key driver of stem cell senescence (Ma et al., 2020).

The role of RNA modifications in aging related organ dysfunctions has also been investigated. Age-related obesity contributes to atherosclerosis, with studies indicating that zinc-finger protein 217 (FP217) can reduce m^6A expression by upregulating the expression of alpha-ketoglutarate-dependent dioxygenase FTO, resulting in increased adipogenesis and obesity (Song et al., 2019). Additionally, methyltransferase-like protein 14 (METTL14) has been shown to directly bind to FOXO1 mRNA, enhancing its translation by increasing m^6A modification, leading to elevated expression of adhesion molecules and exacerbating endothelial inflammation, thereby contributing to atherosclerosis progression (Jian et al., 2020). Furthermore, the deletion of FTO in cardiomyocytes has been linked to accelerated heart failure progression (Berulava et al., 2019). Age-related neurodegenerative diseases are multifactorial, with changes in RNA modifications playing a pivotal role in their pathogenesis. As a prevalent RNA modification in the brain, m^6A modification has been implicated in the development of Alzheimer's disease. Study has shown reduced expression levels of METTL13 and decreased m^6A levels in Alzheimer's disease mice model (Shafik et al., 2021). In another study, conserved reductions of m^6A modifications of synaptic transcripts during aging and neurodegeneration development were demonstrated (Castro-Hernandez et al., 2023). Osteoporosis patients and mouse models exhibit reduced METTL3 expression and m^6A modification levels, which impact bone formation. Mechanically, METTL3 mediates the m^6A methylation of runt-related transcription factor 2 (RUNX2), a key osteogenesis factor, enhancing its stability and thereby promoting osteogenesis (G. Yan et al., 2020). Furthermore, upregulation of FTO by growth differentiation factor 11 (GDF11) during aging and osteoporosis stabilizes PPAR-γ mRNA through m6A demethylation, prompting bone mesenchymal stem cells to differentiate into adipocytes instead of osteoblasts (G. S. Shen et al., 2018). In contrast to DNA and protein methylation modifiers prone to mutations in tumorigenesis, RNA methyltransferases and demethylases are commonly overexpressed in cancer tissues (Lan et al., 2019). Deregulation in the m6A reading process can independently enhance oncogenic signals (Liu et al., 2023). Notably, STC-15, an inhibitor of m6A methyltransferase, has been developed and shown to be effective in stimulating innate immune pathways, inhibiting tumor progression, and boosting the therapeutic response to anti-PD1 therapy, while promoting long-lasting antitumor immunity in preclinical models of colorectal cancer and lymphoma (Vu et al., 2017).

In addition to mRNA, ncRNAs play a crucial role in regulating epigenetic modifications by influencing chromatin structure and interacting with other mechanisms. Various types of ncRNAs, such as microRNAs (miRNAs), lncRNAs, tRNA-derived small RNAs (tsRNAs), ribosomal RNA (rRNA), PIWI-interacting RNAs (piRNAs), and circular RNAs (circRNAs), are involved in these regulatory processes (S. S. Kim & Lee, 2019). Specific miRNAs like miR-29, miR-34a, and miR-9 are linked to aging processes (Owczarz et al., 2017; Ugalde et al., 2011), while miR-1468-3p, miR-217, and miR-203 are correlated with human aging-related cardiac dysfunction(de Yebenes et al., 2020; R. Lin et al., 2020; Zhao, Tang, et al., 2024). Others, such as miR-181a, miR-181ab1, miR-21, and miR-543, play roles in T cell aging and various age-related conditions like fibrosis, stem cell aging, and osteoarthritis (C. Kim et al., 2019; S. Lee et al., 2014; Liu et al., 2020; Vasa-Nicotera et al., 2011; Y. Yan et al., 2019; Ye et al., 2018). In aging-induced osteoporosis, lncRNA Xist and miR-19a-3p impact bone cell functions, with up-regulating miR-19a-3p potentially preventing bone loss and enhancing bone formation (S. Chen et al., 2020). Super-enhancer associated lncRNA NEAT1 is a key regulator of the bone-fat switch in aged bone marrow stem cells (Zhang et al., 2022). ENSMUST00000134285 is implicated in heart cell aging (Chun Yang et al., 2018), H19 influences endothelial

Table 2
Profiles of potential natural products that extend lifespan and ameliorate aging related organ dysfunctions in published studies.

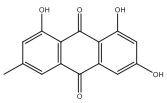
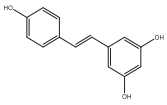
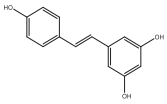
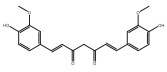
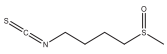
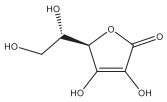
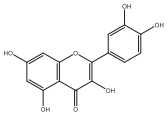
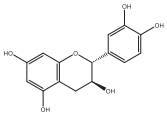
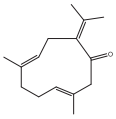
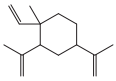
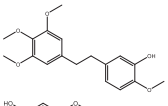
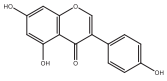
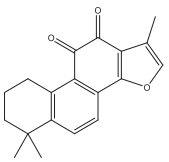
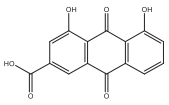
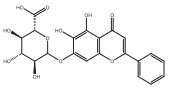
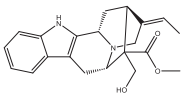
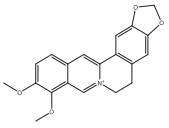
Natural products	Source	Epigenetic reprograming types	Targets	Effects	Reference	Structural formula
Emodin	*Polygonum cuspidatum*	Histone modification	↑H3K27me3; ↑NO; ↓HDAC	Promoting mitophagy and preventing cardiac dysfunction in heart failure	(Dong et al., 2016); (Iwanowycz et al., 2016); (Iwanowycz et al., 2016; Y. Li et al., 2018);(Godoy et al., 2017); (Godoy et al., 2017)	
Resveratrol	Peanuts	Histone modification; DNA methylation; RNA modification	↓ROS; ↓HDAC; ↓IL-6; ↑LIN*E*-1	Improving Ang II-induced cell hypertrophy and anti-heart aging; preventing and/or treating age-related macular degeneration; improving liver function	(Breuss et al., 2019); (Breuss et al., 2019);(Hongyan Zhu et al., 2023; Hosoda et al., 2023; Santos et al., 2023);(Gao & Ye, 2008);(Gaetano et al., 2013);(Akhondzadeh et al., 2020);(Maugeri et al., 2018);(J. Wu, Shi, et al., 2020)	
Epigallocatechin Gallate	Green tea	Histone modification; RNA modification	↓ROS; ↑cTnI; ↑YTHDF2; ↓CCNA2; ↓CDK2	Anti-inflammatory and anti-apoptotic effects; improving cardiac diastolic function	(S. R. Kim et al., 2022; Zuo et al., 2024); (Pan et al., 2017);(R. Wu et al., 2018)	
Curcumin	Curcuma	Histone modification; DNA methylation	↓PPAR-α	Preventing ventricular hypertrophy; reversing non-alcoholic fatty liver disease	(Stachowiak et al., 2024);(H. L. Li et al., 2008);(Vollono et al., 2019);(Y. Y. Li et al., 2018; Patsouris et al., 2006);(S. J. Kim et al., 2008);(Kitani et al., 2007)	
Sulforaphane	Broccoli	Histone modification; DNAmethylation	↑BDNF	Anti-inflammatory and antioxidant stress; promoting brain health and inhibiting AD-associated neurodegeneration	(Ruhee & Suzuki, 2024; Schepici et al., 2020);(J. Kim et al., 2017);(Schepici et al., 2020);(Cao et al., 2023; Kaufman-Szymczyk et al., 2015; Tomasello et al., 2020);(F. Zhao et al., 2018)	
CAscorbic acid	All plants	DNA methylation	↑Foxp3	A potent reducing agent and improving aging-associated diseases	(Padayatty & Levine, 2016);(Boo, 2022);(Sasidharan Nair et al., 2016)	
Quercetin	Apple and various foods	DNA methylation	↓Pgc-1α	Protecting against mitochondrial dysfunction and alleviating HFD-induced obesity and insulin resistance	(Deepika & Maurya, 2022);(Di Petrillo et al., 2022);(Cui et al., 2022; Hosseini et al., 2021);(Devarshi et al., 2017)	
Catechins	Fresh tea leaves	DNA methylation	↓H3K9	Anti-oxidative properties	(Bernatoniene & Kopustinskiene, 2018);(Berletch et al., 2008);(Fang et al., 2003)	
Green tea polyphenols	Green tea	ATP-dependent chromatin remodeling	↓MBD1; ↓MBD4; ↓MeCP2; ↓HDAC 1–3; ↑LysH9/18; ↑H4; ↓HP1α; ↓HP1γ	Prostating cancer chemoprevention	(Pandey et al., 2010);(Ciesielski et al., 2020	
Germacrone	Rhizoma curcuma	ATP-dependent chromatin remodeling	↓ERα	Antitumor activity	("Recent advances in clinical science. Abstracts of the 89th meeting of the Association of Clinical Scientists. May 11 to 14, 1989, Charlottesville, Virginia,"1989)	
β-elemene	Curcuma	RNA modification	↓METTL3 ↓LC3B; ↓ATG5; ↓ATG7	Inhibiting the growth of lung cancer cells	(Liu, Cai, et al., 2020, Liu, Li, et al., 2020);(Feng et al., 2022)	
Erianin	Dendrobium chrysotoxum	RNA modification	↑ALOX12; ↑P53	Treatment on renal cancer	(H. Shen et al., 2023)	
Genistein	Soy	RNA modification	↑E-cadher; ↑ALKBH5; ↓Snail	Improving renal fibrosis	(Ning et al., 2020)	

Table 2 (*continued*)

Natural products	Source	Epigenetic reprograming types	Targets	Effects	Reference	Structural formula
Tanshinone IIA	Salvia	RNA modification	↓ALKBH5	Inhibiting Ang II-induced hypertrophy in vitro and TAC-induced cardiac hypertrophy in vivo	(Zhang, Chen, et al., 2022)	
Rhein	*Rheum palmatum*	RNA modification	↓FTO active site	Reduction of infectivity caused by various coronaviruses, including SARS-CoV-2	(B. Chen et al., 2012; Zannella et al., 2021)	
Baicalin	Dry root of Scutellaria	RNA modification	↓HKDC1; ↓METTL3; ↑HKDC/JAK2/STAT1/caspase-3	Inhibiting the invasion and metastasis of T2D-induced hepatocellular cancer	(H. Jiang et al., 2022)	
Humantenine	Gelsemium elegansa	RNA modification		Inhibiting colon cancer	(Y. Wu et al., 2022)	
Berberine	Coptis chinensis and herbs	RNA modification	↑miR-185-5p; ↑KLF7; ↑5mC ↑Caspase3; ↑DNMTs	Inhibiting gastric cancer	(Babaeenezhad et al., 2024); (Wang, Tang, et al., 2023)	

aging (Hofmann et al., 2019), LncR-SMAL affects cardiac function in aging individuals (Liu, Bai, et al., 2022), and Zeb1os1 plays diverse roles in aging processes (Liu et al., 2024). During aging, tsRNAs and rRNAs typically increase, while piRNAs decrease in organisms such as *C. elegans*(Kato, Chen, Inukai, Zhao, & Slack, 2011). Additionally, circRNAs accumulate in aging brains of Drosophila (Westholm et al., 2014) and *C. elegans* (Cortes-Lopez et al., 2018)." Although the significant role of ncRNAs in aging has been established, the natural products that target ncRNAs and their potential anti-aging effects remain to be explored. The utilization of ncRNAs as genetic tools for the development of anti-aging nucleic acid therapies has emerged as a viable possibility.

4.4.2. Potential anti-aging drugs from natural products targeting RNAmodifications

Despite there is currently a lack of direct evidence linking RNA modification-targeting natural products to aging and age-related disorders, research on identified natural products used for modulating RNA modifications in other diseases can serve as valuable references in the field of aging research.

β-elemene, a sesquiterpenoid compound derived from Curcuma wenyujin, acts as an inhibitor of METTL3. In non-small cell lung cancer (NSCLC), β-elemene reduces autophagy-related proteins like LC3B, ATG5, and ATG7 through METTL3 suppression. This inhibition effectively hinders tumor cell autophagy and proliferation (Liu et al., 2020). Moreover, β-elemene can lower the m6A modification level of phosphatase and tensin homolog (PTEN) mRNA by inhibiting METTL3, leading to increased PTEN protein expression and subsequent inhibition of lung cancer cell growth (Feng et al., 2022).

Erianin, a bibenzyl natural compound derived from Dendrobium chrysotoxum, has been shown to induce ferroptosis in renal cancer stem cells. This mechanism involves enhancing m6A modification of polyunsaturated fatty acid lipoxygenase ALOX12 and cellular tumor antigen p53 mRNA. Ultimately, this process exerts a therapeutic effect on renal cancer. (H. Shen, Geng, Nie, & Liu, 2023).

Genistein, a key component in soy isoflavones, shares structural similarities with mammalian estrogen-estradiol, possessing a diphenolic hydroxyl group typical of estrogen. This structure grants Genistein various physiological activities akin to estrogen's effects. Research suggests that Genistein boosts E-cadherin expression while diminishing snail expression through the upregulation of alkylated DNA repair protein ALKBH5, ultimately ameliorating renal fibrosis (Ning et al., 2020).

Resveratrol reduces Aflatoxin B1 (AFB1)-induced ROS accumulation, altering m6A modification-related proteins like METTL3, FTO, and YTHDF2, improving liver function (Wu et al., 2020). EGCG elevates YTHDF2 expression, decreasing Cyclin-A2 (CCNA2) and CDK2 levels, which halts mitotic clonal expansion and inhibits adipogenesis (R. Wu et al., 2018). Tanshinone IIA (Tan IIA) inhibits ALKBH5-mediated m6A modification of galectin-3, preventing angiotensin II-induced and TAC-induced cardiac hypertrophy (Zhang et al., 2022). Rhein competitively binds to the FTO active site, inhibiting m6A demethylation, and reducing infectivity of various coronaviruses (B. Chen et al., 2012; Zannella et al., 2021). Baicalin targets METTL3 to inhibit DNA 5mC and RNA m6A modifications in the HKDC1 gene, suppressing invasion and metastasis in diabetes-induced hepatocellular cancer (H. Jiang et al., 2022). Humantenine induces cell death in colon cancer cells by modulating 11 RNA m6A modification regulators (Y. Wu et al., 2022).

The isoquinoline quaternary alkaloid berberine is derived from medicinal herbs, including Coptis chinensis, Coptis japonica, and Coptis rhizome (Wu, Gan, et al., 2020; R. Wu et al., 2018; Zhang, Chen, et al., 2022; B. Chen et al., 2012; Zannella et al., 2021; H. Jiang et al., 2022; Y. Wu et al., 2022). Study has indicated that berberine modulates the expression of miR-185-5p, krueppel-like factor 7 (KLF7), caspase-3, and DNMTs and increases 5mC levels in gastric cancer cells, while formulated novel chitosan/pectin nanoparticles (NPs) loaded with berberine enhanced above effects (Babaeenezhad, Rashidipour, Jangravi, Moradi Sarabi, & Shahriary, 2024). Berberine has been shown to act as an effective insulin sensitizer, with similar properties to metformin (J. Yang et al., 2012). It has also been used to improve insulin resistance and enhance ovulation in women with polycystic ovary syndrome (PCOS) (An et al., 2014; Y. Li et al., 2013). In cardiovascular research, a study on acute coronary syndrome showed that berberine in addition to standard

therapy significantly reduced markers of inflammation, such as ICAM-1, MMP-9, CRP, IL-6, VCAM-1, and MCP-1, suggesting that berberine may improve clinical outcomes through its anti-inflammatory effects (Meng et al., 2012). Furthermore, a study published by our group unveiled the anti-heart aging effects of berberine and its derivative tetrahydroberberrubine, which can be attributed to the promotion of mitophagy by enhancing PHB2 mRNA stability, highlighting the potential anti-aging properties of berberine (Wang, Tang, et al., 2023).

In short, RNA modification genes involved in plays a pivotal role in various age-related diseases by influencing RNA stability, translation, and protein levels of key disease-related genes. Exploring natural products that modulate RNA modification offers new avenues for potential therapeutic interventions in age-related conditions.

5. Conclusions and perspectives

Epigenetic changes are crucial in controlling longevity and the dysfunctions of age-related organs. However, research on natural products targeting epigenetic reprogramming and their potential role in delaying aging is currently limited (Table 2). This scarcity can be attributed to two main reasons: Firstly, the majority of epigenetic modifications occur within the cell nucleus, yet the limited number of natural products capable of effectively penetrating the nucleus restricts their direct regulatory effect on these modifications. Secondly, despite many natural products exhibit pronounced protective effects in vitro experiments, challenges related to low bioavailability or unstable physicochemical properties in vivo hinder their further development. It is worth noting that some natural products have already been included in the list of health supplements as dietary ingredients. For example, flavonoids grape seed extract could improve inflammation, blood glucose and oxidative stress in cardiovascular high-risk subjects (Kar, Laight, Rooprai, Shaw, & Cummings, 2009). Adding curcumin to diet can effectively prevent and treat obesity, diabetes, atherosclerosis, metabolic syndrome and other diseases (Aggarwal, 2010), berberine hydrochloride capsules can improve the heart metabolism of patients with diabetes (Nematollahi et al., 2022). Given the positive impact of natural products on human health and aging related diseases. In the future, there will definitely be more natural products entering the ranks of health supplements to help human health and aging. Although the recognized importance of natural products currently, there is a critical need to leverage modern biotechnological research tools, such as computer-aided drug design and screening, structural modification of natural product lead compounds, construction of nanodrug delivery systems and the re-development of natural products associated with Antibody-Drug Conjugate (ADC), to advance the development of natural products with demonstrated anti-aging and epigenetic regulatory properties. In conclusion, this review offers an overview of both established and promising natural products for delaying aging, serving as a valuable reference for advancing the clinical translation of natural products in anti-aging interventions.

CRediT authorship contribution statement

Xin Liu: Writing – review & editing, Writing – original draft. **Jing Feng:** Writing – original draft. **Madi Guo:** Writing – original draft. **Chen Chen:** Writing – original draft. **Tong Zhao:** Writing – original draft. **Xiuxiu Sun:** Writing – original draft. **Yong Zhang:** Writing – review & editing, Writing – original draft, Supervision.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (82273919, 82270396, U24A20813).

References

Abdelgawad, I. Y., Sadak, K. T., Lone, D. W., Dabour, M. S., Niedernhofer, L. J., & Zordoky, B. N. (2021). Molecular mechanisms and cardiovascular implications of cancer therapy-induced senescence. *Pharmacology & Therapeutics 221*, Article 107751.

Adelman, E. R., Huang, H. T., Roisman, A., Olsson, A., Colaprico, A., Qin, T., ... Figueroa, M. E. (2019). Aging human hematopoietic stem cells manifest profound epigenetic reprogramming of enhancers that may predispose to leukemia. *Cancer Discovery 9*, 1080–1101.

Aggarwal, B. B. (2010). Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annual Review of Nutrition 30*, 173–199.

Akhondzadeh, F., Astani, A., Najjari, R., Samadi, M., Rezvani, M. E., Zare, F., ... Safari, F. (2020). Resveratrol suppresses interleukin-6 expression through activation of sirtuin 1 in hypertrophied H9c2 cardiomyoblasts. *Journal of Cellular Physiology 235*, 6969–6977.

Alle, Q., Le Borgne, E., Bensadoun, P., Lemey, C., Bechir, N., Gabanou, M., ... Lemaitre, J. M. (2022). A single short reprogramming early in life initiates and propagates an epigenetically related mechanism improving fitness and promoting an increased healthy lifespan. *Aging Cell 21*, Article e13714.

An, Y., Sun, Z., Zhang, Y., Liu, B., Guan, Y., & Lu, M. (2014). The use of berberine for women with polycystic ovary syndrome undergoing IVF treatment. *Clinical Endocrinology 80*, 425–431.

Andrews, C., Nettle, D., Larriva, M., Gillespie, R., Reichert, S., Brilot, B. O., ... Bateson, M. (2017). A marker of biological age explains individual variation in the strength of the adult stress response. *Royal Society Open Science 4*, Article 171208.

Asadi Shahmirzadi, A., Edgar, D., Liao, C. Y., Hsu, Y. M., Lucanic, M., Asadi Shahmirzadi, A., ... Lithgow, G. J. (2020). Alpha-ketoglutarate, an endogenous metabolite, extends lifespan and compresses morbidity in aging mice. *Cell Metabolism 32*(447–456), Article e446.

Ashton, N. J., Janelidze, S., Al Khleifat, A., Leuzy, A., van der Ende, E. L., Karikari, T. K., ... Hansson, O. (2021). A multicentre validation study of the diagnostic value of plasma neurofilament light. *Nature Communications 12*, 3400.

Auro, K., Joensuu, A., Fischer, K., Kettunen, J., Salo, P., Mattsson, H., ... Perola, M. (2014). A metabolic view on menopause and ageing. *Nature Communications 5*, 4708.

Babaeenezhad, E., Rashidipour, M., Jangravi, Z., Moradi Sarabi, M., & Shahriary, A. (2024). Cytotoxic and epigenetic effects of berberine-loaded chitosan/pectin nanoparticles on AGS gastric cancer cells: Role of the miR-185-5p/KLF7 axis, DNMTs, and global DNA methylation. *International Journal of Biological Macromolecules 260*, Article 129618.

Barcena, C., Lopez-Otin, C., & Kroemer, G. (2019). Methionine restriction for improving progeria: Another autophagy-inducing anti-aging strategy? *Autophagy 15*, 558–559.

Basnet, S., & Kamble, S. T. (2018). Knockdown of the chromatin remodeling gene Brahma by RNA interference reduces reproductive fitness and lifespan in common bed bug (Hemiptera: Cimicidae). *Journal of Medical Entomology 55*, 534–539.

Beausejour, C. M., Krtolica, A., Galimi, F., Narita, M., Lowe, S. W., Yaswen, P., & Campisi, J. (2003). Reversal of human cellular senescence: Roles of the p53 and p16 pathways. *The EMBO Journal 22*, 4212–4222.

Belsky, D. W., Caspi, A., Arseneault, L., Baccarelli, A., Corcoran, D. L., Gao, X., ... Moffitt, T. E. (2020). Quantification of the pace of biological aging in humans through a blood test, the DunedinPoAm DNA methylation algorithm. *Elife 9*.

Ben-Zvi, A., Miller, E. A., & Morimoto, R. I. (2009). Collapse of proteostasis represents an early molecular event in Caenorhabditis elegans aging. *Proceedings of the National Academy of Sciences of the United States of America 106*, 14914–14919.

Berdyshev, G. D., Korotaev, G. K., Boiarskikh, G. V., & Vaniushin, B. F. (1967). Nucleotide composition of DNA and RNA from somatic tissues of humpback and its changes during spawning. *Biokhimiia 32*, 988–993.

Berletch, J. B., Liu, C., Love, W. K., Andrews, L. G., Katiyar, S. K., & Tollefsbol, T. O. (2008). Epigenetic and genetic mechanisms contribute to telomerase inhibition by EGCG. *Journal of Cellular Biochemistry 103*, 509–519.

Bernatoniene, J., & Kopustinskiene, D. M. (2018). The role of Catechins in cellular responses to oxidative stress. *Molecules 23*.

Berulava, T., Buchholz, E., Elerdashvili, V., Pena, T., Islam, M. R., Lbik, D., ... Toischer, K. (2019). Changes in m6A RNA methylation contribute to heart failure progression by modulating translation. *European Journal of Heart Failure 22*, 54–66.

Bhatt, J. K., Thomas, S., & Nanjan, M. J. (2012). Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. *Nutrition Research 32*, 537–541.

Birch, J., Barnes, P. J., & Passos, J. F. (2018). Mitochondria, telomeres and cell senescence: Implications for lung ageing and disease. *Pharmacology & Therapeutics 183*, 34–49.

Blossey, R., & Schiessel, H. (2018). The latest twists in chromatin remodeling. *Biophysical Journal 114*, 2255–2261.

Boo, Y. C. (2022). Ascorbic acid (vitamin C) as a cosmeceutical to increase dermal collagen for skin antiaging purposes: Emerging combination therapies. *Antioxidants (Basel) 11*.

Bougarne, N., Weyers, B., Desmet, S. J., Deckers, J., Ray, D. W., Staels, B., & De Bosscher, K. (2018). Molecular actions of PPARalpha in lipid metabolism and inflammation. *Endocrine Reviews 39*, 760–802.

Breuss, J. M., Atanasov, A. G., & Uhrin, P. (2019). Resveratrol and its effects on the vascular system. *International Journal of Molecular Sciences 20*.

Bucaciuc Mracica, T., Anghel, A., Ion, C. F., Moraru, C. V., Tacutu, R., & Lazar, G. A. (2020). MetaboAge DB: A repository of known ageing-related changes in the human metabolome. *Biogerontology 21*, 763–771.

Buckley, M. T., Sun, E. D., George, B. M., Liu, L., Schaum, N., Xu, L., ... Brunet, A. (2023). Cell-type-specific aging clocks to quantify aging and rejuvenation in neurogenic regions of the brain. *Nature Aging 3*, 121–137.
Calculli, G., Lee, H. J., Shen, K., Pham, U., Herholz, M., Trifunovic, A., ... Vilchez, D. (2021). Systemic regulation of mitochondria by germline proteostasis prevents protein aggregation in the soma of C. Elegans. *Science Advances 7*.
Cao, S., Hu, S., Jiang, P., Zhang, Z., Li, L., & Wu, Q. (2023). Effects of sulforaphane on breast cancer based on metabolome and microbiome. *Food Science & Nutrition 11*, 2277–2287.
Carroll, R. E., Benya, R. V., Turgeon, D. K., Vareed, S., Neuman, M., Rodriguez, L., ... Brenner, D. E. (2011). Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. *Cancer Prevention Research (Philadelphia, Pa.) 4*, 354–364.
Castellano, J. M., Mosher, K. I., Abbey, R. J., McBride, A. A., James, M. L., Berdnik, D., ... Wyss-Coray, T. (2017). Human umbilical cord plasma proteins revitalize hippocampal function in aged mice. *Nature 544*, 488–492.
Castro-Hernandez, R., Berulava, T., Metelova, M., Epple, R., Pena Centeno, T., Richter, J., ... Fischer, A. (2023). Conserved reduction of m(6)A RNA modifications during aging and neurodegeneration is linked to changes in synaptic transcripts. *Proceedings of the National Academy of Sciences of the United States of America 120*, Article e2204933120.
Chan, J. C., & Maze, I. (2020). Nothing is yet set in (hi)stone: Novel post-translational modifications regulating chromatin function. *Trends in Biochemical Sciences 45*, 829–844.
Chen, B., Ye, F., Yu, L., Jia, G., Huang, X., Zhang, X., ... Yang, C. G. (2012). Development of cell-active N6-methyladenosine RNA demethylase FTO inhibitor. *Journal of the American Chemical Society 134*, 17963–17971.
Chen, K., Wang, S., Sun, Q. W., Zhang, B., Ullah, M., & Sun, Z. (2021). Klotho deficiency causes heart aging via impairing the Nrf2-GR pathway. *Circulation Research 128*, 492–507.
Chen, L., Gao, Y., Xu, S., Yuan, J., Wang, M., Li, T., & Gong, J. (2023). N6-methyladenosine reader YTHDF family in biological processes: Structures, roles, and mechanisms. *Frontiers in Immunology 14*, 1162607.
Chen, S., Li, Y., Zhi, S., Ding, Z., Huang, Y., Wang, W., ... Li, J. (2020). lncRNA Xist regulates osteoblast differentiation by sponging miR-19a-3p in aging-induced osteoporosis. *Aging and Disease 11*, 1058–1068.
Chialastri, A., Sarkar, S., Schauer, E. E., Lamba, S., & Dey, S. S. (2024). Combinatorial quantification of 5mC and 5hmC at individual CpG dyads and the transcriptome in single cells reveals modulators of DNA methylation maintenance fidelity. *Nature Structural & Molecular Biology 31*, 1296–1308.
Chu, D. T., Bui, N. L., Vu Thi, H., & Nguyen Thi, Y. V. (2023). Role of DNA methylation in diabetes and obesity. *Progress in Molecular Biology and Translational Science 197*, 153–170.
Chun Yang, X., Hui Zhao, D., Bond Lau, W., Qiang Liu, K., Yu Tian, J., Chao Cheng, Z., ... Fan, Q. (2018). lncRNA ENSMUST00000134285 increases MAPK11 activity, regulating aging-related myocardial apoptosis. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 73*, 1010–1017.
Ciesielski, O., Biesiekierska, M., & Balcerczyk, A. (2020). Epigallocatechin-3-gallate (EGCG) alters histone acetylation and methylation and impacts chromatin architecture profile in human endothelial cells. *Molecules 25*.
Clapier, C. R., & Cairns, B. R. (2009). The biology of chromatin remodeling complexes. *Annual Review of Biochemistry 78*, 273–304.
Clapier, C. R., Iwasa, J., Cairns, B. R., & Peterson, C. L. (2017). Mechanisms of action and regulation of ATP-dependent chromatin-remodelling complexes. *Nature Reviews. Molecular Cell Biology 18*, 407–422.
Correa, F., Mallard, C., Nilsson, M., & Sandberg, M. (2011). Activated microglia decrease histone acetylation and Nrf2-inducible anti-oxidant defence in astrocytes: Restoring effects of inhibitors of HDACs, p38 MAPK and GSK3beta. *Neurobiology of Disease 44*, 142–151.
Cortes-Lopez, M., Gruner, M. R., Cooper, D. A., Gruner, H. N., Voda, A. I., van der Linden, A. M., & Miura, P. (2018). Global accumulation of circRNAs during aging in Caenorhabditis elegans. *BMC Genomics 19*, 8.
Csekes, E., & Rackova, L. (2021). Skin aging, cellular senescence and natural polyphenols. *International Journal of Molecular Sciences 22*.
Cui, Z., Zhao, X., Amevor, F. K., Du, X., Wang, Y., Li, D., ... Zhao, X. (2022). Therapeutic application of quercetin in aging-related diseases: SIRT1 as a potential mechanism. *Frontiers in Immunology 13*, Article 943321.
Deepika, & Maurya, P. K. (2022). Health benefits of quercetin in age-related diseases. *Molecules 27*.
Deng, Y., Chu, X., Li, Q., Zhu, G., Hu, J., Sun, J., Zeng, H., Huang, J., & Ge, G. (2024). Xanthohumol ameliorates drug-induced hepatic ferroptosis via activating Nrf2/xCT/GPX4 signaling pathway. *Phytomedicine 126*, Article 155458.
Denomme, M. M., McCallie, B. R., Haywood, M. E., Parks, J. C., Schoolcraft, W. B., & Katz-Jaffe, M. G. (2024). Paternal aging impacts expression and epigenetic markers as early as the first embryonic tissue lineage differentiation. *Human Genomics 18*, 32.
Devarshi, P. P., Jones, A. D., Taylor, E. M., Stefanska, B., & Henagan, T. M. (2017). Quercetin and quercetin-rich red onion extract Alter Pgc-1α promoter methylation and splice variant expression. *PPAR Research 2017*, 3235693.
Di Petrillo, A., Orrù, G., Fais, A., & Fantini, M. C. (2022). Quercetin and its derivates as antiviral potentials: A comprehensive review. *Phytotherapy Research 36*, 266–278.
Di Zhu, X. W., Zhou, J., Li, X., Huang, X., Li, J., Wu, J., ... Tian, Y. (2020). NuRD mediates mitochondrial stress–induced longevity via chromatin remodeling in response to acetyl-CoA level. *Science Advances 6*, eabb2529.
Dilberger, B., Baumanns, S., Schmitt, F., Schmiedl, T., Hardt, M., Wenzel, U., & Eckert, G. P. (2019). Mitochondrial oxidative stress impairs energy metabolism and reduces stress resistance and longevity of *C. elegans*. *Oxidative Medicine and Cellular Longevity 2019*, 6840540.
Dong, X., Fu, J., Yin, X., Cao, S., Li, X., Lin, L., ... Ni (2016). Emodin: A review of its pharmacology, toxicity and pharmacokinetics. *Phytotherapy Research 30*, 1207–1218.
Draceni, Y., & Pechmann, S. (2019). Pervasive convergent evolution and extreme phenotypes define chaperone requirements of protein homeostasis. *Proceedings of the National Academy of Sciences of the United States of America 116*, 20009–20014.
Dube, C. T., Jahan, F. R. S., & Lim, C. Y. (2022). Key changes in chromatin mark mammalian epidermal differentiation and ageing. *Epigenetics 17*, 444–459.
Earls, J. C., Rappaport, N., Heath, L., Wilmanski, T., Magis, A. T., Schork, N. J., ... Price, N. D. (2019). Multi-Omic biological age estimation and its correlation with wellness and disease phenotypes: A longitudinal study of 3,558 individuals. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 74*, S52–S60.
Enomoto, M., Adachi, H., Fukami, A., Furuki, K., Satoh, A., Otsuka, M., ... Imaizumi, T. (2008). Serum dehydroepiandrosterone sulfate levels predict longevity in men: 27-year follow-up study in a community-based cohort (Tanushimaru study). *Journal of the American Geriatrics Society 56*, 994–998.
Fan, Y., Lv, X., Chen, Z., Peng, Y., & Zhang, M. (2023). m6A methylation: Critical roles in aging and neurological diseases. *Frontiers in Molecular Neuroscience 16*, 1102147.
Fang, M. Z., Wang, Y., Ai, N., Hou, Z., Sun, Y., Lu, H., ... Yang, C. S. (2003). Tea polyphenol (−)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. *Cancer Research 63*, 7563–7570.
Feng, Y., Li, C., Liu, S., Yan, F., Teng, Y., Li, X., & Sun, Y. (2022). B-Elemene restrains PTEN mRNA degradation to restrain the growth of lung Cancer cells via METTL3-mediated N(6) Methyladenosine modification. *Journal of Oncology 2022*, 3472745.
Feser, J., Truong, D., Das, C., Carson, J. J., Kieft, J., Harkness, T., & Tyler, J. K. (2010). Elevated histone expression promotes life span extension. *Molecular Cell 39*, 724–735.
Feser, J., & Tyler, J. (2011). Chromatin structure as a mediator of aging. *FEBS Letters 585*, 2041–2048.
Fournet, M., Bonte, F., & Desmouliere, A. (2018). Glycation damage: A possible hub for major pathophysiological disorders and aging. *Aging and Disease 9*, 880–900.
Franco, F. N., Arrieta, O. A. P., de Mello Silva, B., Aragao, M. M., Nagem, R. A. P., de Araujo, G. R., & Chaves, M. M. (2024). Nrf2 cell signaling pathway is responsible for the antioxidant effect of resveratrol in aging. *Geriatrics & Gerontology International 24*, 954–961.
Freedman, M. S., Gnanapavan, S., Booth, R. A., Calabresi, P. A., Khalil, M., Kuhle, J., ... Consortium of Multiple Sclerosis, C (2024). Guidance for use of neurofilament light chain as a cerebrospinal fluid and blood biomarker in multiple sclerosis management. *EBioMedicine 101*, Article 104970.
Fyodorov, D. V., Zhou, B. R., Skoultchi, A. I., & Bai, Y. (2018). Emerging roles of linker histones in regulating chromatin structure and function. *Nature Reviews. Molecular Cell Biology 19*, 192–206.
Gaetano, C., Venturelli, S., Berger, A., Böcker, A., Busch, C., Weiland, T., ... Bitzer, M. (2013). Resveratrol as a Pan-HDAC inhibitor alters the acetylation status of histone proteins in human-derived Hepatoblastoma cells. *PLoS One 8*.
Gao, Z., Xu, M. S., Barnett, T. L., & Xu, C. W. (2011). Resveratrol induces cellular senescence with attenuated mono-ubiquitination of histone H2B in glioma cells. *Biochemical and Biophysical Research Communications 407*, 271–276.
Gao, Z., & Ye, J. (2008). Inhibition of transcriptional activity of c-JUN by SIRT1. *Biochemical and Biophysical Research Communications 376*, 793–796.
George, M., Tharakan, M., Culberson, J., Reddy, A. P., & Reddy, P. H. (2022). Role of Nrf2 in aging, Alzheimer's and other neurodegenerative diseases. *Ageing Research Reviews 82*, Article 101756.
Ghalaut, V. S., Sangwan, L., Dahiya, K., Ghalaut, P. S., Dhankhar, R., & Saharan, R. (2012). Effect of imatinib therapy with and without turmeric powder on nitric oxide levels in chronic myeloid leukemia. *Journal of Oncology Pharmacy Practice 18*, 186–190.
Giorgi, C., Marchi, S., Simoes, I. C. M., Ren, Z., Morciano, G., Perrone, M., ... Wieckowski, M. R. (2018). Mitochondria and reactive oxygen species in aging and age-related diseases. *International Review of Cell and Molecular Biology 340*, 209–344.
Gire, V., & Dulic, V. (2015). Senescence from G2 arrest, revisited. *Cell Cycle 14*, 297–304.
Godoy, L. D., Lucas, J. E., Bender, A. J., Romanick, S. S., & Ferguson, B. S. (2017). Targeting the epigenome: Screening bioactive compounds that regulate histone deacetylase activity. *Molecular Nutrition & Food Research 61*.
Goloubinoff, P., Sassi, A. S., Fauvet, B., Barducci, A., & De Los Rios, P. (2018). Chaperones convert the energy from ATP into the nonequilibrium stabilization of native proteins. *Nature Chemical Biology 14*, 388–395.
Hachinohe, M., Hanaoka, F., & Masumoto, H. (2011). Hst3 and Hst4 histone deacetylases regulate replicative lifespan by preventing genome instability in Saccharomyces cerevisiae. *Genes to Cells 16*, 467–477.
Haghani, A., Li, C. Z., Robeck, T. R., Zhang, J., Lu, A. T., Ablaeva, J., ... Horvath, S. (2023). DNA methylation networks underlying mammalian traits. *Science 381*, eabq5693.
Hahn, O., Gronke, S., Stubbs, T. M., Ficz, G., Hendrich, O., Krueger, F., ... Partridge, L. (2017). Dietary restriction protects from age-associated DNA methylation and induces epigenetic reprogramming of lipid metabolism. *Genome Biology 18*, 56.
Hao Tang, X. F., Xing, J., Liu, Z., Jiang, B., Dou, Y., Gorospe, M., & Wang, W. (2015). NSun2 delays replicative senescence by repressing p27 (KIP1) translation and elevating CDK1 translation. *Aging (Albany NY) 7*, 1143–1158.
Hargreaves, D. C., & Crabtree, G. R. (2011). ATP-dependent chromatin remodeling: Genetics, genomics and mechanisms. *Cell Research 21*, 396–420.
Hausenblas, H. A., Schoulda, J. A., & Smoliga, J. M. (2015). Resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes mellitus–systematic review and meta-analysis. *Molecular Nutrition & Food Research 59*, 147–159.
He, T., Quan, T., Shao, Y., Voorhees, J. J., & Fisher, G. J. (2014). Oxidative exposure impairs TGF-beta pathway via reduction of type II receptor and SMAD3 in human skin fibroblasts. *Age (Dordrecht, Netherlands) 36*, 9623.
He, Y., Xi, J., Fang, J., Zhang, B., & Cai, W. (2023). Aloe-emodin alleviates doxorubicin-induced cardiotoxicity via inhibition of ferroptosis. *Free Radical Biology & Medicine 206*, 13–21.

He, Z. Y., Shi, C. B., Wen, H., Li, F. L., Wang, B. L., & Wang, J. (2011). Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin. *Cancer Investigation 29*, 208–213.
Hofmann, P., Sommer, J., Theodorou, K., Kirchhof, L., Fischer, A., Li, Y., ... Boon, R. A. (2019). Long non-coding RNA H19 regulates endothelial cell aging via inhibition of STAT3 signalling. *Cardiovascular Research 115*, 230–242.
Hongyan Zhu, X., Qiao, M., Sun, X., & Li, G. (2023). Resveratrol alleviates inflammation and ER stress through SIRT1/NRF2 to delay ovarian aging in a short-lived fish. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 78*, 596–602.
Horvath, S. (2013). DNA methylation age of human tissues and cell types. *Genome Biology 14*, R115.
Horvath, S., & Raj, K. (2018). DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nature Reviews. Genetics 19*, 371–384.
Hosoda, R., Nakashima, R., Yano, M., Iwahara, N., Asakura, S., Nojima, I., ... Kuno, A. (2023). Resveratrol, a SIRT1 activator, attenuates aging-associated alterations in skeletal muscle and heart in mice. *Journal of Pharmacological Sciences 152*, 112–122.
Hosseini, A., Razavi, B. M., Banach, M., & Hosseinzadeh, H. (2021). Quercetin and metabolic syndrome: A review. *Phytotherapy Research 35*, 5352–5364.
Hu, Y., McIntosh, G. H., Le Leu, R. K., Somashekar, R., Meng, X. Q., Gopalsamy, G., ... Young, G. P. (2016). Supplementation with Brazil nuts and green tea extract regulates targeted biomarkers related to colorectal cancer risk in humans. *The British Journal of Nutrition 116*, 1901–1911.
Ishimi, Y., Kojima, M., Takeuchi, F., Miyamoto, T., Yamada, M., & Hanaoka, F. (1987). Changes in chromatin structure during aging of human skin fibroblasts. *Experimental Cell Research 169*, 458–467.
Iwanowycz, S., Wang, J., Altomare, D., Hui, Y., & Fan, D. (2016). Emodin Bidirectionally modulates macrophage polarization and epigenetically regulates macrophage memory. *The Journal of Biological Chemistry 291*, 11491–11503.
Jambhekar, A., Dhall, A., & Shi, Y. (2019). Roles and regulation of histone methylation in animal development. *Nature Reviews. Molecular Cell Biology 20*, 625–641.
Jian, D., Wang, Y., Jian, L., Tang, H., Rao, L., Chen, K., Jia, Z., Zhang, W., Liu, Y., Chen, X., Shen, X., Gao, C., Wang, S., & Li, M. (2020). METTL14 aggravates endothelial inflammation and atherosclerosis by increasing FOXO1 N6-methyladeosine modifications. *Theranostics 10*, 8939–8956.
Jiang, D., Li, T., Guo, C., Tang, T. S., & Liu, H. (2023). Small molecule modulators of chromatin remodeling: From neurodevelopment to neurodegeneration. *Cell & Bioscience 13*, 10.
Jiang, H., Yao, Q., An, Y., Fan, L., Wang, J., & Li, H. (2022). Baicalin suppresses the progression of type 2 diabetes-induced liver tumor through regulating METTL3/m(6)A/HKDC1 axis and downstream p-JAK2/STAT1/clevaged Capase3 pathway. *Phytomedicine 94*, Article 153823.
Kalc, P., Dahnke, R., Hoffstaedter, F., Gaser, C., & Alzheimer's Disease Neuroimaging, I (2024). BrainAGE: Revisited and reframed machine learning workflow. *Human Brain Mapping 45*, Article e26632.
Kar, P., Laight, D., Rooprai, H. K., Shaw, K. M., & Cummings, M. (2009). Effects of grape seed extract in type 2 diabetic subjects at high cardiovascular risk: A double blind randomized placebo controlled trial examining metabolic markers, vascular tone, inflammation, oxidative stress and insulin sensitivity. *Diabetic Medicine 26*, 526–531.
Kato, M., Chen, X., Inukai, S., Zhao, H., & Slack, F. J. (2011). Age-associated changes in expression of small, noncoding RNAs, including microRNAs, in C. Elegans. *RNA 17*, 1804–1820.
Kaufman-Szymczyk, A., Majewski, G., Lubecka-Pietruszewska, K., & Fabianowska-Majewska, K. (2015). The role of Sulforaphane in epigenetic mechanisms, including interdependence between histone modification and DNA methylation. *International Journal of Molecular Sciences 16*, 29732–29743.
Kawakami, K., Nakamura, A., Ishigami, A., Goto, S., & Takahashi, R. (2009). Age-related difference of site-specific histone modifications in rat liver. *Biogerontology 10*, 415–421.
Kenneth Day, L. L. W., Thalacker-Mercer, A., West, A., Bamman, M. M., Brooks, J. D., Myers, R. M., & Absher, D. (2013). Differential DNA methylation with age displays both common and dynamic features across human tissues that are influenced by CpG landscape. *Genome Biology 14*, R102.
Kim, C., Jadhav, R. R., Gustafson, C. E., Smithey, M. J., Hirsch, A. J., Uhrlaub, J. L., ... Goronzy, J. J. (2019). Defects in antiviral T cell responses inflicted by aging-associated miR-181a deficiency. *Cell Reports 29*(2202–2216), Article e2205.
Kim, J., Lee, S., Choi, B. R., Yang, H., Hwang, Y., Park, J. H., ... Kim, J. (2017). Sulforaphane epigenetically enhances neuronal BDNF expression and TrkB signaling pathways. *Molecular Nutrition & Food Research 61*.
Kim, M. J., Kim, D. H., Bang, E., Noh, S. G., Chun, P., Yokozawa, T., ... Chung, H. Y. (2021). PPARalpha agonist, MHY3200, alleviates renal inflammation during aging via regulating ROS/Akt/FoxO1 signaling. *Molecules 26*.
Kim, S. J., Son, T. G., Park, H. R., Park, M., Kim, M. S., Kim, H. S., ... Lee, J. (2008). Curcumin stimulates proliferation of embryonic neural progenitor cells and neurogenesis in the adult hippocampus. *The Journal of Biological Chemistry 283*, 14497–14505.
Kim, S. R., Seong, K. J., Kim, W. J., & Jung, J. Y. (2022). Epigallocatechin Gallate protects against hypoxia-induced inflammation in microglia via NF-κB suppression and Nrf-2/HO-1 activation. *International Journal of Molecular Sciences 23*.
Kim, S. S., & Lee, S. V. (2019). Non-coding RNAs in Caenorhabditis elegans aging. *Molecules and Cells 42*, 379–385.
Kitani, K., Osawa, T., & Yokozawa, T. (2007). The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. *Biogerontology 8*, 567–573.
Klutstein, M., Nejman, D., Greenfield, R., & Cedar, H. (2016). DNA methylation in Cancer and aging. *Cancer Research 76*, 3446–3450.
Knop, F. K., Konings, E., Timmers, S., Schrauwen, P., Holst, J. J., & Blaak, E. E. (2013). Thirty days of resveratrol supplementation does not affect postprandial incretin hormone responses, but suppresses postprandial glucagon in obese subjects. *Diabetic Medicine 30*, 1214–1218.
Kouzarides, T. (2007). Chromatin modifications and their function. *Cell 128*, 693–705.
Labrie, F. (2010). DHEA, important source of sex steroids in men and even more in women. *Progress in Brain Research 182*, 97–148.
Lan, Q., Liu, P. Y., Haase, J., Bell, J. L., Huttelmaier, S., & Liu, T. (2019). The critical role of RNA m(6)A methylation in Cancer. *Cancer Research 79*, 1285–1292.
Larson, K., Yan, S. J., Tsurumi, A., Liu, J., Zhou, J., Gaur, K., ... Li, W. X. (2012). Heterochromatin formation promotes longevity and represses ribosomal RNA synthesis. *PLoS Genetics 8*, Article e1002473.
Le Gall, J. Y., & Ardaillou, R. (2009). The biology of aging. *Bulletin de l'Académie Nationale de Médecine 193*, 365–402 discussion 402-364.
Lee, A. V., Nestler, K. A., & Chiappinelli, K. B. (2024). Therapeutic targeting of DNA methylation alterations in cancer. *Pharmacology & Therapeutics 258*, Article 108640.
Lee, S., Yu, K. R., Ryu, Y. S., Oh, Y. S., Hong, I. S., Kim, H. S., ... Kang, K. S. (2014). miR-543 and miR-590-3p regulate human mesenchymal stem cell aging via direct targeting of AIMP3/p18. *Age (Dordrecht, Netherlands) 36*, 9724.
Levine, M. E., Lu, A. T., Quach, A., Chen, B. H., Assimes, T. L., Bandinelli, S., ... Horvath, S. (2018). An epigenetic biomarker of aging for lifespan and healthspan. *Aging (Albany NY) 10*, 573–591.
Li, H. L., Liu, C., de Couto, G., Ouzounian, M., Sun, M., Wang, A. B., ... Liu, P. P. (2008). Curcumin prevents and reverses murine cardiac hypertrophy. *The Journal of Clinical Investigation 118*, 879–893.
Li, J., Xiong, M., Fu, X. H., Fan, Y., Dong, C., Sun, X., ... Liu, G. H. (2023). Determining a multimodal aging clock in a cohort of Chinese women. *Med 4*(825–848), Article e813.
Li, Q., Li, X., Tang, H., Jiang, B., Dou, Y., Gorospe, M., & Wang, W. (2017). NSUN2-mediated m5C methylation and METTL3/METTL14-mediated m6A methylation cooperatively enhance p21 translation. *Journal of Cellular Biochemistry 118*, 2587–2598.
Li, Q., Zhang, W., Cheng, N., Zhu, Y., Li, H., Zhang, S., Guo, W., & Ge, G. (2023). Pectolinarigenin ameliorates acetaminophen-induced acute liver injury via attenuating oxidative stress and inflammatory response in Nrf2 and PPARa dependent manners. *Phytomedicine 113*, Article 154726.
Li, R., & Roy, R. (2023). Gut microbiota and its role in anti-aging phenomenon: Evidence-based review. *Applied Biochemistry and Biotechnology 195*, 6809–6823.
Li, X., Li, J., Zhu, D., Zhang, N., Hao, X., Zhang, W., ... Tian, Y. (2022). Protein disulfide isomerase PDI-6 regulates Wnt secretion to coordinate inter-tissue UPR(mt) activation and lifespan extension in C. Elegans. *Cell Reports 39*, Article 110931.
Li, Y., Kuang, H., Shen, W., Ma, H., Zhang, Y., Stener-Victorin, E., ... Wu, X. (2013). Letrozole, berberine, or their combination for anovulatory infertility in women with polycystic ovary syndrome: Study design of a double-blind randomised controlled trial. *BMJ Open 3*, Article e003934.
Li, Y. Y., Tang, D., Du, Y. L., Cao, C. Y., Nie, Y. Q., Cao, J., & Zhou, Y. J. (2018). Fatty liver mediated by peroxisome proliferator-activated receptor-alpha DNA methylation can be reversed by a methylation inhibitor and curcumin. *Journal of Digestive Diseases 19*, 421–430.
Lin, R., Rahtu-Korpela, L., Magga, J., Ulvila, J., Swan, J., Kemppi, A., ... Kerkela, R. (2020). miR-1468-3p promotes aging-related cardiac fibrosis. *Molecular Therapy - Nucleic Acids 20*, 589–605.
Lin, Z., Huang, L., Cao, Q., Luo, H., Yao, W., & Zhang, J. C. (2023). Inhibition of abnormal C/EBPbeta/alpha-Syn signaling pathway through activation of Nrf2 ameliorates Parkinson's disease-like pathology. *Aging Cell 22*, Article e13958.
Liu, H., Zhang, H., Lou, H., Wang, J., Hao, S., Chen, H., ... Zhang, Y. (2024). ZEB1-AS1 AS a TRPML1 inhibitor to cause lysosome dysfunction and cardiac damage in aged mice. *Engineering 43*, 183–200.
Liu, J. R., Cai, G. Y., Ning, Y. C., Wang, J. C., Lv, Y., Guo, Y. N., ... Chen, X. M. (2020). Caloric restriction alleviates aging-related fibrosis of kidney through downregulation of miR-21 in extracellular vesicles. *Aging (Albany NY) 12*, 18052–18072.
Liu, R., Zhao, E., Yu, H., Yuan, C., Abbas, M. N., & Cui, H. (2023). Methylation across the central dogma in health and diseases: New therapeutic strategies. *Signal Transduction and Targeted Therapy 8*, 310.
Liu, S., Li, Q., Li, G., Zhang, Q., Zhuo, L., Han, X., ... Xie, T. (2020). The mechanism of m(6)A methyltransferase METTL3-mediated autophagy in reversing gefitinib resistance in NSCLC cells by beta-elemene. *Cell Death & Disease 11*, 969.
Liu, X., Bai, X., Liu, H., Hong, Y., Cui, H., Wang, L., ... Zhang, Y. (2022). LncRNA LOC105378097 inhibits cardiac mitophagy in natural ageing mice. *Clinical and Translational Medicine 12*, Article e908.
Liu, Z., Li, W., Geng, L., Sun, L., Wang, Q., Yu, Y., ... Liu, G. H. (2022). Cross-species metabolomic analysis identifies uridine as a potent regeneration promoting factor. *Cell Discovery 8*, 6.
Liu, Z., Liang, Q., Ren, Y., Guo, C., Ge, X., Wang, L., ... Han, X. (2023). Immunosenescence: Molecular mechanisms and diseases. *Signal Transduction and Targeted Therapy 8*, 200.
Lopez-Otin, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The hallmarks of aging. *Cell 153*, 1194–1217.
Lu, A. T., Quach, A., Wilson, J. G., Reiner, A. P., Aviv, A., Raj, K., ... Horvath, S. (2019). DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging (Albany NY) 11*, 303–327.
Lu, C., Li, B., Zhang, Q., Chen, X., Pang, Y., Lu, F., ... Chen, H. (2023). An individual-level weighted artificial neural network method to improve the systematic bias in BrainAGE analysis. *Cerebral Cortex 33*, 6132–6138.
Luo, Z., Yin, F., Wang, X., & Kong, L. (2024). Progress in approved drugs from natural product resources. *Chinese Journal of Natural Medicines 22*, 195–211.
Ma, S., Sun, S., Geng, L., Song, M., Wang, W., Ye, Y., ... Liu, G. H. (2020). Caloric restriction reprograms the single-cell transcriptional landscape of Rattus Norvegicus aging. *Cell 180*(984–1001), Article e1022.
Macdonald-Dunlop, E., Taba, N., Klaric, L., Frkatovic, A., Walker, R., Hayward, C., ... Joshi, P. K. (2022). A catalogue of omics biological ageing clocks reveals substantial commonality and associations with disease risk. *Aging (Albany NY) 14*, 623–659.

Mamoshina, P., Kochetov, K., Putin, E., Cortese, F., Aliper, A., Lee, W. S., ... Zhavoronkov, A. (2018). Population specific biomarkers of human aging: A big data study using South Korean, Canadian, and eastern European patient populations. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 73*, 1482–1490.

Martinez-Iglesias, O., Carrera, I., Carril, J. C., Fernandez-Novoa, L., Cacabelos, N., & Cacabelos, R. (2020). DNA methylation in neurodegenerative and cerebrovascular disorders. *International Journal of Molecular Sciences 21*.

Mattei, A. L., Bailly, N., & Meissner, A. (2022). DNA methylation: A historical perspective. *Trends in Genetics 38*, 676–707.

Maugeri, A., Barchitta, M., Mazzone, M. G., Giuliano, F., Basile, G., & Agodi, A. (2018). Resveratrol modulates SIRT1 and DNMT functions and restores LINE-1 methylation levels in ARPE-19 cells under oxidative stress and inflammation. *International Journal of Molecular Sciences 19*.

McCrory, C., Fiorito, G., Hernandez, B., Polidoro, S., O'Halloran, A. M., Hever, A., ... Kenny, R. A. (2021). GrimAge outperforms other epigenetic clocks in the prediction of age-related clinical phenotypes and all-cause mortality. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 76*, 741–749.

McEwen, L. M., O'Donnell, K. J., McGill, M. G., Edgar, R. D., Jones, M. J., MacIsaac, J. L., ... Kobor, M. S. (2020). The PedBE clock accurately estimates DNA methylation age in pediatric buccal cells. *Proceedings of the National Academy of Sciences of the United States of America 117*, 23329–23335.

Meng, S., Wang, L. S., Huang, Z. Q., Zhou, Q., Sun, Y. G., Cao, J. T., ... Wang, C. Q. (2012). Berberine ameliorates inflammation in patients with acute coronary syndrome following percutaneous coronary intervention. *Clinical and Experimental Pharmacology & Physiology 39*, 406–411.

Meyer, D. H., & Schumacher, B. (2021). BiT age: A transcriptome-based aging clock near the theoretical limit of accuracy. *Aging Cell 20*, Article e13320.

Milosic, F., Hengstschlager, M., & Osmanagic-Myers, S. (2023). Premature aging in genetic diseases: What conclusions can be drawn for physiological aging. *Frontiers in Aging 4*, 1327833.

Min, K. W., Zealy, R. W., Davila, S., Fomin, M., Cummings, J. C., Makowsky, D., ... Yoon, J. H. (2018). Profiling of m6A RNA modifications identified an age-associated regulation of AGO2 mRNA stability. *Aging Cell 17*, Article e12753.

Moore, L. D., Le, T., & Fan, G. (2012). DNA methylation and its basic function. *Neuropsychopharmacology 38*, 23–38.

Morisaki, N., Moriwaki, S., Sugiyama-Nakagiri, Y., Haketa, K., Takema, Y., & Imokawa, G. (2010). Neprilysin is identical to skin fibroblast elastase: Its role in skin aging and UV responses. *The Journal of Biological Chemistry 285*, 39819–39827.

Movahed, A., Nabipour, I., Lieben Louis, X., Thandapilly, S. J., Yu, L., Kalantarhormozi, M., ... Netticadan, T. (2013). Antihyperglycemic effects of short term resveratrol supplementation in type 2 diabetic patients. *Evidence-based Complementary and Alternative Medicine 2013*, Article 851267.

Murach, K. A., Dimet-Wiley, A. L., Wen, Y., Brightwell, C. R., Latham, C. M., Dungan, C. M., ... Watowich, S. J. (2022). Late-life exercise mitigates skeletal muscle epigenetic aging. *Aging Cell 21*, Article e13527.

Narita, M., Nunez, S., Heard, E., Narita, M., Lin, A. W., Hearn, S. A., ... Lowe, S. W. (2003). Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence. *Cell 113*, 703–716.

Neelamegham, S., & Mahal, L. K. (2016). Multi-level regulation of cellular glycosylation: From genes to transcript to enzyme to structure. *Current Opinion in Structural Biology 40*, 145–152.

Nematollahi, S., Pishdad, G. R., Zakerkish, M., Namjoyan, F., Ahmadi Angali, K., & Borazjani, F. (2022). The effect of berberine and fenugreek seed co-supplementation on inflammatory factor, lipid and glycemic profile in patients with type 2 diabetes mellitus: A double-blind controlled randomized clinical trial. *Diabetology and Metabolic Syndrome 14*, 120.

Nie, C., Li, Y., Li, R., Yan, Y., Zhang, D., Li, T., ... Xu, X. (2022). Distinct biological ages of organs and systems identified from a multi-omics study. *Cell Reports 38*, Article 110459.

Ning, Y., Chen, J., Shi, Y., Song, N., Yu, X., Fang, Y., & Ding, X. (2020). Genistein ameliorates renal fibrosis through regulation snail via m6A RNA demethylase ALKBH5. *Frontiers in Pharmacology 11*, Article 579265.

Nishiyama, A., & Nakanishi, M. (2021). Navigating the DNA methylation landscape of cancer. *Trends in Genetics 37*, 1012–1027.

Norby, J. G., & Jensen, J. (1989). A model for the stepwise radiation inactivation of the alpha 2-dimer of Na,K-ATPase. *The Journal of Biological Chemistry 264*, 19548–19558.

North, B. J., & Sinclair, D. A. (2012). The intersection between aging and cardiovascular disease. *Circulation Research 110*, 1097–1108.

Otto, J. E., Ursu, O., Wu, A. P., Winter, E. B., Cuoco, M. S., Ma, S., ... Kadoch, C. (2023). Structural and functional properties of mSWI/SNF chromatin remodeling complexes revealed through single-cell perturbation screens. *Molecular Cell 83*, 1350–1367.e1357.

Owczarz, M., Budzinska, M., Domaszewska-Szostek, A., Borkowska, J., Polosak, J., Gewartowska, M., ... Puzianowska-Kuznicka, M. (2017). miR-34a and miR-9 are overexpressed and SIRT genes are downregulated in peripheral blood mononuclear cells of aging humans. *Experimental Biology and Medicine (Maywood, N.J.) 242*, 1453–1461.

Padayatty, S. J., & Levine, M. (2016). Vitamin C: The known and the unknown and goldilocks. *Oral Diseases 22*, 463–493.

Pan, B., Quan, J., Liu, L., Xu, Z., Zhu, J., Huang, X., & Tian, J. (2017). Epigallocatechin gallate reverses cTnI-low expression-induced age-related heart diastolic dysfunction through histone acetylation modification. *Journal of Cellular and Molecular Medicine 21*, 2481–2490.

Pandey, M., Shukla, S., & Gupta, S. (2010). Promoter demethylation and chromatin remodeling by green tea polyphenols leads to re-expression of GSTP1 in human prostate cancer cells. *International Journal of Cancer 126*, 2520–2533.

Panwar, P., Lamour, G., Mackenzie, N. C., Yang, H., Ko, F., Li, H., & Bromme, D. (2015). Changes in structural-mechanical properties and degradability of collagen during aging-associated modifications. *The Journal of Biological Chemistry 290*, 23291–23306.

Paolisso, G., Barbieri, M., Bonafe, M., & Franceschi, C. (2000). Metabolic age modelling: The lesson from centenarians. *European Journal of Clinical Investigation 30*, 888–894.

Park, S. C., Lee, Y. S., Cho, K. A., Kim, S. Y., Lee, Y. I., Lee, S. R., & Lim, I. K. (2023). What matters in aging is signaling for responsiveness. *Pharmacology & Therapeutics 252*, Article 108560.

Patsouris, D., Reddy, J. K., Muller, M., & Kersten, S. (2006). Peroxisome proliferator-activated receptor alpha mediates the effects of high-fat diet on hepatic gene expression. *Endocrinology 147*, 1508–1516.

Payne, B. A., & Chinnery, P. F. (2015). Mitochondrial dysfunction in aging: Much progress but many unresolved questions. *Biochimica et Biophysica Acta 1847*, 1347–1353.

Peters, M. J., Joehanes, R., Pilling, L. C., Schurmann, C., Conneely, K. N., Powell, J., ... Johnson, A. D. (2015). The transcriptional landscape of age in human peripheral blood. *Nature Communications 6*, 8570.

Porcuna, J., Minguez-Martinez, J., & Ricote, M. (2021). The PPARalpha and PPARgamma epigenetic landscape in Cancer and immune and metabolic disorders. *International Journal of Molecular Sciences 22*.

Pouikli, A., Parekh, S., Maleszewska, M., Nikopoulou, C., Baghdadi, M., Tripodi, I., ... Tessarz, P. (2021). Chromatin remodeling due to degradation of citrate carrier impairs osteogenesis of aged mesenchymal stem cells. *Nature Aging 1*, 810–825.

Puzianowska-Kuznicka, M., Owczarz, M., Wieczorowska-Tobis, K., Nadrowski, P., Chudek, J., Slusarczyk, P., ... Mossakowska, M. (2016). Interleukin-6 and C-reactive protein, successful aging, and mortality: The PolSenior study. *Immunity & Ageing 13*, 21.

Pyrkov, T. V., Avchaciov, K., Tarkhov, A. E., Menshikov, L. I., Gudkov, A. V., & Fedichev, P. O. (2021). Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit. *Nature Communications 12*, 2765.

Qin, Z., Fisher, G. J., & Quan, T. (2013). Cysteine-rich protein 61 (CCN1) domain-specific stimulation of matrix metalloproteinase-1 expression through alphaVbeta3 integrin in human skin fibroblasts. *The Journal of Biological Chemistry 288*, 12386–12394.

Quan, T., & Fisher, G. J. (2015). Role of age-associated alterations of the dermal extracellular matrix microenvironment in human skin aging: A Mini-review. *Gerontology 61*, 427–434.

Quan, T., He, T., Shao, Y., Lin, L., Kang, S., Voorhees, J. J., & Fisher, G. J. (2006). Elevated cysteine-rich 61 mediates aberrant collagen homeostasis in chronologically aged and photoaged human skin. *The American Journal of Pathology 169*, 482–490.

Quan, T., Qin, Z., Xu, Y., He, T., Kang, S., Voorhees, J. J., & Fisher, G. J. (2010). Ultraviolet irradiation induces CYR61/CCN1, a mediator of collagen homeostasis, through activation of transcription factor AP-1 in human skin fibroblasts. *The Journal of Investigative Dermatology 130*, 1697–1706.

Quan, T., Shin, S., Qin, Z., & Fisher, G. J. (2009). Expression of CCN family of genes in human skin in vivo and alterations by solar-simulated ultraviolet irradiation. *Journal of Cell Communication and Signaling 3*, 19–23.

Ram, O., Goren, A., Amit, I., Shoresh, N., Yosef, N., Ernst, J., ... Bernstein, B. E. (2011). Combinatorial patterning of chromatin regulators uncovered by genome-wide location analysis in human cells. *Cell 147*, 1628–1639.

Ray, P. D., Huang, B. W., & Tsuji, Y. (2015). Coordinated regulation of Nrf2 and histone H3 serine 10 phosphorylation in arsenite-activated transcription of the human heme oxygenase-1 gene. *Biochimica et Biophysica Acta 1849*, 1277–1288.

Recent advances in clinical science. Abstracts of the 89th meeting of the Association of Clinical Scientists. May 11 to 14, 1989, Charlottesville, Virginia. (1989). Annals of Clinical and Laboratory Science, 19, 287–318.

Reid, M. A., Dai, Z., & Locasale, J. W. (2017). The impact of cellular metabolism on chromatin dynamics and epigenetics. *Nature Cell Biology 19*, 1298–1306.

Riedel, C. G., Dowen, R. H., Lourenco, G. F., Kirienko, N. V., Heimbucher, T., West, J. A., ... Ruvkun, G. (2013). DAF-16 employs the chromatin remodeller SWI/SNF to promote stress resistance and longevity. *Nature Cell Biology 15*, 491–501.

Roberts, S. B., Sanicola, M., Emmons, S. W., & Childs, G. (1987). Molecular characterization of the histone gene family of Caenorhabditis elegans. *Journal of Molecular Biology 196*, 27–38.

Roignant, J. Y., & Soller, M. (2017). M(6)A in mRNA: An ancient mechanism for fine-tuning gene expression. *Trends in Genetics 33*, 380–390.

Roundtree, I. A., Evans, M. E., Pan, T., & He, C. (2017). Dynamic RNA modifications in gene expression regulation. *Cell 169*, 1187–1200.

Ruhee, R. T., & Suzuki, K. (2024). The immunomodulatory effects of Sulforaphane in exercise-induced inflammation and oxidative stress: A prospective nutraceutical. *International Journal of Molecular Sciences 25*.

Salminen, A. (2022). Role of indoleamine 2,3-dioxygenase 1 (IDO1) and kynurenine pathway in the regulation of the aging process. *Ageing Research Reviews 75*, Article 101573.

Sanjay Sharma, A., & Lee, H. J. (2021). Role of Phytoconstituents as PPAR agonists: Implications for neurodegenerative disorders. *Biomedicines 9*.

Santos, M. A., Franco, F. N., Caldeira, C. A., de Araujo, G. R., Vieira, A., & Chaves, M. M. (2023). Resveratrol has its antioxidant and anti-inflammatory protective mechanisms decreased in aging. *Archives of Gerontology and Geriatrics 107*, Article 104895.

Sanz, A., & Stefanatos, R. K. (2008). The mitochondrial free radical theory of aging: A critical view. *Current Aging Science 1*, 10–21.

Sasidharan Nair, V., Song, M. H., & Oh, K. I. (2016). Vitamin C facilitates demethylation of the Foxp3 enhancer in a Tet-dependent manner. *Journal of Immunology 196*, 2119–2131.

Sayed, N., Huang, Y., Nguyen, K., Krejciova-Rajaniemi, Z., Grawe, A. P., Gao, T., ... Furman, D. (2021). An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. *Nature Aging 1*, 598–615.

Schepici, G., Bramanti, P., & Mazzon, E. (2020). Efficacy of Sulforaphane in neurodegenerative diseases. *International Journal of Molecular Sciences 21*.

Schneider, J. L., Rowe, J. H., Garcia-de-Alba, C., Kim, C. F., Sharpe, A. H., & Haigis, M. C. (2021). The aging lung: Physiology, disease, and immunity. *Cell 184*, 1990–2019.

Schoberleitner, I., Bauer, I., Huang, A., Andreyeva, E. N., Sebald, J., Pascher, K., ... Lusser, A. (2021). CHD1 controls H3.3 incorporation in adult brain chromatin to maintain metabolic homeostasis and normal lifespan. *Cell Reports 37*, Article 109769.
Schubeler, D. (2015). Function and information content of DNA methylation. *Nature 517*, 321–326.
Sedelnikova, O. A., Horikawa, I., Redon, C., Nakamura, A., Zimonjic, D. B., Popescu, N. C., & Bonner, W. M. (2008). Delayed kinetics of DNA double-strand break processing in normal and pathological aging. *Aging Cell 7*, 89–100.
Shafik, A. M., Zhang, F., Guo, Z., Dai, Q., Pajdzik, K., Li, Y., ... Jin, P. (2021). N6-methyladenosine dynamics in neurodevelopment and aging, and its potential role in Alzheimer's disease. *Genome Biology 22*, 17.
Sharma, R. A., McLelland, H. R., Hill, K. A., Ireson, C. R., Euden, S. A., Manson, M. M., ... Steward, W. P. (2001). Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clinical Cancer Research 7*, 1894–1900.
Shen, G. S., Zhou, H. B., Zhang, H., Chen, B., Liu, Z. P., Yuan, Y., ... Xu, Y. J. (2018). The GDF11-FTO-PPARgamma axis controls the shift of osteoporotic MSC fate to adipocyte and inhibits bone formation during osteoporosis. *Biochimica et Biophysica Acta - Molecular Basis of Disease 1864*, 3644–3654.
Shen, H., Geng, Z., Nie, X., & Liu, T. (2023). Erianin induces Ferroptosis of renal Cancer stem cells via promoting ALOX12/P53 mRNA N6-methyladenosine modification. *Journal of Cancer 14*, 367–378.
Shen, X., Wang, C., Zhou, X., Zhou, W., Hornburg, D., Wu, S., & Snyder, M. P. (2024). Nonlinear dynamics of multi-omics profiles during human aging. *Nature Aging 4*, 1619–1634.
Shi, W., Scialdone, A. P., Emerson, J. I., Mei, L., Wasson, L. K., Davies, H. A., ... Conlon, F. L. (2023). Missense mutation in human CHD4 causes ventricular noncompaction by repressing ADAMTS1. *Circulation Research 133*, 48–67.
Shin, J. W., Kwon, S. H., Choi, J. Y., Na, J. I., Huh, C. H., Choi, H. R., & Park, K. C. (2019). Molecular mechanisms of dermal aging and antiaging approaches. *International Journal of Molecular Sciences 20*.
Siddiqui, N., Sharma, A., Kesharwani, A., & Parihar, V. K. (2024). Exploring role of natural compounds in molecular alterations associated with brain ageing: A perspective towards nutrition for ageing brain. *Ageing Research Reviews 97*, Article 102282.
Song, T., Yang, Y., Wei, H., Xie, X., Lu, J., Zeng, Q., ... Peng, J. (2019). Zfp217 mediates m6A mRNA methylation to orchestrate transcriptional and post-transcriptional regulation to promote adipogenic differentiation. *Nucleic Acids Research 47*, 6130–6144.
Stachowiak, M., Mlynarczyk, D. T., & Dlugaszewska, J. (2024). Wondrous yellow molecule: Are hydrogels a successful strategy to overcome the limitations of curcumin? *Molecules 29*.
Sun, J., Cheng, B., Su, Y., Li, M., Ma, S., Zhang, Y., ... Zhu, P. (2022). The potential role of m6A RNA methylation in the aging process and aging-associated diseases. *Frontiers in Genetics 13*, Article 869950.
Swer, P. B., & Sharma, R. (2021). ATP-dependent chromatin remodelers in ageing and age-related disorders. *Biogerontology 22*, 1–17.
Tabrizi, R., Tamtaji, O. R., Lankarani, K. B., Akbari, M., Dadgostar, E., Dabbaghmanesh, M. H., ... Asemi, Z. (2020). The effects of resveratrol intake on weight loss: A systematic review and meta-analysis of randomized controlled trials. *Critical Reviews in Food Science and Nutrition 60*, 375–390.
Tang, S., Zhang, Y., Botchway, B. O. A., Wang, X., Huang, M., & Liu, X. (2024). Epigallocatechin-3-Gallate inhibits oxidative stress through the Keap1/Nrf2 signaling pathway to improve Alzheimer disease. *Molecular Neurobiology, 62, 3493-3507.*.
Tomasello, B., Di Mauro, M. D., Malfa, G. A., Acquaviva, R., Sinatra, F., Spampinato, G., ... Renis, M. (2020). Rapha Myr((R)), a blend of sulforaphane and myrosinase, exerts antitumor and anoikis-sensitizing effects on human astrocytoma cells modulating sirtuins and dna methylation. *International Journal of Molecular Sciences 21*.
Tome-Carneiro, J., Larrosa, M., Yanez-Gascon, M. J., Davalos, A., Gil-Zamorano, J., Gonzalvez, M., ... Garcia-Conesa, M. T. (2013). One-year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease. *Pharmacological Research 72*, 69–82.
Torres, I. O., & Fujimori, D. G. (2015). Functional coupling between writers, erasers and readers of histone and DNA methylation. *Current Opinion in Structural Biology 35*, 68–75.
Tuoc, T., Dere, E., Radyushkin, K., Pham, L., Nguyen, H., Tonchev, A. B., ... Stoykova, A. (2017). Ablation of BAF170 in developing and postnatal dentate gyrus affects neural stem cell proliferation, differentiation, and learning. *Molecular Neurobiology 54*, 4618–4635.
Ugalde, A. P., Ramsay, A. J., de la Rosa, J., Varela, I., Marino, G., Cadinanos, J., ... Lopez-Otin, C. (2011). Aging and chronic DNA damage response activate a regulatory pathway involving miR-29 and p53. *The EMBO Journal 30*, 2219–2232.
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.
Vaid, M., Prasad, R., Singh, T., Jones, V., & Katiyar, S. K. (2012). Grape seed proanthocyanidins reactivate silenced tumor suppressor genes in human skin cancer cells by targeting epigenetic regulators. *Toxicology and Applied Pharmacology 263*, 122–130.
Vasa-Nicotera, M., Chen, H., Tucci, P., Yang, A. L., Saintigny, G., Menghini, R., ... Federici, M. (2011). miR-146a is modulated in human endothelial cell with aging. *Atherosclerosis 217*, 326–330.
Visconti, V. V., Cariati, I., Fittipaldi, S., Iundusi, R., Gasbarra, E., Tarantino, U., & Botta, A. (2021). DNA methylation signatures of bone metabolism in osteoporosis and osteoarthritis aging-related diseases: An updated review. *International Journal of Molecular Sciences 22*.
Vollono, L., Falconi, M., Gaziano, R., Iacovelli, F., Dika, E., Terracciano, C., ... Campione, E. (2019). Potential of curcumin in skin disorders. *Nutrients 11*.
Vu, L. P., Pickering, B. F., Cheng, Y., Zaccara, S., Nguyen, D., Minuesa, G., ... Kharas, M. G. (2017). The N(6)-methyladenosine (m(6)A)-forming enzyme METTL3 controls myeloid differentiation of normal hematopoietic and leukemia cells. *Nature Medicine 23*, 1369–1376.
Waaijer, M. E., Parish, W. E., Strongitharm, B. H., van Heemst, D., Slagboom, P. E., de Craen, A. J., ... Maier, A. B. (2012). The number of p16INK4a positive cells in human skin reflects biological age. *Aging Cell 11*, 722–725.
Wang, B., Yao, M., Lv, L., Ling, Z., & Li, L. (2017). The human microbiota in health and disease. *Engineering 3*, 71–82.
Wang, K., Liu, H., Hu, Q., Wang, L., Liu, J., Zheng, Z., ... Liu, G. H. (2022). Epigenetic regulation of aging: Implications for interventions of aging and diseases. *Signal Transduction and Targeted Therapy 7*, 374.
Wang, L., Tang, X. Q., Shi, Y., Li, H. M., Meng, Z. Y., Chen, H., ... Zhang, Y. (2023). Tetrahydroberberrubine retards heart aging in mice by promoting PHB2-mediated mitophagy. *Acta Pharmacologica Sinica 44*, 332–344.
Wang, L., Xu, X., Jiang, Z., & You, Q. (2020). Modulation of protein fate decision by small molecules: Targeting molecular chaperone machinery. *Acta Pharmaceutica Sinica B 10*, 1904–1925.
Wang, L., Zheng, W., Men, Q., Ren, X., Song, S., & Ai, C. (2024). Curcumin-loaded polysaccharide microparticles alleviated DSS-induced ulcerative colitis by improving intestinal microecology and regulating MAPK/NF-kappaB/Nrf2/NLRP3 pathways. *International Journal of Biological Macromolecules 281*, Article 136687.
Wang, P., Aronson, W. J., Huang, M., Zhang, Y., Lee, R. P., Heber, D., & Henning, S. M. (2010). Green tea polyphenols and metabolites in prostatectomy tissue: Implications for cancer prevention. *Cancer Prevention Research (Philadelphia, Pa.) 3*, 985–993.
Wang, W. (2023). Glycomedicine: The current state of the art. *Engineering 26*, 12–15.
Wang, X., Yuan, Q., Xiao, Y., Cai, X., Yang, Z., Zeng, W., ... Zhang, C. (2024). Pterostilbene, a resveratrol derivative, improves ovary function by upregulating antioxidant defenses in the aging chickens via increased SIRT1/Nrf2 expression. *Antioxidants (Basel) 13*.
Wang, Y., Wang, Y., Patel, H., Chen, J., Wang, J., Chen, Z. S., & Wang, H. (2023). Epigenetic modification of m(6)A regulator proteins in cancer. *Molecular Cancer 22*, 102.
Wang, Y., Yuan, Q., & Xie, L. (2018). Histone modifications in aging: The underlying mechanisms and implications. *Current Stem Cell Research & Therapy 13*, 125–135.
Warren, J. S., Oka, S. I., Zablocki, D., & Sadoshima, J. (2017). Metabolic reprogramming via PPARalpha signaling in cardiac hypertrophy and failure: From metabolomics to epigenetics. *American Journal of Physiology. Heart and Circulatory Physiology 313*, H584–H596.
Warthin, A. S. (1928). The pathology of the aging process. *Bulletin of the New York Academy of Medicine 4*, 1006–1046.
Wen, Q., Zhou, J., Tian, C., Li, X., Song, G., Gao, Y., ... Gan, H. (2023). Symmetric inheritance of parental histones contributes to safeguarding the fate of mouse embryonic stem cells during differentiation. *Nature Genetics 55*, 1555–1566.
Weng, C., Yu, F., Yang, D., Poeschla, M., Liggett, L. A., Jones, M. G., ... Sankaran, V. G. (2024). Deciphering cell states and genealogies of human haematopoiesis. *Nature 627*, 389–398.
Westerman, K. E., & Ordovas, J. M. (2020). DNA methylation and incident cardiovascular disease. *Current Opinion in Clinical Nutrition and Metabolic Care 23*, 236–240.
Westholm, J. O., Miura, P., Olson, S., Shenker, S., Joseph, B., Sanfilippo, P., ... Lai, E. C. (2014). Genome-wide analysis of drosophila circular RNAs reveals their structural and sequence properties and age-dependent neural accumulation. *Cell Reports 9*, 1966–1980.
Wilmanski, T., Diener, C., Rappaport, N., Patwardhan, S., Wiedrick, J., Lapidus, J., ... Price, N. D. (2021). Gut microbiome pattern reflects healthy ageing and predicts survival in humans. *Nature Metabolism 3*, 274–286.
Wilson, V. L., & Jones, P. A. (1983). DNA methylation decreases in aging but not in immortal cells. *Science 220*, 1055–1057.
Wu, J., Gan, Z., Zhuo, R., Zhang, L., Wang, T., & Zhong, X. (2020). Resveratrol attenuates aflatoxin B(1)-induced ROS formation and increase of m(6)A RNA methylation. *Animals (Basel) 10*.
Wu, J. N., & Roberts, C. W. (2013). ARID1A mutations in cancer: Another epigenetic tumor suppressor? *Cancer Discovery 3*, 35–43.
Wu, J. W., Yaqub, A., Ma, Y., Koudstaal, W., Hofman, A., Ikram, M. A., ... Goudsmit, J. (2021). Biological age in healthy elderly predicts aging-related diseases including dementia. *Scientific Reports 11*, 15929.
Wu, R., Yao, Y., Jiang, Q., Cai, M., Liu, Q., Wang, Y., & Wang, X. (2018). Epigallocatechin gallate targets FTO and inhibits adipogenesis in an mRNA m(6)A-YTHDF2-dependent manner. *International Journal of Obesity 42*, 1378–1388.
Wu, Y., Chen, X., Bao, W., Hong, X., Li, C., Lu, J., ... Zhu, A. (2022). Effect of Humantenine on mRNA m6A modification and expression in human Colon Cancer cell Line HCT116. *Genes (Basel) 13*.
Wu, Z., Shi, Y., Lu, M., Song, M., Yu, Z., Wang, J., ... Qu, J. (2020). METTL3 counteracts premature aging via m6A-dependent stabilization of MIS12 mRNA. *Nucleic Acids Research 48*, 11083–11096.
Xia, W., Hammerberg, C., Li, Y., He, T., Quan, T., Voorhees, J. J., & Fisher, G. J. (2013). Expression of catalytically active matrix metalloproteinase-1 in dermal fibroblasts induces collagen fragmentation and functional alterations that resemble aged human skin. *Aging Cell 12*, 661–671.
Xing, J., Yi, J., Cai, X., Tang, H., Liu, Z., Zhang, X., ... Wang, W. (2015). NSun2 promotes cell growth via elevating cyclin-dependent kinase 1 translation. *Molecular and Cellular Biology 35*, 4043–4052.
Xiong, W., Fang, B., Wang, X., Zhang, M., Du, M., Sun, J., ... Ren, F. (2023). Dietary lipid intervention in the prevention of brain aging. *Engineering 37*, 128–137.

Xiong, Y., Li, X., Liu, J., Luo, P., Zhang, H., Zhou, H., ... Zhou, L. (2024). Omega-3 PUFAs slow organ aging through promoting energy metabolism. *Pharmacological Research 208*, Article 107384.
Yagi, M., Kabata, M., Tanaka, A., Ukai, T., Ohta, S., Nakabayashi, K., ... Yamada, Y. (2020). Identification of distinct loci for de novo DNA methylation by DNMT3A and DNMT3B during mammalian development. *Nature Communications 11*, 3199.
Yan, F., Li, Z., Powell, C. A., & Wang, X. (2022). Forward single-cell sequencing into clinical application: Understanding of ageing and rejuvenation from clinical observation to single-cell solution. *Clinical and Translational Medicine 12*, Article e827.
Yan, G., Yuan, Y., He, M., Gong, R., Lei, H., Zhou, H., ... Yang, L. (2020). M(6)A methylation of precursor-miR-320/RUNX2 controls osteogenic potential of bone marrow-derived mesenchymal stem cells. *Molecular Therapy - Nucleic Acids 19*, 421–436.
Yan, Y., Qin, D., Hu, B., Zhang, C., Liu, S., Wu, D., ... Zhang, L. (2019). Deletion of miR-126a promotes hepatic aging and inflammation in a mouse model of cholestasis. *Molecular Therapy - Nucleic Acids 16*, 494–504.
Yang, J., Yin, J., Gao, H., Xu, L., Wang, Y., Xu, L., & Li, M. (2012). Berberine improves insulin sensitivity by inhibiting fat store and adjusting adipokines profile in human preadipocytes and metabolic syndrome patients. *Evidence-based Complementary and Alternative Medicine 2012*, Article 363845.
Yang, L., Lin, X., Tang, H., Fan, Y., Zeng, S., Jia, L., Li, Y., Shi, Y., He, S., Wang, H., Hu, Z., Gong, X., Liang, X., Yang, Y., & Liu, X. (2020). Mitochondrial DNA mutation exacerbates female reproductive aging via impairment of the NADH/NAD(+) redox. *Aging Cell 19*, Article e13206.
Yang, Y., Zhang, M., & Wang, Y. (2022). The roles of histone modifications in tumorigenesis and associated inhibitors in cancer therapy. *Journal of the National Cancer Center 2*, 277–290.
Ye, Z., Li, G., Kim, C., Hu, B., Jadhav, R. R., Weyand, C. M., & Goronzy, J. J. (2018). Regulation of miR-181a expression in T cell aging. *Nature Communications 9*, 3060.
de Yebenes, V. G., Briones, A. M., Martos-Folgado, I., Mur, S. M., Oller, J., Bilal, F., ... Ramiro, A. R. (2020). Aging-associated miR-217 aggravates atherosclerosis and promotes cardiovascular dysfunction. *Arteriosclerosis, Thrombosis, and Vascular Biology 40*, 2408–2424.
Yoshida, Y., Nakanishi, K., Daimon, M., Ishiwata, J., Sawada, N., Hirokawa, M., ... Komuro, I. (2019). Alteration of cardiac performance and serum B-type natriuretic peptide level in healthy aging. *Journal of the American College of Cardiology 74*, 1789–1800.
Yu, X., & Wang, W. (2021). A rapidly aging world in the 21st century: Hopes from Glycomics and unraveling the biomarkers of aging with the sugar code. *OMICS 25*, 242–248.
Zannella, C., Rinaldi, L., Boccia, G., Chianese, A., Sasso, F. C., De Caro, F., ... Galdiero, M. (2021). Regulation of m6A methylation as a new therapeutic option against COVID-19. *Pharmaceuticals (Basel) 14*.
Zhang, C., Zhang, X., Huang, L., Guan, Y., Huang, X., Tian, X. L., ... Tao, W. (2021). ATF3 drives senescence by reconstructing accessible chromatin profiles. *Aging Cell 20*.
Zhang, H., Ryu, D., Wu, Y., Gariani, K., Wang, X., Luan, P., ... Auwerx, J. (2016). NAD(+) repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science 352*, 1436–1443.
Zhang, H., Xu, R., Li, B., Xin, Z., Ling, Z., Zhu, W., ... Jiang, H. (2022). LncRNA NEAT1 controls the lineage fates of BMSCs during skeletal aging by impairing mitochondrial function and pluripotency maintenance. *Cell Death and Differentiation 29*, 351–365.
Zhang, L., Song, J., Kong, L., Yuan, T., Li, W., Zhang, W., ... Du, G. (2020). The strategies and techniques of drug discovery from natural products. *Pharmacology & Therapeutics 216*, Article 107686.
Zhang, M., Chen, Y., Chen, H., Shen, Y., Pang, L., Wu, W., & Yu, Z. (2022). Tanshinone IIA alleviates cardiac hypertrophy through m6A modification of galectin-3. *Bioengineered 13*, 4260–4270.
Zhang, W., Qu, J., Liu, G. H., & Belmonte, J. C. I. (2020). The ageing epigenome and its rejuvenation. *Nature Reviews. Molecular Cell Biology 21*, 137–150.
Zhang, X., Liu, Z., Yi, J., Tang, H., Xing, J., Yu, M., ... Wang, W. (2012). The tRNA methyltransferase NSun2 stabilizes p16INK(4) mRNA by methylating the 3′-untranslated region of p16. *Nature Communications 3*, 712.
Zhang, X., Zhang, D., Fan, A., Zhou, X., Yang, C., Zhou, J., ... Tao, J. (2024). A novel effect of sulforaphane on promoting mouse granulosa cells proliferation via the NRF2-TKT pathway. *Journal of Advanced Research 24*, 00422–00423.
Zhao, F., Zhang, J., & Chang, N. (2018). Epigenetic modification of Nrf2 by sulforaphane increases the antioxidative and anti-inflammatory capacity in a cellular model of Alzheimer's disease. *European Journal of Pharmacology 824*, 1–10.
Zhao, H., Song, A., Zhang, Y., Shu, L., Song, G., & Ma, H. (2019). Effect of resveratrol on blood lipid levels in patients with type 2 diabetes: A systematic review and Meta-analysis. *Obesity (Silver Spring) 27*, 94–102.
Zhao, J., Sun, H., Wang, C., & Shang, D. (2024). Breast cancer therapy: From the perspective of glucose metabolism and glycosylation. *Molecular Biology Reports 51*, 546.
Zhao, L., Tang, P., Lin, Y., Du, M., Li, H., Jiang, L., Xu, H., Sun, H., Han, J., Sun, Z., Xu, R., Lou, H., Chen, Z., Kopylov, P., Liu, X., & Zhang, Y. (2024). MiR-203 improves cardiac dysfunction by targeting PARP1-NAD(+) axis in aging murine. *Aging Cell 23*, Article e14063.
Zhao, L. Y., Song, J., Liu, Y., Song, C. X., & Yi, C. (2020). Mapping the epigenetic modifications of DNA and RNA. *Protein & Cell 11*, 792–808.
Zhao, Z., & Shilatifard, A. (2019). Epigenetic modifications of histones in cancer. *Genome Biology 20*, 245.
Zhou, W., Liu, H., Yuan, Z., Zundell, J., Towers, M., Lin, J., ... Zhang, R. (2023). Targeting the mevalonate pathway suppresses ARID1A-inactivated cancers by promoting pyroptosis. *Cancer Cell 41*(740–756), Article e710.
Zhu, D., Li, X., & Tian, Y. (2022). Mitochondrial-to-nuclear communication in aging: An epigenetic perspective. *Trends in Biochemical Sciences 47*, 645–659.
Zhu, H., Chen, J., Liu, K., Gao, L., Wu, H., Ma, L., ... Han, J. J. (2023). Human PBMC scRNA-seq-based aging clocks reveal ribosome to inflammation balance as a single-cell aging hallmark and super longevity. *Science Advances 9*, eabq7599.
Zuo, G., Chen, M., Zuo, Y., Liu, F., Yang, Y., Li, J., ... Lin, Y. (2024). Tea polyphenol epigallocatechin Gallate protects against nonalcoholic fatty liver disease and associated Endotoxemia in rats via modulating gut microbiota Dysbiosis and alleviating intestinal barrier dysfunction and related inflammation. *Journal of Agricultural and Food Chemistry 72*, 9067–9086.