

Senolytics from natural products for extending health and lifespan

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Senescence, a multifaceted cellular process, intricately regulates organismal aging by imposing irreversible growth arrest on cells. This phenomenon, characterized by altered gene expression and the accumulation of senescent cells, significantly contributes to age-related physiological decline and the onset of various age-associated pathologies [1]. Cellular senescence, the irreversible cessation of cell division, is intricately linked to the aging process in individuals [2]. As organisms age, the accumulation of senescent cells increases, contributing to tissue dysfunction and the development of age-related pathologies. Understanding the mechanisms underlying cellular senescence holds promise for elucidating the fundamental processes governing aging and may pave the way for targeted interventions to mitigate age-associated decline [3]. Senolytics are compounds that target and eliminate senescent cells, which are aged or damaged cells that accumulate in tissues and contribute to aging and age-related diseases [4]. Senolytics represent a class of pharmacological agents designed to selectively target and eliminate senescent cells, thereby mitigating the deleterious effects of cellular senescence on tissue homeostasis and organismal health. This emerging therapeutic approach holds promise in attenuating age-related pathologies and extending a healthy lifespan by modulating the senescent cell burden within tissues.

Many senolytics are synthetic compounds, while some natural products also exhibit senolytic properties. Such as flavonoids, containing quercetin, fisetin and apigenin, polyphenols, containing resveratrol and epigallocatechin gallate, gingerenone A, berberine and so on (Figure 1) [5–12]. Niki et al. identified quercetin and its derivative as a potent proteasome activator with anti-oxidant properties that consequently influence cellular lifespan, survival, and viability [5]. Furthermore, the combination of the senolytic drugs dasatinib and quercetin is renowned for diminishing the abundance of senescent cells in aged mice [13–15]. Matthew et al. demonstrated

that fisetin can effectively reduce the biomarkers of senescence and senescence-associated secretory phenotype in multiple tissues from progeroid and wild-type mice, via both acute (oral) and chronic (dietary) treatment [7]. They found that administration of fisetin to wild-type mice late in life, can restore tissue homeostasis, reduce age-related pathology, and extend median and maximum lifespan. Resveratrol exhibits diverse bioactivities, including antioxidant, anti-inflammatory, cardiovascular protective, anticancer, antidiabetic, antiobesity, neuroprotective, and anti-aging properties. Its anti-aging effects primarily involve mitigating oxidative stress, alleviating inflammatory responses, enhancing mitochondrial function, and modulating apoptosis. Thus, resveratrol holds promise as a potent and safe agent for both preventing and treating aging and age-related ailments [9].

Senolytics derived from natural products possess several characteristic features and merits that distinguish them from synthetic compounds and conventional therapies. Many natural products have been consumed as dietary supplements or traditional medicines for centuries, demonstrating a relatively low toxicity and favorable safety profile in humans. Compared to synthetic drugs, natural product-based senolytics may offer a potential alternative with minimal adverse effects. Besides, natural products often exhibit pleiotropic pharmacological activities, targeting multiple cellular pathways and molecular targets implicated in senescence, inflammation, and disease progression. This multifaceted mode of action may confer synergistic or additive effects, enhancing the anti-aging efficacy. In addition, many natural products with senolytic activity are commonly found in dietary sources, making them accessible for incorporation into functional foods, nutraceuticals, and dietary supplements. The integration of senolytic compounds into everyday diets may offer preventive and therapeutic benefits against aging and age-related diseases.

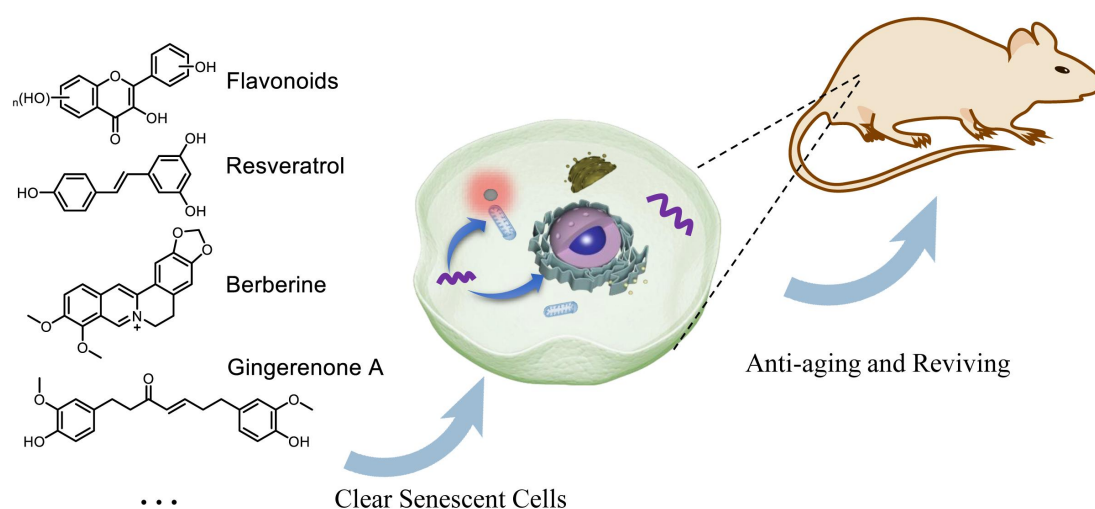


Figure 1 Natural senolytics for extending health and lifespan

Natural products have garnered considerable attention as potential senolytics, compounds that target senescent cells to alleviate age-related diseases. However, their utility is hindered by several shortages. Natural products exhibit diverse chemical structures, posing challenges in identifying specific senolytic mechanisms and optimizing efficacy. Additionally, their bioavailability and pharmacokinetic profiles vary, impeding consistent therapeutic outcomes. Meanwhile, sourcing and purification of natural products may be economically and environmentally unsustainable. Lastly, regulatory hurdles often impede the clinical translation of natural compounds. Addressing these shortages necessitates rigorous elucidation of their mechanisms, development of standardized formulations, and strategic integration into clinical practice, ensuring their effective utilization as senolytics.

Natural occurred senolytics offer promising approaches in anti-aging research, presenting novel avenues to combat age-related decline and extend lifespan. These compounds, abundant in bioactive agents with diverse pharmacological activities, hold the potential to selectively target and eliminate senescent cells, thereby attenuating chronic inflammation, tissue dysfunction, and organ decline associated with aging. Beyond disease intervention, natural product-based senolytics may rejuvenate aged tissues and organs, improving physiological function and quality of life in elderly individuals. Moreover, their safety profile and pleiotropic effects underscore their potential as sustainable and eco-friendly interventions for anti-aging. As research progresses, translating these compounds from preclinical studies to clinical trials holds promise for unlocking their therapeutic potential in promoting healthy aging and extending lifespan. However, further investigations are necessary to elucidate mechanisms of action, optimize therapeutic efficacy, and assess long-term safety and efficacy in human populations. Overall, senolytics from natural products represent a compelling strategy for healthier and more vibrant aging in the future.

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Author contributions

Chen J wrote the draft. Ma DP, He LM, and Yang DL collected relevant information. He LM and Yang DL revised and edited the manuscript. All authors have reviewed and agreed to the final draft.

Competing interests

The authors declare no conflicts of interest.

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