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Genetic And Biotechnological Advances in Plant-Based Geroprotectors: Toward Molecular Strategies for Healthy Aging

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Abstract
Plant-based geroprotectors represent a promising class of natural compounds capable of slowing down aging and promoting increased lifespan. This review explores recent advancements in biotechnology and genetic engineering, including genome editing (CRISPR/Cas9), omics approaches, and in vitro culture methods, all aimed at enhancing the bioavailability and efficacy of phytochemicals with geroprotective properties. The molecular mechanisms of action of key compounds (resveratrol, polydatin, flavonoids) are summarized, along with data from preclinical and clinical studies. In addition, the review highlights current challenges and future perspectives regarding the integration of these substances into clinical practice.

Keywords: Geroprotectors, phytochemistry, CRISPR/Cas9, resveratrol, aging, biotechnology, signaling pathways SIRT1, AMPK, mTOR.

Introduction

Aging is a complex biological process accompanied by a decline in physiological functions and the onset of chronic diseases.

The aim of this article is to summarize current scientific data on natural plant-based geroprotectors, their molecular targets, biotechnological strategies for production, and potential for application in clinical gerontology, with a focus on genetic and bioengineering approaches to enhance their efficacy.

According to the World Health Organization, by 2050 the proportion of people over the age of 60 worldwide will reach 2 billion. In this context, the search for compounds capable of slowing aging and improving the quality of life for the elderly has become increasingly relevant. Of particular interest are natural compounds of plant origin—phytogeroprotectors (Moskalev et al., 2016).

One of the most studied and promising classes of phytogeroprotectors is **polyphenols** (Tresserra-Rimbau, A., Rimm, E. B., Medina-Remón, A., et al., 2014). Among them, **resveratrol**, a

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compound found in grape skins and certain berries (Fig. 1), attracts special attention. It activates sirtuins (particularly SIRT1), which are associated with lifespan extension and improved metabolic function (Baur, J. A., & Sinclair, D. A., 2006). Resveratrol has been the subject of numerous studies demonstrating its potential to prolong lifespan in model organisms.

Figure 1. High-potency resveratrol, 350 mg, 60 vegetarian capsules (https://uz.iherb.com)

Another significant compound is polydatin, a natural glucoside of resveratrol. Due to its chemical structure, polydatin exhibits improved bioavailability, resistance to enzymatic degradation, and provides a prolonged effect in the body. It demonstrates pronounced antioxidant, anti-inflammatory, and metabolic properties, making it a strong candidate as a geroprotective agent (Wang et al., 2022).

Among the most widespread classes of plant-derived geroprotectors are **flavonoids**, including quercetin, catechins, rutin, and others. These compounds regulate cellular signaling pathways (such as mTOR, AMPK, and NRF2), help reduce oxidative stress, induce autophagy, and improve vascular function (Fig. 2). They are also actively studied in the clinical context as part of preventive gerontology (D'Andrea, G., 2015).

Figure 2. Foods containing flavonoids.

Equally important are **carotenoids** (beta-carotene, lycopene) and **coumarins**, which exhibit antioxidant, photoprotective, and immunomodulatory activities (Davinelli, S., Ali, S., Solfrizzi, V., et al., 2022). Their role in modulating the cell cycle and protecting against age-related changes is being actively investigated, including through genetic and biotechnological approaches.

However, despite the great potential of plant-based geroprotectors, their clinical application is limited by several factors: low bioavailability, rapid metabolism, and instability of compounds within the body (Yang, C. S., Sang, S., Lambert, J. D., & Lee, M. J., 2008). These limitations necessitate the development of new delivery strategies, enhancement of synthesis efficiency, and improvement of the pharmacokinetic properties of the compounds. Therefore, the use of genetic engineering, cellular biotechnology, synthetic biology, and systemic analysis of omics data has become especially relevant to enhance the therapeutic potential of phytogeroprotectors.

2. Genetic Engineering of Geroprotective Compounds in Plants

The use of **CRISPR/Cas9** in plant metabolic engineering allows for targeted enhancement of the synthesis of valuable compounds (Singh, A., & Singh, N., 2020):

- In Vitis davidii cells, mutation of the **CHS2** gene led to a fourfold increase in resveratrol and a fivefold increase in piceid levels (Lai et al., 2025).
- Genetically modified tomatoes and grapes with enhanced expression of phytoalexin biosynthesis pathways demonstrate greater resistance and increased antioxidant production.
- **Omics** technologies (transcriptomics, metabolomics) help identify key biosynthetic enzymes (PAL, STS, UGTs) and regulate their activity.

3. Biotechnological Production of Phytogeroprotectors

To increase the yield of geroprotectors, the following methods are used:

- In vitro cultures (callus, hairy roots) with elicitors.
- Bioreactors and suspension cultures.
- **Synthetic biology**: expression of plant metabolic pathways in yeast and bacteria for industrial-scale production of resveratrol.

Example: Saccharomyces cerevisiae yeast modified with grape genes can produce resveratrol at levels up to 800 mg/L (Li et al., 2023).

4. Molecular Targets of Geroprotectors

Phytogeroprotectors act on key aging-related signaling pathways:

- **SIRT1** — activated by resveratrol, regulates mitochondria, longevity genes, and autophagy.
- **AMPK** — an energy sensor activated by phytonutrients, inhibits mTOR.
- **mTOR** — a central metabolic regulator inhibited by caloric restriction and phytochemicals.
- **NRF2** — controls antioxidant defense and is induced by quercetin and catechins (Scapagnini, G., Vasto, S., Abraham, N. G., Caruso, C., Zella, D., & Fabio, G., 2011).

5. Preclinical and Clinical Studies

In animal models:

- Resveratrol has been shown to increase the lifespan of mice by 18–21% on a high-fat diet.
- Polydatin demonstrates hepatoprotective and neuroprotective properties (Wang et al., 2022).

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In clinical studies:

- A meta-analysis of 11 RCTs confirmed the anti-inflammatory effects of resveratrol in elderly patients.
- **Bioavailability remains a critical issue** — innovations include nanocapsules, liposomes, and transport systems to improve delivery.

6. Perspectives and Challenges

Despite significant progress in the study of phytogeroprotectors, there remain several major challenges that hinder their widespread adoption in clinical settings.

First, **low bioavailability** of most phytochemicals remains a key limitation. This reduces their therapeutic potential, as even high doses often result in poor absorption in the gastrointestinal tract. Addressing this issue requires the development of novel delivery systems, including **liposomal formulations, nanocapsules, and biodegradable polymers** capable of ensuring sustained and targeted release of active substances.

Secondly, there is currently no unified regulatory framework for assessing the safety and efficacy of phytogeroprotectors, which hinders their standardization and registration as medicinal products. This necessitates the development of international standards and testing protocols, similar to those applied to pharmaceutical drugs.

Thirdly, there is insufficient standardization regarding dosages, raw material sources, and purification methods. Plant extracts—even when obtained from the same species—can vary significantly in composition depending on cultivation conditions, climate factors, and extraction methods. This compromises reproducibility and calls for the implementation of strict quality standards.

Finally, an important unresolved issue is the translation of laboratory and preclinical research findings into clinical practice. Despite compelling in vitro and animal model data, there is a lack of large-scale cohort and randomized clinical trials in humans. This gap slows the integration of phytogeroprotectors into preventive protocols for age-related diseases.

Conclusion

Plant-based geroprotectors represent a promising direction in preventive and personalized medicine aimed at promoting active and healthy longevity. Their ability to modulate key aging-related signaling pathways (SIRT1, AMPK, mTOR), reduce oxidative stress, activate autophagy, and improve metabolic parameters has been confirmed in both preclinical and several clinical studies. Particular attention is given to polyphenols, flavonoids, and carotenoids, which exhibit high biological activity but still require improvement in terms of bioavailability and stability.

Modern biotechnological and genetic approaches, including in vitro cultures, CRISPR/Cas9, synthetic biology, and omics technologies, open new opportunities for enhancing the efficacy and standardization of phytogeroprotectors. Nevertheless, challenges remain related to the lack of unified regulations on dosage and safety, as well as the need for large-scale clinical trials.

Thus, phytogeroprotectors hold significant potential for integration into gerontological practice; however, their widespread adoption will require a comprehensive interdisciplinary approach involving pharmacology, genetics, biotechnology, and clinical medicine.

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