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PHYTOTHERAPY TARGETING IMMUNOSENESCENCE: MECHANISTIC PERSPECTIVES FOR HEALTHY AGEING (MINI-REVIEW)

Actuality. *Aging is a complex process marked by molecular and cellular damage, leading to immunosenescence and increased risk of chronic diseases. Phytotherapeutic interventions are widely used and show multifunctional potential, including modulation of signaling pathways, neuroprotective and cardiovascular benefits, and epigenetic regulation. Although phytochemicals interact with immune-associated pathways, their effects on ageing-related immune dysfunction and associated health conditions remain incompletely understood.*

Purpose of the work. *This review highlights the role of medicinal plants and phytochemicals in supporting immune-related healthy aging through multi-targeted mechanisms.*

Material and methods. *A comprehensive literature search was conducted between August and December 2025 using academic databases such as PubMed, Scopus, Google Scholar, ScienceDirect, and Elsevier.*

Research results. *Phytochemicals, including polyphenols, flavonoids, terpenoids, saponins, and alkaloids, possess multifaceted therapeutic potential in counteracting age-related immune decline. Key compounds, such as curcumin, resveratrol, EGCG, quercetin, ginsenosides, berberine, and piperine, modulate key cellular processes. For instance, our analysis reveals that curcumin, resveratrol, and berberine primarily counteract immunosenescence by promoting autophagy and activating the Klotho/Sirtuin 1 pathway, while simultaneously neutralizing oxidative stress to maintain mitochondrial integrity and stem cell viability. In parallel, epigallocatechin gallate and quercetin exert their effects by limiting vascular and thymic atrophy and restoring redox balance. They bolster antioxidant defenses by activating the Nrf2/HO-1 signaling axis, stimulating interleukin-2 secretion, and enhancing nitric oxide production. Furthermore, ginsenosides, piperlongumine, and piperine function as potent senotherapeutics; they suppress the senescence-associated secretory phenotype and attenuate chronic inflammation by modulating STAT3/mTOR and MAPK signaling. Simultaneously, they counteract immunosenescence by optimizing T-cell metabolic fitness and rejuvenating lymphoid organ function, thereby rebalancing the cytokine milieu for sustained immune health.*

Conclusion. *Collectively, these findings underscore the therapeutic promise of phytochemicals as multi-targeted agents capable of mitigating oxidative damage and driving epigenetic regulation. By shifting the cellular environment from a pro-inflammatory state toward systemic homeostasis, these bioactive compounds offer a potent, complementary strategy for preserving immune resilience and reducing the risk of age-associated pathologies.*

Key words: *Phytotherapy, Healthy aging, immunosenescence, Chronic diseases, Cytokine.*

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ФІТОТЕРАПІЯ, СПРЯМОВАНА НА ІМУНОСЕНЕСЦЕНЦІЮ: МЕХАНІСТИЧНІ ПЕРСПЕКТИВИ ДЛЯ ЗДОРОВОГО СТАРІННЯ (МІНІОГЛЯД)

Актуальність. *Старіння – це складний процес, який характеризується молекулярними та клітинними пошкодженнями, що призводить до імуносенесценції (старіння імунної системи) та підвищеного ризику хронічних захворювань. Фітотерапевтичні втручання широко використовуються та демонструють багатофункціональний потенціал, включаючи модуляцію сигнальних шляхів, нейропротекторні та серцево-судинні переваги, а також епігенетичну регуляцію. Хоча фітохімічні речовини взаємодіють з імунозалежними сигнальними шляхами, їхній вплив на пов'язану зі старінням імунну дисфункцію та пов'язані з нею стани здоров'я залишається недостатньо вивченим.*

Мета дослідження. *Цей огляд підкреслює роль лікарських рослин та фітохімічних сполук у підтримці здорового старіння, пов'язаного з імунною системою, за допомогою багатоцільових механізмів.*

Матеріал і методи. *Комплексний пошук літератури було проведено із серпня по грудень 2025 р. з використанням академічних баз даних, таких як PubMed, Scopus, Google Scholar, ScienceDirect та Elsevier.*

Результати дослідження. *Фітохімічні сполуки, зокрема поліфеноли, флавоноїди, терпеноїди, сапоніни та алкалоїди, мають багатогранний терапевтичний потенціал, у протидії віковому зниженню функцій імунної системи. Ключові сполуки, такі як куркумін, ресвератрол, EGCG, кверцетин, гінзенозиди, берберин і піперин, модулюють важливі клітинні процеси. Зокрема, наш аналіз указує, що куркумін, ресвератрол і берберин переважно протидіють імуностарінню шляхом стимуляції аутофагії та активації сигнального шляху Klotho/Sirtuin 1, одночасно нейтралізуючи оксидативний стрес для підтримання цілісності мітохондрій і життєздатності стовбурових клітин. Водночас епігалокатехін галат і кверцетин реалізують свої ефекти шляхом обмеження судинної і тимічної атрофії та відновлення редокс-балансу. Вони посилюють антиоксидантний захист через активацію сигнальної осі Nrf2/HO-1, стимуляцію секреції інтерлейкіну-2 та підвищення продукції оксиду азоту. Окрім того, гінзенозиди, піперлонгумін і піперин діють як потужні сенотерапевтичні агенти: вони пригнічують сенесцент-асоційований секреторний фенотип та послаблюють хронічне запалення шляхом модуляції сигнальних шляхів STAT3/mTOR і MAPK. Водночас вони протидіють імуностарінню, оптимізуючи метаболічну активність Т-лімфоцитів і відновлюючи функцію лімфоїдних органів, що сприяє нормалізації цитокінового середовища та підтриманню тривалого імунного здоров'я.*

Висновок. *Загалом отримані дані підкреслюють терапевтичну перспективність фітохімічних сполук як багатоцільових агентів, здатних зменшувати оксидативне пошкодження та регулювати епігенетичні процеси. Змінюючи клітинне середовище від прозапального стану до системного гомеостазу, ці біологічно активні сполуки пропонують ефективну взаємодоповнюючу стратегію для збереження імунної стійкості та зниження ризику розвитку вікових патологій.*

Ключові слова: *фітотерапія, здорове старіння, імуносенесценція, хронічні захворювання, цитокіни.*

Actuality. The World Health Organization (WHO), through its Technical Advisory Group, has established a comprehensive framework for monitoring progress under the UN Decade of Healthy Aging (2021–2030). Within this framework, aging is defined as a progressive and multifaceted process involving physical, cognitive, and social transformations over time. Biologically, it is characterized by the progressive accumulation of molecular and cellular damage, which gradually compromises physiological capacity, increases susceptibility to disease, and ultimately results in the deterioration of functional integrity and survival (WHO, 2025). Although we adopt the widely used term «aging», it encompasses a complex biological process, often characterized as the gradual breakdown of self-organizing systems and a diminished capacity to adapt to environmental changes, which relies on mechanisms that are still only partially understood (da Costa, 2016: 90–112). Recent discoveries in biogerontology suggest that aging may be governed by a genetic program activated after maturity and may serve an adaptive role at the population or species level (Pamplona, 2023). Immunosenescence is the age-related decline in immune function, involving structural and functional changes in both innate and adaptive immunity. Key features include thymic atrophy, reduced immune repertoire diversity, impaired antigen response, and chronic low-grade inflammation («inflamm-aging») (Wang, 2025). Moreover, dysregulation of the immune system contributes to neurodegenerative, cardiovascular, autoimmune diseases, and cancers, partly through the actions of senescence-associated secretory phenotype (SASP) mediators, which influence immune activity, fibrosis, and inflammation (Wang, 2022). The principal aim of aging research is to identify strategies that

delay the onset of age-related diseases, extend healthy lifespan, and sustain overall health (Hilmer, 2025). Understanding the fundamental mechanisms of the aging process is expected to support the identification of novel therapeutic targets (Guo, 2022), including phytotherapeutic interventions.

Relying on data gathered between April 2023 and March 2024, the WHO's Global Dashboards for Traditional, Complementary, and Integrative Medicine (TCIM), developed on the basis of the Third WHO Global Survey on TCIM, offer comprehensive insights into the availability, production standards, and safety regulations governing herbal medicines across Member States (WHO, 2025). These findings provide clear evidence of the widespread use of medicinal plants across diverse cultural and healthcare settings, underscoring their vital role in medical practice as accessible, culturally integrated, and therapeutically valuable components of both traditional and modern clinical contexts.

The multifunctional therapeutic and preventive potential of phytoconstituent mixtures, as highlighted in recent studies (Pereira, 2025; Ansari, 2023), is particularly effective in addressing the complex multi-factorial pathophysiology of chronic age-related disorders. The therapeutic efficacy of these formulations is driven by the synergistic interplay of individual constituents; such combination not only amplifies the primary medicinal effect but also attenuates potential side effects through multi-target modulation (Zhang, 2019). Consequently, these plant-based interventions can regulate key signaling pathways across various systems, fostering neuroprotection and cardiovascular health in aging populations (Paul, 2024). A significant advantage of this approach is the favorable safety profile associated with these remedies (Fazilat, 2024), which is paramount for elderly patients managed under complex polypharmacy protocols. Beyond acute cellular responses, phytochemicals offer a sustained, non-toxic means of modulating epigenetic regulation over a lifetime, potentially slowing the progression of age-associated metabolic (Nurkolis, 2025) and neurodegenerative diseases (Prasanth, 2024). In distinct contrast to conventional synthetic analogs – which typically target isolated receptors – plant-derived bioactive compounds function as pleiotropic modulators that interact with complex cellular networks to restore immune homeostasis (Parchami Ghazaee, 2025). While this multi-targeted potential is evident, the precise mechanisms by which these compounds govern the interplay between age-related immune dysfunction and systemic health remain a critical frontier for investigation.

Purpose of the work. This review provides an updated overview of investigations into phytopreventive strategies in the context of immune-related healthy aging. Particular emphasis is placed on the capacity of phytochemicals and medicinal plants to delay or modulate disease progression through multi-targeted mechanisms. Moreover, this review bridges Eastern and Western medical philosophies by framing them within the context of systems biology. While Western medicine focuses on molecular homeostasis and specific biomarkers of immunosenescence, Eastern paradigms emphasize «harmony» and the maintenance of «vital reserve». Scientifically, this article addresses these dual perspectives through the lenses of pleiotropy and hormesis – demonstrating how phytochemicals act not as single-target drugs, but as systemic modulators that restore immune connectivity and resilience (Zhang, 2019). By aligning the Eastern goal of systemic balance with the Western focus on signaling pathways, this work clarifies how plant-based interventions can effectively treat aging as a holistic network failure.

Material and methods.

1. Sources of information

A comprehensive literature search was conducted between August and December 2025 using academic databases such as PubMed, Scopus, Google Scholar, ScienceDirect, and Elsevier. Peer-reviewed articles published between January 2020 and May 2026 were included to ensure the incorporation of recent findings in the field. To enhance the completeness of the review, reference lists of selected studies were also screened for additional relevant sources.

2. Search terms

The reviewers independently conducted manual literature searches, applying a multi-query strategy that incorporated terms such as «phytotherapy», «herbal medicine», «medicinal plants», «age-associated diseases», «chronic diseases», and other condition-specific keywords pertinent to the topic.

3. Selection criteria

Inclusion criteria were restricted to original, high-quality English-language publications addressing the use of medicinal plants or phytochemicals in the prevention or management of aging-related diseases. Eligible studies included *in vivo*, *in vitro*, in silico investigations, clinical trials, meta-analyses, questionnaire-based surveys, technical reports, and narrative reviews focusing specifically on herbal interventions. Exclusion criteria comprised outdated data, irrelevant topics, case reports, study protocols, and letters to the editor. To maintain a focused scope, studies exploring phytotherapy in combination with other complementary and alternative medicine modalities were not considered.

Results. The analysis included articles addressing strategies for the prevention and management of

aging-related conditions. Particular attention was given to research examining the effects of major plant secondary metabolites on immunosenescence. Recent publications were incorporated to provide a robust scientific foundation and to elucidate the potential mechanisms underlying the efficacy of applied phytochemicals.

Discussion.

Phytochemical Approaches to Immunosenescence and Healthy Aging

Phytochemicals exert geroprotective effects by modulating complex cellular networks, acting as biochemical signals that reprogram the aging cell. The therapeutic potential of these agents is categorized into three major bioactive classes, each contributing unique molecular signatures to the preservation of immune resilience.

1. Polyphenols & Flavonoids

Curcumin, a polyphenolic compound extracted from plants of the Zingiberaceae family (*Curcuma longa* L.), has garnered significant attention in medicine due to its broad-spectrum pharmacological properties, including anti-inflammatory, antioxidant, immunomodulatory, and potential anti-aging effects. It emerges as a promising agent against immune aging and inflammation-driven tissue damage by orchestrating multiple cellular protective mechanisms (Allegra, 2022). Treatment of canine bone marrow mesenchymal stem cells (cBMSCs) with curcumin during long-term *in vitro* cultivation (to model premature senescence) resulted in a significant reduction in senescence-associated β-galactosidase (SA-β-gal)-positive cells. Notably, 1 μM curcumin exerted pronounced cytoprotective effects, delaying cellular senescence, as evidenced by downregulation of the senescence marker p16 and the pro-inflammatory cytokines IL-6 and Tumor Necrosis Factor-α (TNF-α), along with upregulation of the pluripotency-related transcription factors Nanog and SOX-2. Furthermore, curcumin induced a dose-dependent increase in autophagic activity, as evidenced by enhanced autophagosome and autolysosome formation after 24 h of exposure. Importantly, pharmacological inhibition of autophagy accelerated cBMSC senescence, further supporting the role of autophagy in maintaining stem cell viability and in delaying senescence (Deng, 2021). *In vitro* experiments using senescence-induced rat BMSCs (rBMSCs) revealed that treatment with curcumin liposomes significantly downregulated the expression of senescence markers p16, p21, and p53 ($p < 0.05$, $p < 0.01$). This treatment also restored mitochondrial function, as evidenced by a reduction in mitochondrial reactive oxygen species (mtROS) levels ($p < 0.01$) and an increase in mitochondrial membrane potential (mtΔψm) ($p < 0.05$) along with improved rBMSC proliferation. Additionally, treatment with 10 μM/L liposomal curcumin elevated the expression of mitophagy-related proteins PINK1 and LC3B-II/I, indicating restored mitochondrial homeostasis and reduced cellular damage (Li, 2024). Beyond their role as stromal progenitors, MSCs also contribute to the maintenance of the hematopoietic stem cell niche. This interaction is vital for supporting hematopoiesis and the generation of immune cells (Castillo, 2007: 76–80). Thus, rejuvenation of senescent MSCs via liposomal curcumin may offer a strategy for preserving the bone marrow microenvironment and mitigating age-related immune decline. Recent findings (Li, 2026) demonstrate that curcumin—in a dose-dependent manner (50–100 μmol/L) – suppresses autoimmune inflammation by modulating the nuclear factor erythroid 2-related factor 2 (Nrf2)/cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING)/nuclear factor-kappa B (NF-κB) signaling axis. Mechanistically, curcumin-mediated NRF2 activation directly inhibits the cGAS-STING pathway, thereby preventing the downstream activation of NF-κB and significantly reducing pathological cell invasion and cytokine release. This multi-layered modulation positions curcumin as a critical bridge between antioxidant defense and innate immune sensing, effectively restoring systemic homeostasis in the context of chronic inflammation.

Resveratrol (trans-3,4,5-trihydroxystilbene) is a naturally occurring polyphenol found in red wine, rhubarb, and fruits including blueberries, numerous red grape varieties, and peanuts, exhibiting a broad spectrum of biological activities. The immunomodulatory properties of resveratrol have been extensively reviewed by Malaguarnera (2019). The B cell-activating factor (BAFF) system regulates B cell differentiation and maturation in adaptive immunity; however, its overexpression contributes to autoimmune pathology. In ageing, dysregulated cytokine signalling increases BAFF production, promoting survival of autoreactive B cells, autoantibody formation, and loss of B cell tolerance (Möckel, 2021).

Resveratrol has been shown to counteract these effects by inducing autophagy, thereby suppressing BAFF-induced proliferation and survival of murine primary B lymphocytes and human Raji B-lymphoid cells (Yao, 2022) . In addition, resveratrol increases the expression of antioxidant factors, including catalase and SIRT1, while reducing pro-inflammatory cytokines (IL-1β, TNF-α, IL-10) and chemokines (CCL2, CCL5) in peripheral blood mononuclear cells after Toll-like receptor stimulation, suggesting its potential to modulate excessive inflammatory responses during ageing (Fernandes, 2025). Moreover, Resveratrol adminis-

tration in *Nothobranchius guentheri* reduced thymic senescent cells, increased SIRT1 and SIRT3 expression, and decreased NF-κB activity, indicating diminished inflammatory signaling. Similar protective effects were observed in the kidney, including reduced fibrosis and senescence markers (Hou, 2023). Overall, resveratrol appears to delay age-related degenerative changes and mitigate immunosenescence through autophagy activation, oxidative stress reduction, and modulation of inflammation.

Epigallocatechin gallate (EGCG), the major catechin in green tea, has been associated with modulation of cellular senescence, delayed ageing, and reduced age-related pathology (Wan, 2023). It decreased senescence markers and SASP factors, suppressed monocyte activation, and restored immune homeostasis in ageing-related vascular models, supporting its senotherapeutic potential (Patel, 2025). In addition, gallic acid restored thymic architecture, increased thymocyte and $CD4^+$ T cell numbers, enhanced proliferation, and reduced apoptosis in an ageing mouse model (Guo, 2020). Furthermore, a review by Mokra et al. (2022) demonstrated that EGCG exerts antioxidant and anti-inflammatory effects by activating the Nrf2/HO-1 (heme oxygenase-1) pathway. Collectively, these findings indicate that phytochemicals may counteract age-related immune decline by targeting senescent cell burden and inflammatory signaling.

Quercetin and fisetin are flavonoids present in various fruits and vegetables, known for their broad pharmacological properties, including anti-inflammatory, antioxidant, anti-apoptotic, and their ability to modulate cancer signaling pathways (Zolfaghari, 2025). Their senolytic properties have also been explored, as evidenced by a study in aged rhesus monkeys in which a combined oral dose of dasatinib (D, 5 mg/kg) and fisetin (100 mg/kg) significantly reduced epidermal markers of cellular senescence, specifically $p16^+$ and $p21^+$ cells (Colman, 2020).Taken together, these findings suggest that quercetin and fisetin exert their immunomodulatory effects not merely through antioxidant activity, but by selectively targeting senescent cell populations and inflammatory signaling pathways, thereby contributing to the preservation of immune function during aging. Quercetin has been shown to restore immune function in PBMCs from aged mice by enhancing proliferation, increasing IL-2 and nitric oxide (NO) production, strengthening antioxidant defenses, and reducing oxidative stress, highlighting its potential as a dietary adjuvant to counteract immunosenescence in the elderly (Bouamama, 2023). Regarding age-related changes in the immune system, an *in vivo* experiment showed that lungs of aged influenza infected mice exhibited a significantly higher proportion of Forkhead box P3 (FoxP3)-expressing $CD4^+$ T cells and elevated levels of transforming growth factor-beta (TGF-β), a pleiotropic cytokine that contributes to the maintenance of the senescent phenotype. Senolytic treatment with dasatinib plus quercetin in aged mice partially restored T helper cell differentiation by reducing FoxP3 expression and shifting toward a Th2 profile, potentially via suppression of elevated TGF-β in the aged lung environment (Lorenzo, 2022). However, follow-up experiments using the same agents failed to show therapeutic benefit, with no improvements in weight loss, lung pathology, antibody production, or pro-inflammatory markers (Torrance, 2023). While senolytics hold promise, their effects on immune responses, particularly between primary and memory phases, remain unclear, requiring further investigation in older populations.

2. Terpenoids & Saponins

A recent comprehensive review by Iqbal *et al*. highlighted the therapeutic potential of ginseng and its active components, ginsenosides, in attenuating age-related diseases through multiple mechanisms demonstrated by *in vivo* and *in vitro* models (Iqbal, 2025). The regulation of Treg cell function during aging is closely linked to oxidative stress, redox status, and immune homeostasis. Red ginseng extract (RGE, 10 and 100 μg/mL) has been shown to increase mitochondrial oxygen consumption rate in $CD4^+$ T cells from both young and aged mice, with stronger effects in the aged group, indicating enhanced mitochondrial and glycolytic activity. In aged mice, RGE increased naïve $CD4^+$ and $CD8^+$ T cells, reduced memory T cells, downregulated Major Histocompatibility Complex class II on macrophages, and lowered pro-inflammatory cytokine production. RGE also decreased senescence-related and exhaustion markers in T cells, while shifting macrophages toward a less inflammatory profile by suppressing *Tnf*, *IL1b*, *Cd80*, and *Cd86* genes. Single-cell transcriptomics revealed reduced pro-inflammatory signaling between immune cells. Overall, RGE appears to counteract immunosenescence by reprogramming T cell metabolism and dampening macrophage-mediated inflammation (Lee, 2025). The primary active components of American ginseng are saponins, particularly Rb1 and Re. Administration of these saponins (Rb1, 30 mg/kg and Re, 15 mg/kg) significantly increased thymus and spleen indices and promoted weight gain in aged mice. Thymic apoptosis was slightly reduced, decreasing the proportion of apoptotic cells. Treatment with individual saponins elevated blood IgA and IgG levels, while combined administration of Rb1 and Re markedly increased IgG. Furthermore, Rb1 and Re, particularly when given together, restored anti-inflammatory cytokines, including IL-2, IL-4,

IL-10, and suppressed most pro-inflammatory cytokines (IL-6, IL-17, IL-27, TNF, and interferon), counteracting the typical age-related decline in anti-inflammatory cytokines and rise in pro-inflammatory mediators (Shi, 2024). NF-κB, a central regulator of immune and inflammatory responses, contributes to photoaging by promoting the expression of matrix metalloproteinases (MMPs), driving collagen degradation, stimulating pro-inflammatory cytokine release, and recruiting collagenase-producing neutrophils into UVB-damaged skin. The active constituents of *Astragalus membranaceus,* including flavonoids, polysaccharides, and astragalosides, the major triterpenoid saponins, have been shown to inhibit NF-κB activation and downregulate its downstream inflammatory mediators. By reducing ROS generation, suppressing NF-κB–induced cytokines (TNFα, IL-1β, IL-6, IL-8), and limiting MMP expression, they can attenuate UV-induced inflammation and extracellular matrix breakdown. This combined antioxidant and anti-inflammatory action underscores their potential as anti-aging agents for preserving skin structure and function (Borowicz, 2025). Beyond skin protection, Astragaloside IV, at various concentrations, has also been demonstrated to target immune signaling relevant to aging-related conditions. In macrophages, it suppressed senescence, alleviated mitochondrial dysfunction, and shifted polarization from pro-inflammatory M1 to reparative M2 phenotypes by inhibiting the STING/NF-κB pathway. These immunomodulatory effects subsequently enhanced the osteogenic potential of BMSCs and, *in vivo*, improved bone microstructure while preventing bone loss, highlighting the broader protective role of Astragaloside IV in age-associated tissue degeneration (Li, 2024). These findings collectively support a pathway-oriented framework in which immune aging is shaped by coordinated metabolic and inflammatory networks, providing a rationale for considering phytochemicals within systems-level strategies rather than compound-specific approaches.

3. Alkaloids

Berberine (BBR), a benzylisoquinoline alkaloid found in plants such as barberry (*Berberis* spp.), has been comprehensively reviewed by Mushtaq et al. regarding its mechanistic pharmacological effects against cancer, DM, obesity, allergy, hypertension, and oxidative stress, as well as its anti-aging properties (Mushtaq, 2023). Furthermore, evidence from both *in vitro* and *in vivo* investigations demonstrates that BBR significantly attenuates the production of pro-inflammatory mediators, including TNF-α, IL-6, IL-1β, PGE_2, and NO. Mechanistically, BBR downregulates the mRNA expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) while concurrently modulating the Nrf2 signaling axis to restore redox homeostasis, suggesting its potential as a safe and effective strategy for the treatment of autoimmune diseases (Mentese, 2026; Qin, 2024). BBR has been shown to alleviate oxidative and inflammatory lung injury by in rats.

BBR was shown to extend lifespan in *Caenorhabditis elegans* in a dose-dependent manner, with 80 μg/mL producing the most pronounced benefit without affecting growth, feeding, or reproduction. It was reported to enhance locomotor activity, reduce ROS and lipofuscin accumulation, and improve stress tolerance, reflecting its antioxidant and cellular protective properties. Transcriptomic analyses have indicated that BBR modulates metabolism, particularly via cytochrome P450 and UDP-glucuronosyltransferase genes, lipid metabolism (*daf-12*, *nhr-80*, *fard-1*, *fat-6*), autophagy-lysosome pathways, and stress responses via mitogen-activated protein kinase (MAPK) signaling. These multifaceted actions collectively enhance cellular health, metabolic regulation, and longevity in *C. elegans* (Bei, 2025).

Along with this, an *in vitro* investigation of H9c2 cardiac cells and blood samples from aged rats demonstrated that dietary BBR (1 and 2 g/kg) restored cell viability and telomere length, and inhibited p53 and p21 upregulation, proposing that the anti-senescent action of BBR depends on Klotho (KL) protein. BBR mitigated oxidative stress, apoptosis, and mitochondrial dysfunction, normalizing ROS levels, Bcl-2-associated X protein (Bax)/B-cell lymphoma 2 (Bcl-2) ratio, and mitochondrial respiration. In aged rats, BBR improved myocardial structure, reduced fibrosis, and hypertrophy markers, including atrial natriuretic peptide, α-and β-myosin heavy chain, lowered serum creatine kinase, and restored *KL* and *SIRT1* expression. These findings suggest that BBR protects against cardiac senescence and age-related cardiac damage through the KL/SIRT1 signaling pathway, highlighting its potential as a cardioprotective and anti-aging intervention (Li, 2022). Through overlapping mechanisms, such as enhanced antioxidant defenses, autophagy, and metabolic homeostasis, as well as the protective role of KL against immunosenescent-like phenotypes in monocytes (Mytych, 2018), BBR may contribute to preserving immune function and mitigating immunosenescence. However, further studies are needed to confirm these effects in mammalian systems and to elucidate the precise molecular mechanisms underlying its immunomodulatory potential.

Piperlongumine (PPL) and piperine, an amide alkaloid isolated from *Piper longum* L. (long pepper) and other Piper species, have been investigated for diverse medicinal applications, including anticancer, antidiabetic,

anti-obesity, and cardiovascular effects (Sinha, 2025). A novel alkaloid, PPLA, was isolated from *P. longum* leaves and demonstrated potent anti-inflammatory activity by inhibiting NO, IL-6, iNOS, and COX-2 in lipopolysaccharide (LPS)-stimulated cells. Molecular docking studies suggested that it binds effectively to IL-6, TNF-α, and iNOS, supporting its potential as a lead compound for anti-inflammatory drug development (Tran, 2024). Additionally, fruits of *P. longum* L., at concentrations ranging from 0–100 μg/mL, exhibited anti-inflammatory effects by modulating the MAPK pathway, indicating their potential as therapeutic agents for inflammatory diseases *in vitro* (Phan, 2024). These alkaloids have been proposed as novel anti-aging therapies. Piperine (70 μM) was shown to reduce SA-β-gal activity in senescent human dermal fibroblasts without affecting cell morphology. It restored mitochondrial membrane potential and decreased intracellular ROS levels. Moreover, piperine significantly suppressed the SASP, reducing secretion of IL-6, IL-8, and TGF-β1 in senescent cells. These findings suggest that piperine can restore senescent cell functions and serves as a potential senotherapeutic agent through modulation of SASP (Lim, 2022). PPL exhibits multi-level anti-inflammatory and senotherapeutic effects. In imiquimod-induced psoriatic mice, topical (10–30 mg/kg) and subcutaneous (1 mg/kg) administration of PPL attenuated skin inflammation, reduced splenomegaly, and suppressed keratinocyte hyperproliferation, while restoring normal tissue architecture by inhibiting Akt/mTOR and p70S6K signaling and downregulating proliferation markers, including Ki67, Cyclin D1, and Bcl-2. At 5–10 μM, PPL induced ROS-mediated apoptosis, improved mitochondrial function, and downregulated aberrant keratin 17 expression via STAT3 inhibition. It also suppressed pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, IL-17, IL-22, TGF-β and chemokine networks, while inhibiting NF-κB/p65 and c-Jun N-terminal kinase (JNK) signaling in macrophages, thereby reducing immune cell recruitment. Notably, PPL exerted epigenetic modulation through Histone Deacetylase (HDAC) inhibition, lowering HDAC1, 2, 3, and 6 expression both *in vitro* and *in vivo* (Thatikonda, 2020). Given that hyperactivation of STAT3 and mTOR drives the production of pro-inflammatory cytokines, including IL-6 and IL-23, which contribute to the SASP and sustain chronic inflammatory signaling (Fu, 2025), this evidence supports the view that alkaloid phytochemicals act on shared longevity and inflammatory signaling networks, providing indirect but biologically plausible links to the modulation of immunosenescence. Table summarizes the immunosenescence-modulating properties of plant secondary metabolites. Mechanistic Landscape of Phytochemical-Mediated Immune Resilience is illustrated in fig.

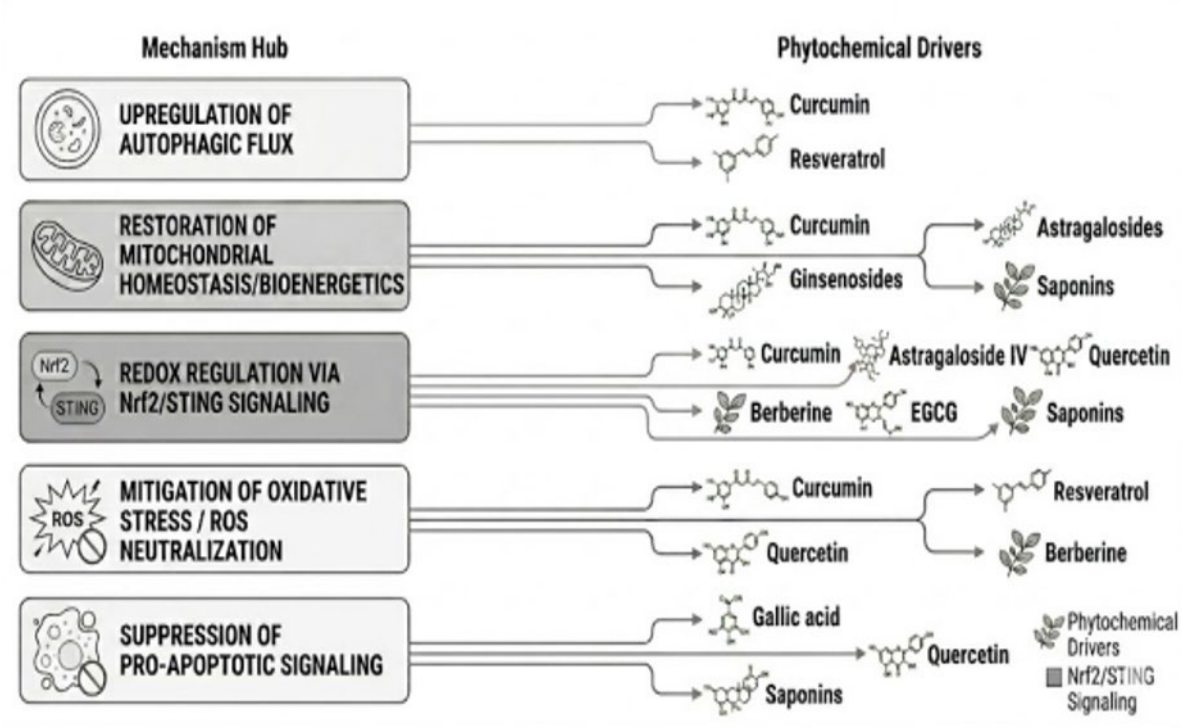

Fig. Mechanistic Landscape of Phytochemical-Mediated Immune Resilience

Table

Modulation of Immunosenescence by Plant Secondary Metabolites

Plant secondary metabolites	Phytoconstituents/Medicinal plants/ Concentrations		Experimental models	Biological effects
Polyphenols & Flavonoids	Curcunin	1-10 μM	cBMSCs	downregulation of the senescence marker and pro-inflammatory cytokines, increasing autophagic activity (Deng et al.)
		10-100 μmol/L	human rheumatoid arthritis fibroblast-like synoviocyte cell line	Modulation of Nrf2-cGAS-STING-NF-κB signaling axis (Li et al.)
	curcumin liposomes	5-10 μM	rBMSCs	reduction in mtROS (Li et al.)
	Resveratrol	0–20 μM	murine B lymphocytes and neoplastic human B-lymphoid Raji cells	inducing autophagy (Yao et al.)
		100μM	PBMCs obtained from women across agев groups	autophagy activation, oxidative stress reduction, and inflammation modulation (Fernandes et al.)
		25, 50, or 100 mg/kg mbw	D-galactose-induced aging mouse	improving thymic architecture (Hou et al.)
	EGCG	100 μM	aging-induced human umbilical vein endothelial cells	reducing senescence markers, suppressing monocyte activation, and restoring immune homeostasis (Patel et al.)
		–	Results of a review article	activating the Nrf2/HO-1 pathway (Mokra et al.)
	Gallic acid	200, 250, and 500 mg/kg mbw/day	D-galactose-induced aging mic	increasing thymocyte and $CD4^+$ T cell numbers, reducing apoptosis (Guo, et al.)
	Dasatinib+fisetin	5+100 mg/kg (orally)	aged rhesus monkeys	reducing epidermal markers of cellular senescence, specifically $p16^+$ and $p21^+$ cells (Colman, et al.)
	Quercetin	NA	PBMCs from aged mice	restoring immune function, reducing oxidative stress (Bouamama et al.)
	Dasatinib+ quercetin	5mg/kg/day+ 50 mg/kg/day	aged influenza infected mice	restoring Th cell differentiation (Lorenzo et al.)
	Dasatinib+ quercetin	5mg/kg/mbwday+ 50 mg/kgmbw/day	aged influenza infected mice	no therapeutic benefits (Torrance et al.)
Terpenoids & Saponins	RGE	10 and 100 μg/mL of RGE	*in vivo*: aged mice administered RGE, *in vitro*: $CD4^+$ T cells from young and aged mice treated with RGE	boosting T cell metabolism, increasing naïve T cells, reducing inflammation, decreasing senescence/exhaustion markers (Lee et al.)
	Saponins Rb1 and Re	30 mg/kgmbw and 15 mg/kgmbw	*in vivo*: aged mice	increasing thymus and spleen indices, restoring anti-inflammatory cytokines, and suppressing pro-inflammatory cytokines (Shi et al.)
	Astragalus membranaceus	–	results of a review article	Antioxidant effect, reducing pro-inflammatory cytokins (Borowic , & Jach)
	Astragaloside IV	various concentrations	senescent macrophage model	Suppressing macrophage senescence, improving mitochondrial function (Li et al.)

Table continuation

Plant secondary metabolites	Phytoconstituents/Medicinal plants/ Concentrations		Experimental models	Biological effects
Alkaloids	BBR	40, 80, 160 μg/mL of BBR	*C. elegans* model organism	extending *C. elegans* lifespan, reducing ROS, modulat metabolic, autophagy (Bei et al.)
		1-2 g/kgmbw	*in vitro* (H9c2 cells), *ex vivo* (blood from aged rats)	reduced oxidative stress, apoptosis, and fibrosis, restored telomere length and KL/SIRT1 (Li et al.)
		1-2 g/kgmbw	*in vivo:* systemic methotrexate-induced pulmonotoxicity	Suppression of Nrf2 levels, attenuation of degenerative biochemical markers and pulmonary histopathological alterations (Mentese et al.)
	piperlongumine A	2 μM	LPS-stimulated RAW 264.7 cells	anti-inflammatory, restoring KL/SIRT1 pathway (Tran et al.)
	Piper longum L.friut	0–100 μg/mL	RAW 264.7 cells	anti-inflammatory effects via MAPK pathway modulation (Phan et al.)
	Piperine	70 μM	various cancer cell lines	reduced SA-β-gal activity, lowered ROS, and suppressed SASP, restored MMP (Lim et al.)
	PPL	10–30 mg/ kgmbw topically, 1 mg/kgmbw subcutaneously, and 5–10 μM *in vitro*	*in vivo*: imiquimod-induced psoriatic mice, *in vitro*: keratinocytes and macrophages cultures	reducing inflammation and hyperproliferation, restoring tissue architecture, inducing apoptosis, suppressing cytokines, inhibited NF-κB/JNK and HDACs (Thatikonda et al.)

Note: Some abbreviations are defined in the main text; NA-Not available; mbw-mouse body weight

Challenges and Future Directions. Given the complex interplay between oxidative stress, polypharmacy, and age-related diseases, there is a pressing need to explore alternative or complementary strategies that maintain antioxidant balance while minimizing adverse effects (Rojas-Solé, 2024). Moreover, immunosenescence significantly contributes to the increased incidence of age-related diseases, ultimately leading to organ failure and death. Recent advances in single-cell technologies provide valuable insights into the molecular and cellular mechanisms driving immunosenescence, thereby informing targeted strategies to promote healthy aging (Tran, 2024). Although ageing itself is not yet an officially recognized therapeutic target, current clinical trials primarily focus on preventing age-related diseases in high-risk populations. Concurrently, a deeper understanding of the hallmarks of aging provides a robust framework for developing more effective interventions (López-Otín, 2023). Within this context, phytochemicals, owing to their multi-target antioxidant and anti-inflammatory actions, emerge as promising candidates for early intervention. By modulating interconnected aging pathways, phytochemicals hold potential to delay the onset of age-related pathologies and enhance the safety and efficacy of anti-ageing strategies. Future research should focus on elucidating the precise mechanisms through which these natural compounds interact with biological pathways affected by aging and medication use. While the bioactive potential of these compounds is well-supported by *in vitro* and *in vivo* data, translating these findings into clinical reality requires careful consideration of pharmacokinetics. Challenges such as low systemic bioavailability and potential herb-drug interactions must be addressed to ensure safety and efficacy. Consequently, a transition toward well-designed clinical trials is essential to determine pharmacokinetic profiles, optimize dosing, and evaluate the safety of phytochemical interventions in older populations often burdened by polypharmacy and multi-morbidity. Furthermore, the role of the diet-microbiota-immunity axis represents a critical frontier in understanding phytochemical efficacy. Given that gut microbial biotransformation is often a prerequisite for the activation of many plant-derived metabolites, future research should explore how age-related changes in the microbiome dictate the individual response to phytochemical therapy. Ultimately, integrating phytoconstituents into personalized interventions could help mitigate the detrimental effects of oxidative imbalance and polypharmacy, advancing healthier, more resilient aging.

Study limitations. Despite the valuable insights provided by this study, several limitations should be acknowledged. First, the effects of phytochemicals on other age-related disorders, such as neurodegenerative diseases, cardiovascular diseases, and cancer, were not addressed. Second, although other autophagy activators in senescent cells beyond immune cells have been investigated, they were not covered in this review. Finally, as the discussion primarily focused on mechanistic strategies, the exploration of different herbs across various traditional systems of medicine was not included and is recommended for future studies.

Conclusions. Phytochemicals, including polyphenols, flavonoids, terpenoids, saponins, and alkaloids, exhibit multifaceted therapeutic potential in counteracting age-related immune decline. Compounds such as curcumin, resveratrol, EGCG, quercetin, ginsenosides, berberine, and piperine modulate key cellular processes, including autophagy, mitochondrial function, oxidative stress, and inflammatory signaling, while targeting senescent cells and the senescence-associated secretory phenotype. These actions collectively support the preservation of immune function, attenuation of chronic inflammation, and mitigation of tissue degeneration associated with aging. The evidence underscores the promise of plant-derived interventions as multi-targeted strategies for promoting healthy aging and immunoprotection, although further in vivo and clinical studies are warranted to fully elucidate their mechanisms and therapeutic potential.

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Authors' Contributions

Parchami Ghazaee S. – conceiving and designing the study, writing the manuscript, providing administrative, technical, and material support;

Gorova E.V. – collecting the sources of the article, corrections and literary edition;

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