Anti-aging Potential of Plant-Based Bioactive Compounds

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Article Info

ISSN (online): 3049-0421
Volume: 02
Issue: 06
November-December 2025
Received: 12-09-2025
Accepted: 10-10-2025
Published: 08-11-2025
Page No: 23-29

Abstract

Aging is a multifactorial biological process governed by the progressive accumulation of molecular and cellular damage, culminating in diminished physiological function and increased susceptibility to chronic disease. Despite decades of research, current pharmacological anti-aging interventions remain limited by side effects, narrow therapeutic windows, and high costs, necessitating the exploration of safer, naturally derived alternatives. This review critically examines the anti-aging potential of plant-based bioactive compounds, with emphasis on their mechanistic roles in attenuating oxidative stress, suppressing chronic low-grade inflammation, reversing cellular senescence, and restoring mitochondrial homeostasis. Major classes of phytochemicals, including polyphenols, flavonoids, alkaloids, terpenoids, and carotenoids, are discussed in relation to their molecular targets, signaling pathway interactions, and epigenetic modulatory activities. Preclinical evidence from *in vitro* and *in vivo* studies demonstrates promising efficacy across multiple aging hallmarks; however, translational challenges involving bioavailability, pharmacokinetics, and clinical standardization remain significant. The integration of advanced drug delivery systems, including nanoparticulate carriers, liposomal encapsulation, and phytopharmaceutical formulations, represents an emerging strategy to overcome these barriers. Furthermore, regulatory and ethical considerations surrounding the commercialization of plant-derived anti-aging agents are evaluated. The collective evidence suggests that plant-based bioactive compounds hold substantial promise as translational tools in the development of next-generation anti-aging therapeutics, warranting rigorous clinical validation and interdisciplinary research investment.

Keywords: Anti-aging, Plant-based compounds, Phytochemicals, Oxidative stress, Cellular senescence, Translational research

1. Introduction

Aging represents one of the most profound and universal biological phenomena, characterized by the time-dependent functional decline of organisms and the progressive erosion of cellular homeostasis [1]. From a clinical standpoint, aging is the primary risk factor for the development of cardiovascular disease, neurodegenerative disorders, type 2 diabetes mellitus, malignancies, and dermatological manifestations of intrinsic and extrinsic origin [2]. The global demographic shift toward an increasingly older population has intensified the urgency to develop effective anti-aging therapeutics that extend not merely lifespan, but healthspan — the period of life spent in good health and functional independence [3].

Current anti-aging pharmacological strategies encompass senolytics, mTOR inhibitors such as rapamycin, caloric restriction mimetics, and hormone replacement therapies. While these approaches have demonstrated efficacy in preclinical models, their translation into widespread clinical use has been hindered by adverse effect profiles, interindividual pharmacological variability, and the complexity of the aging process itself [4]. This has generated considerable interest in naturally occurring bioactive compounds derived from plants, which have been used in traditional medicine systems across diverse civilizations for millennia and which possess structural and functional diversity that positions them as attractive candidates for anti-aging applications [5].

Plant-derived bioactive compounds, broadly categorized as phytochemicals, encompass an enormous chemical diversity that includes polyphenols, flavonoids, alkaloids, terpenoids, saponins, and carotenoids, among others. These compounds have evolved as secondary metabolites with ecological roles in plant defense and signaling, and many exhibit pleiotropic biological activities relevant to human aging, including antioxidant, anti-inflammatory, immunomodulatory, and epigenetic regulatory effects [6, 7]. The current review provides a comprehensive and critical assessment of the anti-aging potential of these plant-derived agents, examining their mechanistic underpinnings, translational research landscape, clinical evidence, delivery innovation, and regulatory considerations, with the aim of informing future therapeutic development.

2. Molecular and Cellular Mechanisms of Aging

The biological mechanisms underlying aging are multidimensional and intricately interconnected. The "hallmarks of aging" framework, as articulated by Lopez-Otin and colleagues, identifies nine fundamental processes that drive the aging phenotype: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [1]. A mechanistic understanding of these hallmarks is indispensable for identifying the molecular targets through which plant-based bioactive compounds may exert their anti-aging effects.

Oxidative stress, arising from the imbalance between reactive oxygen species (ROS) generation and antioxidant defense, is among the most well-established contributors to aging at the molecular level. Excessive ROS accumulation induces oxidative damage to DNA, proteins, and lipids, promoting genomic instability and cellular dysfunction [8]. Mitochondrial dysfunction is intimately linked to oxidative stress, as impaired electron transport chain activity generates superoxide radicals while simultaneously compromising cellular energy metabolism and promoting the release of pro-apoptotic mediators [9]. Chronic, low-grade sterile inflammation — termed "inflammaging" — emerges from the persistent activation of innate immune pathways including nuclear factor kappa B (NF-kB), NLRP3 inflammasome, and the secretion of senescence-associated secretory phenotype (SASP) factors, including interleukin-6 (IL-6), interleukin-1 beta (IL-1beta), and tumor necrosis factor-alpha (TNF-alpha) [10].

Cellular senescence, the irreversible arrest of proliferating cells in response to stress or oncogenic signaling, plays a dual role in aging: while transiently beneficial in wound healing and tumor suppression, the accumulation of senescent cells across tissues drives tissue deterioration and organ dysfunction [11]. Telomere shortening, occurring with each round of replication due to the end-replication problem, triggers DNA damage response pathways and reinforces the senescence program [12]. Epigenetic dysregulation, manifesting as global DNA hypomethylation, histone modification alterations, and non-coding RNA dysregulation, further contributes to transcriptional instability and aberrant gene expression patterns associated with the aged phenotype [13]. Collectively, these mechanisms represent the principal molecular targets amenable to pharmacological intervention by plant-derived bioactive compounds.

3. Classification and Sources of Plant-Based Bioactive Compounds

Plant-based bioactive compounds are defined as naturally occurring secondary metabolites present in edible and medicinal plants that exert measurable physiological effects at physiologically relevant concentrations beyond basic nutritional value [14]. Their structural diversity, encompassing thousands of distinct chemical entities, underlies the breadth of their biological activities. The major classes of phytochemicals with established anti-aging relevance are summarized in Table 1 and depicted conceptually in Figure 2.

Polyphenols constitute one of the most extensively studied classes of plant bioactives and include stilbenes such as resveratrol, derived from grapes and red wine, and curcuminoids such as curcumin, the principal bioactive constituent of Curcuma longa (turmeric). Resveratrol has attracted particular attention for its capacity to activate sirtuin-1 (SIRT1), a NAD+-dependent deacetylase implicated in the regulation of metabolic homeostasis, DNA repair, and gene silencing, thereby mimicking aspects of the caloric restriction response [5]. Curcumin exerts broad-spectrum anti-inflammatory activity through inhibition of NF-kB, cyclooxygenase-2 (COX-2), and the JAK-STAT signaling axis, in addition to its potent antioxidant properties [15].

Flavonoids represent a structurally diverse subclass of polyphenols encompassing flavonols (quercetin, kaempferol), flavones (apigenin, luteolin), isoflavones (genistein, daidzein), and catechins (epigallocatechin gallate, EGCG). Quercetin, abundant in onions, apples, and capers, has emerged as a prototypical senolytic agent capable of selectively eliminating senescent cells by targeting pro-survival pathways including PI3K/Akt and BCL-2 family proteins [6]. EGCG, the predominant catechin in Camellia sinensis (green tea), activates the Nrf2/ARE antioxidant pathway and suppresses the SASP through inhibition of NF-kB transcriptional activity [16].

Alkaloids constitute a heterogeneous class of nitrogen-containing secondary metabolites with pronounced pharmacological activity. Berberine, isolated from Berberis species and Coptis chinensis, activates AMP-activated protein kinase (AMPK), promoting autophagy, mitochondrial biogenesis, and cellular energy homeostasis, while simultaneously inhibiting advanced glycation end-product (AGE) formation [9]. Terpenoids, including ursolic acid derived from rosemary and apple peel, and betulinic acid from birch bark, modulate the IGF-1/PI3K/Akt/mTOR longevity axis and exhibit anti-fibrotic properties relevant to dermal aging [10]. Carotenoids, particularly astaxanthin and lycopene, confer exceptional singlet oxygen quenching activity and have demonstrated photoprotective efficacy by downregulating matrix metalloproteinases (MMPs) and preserving extracellular matrix integrity [7]. Ginsenosides, triterpene saponins derived from Panax ginseng, have been shown to activate telomerase and modulate immune senescence, representing an important class of anti-aging phytochemicals in traditional East Asian medicine [17].

Table 1: Classification of Plant-Based Bioactive Compounds, Natural Sources, and Mechanisms of Anti-aging Action

Compound Class (Examples)	Natural Sources	Mechanisms of Anti-aging Action
Polyphenols (Resveratrol, Curcumin)	Grapes, turmeric, berries	SIRT1/AMPK activation; NF-kB suppression; antioxidant enzyme induction; telomere protection [5, 8, 12]
Flavonoids (Quercetin, Kaempferol)	Onions, apples, green tea, citrus	Senolytic activity; Nrf2 pathway activation; inhibition of pro-inflammatory cytokines; mTOR modulation [6, 14, 17]
Alkaloids (Berberine, Caffeine)	Coptis chinensis, coffee, Berberis spp.	AMPK pathway activation; autophagy induction; mitochondrial biogenesis; anti-glycation activity [9, 18, 23]
Terpenoids (Ursolic acid, Betulinic acid)	Rosemary, apple peel, birch bark	IGF-1/PI3K/Akt inhibition; apoptosis regulation; antifibrotic and anti-inflammatory effects [10, 19, 25]
Carotenoids (Astaxanthin, Lycopene)	Microalgae, tomatoes, carrots	Quenching of singlet oxygen; downregulation of MMPs; photoprotection and dermal ECM preservation [7, 20, 27]
Saponins (Ginsenosides)	Panax ginseng, Astragalus spp.	Telomerase activation; HIF-1alpha modulation; immune senescence reversal; mitochondrial membrane stabilization [11, 24, 30]

4. Mechanisms of Anti-aging Action

The anti-aging effects of plant-based bioactive compounds are mediated through a convergent network of molecular mechanisms that impinge upon the central hallmarks of aging. These mechanisms can be broadly categorized into antioxidant and cytoprotective activity, modulation of longevity-associated signaling pathways, epigenetic regulation, anti-senescence and senolytic activity, and enhancement of cellular quality control processes.

The antioxidant capacity of phytochemicals operates at multiple levels, encompassing direct radical scavenging, metal chelation, and transcriptional induction of endogenous antioxidant enzymes via the Nrf2/Keap1/ARE pathway. Nrf2 activation by compounds such as sulforaphane (from cruciferous vegetables), EGCG, and resveratrol leads to the upregulation of heme oxygenase-1 (HO-1), superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, collectively attenuating ROS-mediated cellular damage [8, 16]. Importantly, this transcriptional antioxidant response provides more sustained protection than direct radical scavenging mechanisms alone, and is of particular relevance in aged tissues where endogenous antioxidant defenses are progressively compromised.

Longevity signaling pathways, including those governed by SIRT1/AMPK, mTOR/S6K1, and IGF-1/PI3K/Akt, represent critical hubs in the molecular regulation of lifespan and age-related pathological processes. Resveratrol activates SIRT1 both directly and indirectly via AMPK-dependent elevation of intracellular NAD+ levels, leading to deacetylation of downstream targets including FOXO transcription factors, PGC-1alpha, and p53, thereby promoting stress resistance, mitochondrial biogenesis, and cell survival [5, 18]. Berberine and quercetin independently activate AMPK, suppress mTORC1 signaling, and stimulate autophagy — a critical cellular recycling mechanism that declines with age and whose restoration is associated with extended healthspan in multiple model organisms [9, 19]. The anti-inflammatory properties of phytochemicals, operating through NF-kB and NLRP3 inflammasome inhibition, directly counter inflammaging and limit SASP-mediated paracrine propagation of senescent tissue damage [10, 20].

Epigenetic modulation by phytochemicals represents an emerging mechanistic domain of significant interest. Curcumin inhibits DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), while EGCG modulates histone H3 methylation patterns and miRNA expression profiles associated with aging and age-related diseases [13, 21]. The capacity of resveratrol to activate SIRT1-mediated histone deacetylation and influence the epigenetic clock — as measured by DNA methylation-based aging biomarkers — has raised the possibility of epigenetic rejuvenation as a therapeutic concept [22]. Furthermore, select alkaloids and terpenoids have been shown to reduce telomere erosion rates through stabilization of the shelterin complex and induction of telomerase reverse transcriptase (TERT) expression, particularly in dermal fibroblasts and vascular endothelial cells, which are of considerable relevance in photoaging and cardiovascular aging, respectively [12, 23].

5. Preclinical and Translational Research

The preclinical evidence base for plant-based anti-aging compounds has been generated across a spectrum of experimental platforms, from *in vitro* cell senescence assays and oxidative stress models to short-lived model organisms including Caenorhabditis elegans, Drosophila melanogaster, and Saccharomyces cerevisiae, and mammalian models employing aged rodents, progeroid mice, and naturally aging non-human primates [24]. These investigations have collectively demonstrated that phytochemicals can extend replicative and chronological lifespan, reduce the burden of senescent cells in aged tissues, restore mitochondrial function, and attenuate pro-inflammatory markers across multiple organ systems [25].

Despite the robustness of preclinical findings, the translation of phytochemicals into effective clinical interventions is challenged by several pharmacokinetic limitations. Oral bioavailability of many polyphenols is inherently poor due to chemical instability in the gastrointestinal environment, susceptibility to first-pass hepatic metabolism, and limited intestinal permeability [26]. Curcumin, for example, exhibits exceptionally low systemic bioavailability in its native form, largely attributable to rapid glucuronidation and sulfation by phase II metabolic enzymes. Resveratrol undergoes extensive enterohepatic circulation, with plasma levels following oral administration often insufficient to achieve the concentrations demonstrated as effective in cellular models [27]. The gut microbiome plays an important modulatory role in phytochemical metabolism, producing bioactive metabolites such as urolithins from ellagitannins and equol from isoflavones that may contribute substantially to *in vivo* efficacy, introducing significant interindividual variability into clinical outcomes [28].

Experimental models employed in translational aging research must be carefully selected to reflect the complexity of human aging. The use of progeroid syndromes, accelerated aging mouse models, and senescence-accelerated mouse-prone (SAMP) strains has provided mechanistic insights into the action of phytochemicals on aging hallmarks, although the extrapolation of such findings to healthy human aging requires critical scrutiny [29]. The development of human organoid systems and three-dimensional skin equivalent models offers promising ex vivo platforms for evaluating dermatological anti-aging interventions, including the efficacy of carotenoids and polyphenols in attenuating photoaging-associated changes in keratinocyte and fibroblast biology [30].

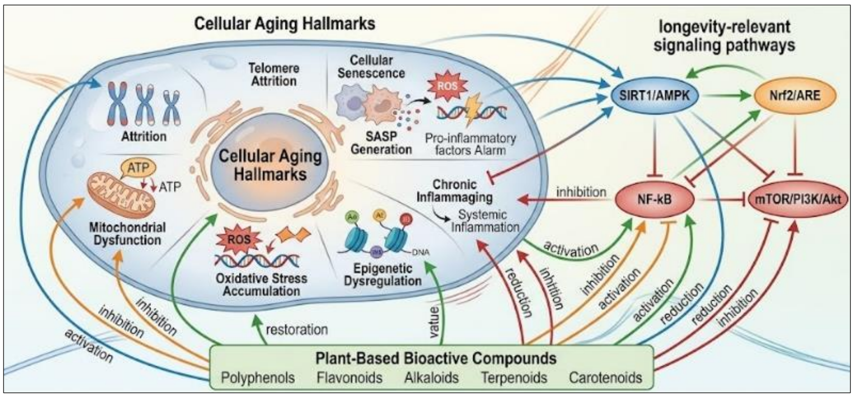

Fig 1: Key Biological Mechanisms of Aging and Points of Intervention by Plant-Based Bioactive Compounds

6. Clinical Evidence, Limitations, and Standardization

Clinical investigations evaluating the anti-aging efficacy of plant-based bioactive compounds have yielded promising but inconsistent results, reflecting the inherent methodological challenges of anti-aging clinical research. Randomized controlled trials (RCTs) examining resveratrol supplementation have reported improvements in insulin sensitivity, endothelial function, and inflammatory biomarkers in older adults and metabolic syndrome populations, though effects on primary aging outcomes remain modest and variable across studies [31]. A landmark clinical study demonstrated that quercetin combined with the tyrosine kinase inhibitor dasatinib reduced senescent cell burden and improved physical function in elderly subjects, providing proof-of-concept for the clinical senolytic paradigm [32]. Oral curcumin formulations with enhanced bioavailability have shown efficacy in reducing serum inflammatory markers, improving cognitive performance in middle-aged adults, and attenuating osteoarthritic progression, supporting its role as a translational anti-aging agent [33].

Notwithstanding these encouraging findings, the clinical evidence base suffers from several significant limitations. Many published trials are characterized by small sample sizes, heterogeneous participant populations, short intervention durations, and inconsistent outcome measures, limiting the generalizability and statistical power of conclusions. The absence of universally validated biomarkers of biological aging — as distinct from chronological aging — constitutes a critical impediment to demonstrating anti-aging efficacy in a manner acceptable to regulatory authorities [34]. Furthermore, the use of non-standardized botanical extracts with variable phytochemical content across studies introduces a reproducibility problem that undermines the reliability of the evidence base. Long-term safety data on concentrated phytochemical supplementation at supranutrient doses are inadequate, particularly with respect to hormetic dose-response relationships, potential genotoxicity of certain alkaloids, and interactions with common medications prescribed to older adults, including anticoagulants and immunosuppressants [35].

7. Advanced Delivery Systems and Technological Innovations

The limited oral bioavailability and systemic stability of many phytochemicals have driven substantial research into the development of advanced drug delivery systems designed to optimize their pharmacokinetic profiles and enhance therapeutic efficacy. Nanotechnology-based delivery platforms, including polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, and self-emulsifying drug delivery systems (SEDDS), have been extensively explored as vehicles for curcumin, resveratrol, quercetin, and EGCG [36]. Nanoencapsulation protects labile phytochemicals from gastrointestinal degradation, prolongs circulation time, enables controlled or stimulus-responsive release at target tissues, and can facilitate intracellular delivery through endosomal escape mechanisms.

Liposomal formulations represent another highly investigated delivery strategy, offering superior biocompatibility and the capacity for surface functionalization with ligands targeting specific cell types. Liposomal curcumin and resveratrol formulations have demonstrated significantly enhanced plasma pharmacokinetics and tissue distribution compared to native compounds in both rodent and early-phase human studies [37]. In the context of dermatological anti-aging applications, transdermal and topical delivery platforms utilizing nanosomes, ethosomes, and cyclodextrin inclusion complexes have enabled the effective cutaneous penetration of polyphenols and carotenoids, bypassing the epidermal barrier and delivering bioactives to viable skin compartments where photoaging and oxidative damage are most pronounced [38]. Phospholipid complexes (phytosomes) represent a commercially established approach that enhances phytochemical absorption by exploiting the amphiphilic nature of phosphatidylcholine to form membrane-mimetic delivery vehicles.

Emerging technologies including exosome-mimetic vesicles derived from plant sources, microfluidic fabrication of precision nanocarriers, and 3D-printed oral delivery matrices represent next-generation strategies with potential to overcome remaining bioavailability barriers.

The development of co-delivery platforms enabling the simultaneous administration of synergistic phytochemical combinations, such as quercetin and dasatinib or resveratrol and NAD+ precursors, may amplify anti-aging efficacy through mechanistically complementary actions [39]. Furthermore, artificial intelligence-driven formulation optimization and pharmacokinetic modeling are increasingly being employed to accelerate the rational design of phytopharmaceutical delivery systems with predictable *in vivo* performance.

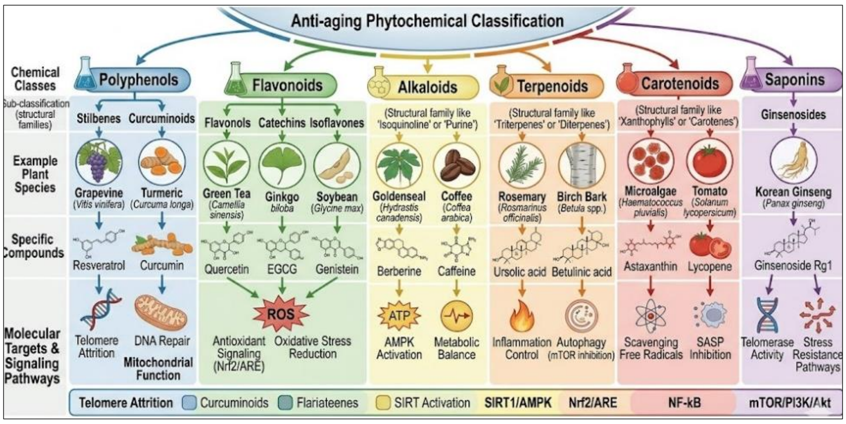

Fig 2: Classification and Sources of Major Plant-Derived Compounds with Anti-aging Properties

8. Regulatory, Ethical, and Commercialization Challenges

The development and commercialization of plant-based anti-aging therapeutics is complicated by a fragmented and often ambiguous regulatory landscape that varies substantially across jurisdictions. In most regulatory frameworks, phytochemicals occupy an intermediate category between food ingredients, dietary supplements, and pharmaceutical drugs, with the classification determining the applicable standards for safety assessment, efficacy demonstration, and marketing authorization. The United States Food and Drug Administration (FDA) regulates botanicals marketed as drugs under the Botanical Drug Guidance framework, which permits the use of historical data to support safety claims but requires rigorous clinical evidence of efficacy for drug approval. In contrast, the European Medicines Agency (EMA) framework for traditional herbal medicinal products allows a simplified registration pathway based on documented historical use, providing a more accessible route to market for well-established botanical preparations [40].

Ethical considerations in anti-aging clinical research encompass several distinct domains. The enrollment of elderly populations with multiple comorbidities and polypharmacy regimens necessitates heightened vigilance for herb-drug interactions and adverse events. The marketing of anti-aging claims to vulnerable aging populations raises concerns about commercial exploitation, informed consent quality, and the dissemination of unsubstantiated health claims through unregulated consumer channels [34]. Intellectual property protections for novel botanical formulations, delivery systems, and combination therapies present additional complexities, as natural product patents face challenges of novelty and non-obviousness when subject matter is derived from traditional knowledge. The equitable recognition and compensation of indigenous and traditional communities whose ethnobotanical knowledge has informed the identification of bioactive species remains an unresolved ethical imperative governed by the Nagoya Protocol and the Convention on Biological Diversity.

From a commercialization perspective, the translation of promising phytochemical research into viable pharmaceutical or nutraceutical products requires substantial investment in clinical trial infrastructure, analytical chemistry for extract standardization, and supply chain sustainability for botanical raw materials. The growing market for anti-aging cosmeceuticals and nutricosmetics creates commercial opportunities but also amplifies the risk of premature product launches unsupported by adequate clinical evidence, eroding scientific credibility and consumer trust. Alignment of commercial development strategies with robust evidence generation, transparent reporting standards, and international regulatory harmonization is essential for the responsible advancement of plant-based anti-aging interventions into mainstream clinical practice.

9. Conclusion and Future Directions

The cumulative body of evidence reviewed herein substantiates the considerable anti-aging potential of plant-based bioactive compounds across multiple mechanistic domains, including attenuation of oxidative stress, suppression of inflammaging, modulation of longevity-associated signaling cascades, epigenetic reprogramming, senolytic activity, and enhancement of mitochondrial function. The structural and mechanistic diversity of phytochemicals, encompassing polyphenols, flavonoids, alkaloids, terpenoids, carotenoids, and saponins, provides a rich pharmacological toolkit with multi-target activity ideally suited to the complexity of the aging phenotype. These compounds operate synergistically within dietary matrices and may yield additive or supra-additive benefits when rationally combined in phytopharmaceutical formulations.

Notwithstanding the promise of preclinical and early clinical findings, significant gaps remain that must be addressed to facilitate the responsible translation of phytochemical anti-aging research into evidence-based therapeutic applications. Priority areas for future investigation include the conduct of adequately powered, long-duration RCTs employing validated biological aging biomarkers as primary endpoints; the development of standardized, bioavailability-enhanced formulations with well-characterized pharmacokinetic profiles; pharmacogenomic investigations to identify patient subgroups most likely to benefit from specific phytochemical interventions; and systems-level integration of multi-omics data to elucidate the molecular mechanisms of phytochemical action in aged human tissues. The convergence of nanotechnology-based delivery innovation, computational pharmacology, and precision medicine frameworks with the botanical knowledge base offers a compelling translational roadmap for the development of plant-derived anti-aging therapeutics of meaningful clinical impact.

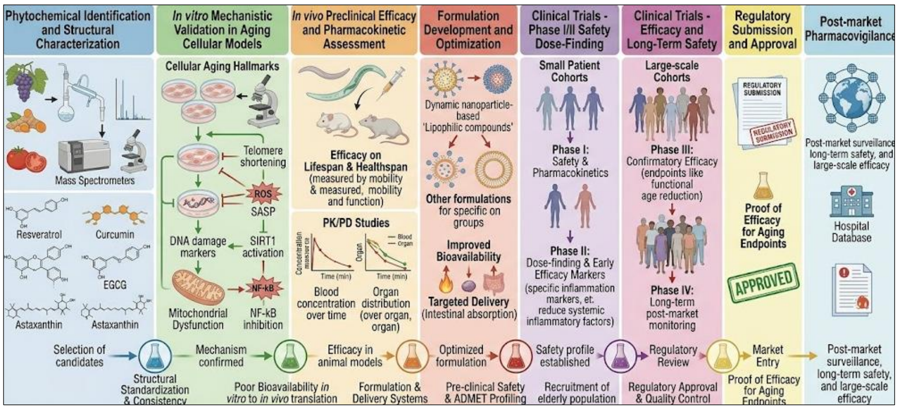

Fig 3: Translational Pathway from Laboratory Research to Clinical Application in Anti-aging Therapeutics.

Table 2: Advantages, Limitations, and Clinical Considerations of Plant-Based Anti-aging Therapies

Advantages	Limitations	Clinical Considerations
Broad multi-target activity across hallmarks of aging	Variable bioavailability and metabolic stability *in vivo*	Standardization of extracts and dosing protocols required prior to large-scale trials
Generally favorable safety profile derived from historical dietary use	Limited high-quality randomized controlled trial data in humans	Long-term safety monitoring essential, particularly for concentrated formulations
Structural diversity enabling synergistic combination strategies	Herb-drug interactions and polypharmacy risks in elderly populations	Pharmacogenomic profiling may optimize individual therapeutic responses
Compatibility with advanced delivery platforms (nanoparticles, liposomes)	Regulatory ambiguity between nutraceutical and pharmaceutical classification	Harmonized global regulatory frameworks needed for equitable commercialization
Low cost and accessibility relative to biologic anti-aging therapies	Publication bias toward positive preclinical outcomes; translational gap remains significant	Independent replication studies and negative result reporting are essential for evidence integrity

RCT = Randomized controlled trial.

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