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The Anti-aging Mechanisms of Plant Polyphenols and Challenges to Their Bioavailability: A Systematic Literature Review

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Abstract: As natural bioactive compounds obtained from the daily diet, plant polyphenols have shown potential in anti-aging research to exert their effects through multi-target regulatory networks, such as the AMPK/SIRT1 axis and inflammatory and oxidative stress pathways. However, their oral bioavailability is quite low, which has become a major obstacle limiting their progression towards clinical application. This review provides a systematic overview of progress in this field and further explores the potential applications of plant polyphenols in supportive cancer therapy through their intervention in the aging process. It notes that although current research is becoming increasingly detailed in its exploration of mechanisms, there remain widespread shortcomings, such as insufficient physiological relevance and relatively weak clinical evidence. Future work should focus more on validating mechanisms in physiologically relevant models and promoting the design of more rigorous clinical trials; only then can plant polyphenols truly be transformed from laboratory potential into tangible clinical benefits.

Keywords: Plant polyphenols, Anti-aging, Bioavailability, Nanodelivery systems, Clinical translation

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1. Introduction

With the global population aging at an ever-increasing rate, aging and the associated chronic diseases have become central challenges for public health. [1]. Phytochemicals derived from the daily diet, particularly plant polyphenols, have taken a prominent position in the field of anti-aging research due to their wide range of food sources, diverse biological activities and relatively high safety profile [2]. Phytopolyphenols constitute a large class of secondary metabolites widely distributed in plant-based foods such as fruits, vegetables, tea and spices [3].

Numerous preclinical studies have indicated that phytopolyphenols not only scavenge free radicals through direct antioxidant action, but also exert anti-aging effects at multiple levels—including energy metabolism, inflammation and autophagy—by modulating complex cellular signaling pathways [4]. However, a significant gap exists between their exceptional in vitro activity and their unclear in vivo efficacy, primarily attributable to the inherent challenge of low bioavailability [5]; this contradiction constitutes the core tension in research within this field.

This review aims to systematically collate and evaluate recent research progress regarding the anti-aging effects of plant polyphenols and the challenges associated with their bioavailability. The primary objectives of this paper are to summarise the key molecular mechanisms and core targets underlying the anti-aging effects of plant polyphenols, analyze cutting-edge technical strategies for enhancing their bioavailability, assess the limitations and controversies of current research, and identify knowledge gaps, whilst providing directional recommendations for future basic research and clinical translation.

2. Mechanisms of anti-aging: From antioxidant effects to multi-target network regulation

Early research into plant polyphenols focused primarily on their direct antioxidant effects; however, in recent years, studies have clearly demonstrated that plant polyphenols function as part of a complex network regulating biological responses, achieving their effects by modulating several evolutionarily conserved longevity pathways and cellular homeostasis maintenance systems [6].

Key pathways and major findings: The AMPK/SIRT1 energy metabolism axis is regarded as a central hub [7]. Xu and his collaborators noted that many types of polyphenols act as natural activators of AMPK; by modulating cellular energy status, they induce autophagy and improve mitochondrial function [7]. This pathway is closely linked to SIRT1. Yang and Sauve [8] provided a systematic account of the central role of NAD+ metabolism, noting that polyphenols or NAD+ precursors indirectly activate SIRT1 by elevating NAD+ levels, thereby forming the metabolic basis of anti-aging. The suppression of chronic low-grade inflammation is another key mechanism; researchers such as Xiang Lu et al. [9] summarised that quercetin can combat atherosclerosis by inhibiting common inflammatory pathways such as NF-κB and the NLRP3 inflammasome. More in-depth studies, such as that by López-Sánchez et al. [10], found that kaempferol can specifically inhibit complement C3 activation and the generation of pro-inflammatory type A1 astrocytes. Finally, there is the regulation of cell fate; plant polyphenols not only protect normal cells but also induce the death of abnormal cells. For instance, Deng et al. [11] found that okra flavonoids can induce apoptosis, senescence, and autophagy in colorectal cancer cells, whilst Park et al. [4] noted that quercetin induces cell cycle arrest in endometriosis cells by regulating Cyclin D1 and related miRNAs.

Trend Analysis: Research trends in this field have shifted from describing individual antioxidant phenomena to analyzing the regulation of complex signaling networks by polyphenols [7]. An emerging frontier focuses on the interactions between polyphenols and the gut microbiota [12]. Yang Wenhan [13] noted that the anti-aging activity of ferulic acid metabolites produced by the gut microbiota is superior to that of the parent compound. Dong et al.[14] further proposed that anthocyanins eliminate senescent endothelial cells via the ‘gut microbiota + metabolites + vasculature’ axis. This suggests a profound shift in research perspective from a ‘single compound–single target’ model to a systemic interaction model involving ‘dietary components–microbiome–host’ [13-14].

3. Bioavailability challenges and innovations in delivery technologies

Although research into the mechanisms of action is progressing rapidly, the extremely low oral bioavailability commonly encountered with plant polyphenols has become a fundamental bottleneck limiting their translation into clinical applications [5].

Regarding key research findings and methodological evaluations, the pharmacokinetic study by Zabela et al. [15] provides precise quantitative evidence. They observed that following oral administration of kaempferol to rats, the plasma concentration of the parent compound was extremely low, whilst after intravenous administration, its plasma half-life was approximately only 3 minutes, indicating rapid clearance. To overcome this bottleneck, formulation innovation has become a new research focus, with nanotechnology representing the most promising solution [16]. In their review, Mundekkad and Cho [16] noted that formulating curcumin into nanoliposomes, polymeric nanoparticles or micelles can significantly improve its water solubility, stability, targeting ability and bioavailability.

Regarding research trends and innovation, current delivery strategies are evolving from simple solubilization towards intelligent and functionalized approaches [16]. Furthermore, the use of prodrug strategies and the activation of gut microbiota metabolism have emerged as novel concepts for enhancing bioavailability [13].

4. Controversies and the challenges of clinical translation

Although preclinical data are abundant, there remain significant controversies and unresolved discrepancies in the field of plant polyphenol research.

On the one hand, the main point of contention concerns the directness and specificity of the mechanism of action, as exemplified by the relationship between resveratrol and SIRT1. In their review, Rogina and Tissenbaum [17] noted that there is still debate as to whether resveratrol can directly activate SIRT1. This indirectly highlights a common issue in polyphenol research: due to their multi-target nature, it is extremely difficult to identify their most critical and direct targets [17].

Next are the consequences of this double-edged sword and the potential pitfalls in clinical applications. Fernando and his team, in their paper [18], offer a particularly cautionary perspective. They noted that the dual nature of phytochemicals—acting as antioxidants or, conversely, as pro-oxidants—may lead to opposite outcomes when used in conjunction with cancer radiotherapy and chemotherapy. This inconsistency highlights the gap in understanding and the latent dangers involved in transitioning from dietary supplementation to adjuvant therapy [18]. It is worth noting that recent research has increasingly turned its attention to the other side of this 'double-edged sword'—namely, the potential of plant polyphenols to eliminate age-related cells caused by treatment and mitigate the toxicity associated with radiotherapy and chemotherapy, thereby offering potential as an adjunctive therapy [19-20], This demonstrates that the role of plant polyphenols in cancer treatment is not simply one of 'interference' or 'assistance', but is closely linked to dosage, timing of administration, and the specific type of polyphenol involved; more detailed research designs are required to clarify the boundaries of their use.

Setting aside the effects and risks, the lack of clinical evidence and the contradictions within it have become the most fundamental challenges in this field. Benameur and his collaborators state directly in their paper [5] that the primary reason for the inconsistent results of clinical trials using curcumin to treat neurological disorders is its extremely low bioavailability. Braidy and Liu [21], in their analysis of the risks and benefits of NAD+ precursor therapy, also noted that high-quality, long-term human trials remain scarce to date. This translational gap between animal and human studies underscores the significant challenges posed by species differences [5, 21].

Methodological differences also play a role, but these controversies stem in part from variations in research methodologies. For instance, in vitro studies frequently employ polyphenol concentrations far exceeding physiologically achievable levels, whilst clinical trials lack standardized references regarding subject selection, the form of the intervention, dosage, duration of treatment and endpoints [15, 22].

5. Outlook: From anti-aging to supportive cancer care

The mechanisms by which plant polyphenols delay the aging process—such as modulating the AMPK/SIRT1 pathway, suppressing inflammatory responses and oxidative stress, and eliminating senescent cells—are intrinsically linked to some key clinical challenges in cancer treatment. When chemotherapy and radiotherapy kill tumor cells, they often induce a state of 'treatment-induced senescence' in normal cells. This not only leads to delayed adverse effects such as cardiac damage, impaired neurological function and suppressed bone marrow function, but also promotes tumor recurrence and metastasis via the senescence-associated secretory phenotype (SASP) [19-20].

In recent years, due to their favorable safety profile and multifaceted effects, plant polyphenols have begun to be explored as adjunctive therapies in cancer supportive care. Studies have indicated that quercetin can reduce cisplatin-induced lymphocyte DNA damage and oxidative stress [23], resveratrol and curcumin significantly increased the survival rate of cardiomyocytes following doxorubicin treatment in vitro [24], whilst rosmarinic acid has been reported to possess dual effects of reducing chemotherapy toxicity and reversing drug resistance [25], These findings suggest that plant polyphenols, by targeting ageing-related pathways, hold promise in reducing treatment-related toxicity, improving patient tolerance and enhancing quality of life.

It should be noted that the use of plant polyphenols in cancer treatment is still in a relatively preliminary exploratory phase. The 'antioxidant-prooxidant duality' concept proposed by Fernando et al. [18] highlights that the efficacy of polyphenols when used in combination with radiotherapy and chemotherapy depends largely on dosage, timing of administration, and the specific type of polyphenol. Future research must further clarify: the optimal dosage and time window for combining plant polyphenols with chemotherapy or radiotherapy to avoid interfering with antitumour efficacy; the use of biomarkers based on ageing phenotypes to identify patient groups most likely to benefit; high-quality clinical trials to validate their clinical efficacy and safety; and the integration of ageing intervention strategies into the comprehensive management of cancer treatment, which may well become a new pathway for improving patient outcomes.

6. Methodological assessment and general limitations

A critical review and examination of the existing literature at the methodological level facilitates a more objective assessment of the strength of evidence in this field. The strengths of the research as a whole lie in: 1) in-depth exploration of mechanisms [7,10]; 2) innovative integration of technologies [13,26]; and 3) the diversity of research models [11,27]. However, the widespread limitations are more pronounced, as shown in **Table 1** below.

Table 1. Current limitations in polyphenol research and strategies for improvement

Limiting factors	Specific manifestations	Impact and recommendations for improvement
Neglect of bioavailability	A large number of mechanistic studies have conducted in vitro experiments using high concentrations without taking in vivo pharmacokinetics into account, raising doubts about their physiological relevance [15].	Extreme caution should be exercised when extrapolating conclusions. There is a need to strengthen studies combining PK and PD, using concentrations that are more physiologically relevant [15].
Fragmented research	Much of the research has focused on repeatedly validating the roles of a small number of key molecules in the same pathways, whilst there has been insufficient exploration of a broader range of plant resources and more novel mechanisms [22].	This results in limited knowledge gains. Efforts to explore non-star polyphenols and new paradigms of action should be encouraged [22].
Insufficient analysis of complex systems	Although studies on traditional Chinese medicine formulations [27] and crude plant extracts [6] have utilized network pharmacology for prediction, they have largely been limited to compound-target predictions, lacking rigorous experimental validation of synergistic or antagonistic interactions between multiple components [22].	The explanation of the mechanism is superficial. It needs to be validated through quantitative analysis and orthogonal experiments [22].
Weak foundations in clinical translation	There are differences between animal models and human diseases; clinical trials tend to be small in scale, short, and lack standardized endpoints, and there is a dearth of long-term safety data [21].	This represents the greatest bottleneck in the field; there is a need to promote standardized, large-scale RCT studies and to systematically assess the risks and benefits [21].
Individual differences and the lack of precision in application	Very few studies have examined the influence of an individual's genetic background, gut microbiota composition and baseline dietary patterns on the effects of polyphenols [13].	This limits the precision of the application; future research will need to incorporate the principles of personalized nutrition and precision medicine [13].

7. Conclusion

This review systematically summarises research progress on plant polyphenols in the field of anti-aging. Key findings indicate that plant polyphenols establish a complex anti-aging network through multiple mechanisms, including the regulation of the AMPK/SIRT1 energy metabolism axis, the suppression of inflammation and oxidative stress, the modulation of cell fate, and interactions with the gut microbiota [7, 9–11]. However, their extremely low bioavailability severely limits their efficacy in vivo [5, 15], and technological innovations such as nanodelivery have become key strategies for overcoming this bottleneck [16]. Furthermore, although preclinical evidence is abundant, the field still faces issues including direct disputes regarding core mechanisms [17], a severe lack of clinical evidence [5, 21], and a degree of fragmentation in research [22].

The identified research gaps primarily include: (1) the mechanisms of action of polyphenols at physiologically relevant concentrations [15]; (2) in-depth exploration of non-star polyphenols and polyphenol synergistic effects [22]; (3) personalised effects based on human gut microbiota characteristics [13]; and (4) a systematic assessment of the safety and potential risks of long-term high-dose polyphenol supplementation [21].

Recommendations for future research: Firstly, to advance 'physiological relevance' studies, encouraging research in models that more closely mimic the human internal environment, whilst strengthening integrated PK/PD analyses [15]. Secondly, to conduct rigorous clinical translation studies, prioritizing large-scale, long-term, double-blind, randomized controlled trials for specific polyphenol formulations that have undergone delivery technology optimization and demonstrate significantly improved bioavailability [21]. Finally, precision nutrition and integrated intervention strategies should be explored, investigating the contribution of polyphenols within specific dietary patterns, examining synergistic effects with other interventions, and combining individual omics data to develop personalized polyphenol intervention protocols [13].

Implications for related fields: For nutrition and food science, attention should be paid to optimising the retention and bioavailability of polyphenols through food processing technologies and dietary combinations [2]; in the fields of pharmacy and pharmaceutical formulation, the development of highly efficient and safe delivery systems is a matter of urgency [16]; and in clinical medicine and public health, health claims regarding polyphenol supplements should be treated with caution until high-level clinical evidence is available, whilst the consumption of natural polyphenol sources through a varied diet should be actively promoted [18,21].

Disclosure statement

The authors declare no conflict of interest.

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