Open Access Library Journal
2026, Volume 13, e15302
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Research Progress of Polyphenolic Antioxidants in Disease Therapy: Molecular Mechanisms and Clinical Applications

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How to cite this paper: Yang, L.H., Guo, Y.Q., Cheng, W.H., Li, Y.C., Bai, H.W., Chen, W. and Wang, H.F. (2026) Research Progress of Polyphenolic Antioxidants in Disease Therapy: Molecular Mechanisms and Clinical Applications. *Open Access Library Journal*, **13**: e15302.
https://doi.org/10.4236/oalib.1115302

Received: April 4, 2026
Accepted: May 19, 2026
Published: May 22, 2026

Abstract

Polyphenolic antioxidants are a diverse class of plant-derived secondary metabolites ubiquitously found in plant-based foods, highly promising for therapeutic intervention of various diseases. This review systematically covers dietary polyphenols from common food sources, purified compounds, polyphenol-rich plant extracts, and emerging delivery systems for bioavailability enhancement, with a core focus on their molecular mechanisms of action and therapeutic potential in neurodegenerative diseases, cardiovascular diseases, and malignancies. The review details diverse molecular mechanisms underpinning polyphenol efficacy, extending beyond direct antioxidant activity to include modulation of signaling pathways, enzyme inhibition, and gene expression regulation. Evidence demonstrates their potential in mitigating oxidative stress, inflammation, and specific pathological processes characteristic of Alzheimer's disease, Parkinson's disease, atherosclerosis, hypertension, and various cancers. However, significant challenges in pharmacokinetics, particularly poor bioavailability and extensive metabolism, hinder clinical translation. While preclinical evidence is compelling, overcoming bioavailability limitations via novel delivery systems or structural optimization is crucial for clinical advancement.

Subject Areas

Pharmacology

Keywords

Antioxidants, Cancer, Cardiovascular Diseases, Neurodegenerative Diseases, Polyphenols

1. Introduction

Polyphenolic compounds are diverse plant-derived natural products with multiple phenolic hydroxyl groups attached to aromatic rings. They exhibit potent antioxidant effects through three main mechanisms: direct free radical scavenging, transition metal ion chelation, and modulation of endogenous cellular redox and antioxidant systems, along with a broad spectrum of other biological activities. Structurally, they are classified into subclasses, including flavonoids, phenolic acids, tannins, lignans, stilbenes, and coumarins, existing in both monomeric and polymeric forms. These structural features underpin their antioxidant properties. Well-studied examples such as tea catechins, wine resveratrol, and turmeric curcumin can neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby alleviating oxidative stress and its harmful effects on cellular components [1] [2]. Additionally, their ability to chelate transition metals like iron and copper is particularly important, as these metals catalyze the formation of highly reactive hydroxyl radicals that worsen oxidative damage [3] [4].

Recent studies have elucidated that polyphenols modulate key cellular signaling pathways. They upregulate endogenous antioxidant enzymes (e.g., SOD, GPx) to enhance the body's intrinsic defense against oxidative insults [4]. Additionally, they inhibit pro-oxidant enzyme activation, downregulate pro-inflammatory cytokines, and modulate matrix metalloproteinase (MMP) activity involved in tissue remodeling and chronic inflammatory disease pathogenesis [5]. Polyphenol-gut microbiota interactions further amplify health benefits, as microbial metabolism converts them into more bioactive and bioavailable metabolites [6] [7]. Moreover, they exert cardioprotective effects by regulating lipid metabolism, inhibiting platelet hyperactivity, and preserving endothelial function [8] [9]. Collectively, these mechanisms underscore polyphenols' central role in defending against oxidative stress and inflammation, positioning them as promising agents for preventing and managing major chronic diseases [10] [11]. This review systematically summarizes the latest advances in polyphenol classification, structural characteristics, molecular mechanisms and clinical translational potential, aiming to provide a theoretical basis for developing polyphenol-based functional foods and pharmaceuticals.

2. Classification and Structural Characteristics of Polyphenol Antioxidants

2.1. Major Classifications of Polyphenols

Polyphenols are broadly classified into five main categories based on their chemical structures and natural sources: flavonoids, phenolic acids, tannins, lignans, and coumarins. Flavonoids, the largest and most extensively studied group (including isoflavones and anthocyanins), are abundant in fruits, vegetables, tea and wine with diverse biological activities [12] [13]. Phenolic acids are subdivided into hydroxybenzoic acids (e.g., gallic acid) and hydroxycinnamic acids (e.g., ferulic acid, caffeic acid), which are widely distributed in coffee, berries and whole grains [14]. Notably, ellagic acid is a hydrolytic metabolite of hydrolyzable tannins (e.g., ellagitannins) rather than a hydrolyzable tannin itself. Tannins, comprising hydrolyzable tannins (e.g., ellagitannins) and condensed tannins (proanthocyanidins), are present in tea, wine and certain fruits [15]. Each polyphenol class has unique chemical features and biological activities, contributing to their diverse health benefits and therapeutic potential [16].

2.2. Relationship between Structure and Antioxidant Activity

Polyphenols' antioxidant activity is closely associated with their molecular structure, primarily determined by the number and position of hydroxyl groups, glycosylation/methylation modifications, and polymerization degree. Ortho-dihydroxy (catechol) structures on aromatic rings significantly enhance free radical scavenging capacity; flavonoids with multiple adjacent hydroxyl groups are more potent in donating hydrogen and stabilizing radicals [17] [18]. Glycosylation increases water solubility and stability but reduces immediate antioxidant activity by masking free hydroxyls, while enzymatic/microbial deglycosylation in the gut or during fermentation regenerates active aglycones to restore or even enhance activity [19]. Methylation improves membrane permeability and metabolic stability but decreases available free hydroxyls for radical scavenging [20]. Additionally, polymerization degree is positively correlated with antioxidant capacity: highly polymerized polyphenols (e.g., tannins, proanthocyanidins) show stronger radical scavenging and metal-chelating abilities than monomers [21] [22]. In conclusion, polyphenols' antioxidant efficacy is governed by their hydroxylation patterns, chemical modifications, and molecular size.

2.3. Main Sources and Content Distribution

Polyphenols are widely distributed in the plant kingdom, with their abundance varying greatly among different food sources and even different parts of the same plant. Grapes, blueberries and apples are rich sources of polyphenols, and studies have confirmed that polyphenol concentrations in grape skins and seeds, as well as apple peels, are often higher than those in the edible pulp [23]-[25]. Berries (e.g., blue honeysuckle, strawberries) are also rich in polyphenols, and the leaves of some berry plants (e.g., strawberry) have polyphenol concentrations many times higher than their fruits, showing significant variation across plant parts [26] [27]. Vegetables (onions, spinach) and legumes (soybeans, mung beans) are important dietary polyphenol sources, whose contents are affected by cultivation methods, genotype and processing [28] [29].

Tea leaves are rich in polyphenols, with catechins and theaflavins driving their potent antioxidant activity. Spices and medicinal herbs are also major polyphenol sources, valued for their health benefits. Polyphenol content varies markedly across plant parts: pomegranate and grape peels/seeds have higher concentrations than edible pulp, and fruit/vegetable processing by-products (pomace, seed waste) are valuable extraction sources [30] [31]. Similarly, grain processing such as malting significantly alters polyphenol content and antioxidant activity, demonstrating that plant variety and post-harvest processing affect their distribution [32] [33]. Polyphenol distribution and content are highly variable, influenced by species, cultivar, cultivation conditions, plant part and processing, highlighting the need for comprehensive profiling to maximize their dietary and therapeutic benefits [34] [35].

3. Molecular Mechanisms of Polyphenol Antioxidants

3.1. Free Radical Scavenging and Metal Ion Chelation

Polyphenols, especially flavonoids, exert antioxidant effects via two principal mechanisms: direct ROS scavenging and transition metal ion chelation. Direct scavenging relies on their ability to donate hydrogen atoms or electrons to neutralize free radicals. Recent kinetic studies show polyphenol-radical reactions proceed up to 1,000 times faster than previously thought, significantly enhancing cellular antioxidant protection [36]. The presence and position of hydroxyl groups are critical for efficient hydrogen transfer and radical quenching; flavonoids and catechins exhibit robust activity against DPPH, ABTS and hydroxyl radicals in in vitro models [17] [37]-[39]. Additionally, polyphenols chelate Fe^{2+} and Cu^{2+}—key mediators of the Fenton reaction, which generates highly reactive hydroxyl radicals from hydrogen peroxide and amplifies oxidative damage—thus disrupting this reaction and reducing hydroxyl radical formation [3] [40]-[42]. Furthermore, the antioxidant and metal-chelating properties of polyphenols are being utilized to develop metal-polyphenol nanomaterials and coordination complexes, which show promising therapeutic efficacy against inflammation, neurodegeneration and microbial infections [43]-[45] (**Figure 1**).

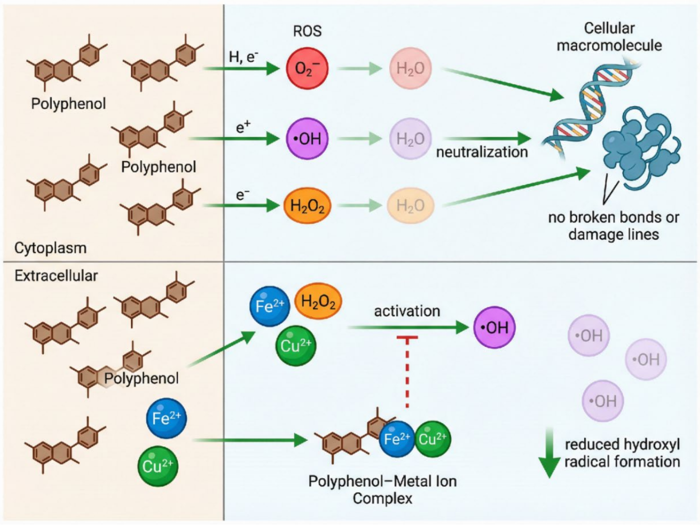

Figure 1. Two mechanisms of Polyphenol Antioxidant Activity: (1) Donate hydrogen atoms or electrons to neutralize reactive substances such as ROS; (2) Block the Fenton reaction by binding to transition metal ions, and reduce the formation of hydroxyl radicals.

3.2. Regulation of Antioxidant Enzyme Systems

Polyphenolic compounds play a pivotal role in modulating endogenous antioxidant enzyme systems including SOD, catalase (CAT) and GPx, which form the primary defense against ROS and oxidative stress involved in multiple disease pathogeneses. Polyphenols upregulate the expression and activity of these enzymes to enhance cellular antioxidative capacity. Dietary polyphenols have been shown to increase SOD, CAT and GPx activities in cell and animal models, improving redox balance and protecting against oxidative damage [46] [47]. This upregulation occurs across diverse contexts, including neurodegenerative diseases, metabolic disorders, and environmental or pharmacological stress conditions [48]-[50]. The underlying molecular mechanism mainly involves activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway. Polyphenol-activated Nrf2 translocates to the nucleus, binds to AREs in target gene promoters, and transcriptionally upregulates antioxidant enzymes including SOD, CAT, GPx, heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1) [46] [51]-[53] (**Figure 2**).

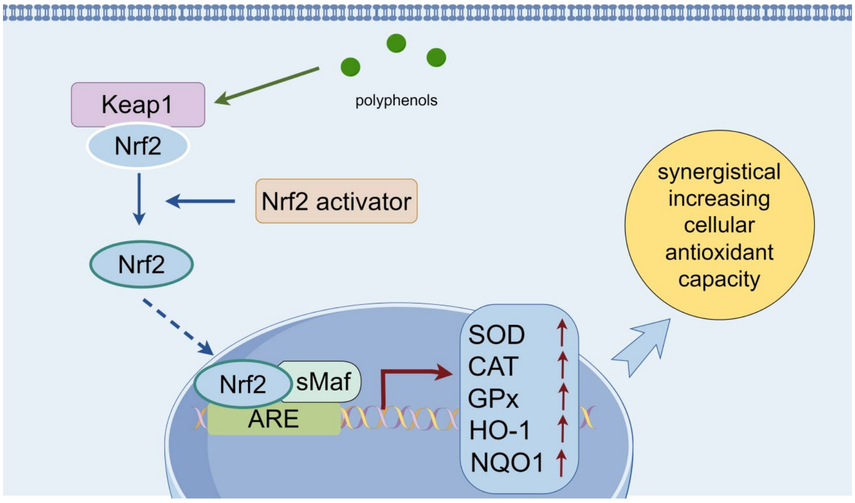

Figure 2. Regulation of Antioxidant Enzyme Systems. Entry of polyphenols into the cell, where they modify and change the conformation of Keap1 protein, and releasing and activating Nrf2. Nrf2 translocates into the nucleus and upregulates the expression of antioxidant enzymes. By Figdraw.

3.3. Inhibition of Lipid Peroxidation and Protein/Nucleic Acid Damage

Polyphenolic antioxidants alleviate oxidative stress-induced cellular damage by inhibiting lipid peroxidation (triggered by ROS attacking membrane PUFAs, generating MDA that disrupts membrane integrity) and protecting proteins and nucleic acids, largely via radical scavenging. Supplementation reduces MDA levels and preserves membrane structure; polyphenol-rich fractions significantly attenuate lipid peroxidation and boost antioxidant enzyme activities in pro-oxidant-exposed human skin cells [54]. Chlorogenic acid and other polyphenols interact with membrane lipids to delay peroxidation and maintain vesicle integrity even with cholesterol present [55]. Animal studies further confirm that chia leaf and Acacia nilotica polyphenolic extracts restore glutathione levels, reduce lipid peroxidation and ameliorate oxidative tissue damage [56] [57]. Beyond lipid protection, polyphenols prevent oxidative protein and DNA modifications, lowering mutagenesis and apoptosis risk. Tea polyphenols attenuate DNA damage and promote DNA repair in neurons under oxidative insults such as methamphetamine-induced neurotoxicity [58]. They also inhibit the formation of protein carbonyls and advanced glycation end-products (oxidative protein damage markers), as shown in muscle and testicular tissue studies [59]. Conjugating polyphenols with proteins or polysaccharides (e.g., chitosan) further enhances their antioxidant capacity, providing synergistic protection against lipid and protein oxidative damage [60] [61] (**Figure 3**).

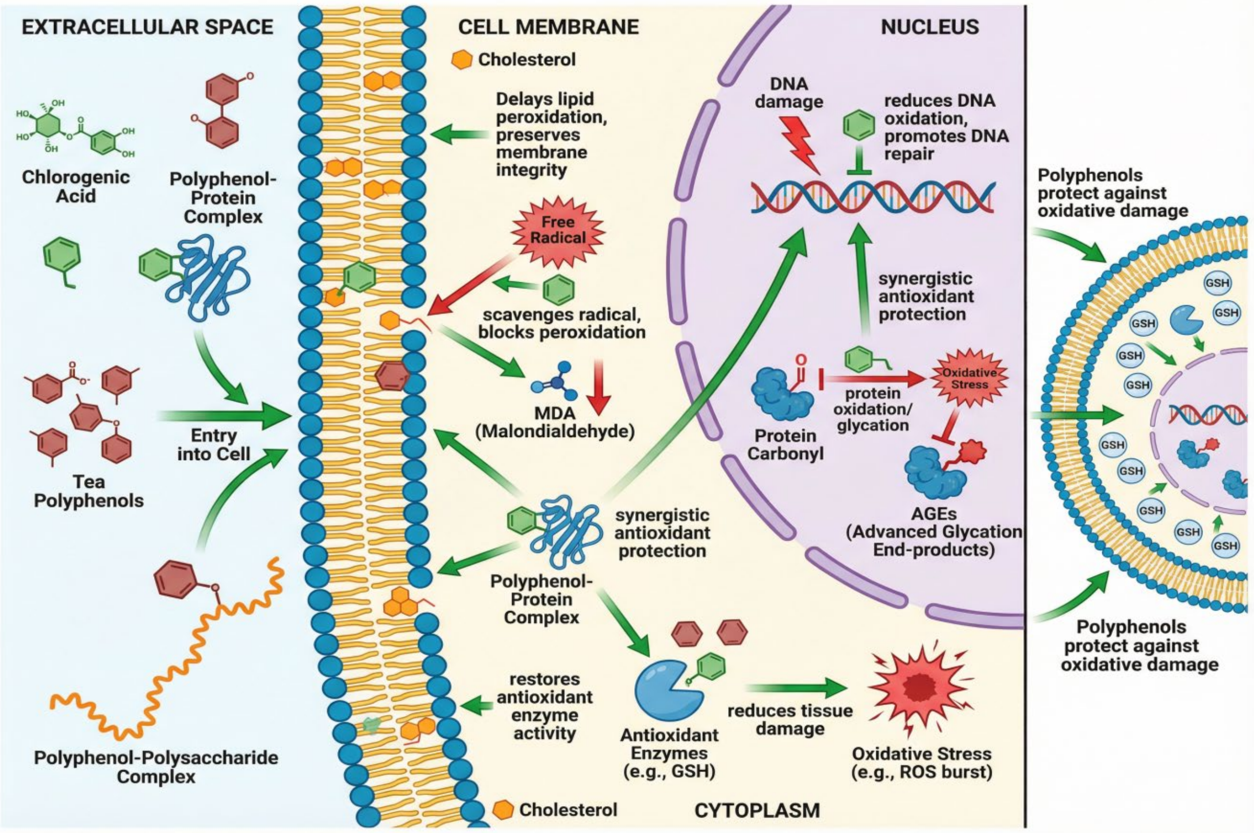

Figure 3. Polyphenols Inhibit Lipid Peroxidation and Protein/Nucleic Acid Damage. ROS attack three major classes of biological macromolecules simultaneously: lipids, proteins, and DNA, triggering respective oxidative damage chain reactions (such as lipid peroxidation producing MDA, protein carbonyl and AGEs formation, and DNA damage). By scavenging free radicals, polyphenols block the attack of ROS at its source, effectively suppressing oxidative damage along each pathway. This results in multiple protective effects, including maintaining cellular structural integrity, reducing oxidative marker levels, and alleviating tissue damage.

3.4. Anti-Inflammatory Effects and Regulation of Cellular Signaling Pathways

Polyphenols modulate inflammatory responses and disease-related signaling pathways primarily by inhibiting NF-κB and MAPK cascades; e.g., jujube peel and Punica granatum L. peel polyphenols suppress NF-κB/MAPK activation in LPS-stimulated macrophages, reducing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and iNOS/COX-2 expression [62] [63]. They also target the TLR4/NF-κB pathway, central to intestinal inflammation and IBD [64]. Additionally, polyphenols regulate cell survival and repair via PI3K/Akt and AMPK pathways: PI3K/Akt activation promotes cell survival and tissue repair, while AMPK stimulation improves metabolic health and alleviates inflammation [65] [66]. This interplay attenuates inflammatory responses and enhances cellular resilience to stress and injury (**Figure 4**), underpinning their therapeutic potential in chronic inflammatory diseases, metabolic disorders, and tissue repair, and warranting further mechanistic and clinical research [67] [68].

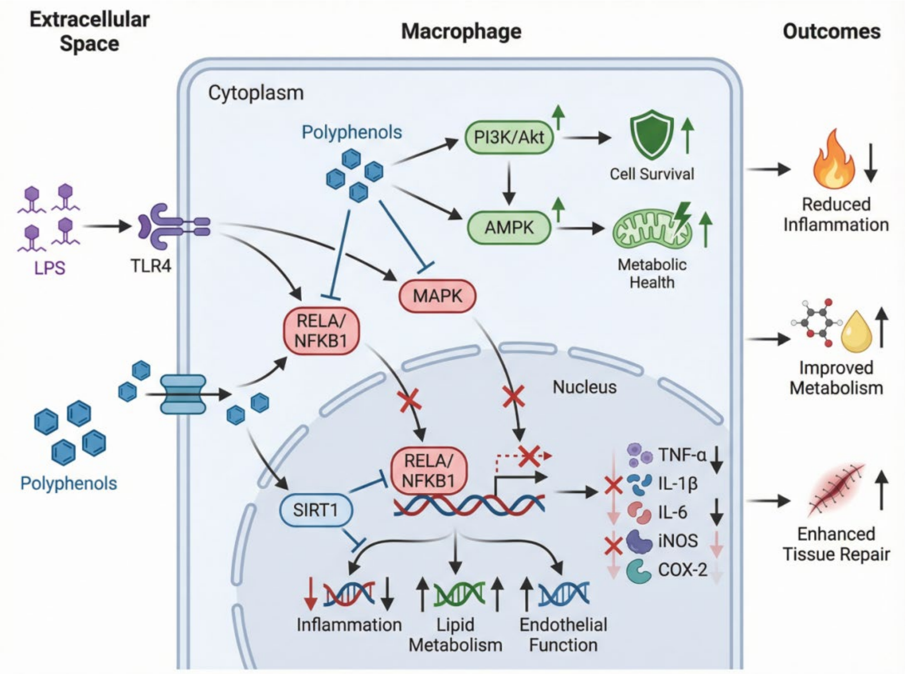

Figure 4. Anti-inflammatory effects and regulation of Cellular Signaling Pathways. Polyphenols suppress the activation of NF-kB and MAPK in LPS-stimulated macrophages, leading to decreased production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as downregulation of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Moreover, polyphenols activate the PI3K/Akt and AMPK signaling pathway promoting cell survival and tissue repair, and improved metabolic health and reduced inflammation.

4. Advances in the Application of Polyphenolic Antioxidants in Neurodegenerative Diseases

4.1. Mechanisms of Polyphenols in Alzheimer's Disease (AD)

The mechanistic findings in this subsection are mainly derived from in vitro cell culture, in vivo animal model studies, and preliminary human observational studies. Polyphenols including quercetin, resveratrol, curcumin and catechins show multifaceted neuroprotective effects against Alzheimer's disease (AD). They directly inhibit amyloid-β (Aβ) aggregation and tau hyperphosphorylation, the two hallmark pathologies of AD, thus reducing neurotoxicity and neuronal damage. Specifically, curcumin inhibits Aβ aggregation, promotes disaggregation of existing amyloid plaques and prevents tau hyperphosphorylation to attenuate neurofibrillary tangle formation [69]. Quercetin and its derivatives from ginger leaf polyphenols mitigate Aβ toxicity by activating antioxidative signaling pathways such as JNK/FOXO, enhancing antioxidase gene expression and reducing neuronal oxidative stress [70].

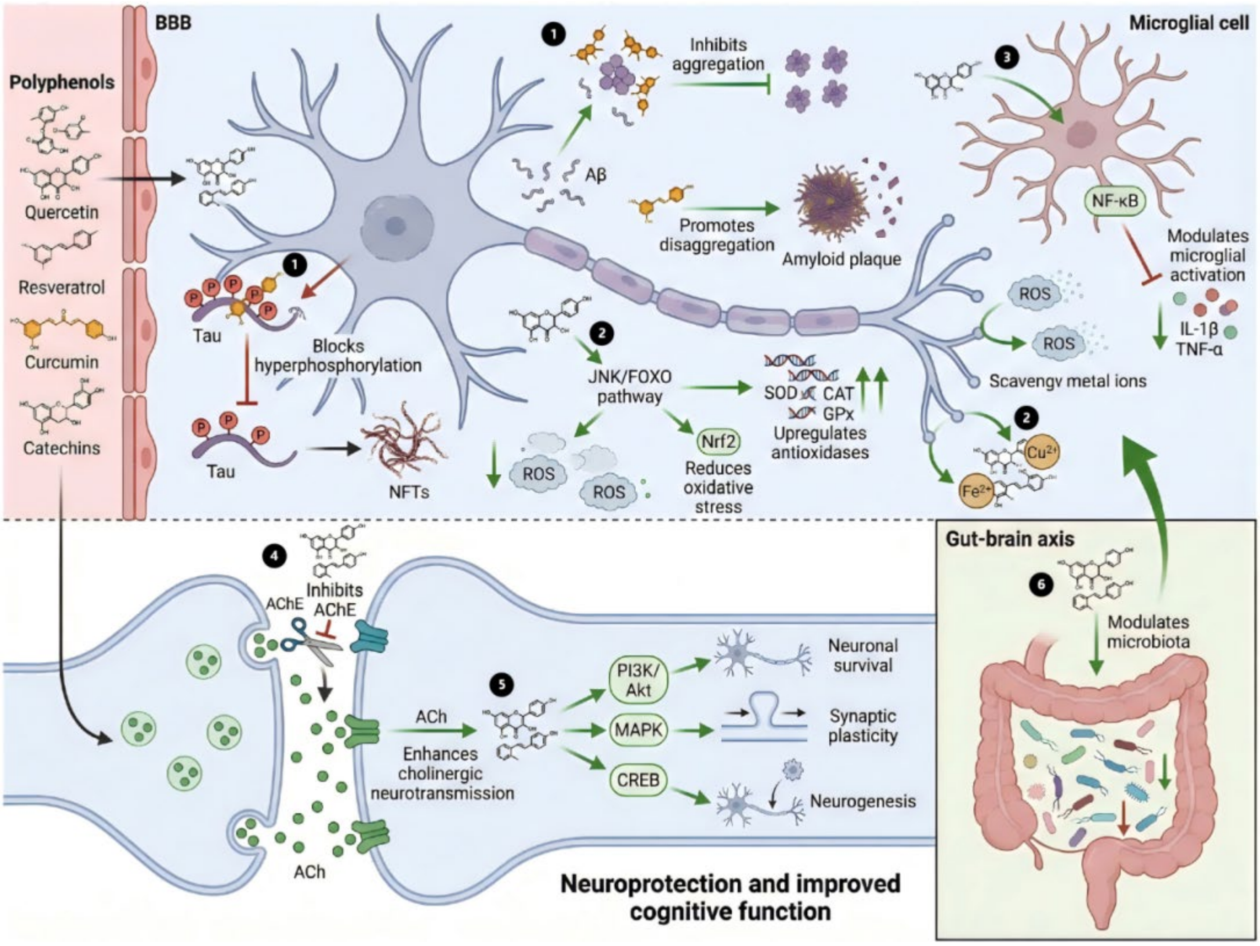

Figure 5. Six core pathways of Polyphenols in Combating Alzheimer's Disease (AD): (1) Directly targeting core pathology. Polyphenols directly intervene in two key hallmarks of AD: Aβ plaques and tau tangles, and reduce the accumulation of toxic proteins at the source. (2) Potent antioxidant effects. Through both direct (scavenging ROS) and indirect (activating pathways such as Nrf2 and JNK/FOXO) mechanisms, polyphenols comprehensively enhance the antioxidant defense capacity of neurons. (3) Suppressing neuroinflammation. Polyphenols inhibit the overactivation of microglia and reduce the damage caused by inflammatory factors to neurons by the NF-κB pathway. (4) Improving neurotransmission. Inhibiting acetylcholinesterase, increasing acetylcholine levels, and benefiting cognitive function. (5) Supporting wellbeing of neurons. Polyphenols modulate key cellular signaling pathways such as PI3K/Akt to promote neuronal survival, plasticity, and regeneration. (6) Regulating the gut-brain axis. As an emerging field of research, polyphenols indirectly protect on the brain through improve gut health.

Beyond direct effects on protein pathology, polyphenols exert potent antioxidant effects by scavenging ROS, chelating redox-active metal ions and upregulating endogenous antioxidant enzymes via the Nrf2 pathway, thus protecting neurons from oxidative damage [3] [71]. Their anti-inflammatory properties are also crucial: they suppress the NF-κB signaling pathway, reduce pro-inflammatory cytokine production and modulate microglial activation, alleviating neuroinflammation that accelerates AD progression [72] [73]. Furthermore, polyphenols inhibit acetylcholinesterase activity to enhance cholinergic neurotransmission and improve cognitive function [74] [75], and regulate key pathways (PI3K/Akt, MAPK, CREB) involved in neuronal survival, synaptic plasticity and neurogenesis, which are essential for cognitive health [76]. Emerging evidence shows that polyphenols modulate the gut-brain axis by fostering beneficial microbiota composition and promoting neuroprotective metabolite production, further enhancing cognitive resilience [77] [78]. (**Figure 5**)

4.2. *In Vitro* and Animal Model Studies

All evidence in this subsection is derived from controlled in vitro cellular and in vivo animal model studies of neurodegenerative diseases. Accumulating experimental evidence demonstrates that polyphenols exert potent antioxidant and neuroprotective effects against neurodegenerative diseases such as AD. In AD mouse models, administration of polyphenol-rich extracts or specific polyphenolic compounds significantly reduces brain oxidative stress markers, correlating with improved cognitive performance and learning-memory abilities. Specifically, marine polyphenols from macroalgae slow neurodegeneration and limit neuronal loss in animal models primarily via antioxidant activity that mitigates oxidative stress-driven AD pathology [79]. Furthermore, polyphenols can modulate neuroinflammatory pathways and increase glutathione (GSH) levels, further supporting neuronal survival under oxidative stress [80].

4.3. Clinical Research and Prospects for Application

The findings in this subsection are derived from human clinical trials, epidemiological studies and translational clinical research on polyphenol interventions for neurodegenerative diseases. Recent studies increasingly highlight the potential of polyphenol-based supplements (e.g., grape polyphenols, green tea extracts) in managing neurodegenerative diseases such as AD, with their multi-targeted neuroprotective, antioxidant and anti-inflammatory effects underlying the benefits in cognitive function and disease progression. Specifically, grape polyphenols can cross the blood-brain barrier, modulate neuroinflammation and reduce oxidative stress, providing a mechanistic basis for their neuroprotective properties [81]-[83]. Polyphenol supplements also have a favorable safety profile, being generally well tolerated with a low incidence of adverse effects according to human trials and nutritional studies [83] [84]. Future research should focus on optimizing polyphenol delivery and bioavailability, elucidating clinical molecular mechanisms, and conducting high-quality RCTs to establish standardized dosing regimens and long-term safety profiles.

5. The Role of Polyphenol Antioxidants in Cardiovascular Diseases, Tumors, and Other Chronic Diseases

5.1. Mechanisms of Cardiovascular Disease Prevention and Treatment

Supported primarily by preclinical studies and corroborated by epidemiological evidence and small clinical trials, polyphenols protect against cardiovascular diseases (CVD) via multiple mechanisms: they reduce LDL oxidation by directly scavenging ROS, thereby slowing atherosclerosis progression and lowering plaque rupture/event risk [85]-[87]; enhance endothelial NO bioavailability to improve vascular tone, lower blood pressure, and maintain integrity [88] [89]; inhibit platelet aggregation to reduce thrombus risk [90] [91]; and modulate signaling pathways to upregulate endogenous antioxidant enzymes and anti-inflammatory mediators [91] [92]. Meta-analyses and epidemiological studies consistently associate polyphenol-rich diets with improved lipid profiles, reduced blood pressure, and lower vascular inflammation markers, supporting cardiovascular risk reduction [93] [94].

5.2. Antioxidant and Anti-Inflammatory Effects in Tumorigenesis and Tumor Progression

The anticancer mechanistic findings here are mainly based on in vitro cancer cell line and in vivo xenograft/genetically modified animal tumor models. Polyphenols exert significant protective effects against tumorigenesis and progression by targeting oxidative stress and inflammation—the two key drivers of cancer. As potent free radical scavengers, they neutralize ROS-induced DNA/protein/lipid damage to reduce mutagenic and carcinogenic events. Additionally, polyphenols modulate key inflammatory pathways including the NF-κB cascade, which is frequently upregulated in cancer and drives pro-inflammatory cytokine/mediator expression that promotes tumor growth, angiogenesis and metastasis [95] [96]. Inhibiting NF-κB suppresses TNF-α, IL-1β, IL-6 and COX-2 production, attenuating the tumor-promoting chronic inflammatory microenvironment [97] [98].

Furthermore, polyphenols induce tumor cell apoptosis via modulating mitochondrial pathways, upregulating pro-apoptotic proteins and downregulating anti-apoptotic factors, thus inhibiting tumor cell proliferation and survival [99] [100]. Across various tumor models, they have been shown to inhibit cancer cell growth, prevent metastasis and enhance chemosensitivity [99] [101], mediated also by epigenetic regulation and modulation of cell cycle/apoptosis-related gene expression [102].

5.3. Application in Other Chronic Diseases

Preclinical and clinical evidence demonstrates polyphenols exert therapeutic effects on diabetes, obesity, and metabolic syndrome by improving insulin resistance, reducing inflammation, and protecting pancreatic β-cells, partly via Nrf2 pathway modulation to mitigate oxidative stress and inflammation—the core drivers of diabetic complications. While preclinical studies confirm Nrf2 activation reduces ROS and improves insulin sensitivity, resveratrol clinical trials show inconsistent glycemic benefits, attributed to bioavailability limitations and individual response differences [103].

Epidemiological studies indicate an inverse relationship between polyphenol intake and metabolic syndrome incidence, mediated by antioxidant/anti-inflammatory effects and regulation of glucose and lipid metabolism [104]; polyphenol-rich dietary interventions enhance plasma antioxidant capacity and reduce oxidative stress markers in obesity, diabetes, and related disorders [105]. Polyphenols also have recognized pharmacological potential for cardiovascular and renal health, with emerging evidence supporting their use as adjunct or alternative therapies for chronic organ dysfunction [106].

5.4. Clinical Applications and Functional Food Development

Based on human clinical research, product development and formulation trials (supported by preclinical delivery system efficacy data), polyphenols' clinical applications have expanded as health-promoting food ingredients and pharmaceutical adjuncts [107] [108]. Abundant in fruits, vegetables, teas and grains, their antioxidant, anti-inflammatory and antimicrobial activities underpin disease prevention, driving incorporation into functional foods, beverages and supplements [109] [110]. The food industry develops innovative polyphenol-based products to enhance nutritional value, antioxidant stability, glycemic modulation and natural preservation [111]. Advances in extraction, purification and encapsulation improve bioavailability and stability by overcoming solubility and degradation limitations [112] [113]; e.g., hydrogels and nanocarriers for targeted drug delivery and tissue regeneration, and polyphenol-protein/polysaccharide complexes for functional food matrices and nutraceuticals [114] [115]. Despite challenges in standardization, dosing and clinical validation, polyphenol-based products have broad market prospects driven by demand for natural, science-backed interventions, positioning them at the forefront of functional food and nutraceutical industries [109] [116].

6. Conclusions

Polyphenolic antioxidants have emerged as a prominent area of research in recent years, owing to their remarkable structural diversity and multifaceted mechanisms of action. As highlighted throughout this review, their capacity to counteract oxidative stress, modulate enzymatic antioxidant systems, suppress inflammation, and regulate cellular signaling pathways underpins their therapeutic potential across a spectrum of chronic diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer. Additionally, the bioavailability of polyphenolic compounds remains a significant obstacle, as many exhibit limited absorption and rapid metabolism in vivo, which may attenuate their therapeutic efficacy. Addressing these challenges requires a balanced approach that integrates findings from basic science with insights gained from clinical research.

Beyond the well-documented challenge of poor bioavailability, several critical and interconnected hurdles significantly impede the clinical translation of these bioactive agents. First, the biological activity of metabolites generated in vivo often proves inconsistent, creating uncertainty regarding therapeutic efficacy [12] [13]. Second, the field suffers from a notable absence of standardized protocols governing dosage, purity, and pharmaceutical formulation [12] [83]. Third, substantial interindividual variation in gut microbial metabolism introduces unpredictable elements into drug processing [6] [7]. Finally, there exists a risk of significant pharmacokinetic interactions when these agents are co-administered with conventional medications, particularly anticoagulants, antidiabetics, and chemotherapeutic drugs [107] [108].

The safety profile of polyphenols, as established by numerous preclinical and clinical investigations, provides a solid foundation for their further development. Future research should prioritize the optimization of polyphenol structures through chemical modifications aimed at enhancing their stability, bioavailability, and target specificity. Advances in formulation technologies, offer promising avenues to improve the delivery and efficacy of these compounds in clinical settings. Ultimately, overcoming the identified translational barriers through interdisciplinary collaboration will be essential to unlock the full therapeutic and public health potential of polyphenolic antioxidants.

Funding

This work was supported by Shanxi Provincial Basic Research Program, No. 202303021211136. Central Fund for Guiding Local Science and Technology Development in Shanxi Province, No. YDZJSX20231A052.

Acknowledgements

All authors thank anonymous reviewers for their careful reading and valuable comments to improve our manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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