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Review

Synergistic Natural Products in Anti-Ageing: Mechanistic Insights, Experimental Evidence, and Translational Perspectives

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ABSTRACT: Ageing is characterised by a progressive decline in physiological function driven by oxidative stress, chronic inflammation, and metabolic imbalance. Natural products contain diverse bioactive compounds capable of regulating these interconnected processes through convergent molecular pathways. This review synthesises current evidence across six major classes of natural bioactives, including polyphenols, terpenoids, polyamines, polysaccharides, fatty acids, and bioactive peptides, and examines their roles within metabolic, redox, inflammatory, and epigenetic networks. Individually, these compounds enhance mitochondrial function, modulate AMP-activated protein kinase (AMPK)–sirtuin 1 (SIRT1)–mechanistic target of rapamycin complex 1 (mTORC1) signalling, activate the nuclear factor erythroid 2-related factor 2 (Nrf2)–antioxidant response element (ARE) antioxidant pathway, suppress nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) activation, and improve cellular stress resilience. When used in combination, they exhibit synergistic interactions that amplify antioxidant, anti-inflammatory, and metabolic benefits, resulting in measurable improvements in lifespan and healthspan. Quantitative analyses demonstrate that rationally designed combinations achieve approximately 20–35 percent greater efficacy than single agents, reflecting coordinated multi-target reinforcement rather than simple additive effects. Overall, these insights highlight the mechanistic rationale, experimental evidence, and translational potential of synergistic natural bioactives as promising strategies for promoting healthy ageing and mitigating age-related decline.

Keywords: Natural bioactives; Anti-ageing mechanisms; AMPK–SIRT1–mTORC1 signalling; Nrf2–ARE pathway; NF-κB regulation; Synergistic combinations; Lifespan and health-span

1. Introduction

1.1. Background for Ageing and Anti-Ageing

Ageing represents a progressive decline in physiological integrity driven by the cumulative effects of molecular and cellular damage over time [1,2]. In contrast, anti-ageing refers to scientific and clinical strategies designed to delay this process, prevent age-related diseases, and preserve physical, functional, and aesthetic health [3,4].

Natural compounds are increasingly recognised as pivotal components of anti-ageing strategies, as they exhibit antioxidant, anti-inflammatory, photoprotective, antimicrobial, wound-healing, and DNA-repair activities [5]. These bioactive molecules, derived from terrestrial and marine organisms, fungi, and microorganisms, include secondary metabolites such as flavonoids, phenolic acids, polysaccharides, and lipopeptides that exert measurable anti-ageing effects through multiple biological mechanisms [6–11].

1.2. Literature Search Strategy

Publications on the anti-ageing effects of natural products were identified through a comprehensive two-stage search conducted across the Web of Science Core Collection, Google Scholar, and the University of Auckland Libraries (2005–2025). The initial scoping stage, using the keywords “anti-ageing”, “natural products”, and “functional food”, was performed to outline overall research trends and thematic distributions. A subsequent targeted search combined “anti-ageing” with polyphenols, terpenoids, polyamines, polysaccharides, fatty acids, bioactive peptides, and multi-component natural products to identify mechanistic and experimental studies. Grey literature and reference verification were included through Google Scholar and institutional resources, while studies restricted to topical or cosmetic formulations were excluded. Additional relevant references were identified through citation tracking.

Keyword co-occurrence and timeline analyses were conducted using CiteSpace (v6.2.R4) to visualise research dynamics within the dataset. The results revealed a progressive shift from early studies focused on general biological processes, such as “mammalian ageing” and “vitamin C”, to more recent research emphasising mechanistic and multi-component strategies involving natural bioactives and dietary interventions (Figure 1). This trend highlights the increasing integration of molecular biology, nutrition, and pharmacognosy in anti-ageing research.

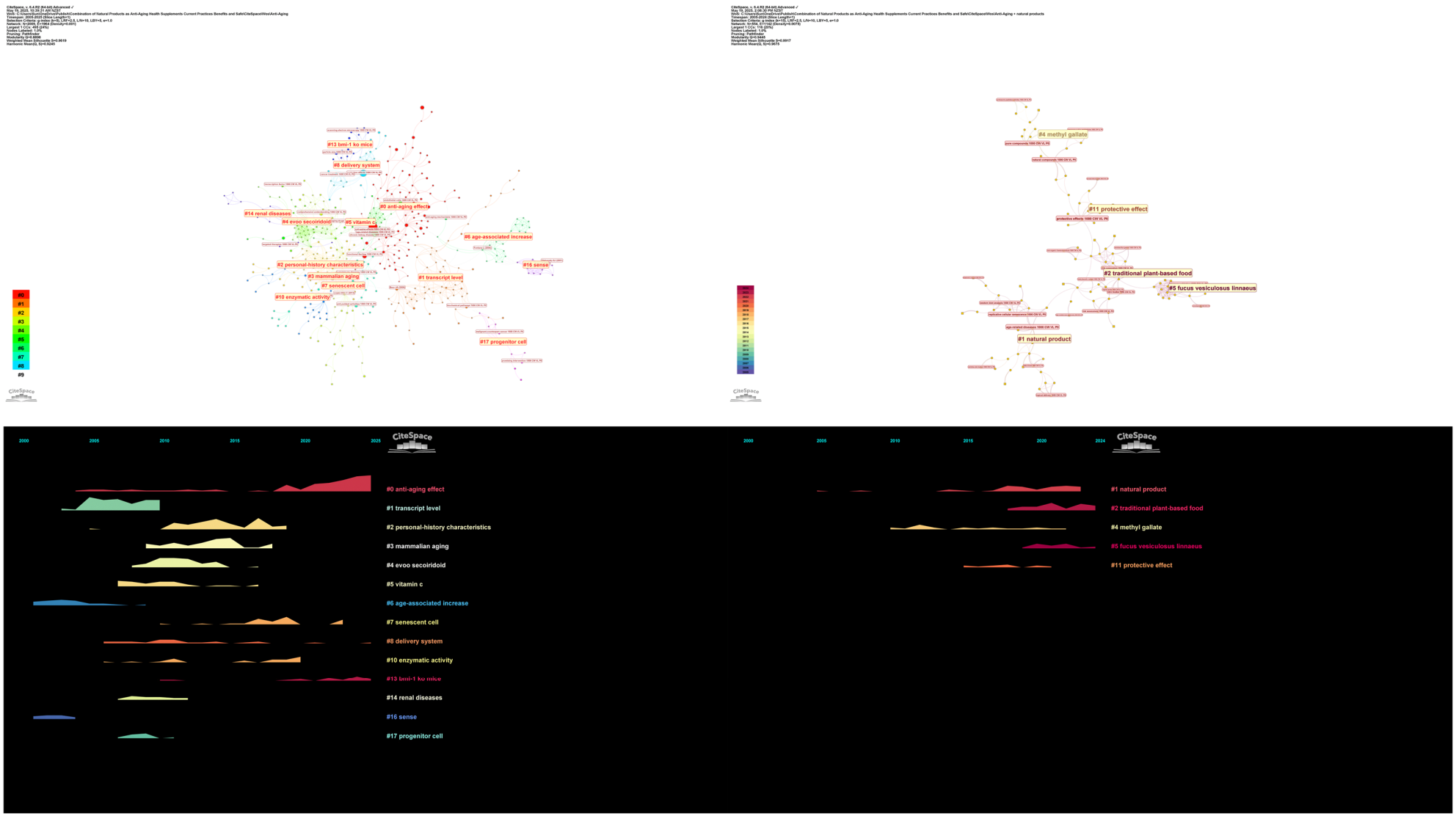

Figure 1. Keyword co-occurrence and timeline mapping of anti-ageing research on natural products (2005–2025). Notes: Upper panels show clustered keyword networks, and lower panels display their temporal evolution. Colours indicate cluster identity and chronological order. Analysis conducted in CiteSpace (v6.2.R4) using data from the Web of Science Core Collection.

1.3. Aim of This Review

This review synthesises current evidence on the anti-ageing potential of major classes of natural bioactives, including polyphenols, terpenoids, polyamines, polysaccharides, fatty acids, and bioactive peptides. It focuses on their roles in modulating oxidative stress, inflammation, mitochondrial function, and cellular senescence, and evaluates naturally derived multi-component products to elucidate how complex compositions contribute to anti-ageing effects. By integrating findings from both single-compound and combined formulations, this review proposes mechanistic hypotheses for synergistic interactions among natural products in mitigating age-related decline.

2. Biological Mechanisms of Ageing and Anti-Ageing Strategies

2.1. Theory of Ageing Causes

Ageing is characterised by a progressive loss of physiological integrity that impairs function, increases vulnerability to stress and disease, and ultimately culminates in organismal mortality [12]. Numerous hypotheses have been proposed to explain age-related changes; however, they often conflict with one another, and no single model can fully account for the complexity of the ageing process [13].

Recent research has introduced novel perspectives, such as the five-factor theory proposed by Obradovic [14], which conceptualises ageing as a multifactorial process driven by structural alterations in cells, the cessation of cell division, and impaired stem-cell signalling that culminates in systemic functional decline. While this framework integrates both cellular and evolutionary perspectives, it remains limited in identifying the precise molecular drivers of these structural changes and in defining the conditions under which stem cells may be reactivated in long-lived species. These acknowledged gaps underscore the importance of situating this model within a broader theoretical context.

Although this theory presents an innovative perspective, it remains limited in several respects. Specifically, it does not clearly define the molecular or environmental factors underlying these structural alterations, nor does it adequately explain the conditions under which stem cells may be reactivated to delay ageing, as observed in certain long-lived species. These limitations, consistent with gaps acknowledged by the original author, underscore the need to situate this theory within the broader context of ageing research.

Contemporary biological theories are broadly categorised into programmed theories and damage- or error-based theories. Programmed theories propose that ageing follows a genetically regulated biological timetable, wherein altered gene expression, hormonal regulation, and immune decline collectively drive physiological deterioration [2,13,15,16]. The programmed longevity theory views ageing as a continuation of developmental processes governed by specific genes. The endocrine theory links age-related hormonal shifts to the regulation of biological clocks. The immunological theory attributes senescence to genetically programmed decline in immune function [17,18] (Table 1).

Table 1. Classical ageing theories and their mechanistic pathways.

Theory Category	Representative Models	Description	Key Mechanistic Features/Targets
Programmed Theories	Programmed Longevity	Ageing is considered a continuation of development regulated by a genetic timetable, resulting from the sequential switching on and off of specific genes.	– Sequential gene activation/inactivation (e.g., DAF-2, ~80 longevity-associated genes) – Yamanaka factors enabling stem cell reprogramming – Programmed decline in mitochondrial bioenergetics (reduced ATP/ADP ratio)
	Endocrine Theory	Biological clocks regulate the pace of ageing through hormones. Hormonal signalling pathways control metabolism, growth, and repair, thereby influencing lifespan.	– Insulin/IGF-1 signalling (IIS) as a central regulator – FOXO transcription factors promoting stress resistance and longevity – Hormonal imbalance impairing cellular maintenance and defence mechanisms
	Immunological Theory	The immune system is genetically programmed to decline with age, leading to increased susceptibility to infections, chronic inflammation, and ageing-related diseases.	– Thymic involution and reduced T-cell production – Decreased antibody responses – Chronic low-grade inflammation (inflammaging) – Immune dysregulation contributing to cardiovascular diseases, Alzheimer's disease, and cancer
Damage/Error Theories	Wear-and-Tear Theory	Ageing results from prolonged functional stress that gradually damages and degrades cells and tissues, leading to organ dysfunction and death.	– Accumulation of cellular and tissue damage due to repeated use and environmental stressors (mechanical, oxidative, metabolic) – Increased macromolecular damage (proteins, lipids, DNA) over time – Impaired repair mechanisms failing to keep pace with damage – Progressive decline in organ function similar to mechanical wear of components
	Rate-of-Living Theory	Higher metabolic rates correlate with shorter lifespans. The theory suggests that organisms with higher energy expenditure age faster and die sooner.	– Energy expenditure accelerates consumption of a finite "vital substance" – Oxygen metabolism by-products ROS, induce molecular damage – Aging rate is proportional to unrepaired oxidative damage – Efficiency of antioxidant and repair mechanisms modulates lifespan

	Cross-Linking Theory	Accumulation of cross-linked proteins impairs cellular and tissue functions.	– Formation of irreversible cross-links between proteins (e.g., collagen, elastin) leading to tissue stiffness – Intracellular cross-links (DNA-protein) inhibit gene expression and protein synthesis – Nonenzymatic glycosylation produces AGEs that promote further cross-linking and cellular dysfunction – Associated with loss of elasticity, vascular stiffening, delayed wound healing, and joint mobility reduction
	Free Radical Theory	Ageing results from the accumulation of cellular damage caused by ROS.	– ROS attack macromolecules (DNA, proteins, lipids), leading to mutations, strand breaks, and cross-linking. – Oxidative damage impairs cellular structure and function. – Endogenous antioxidant enzymes (SOD, CAT, GPx) mitigate ROS damage but decline with age. – Accumulated oxidative damage contributes to progressive cellular dysfunction and organ deterioration.
	Mitochondrial DNA Damage Theory	Ageing is driven by mitochondrial dysfunction and progressive mtDNA damage, which amplify oxidative stress and trigger cell death.	– Mitochondria are the main source of ROS, which damages mtDNA and respiratory chain components. – mtDNA mutations impair oxidative phosphorylation, reduce ATP production, and promote further ROS generation (vicious cycle). – Accumulated mtDNA damage compromises mitochondrial integrity and activates apoptotic pathways. – Emerging evidence suggests ROS also act as signalling molecules, activating stress resistance mechanisms and potentially extending lifespan.

This table summarises the major classical theories of ageing, categorised into programmed and damage/error models. Each theory is briefly described, and its key mechanistic features and molecular targets are outlined to highlight the distinct biological processes implicated in ageing. These mechanistic insights provide a conceptual framework for comparing traditional hypotheses with emerging perspectives and for guiding future research on anti-ageing interventions [2,13,15–23].

In contrast, damage- or error-based theories attribute ageing to the cumulative effects of environmental and metabolic stressors rather than to predetermined genetic programming. These frameworks encompass the wear-and-tear, rate-of-living, cross-linking, free radical, and mitochondrial DNA damage theories. The wear-and-tear theory posits that prolonged functional stress leads to cellular and tissue degradation, whereas the rate-of-living theory associates higher metabolic rates with reduced lifespan [2,13,15]. The cross-linking and free radical theories emphasise molecular damage arising from accumulated protein cross-links and reactive oxygen species (ROS) [19,21,22]. The mitochondrial DNA damage theory further links mitochondrial dysfunction to oxidative stress and cell death [18] (Table 1).

Collectively, these frameworks offer complementary perspectives on the intrinsic and extrinsic drivers of ageing and form a conceptual foundation for anti-ageing research. While each model accounts for only part of the process, together they highlight the multifactorial nature of biological ageing and the intricate interplay among genetic regulation, metabolic homeostasis, and repair mechanisms of cellular damage.

2.2. Theory of Anti-Ageing

The interplay among ageing triggers, phenotypic traits, and age-related diseases, whether genetically inherited or acquired, has attracted growing scientific attention in recent decades. Concurrent advances in biotechnology and biomedical sciences have expanded both the design and the implementation of anti-ageing interventions. Contemporary theories propose that phenotypic ageing arises from dynamic interactions between intrinsic genetic profiles and modifiable environmental factors, including diet, physical activity, and other environmental exposures (Equation (1)). This conceptual model illustrates the interdependence between genetic determinants and environmental factors in shaping the ageing phenotype [24].

Equation (1). Phenotypic Determinants of Ageing

$$\begin{aligned} &Phenotypic\ Ageing \\ &= Genotypes \\ &+ External\ Factors\ (e.g., diet, lifestyle\ and\ environmental\ conditions) \end{aligned} \quad (1)$$

Current anti-ageing strategies are generally classified into three complementary frameworks: geroprotection, which aims to prevent or delay damage accumulation; rejuvenation, which focuses on restoring physiological function; and regeneration, which promotes the repair or replacement of aged or damaged tissues [25,26].

Building upon these foundational principles, a wide range of interventions has emerged, reflecting advances in mechanistic understanding of ageing. These approaches can be broadly categorised into five domains: lifestyle interventions, microbiome modulation, genetic and regenerative strategies, molecular targeting, and emerging technologies [25,27].

Lifestyle-based strategies, including caloric restriction, antioxidant-rich diets, regular physical activity, and adequate sleep, help maintain metabolic balance, reduce oxidative stress, and enhance autophagic turnover, thereby supporting circadian synchrony and systemic homeostasis [24,25]. Molecular and regenerative approaches encompass several interrelated mechanisms, such as nicotinamide adenine dinucleotide (NAD^+) metabolism, senescence clearance, mitochondrial biogenesis, and the use of DNA-methylation clocks to evaluate biological ageing [20,23,26,27].

Finally, emerging technologies, including epigenetic remodelling, synthetic biology, and biomarker-guided feedback systems, represent the frontier of precision ageing medicine [26] (Table 2).

Table 2. Overview of Principal Anti-Ageing Strategies and Their Biological Foundations.

Strategy Category	Representative Examples	Description	Core Biological Focus
Lifestyle Interventions	Caloric restriction, intermittent fasting, antioxidant-rich diet, exercise, and sleep optimisation	Lifestyle-based approaches support systemic homeostasis by reducing oxidative and metabolic stress, enhancing autophagy, and promoting cellular repair. These strategies influence multiple hallmarks of ageing through metabolic and circadian regulation.	Redox balance • Energy metabolism • Circadian synchrony • Autophagic turnover
Microbiome Modulation	Probiotics, prebiotics, high-fibre diet	Improves microbial diversity and intestinal barrier integrity, reducing systemic inflammation and supporting immune–metabolic communication.	Gut–immune axis • Inflammation control • Metabolic resilience
Genetic and Regenerative Approaches	Telomere maintenance (hTERT activation), stem cell therapy, cellular reprogramming	Targets chromosomal stability and cellular renewal to delay senescence and restore tissue function.	DNA repair • Epigenetic stability • Stem-cell regeneration
Molecular Targeting	NAD^+ supplementation, senolytics, mTOR modulators	Modulates signalling pathways associated with cellular stress, autophagy, and senescence to maintain metabolic balance.	Energy sensing • Proteostasis • Cellular senescence control
Emerging Technologies	Epigenetic remodelling, synthetic biology tools, biomarker-guided interventions	Employ advanced biotechnologies for precision monitoring and reprogramming of ageing processes, mostly at the pre-clinical stage.	Epigenetic reversal • Digital biomarker feedback • System-level precision modulation

This table categorises contemporary anti-ageing interventions into five major domains: lifestyle interventions, microbiome modulation, genetic and regenerative approaches, molecular targeting, and emerging technologies. For each category, representative examples are provided along with a concise description and their principal mechanistic features, illustrating how each strategy engages specific biological processes implicated in ageing and age-related functional decline [24–27].

2.3. Molecular Pathways Underlying Ageing and Anti-Ageing Regulation

Ageing arises from a network of interconnected signalling cascades that coordinate metabolism, redox balance, inflammation, autophagy, and cellular renewal. These cascades constitute the molecular foundation of anti-ageing research and represent key targets for nutritional and pharmacological interventions. They act as nodal regulators linking nutrient sensing, energy metabolism, and stress responses, integrating physiological resilience with longevity outcomes [28–32]. Collectively, these signalling cascades form a multilayered regulatory network that integrates metabolic, redox, inflammatory, and immune regulation to modulate ageing (Figure 2) [33–35].

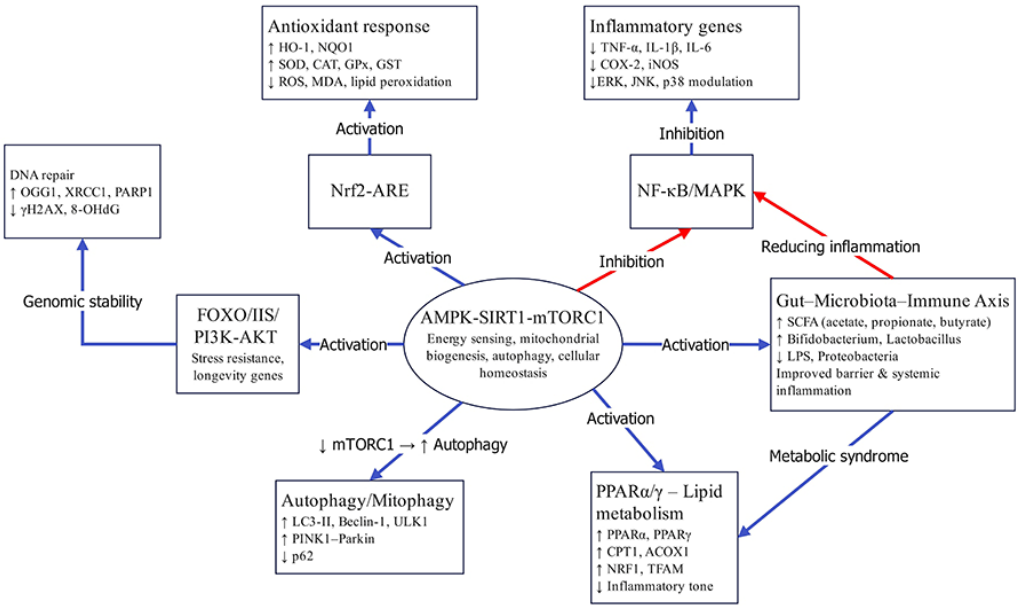

Figure 2. Integrated molecular network underlying anti-ageing regulation by natural products. Notes: Natural products activate the AMPK–SIRT1–mTORC1 axis and its downstream antioxidant, anti-inflammatory, metabolic, autophagic, and microbiota-related pathways, thereby enhancing mitochondrial function, genomic stability, and systemic homeostasis.

2.3.1. AMPK-SIRT1-mTORC1 Axis

The AMP-activated protein kinase (AMPK)–sirtuin 1 (SIRT1)–mechanistic target of rapamycin complex 1 (mTORC1) axis acts as a central metabolic switch that controls energy sensing, mitochondrial biogenesis, and autophagy. Activation of AMPK and SIRT1 enhances catabolic efficiency and cellular stress tolerance through fatty acid oxidation and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α)–mediated mitochondrial function, whereas inhibition of mTOR limits anabolic overactivation and suppresses cellular senescence [36–38]. Convergent evidence from multiple classes of natural products indicates that modulation of this axis improves mitochondrial quality control, attenuates growth factor signalling, and supports chromatin stability [28,30,39].

2.3.2. Nrf2-ARE Pathway

The nuclear factor erythroid 2–related factor 2 (Nrf2)–antioxidant response element (ARE) pathway regulates cellular redox homeostasis. Under oxidative stress, Nrf2 translocates to the nucleus and induces the expression of detoxification and antioxidant genes, including heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and superoxide dismutase (SOD). Sustained activation mitigates ROS accumulation, prevents lipid peroxidation, and protects macromolecules from oxidative damage [40–42]. Studies on polyphenols, terpenoids, and polysaccharides have shown that these compounds enhance Nrf2

nuclear localisation and downstream gene transcription, thereby improving antioxidant capacity and delaying functional decline [33,43,44].

2.3.3. NF-κB and MAPK Cascades

The nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) cascades mediate inflammatory and stress-related transcriptional responses. NF-κB activation upregulates pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and cyclooxygenase-2 (COX-2), whereas MAPK members, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (p38), regulate cellular adaptation to oxidative and metabolic stress. Persistent overactivation of these pathways contributes to inflammageing and tissue degeneration [45,46]. Natural products such as polyphenols, terpenoids, peptides, and unsaturated fatty acids have been shown to inhibit NF-κB nuclear translocation and modulate MAPK phosphorylation, thereby reducing chronic low-grade inflammation and preserving tissue integrity [28,37–39].

2.3.4. FOXO/IIS/PI3K-AKT Signalling Pathway

Forkhead box O (FOXO) transcription factors act downstream of the insulin/IGF-1 signalling (IIS) and phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT) cascades. Reduced IIS or AKT activity promotes FOXO nuclear translocation and the activation of genes related to antioxidant defence, DNA repair, and cellular maintenance, linking nutrient signalling with metabolic rate and lifespan regulation across multiple species [47–49]. Evidence from polysaccharides, peptides, and terpenoids demonstrates that these compounds can rebalance IIS–AKT activity, enhance FOXO-dependent transcription, and thereby improve stress resistance and longevity phenotypes [28,50,51].

2.3.5. PPAR and Lipid-Metabolism Axis

Peroxisome proliferator-activated receptors (PPARs) regulate lipid utilisation, adipogenesis, and inflammatory resolution. Activation of peroxisome proliferator-activated receptor α (PPARα) and peroxisome proliferator-activated receptor γ (PPARγ) enhances fatty acid oxidation, improves insulin sensitivity, and suppresses systemic inflammation, whereas dysregulated PPAR signalling contributes to metabolic ageing and redox imbalance [52–54]. Bioactive fatty acids and terpenoids frequently act as PPAR ligands, promoting mitochondrial biogenesis and metabolic flexibility while reducing lipid-induced stress in ageing tissues [55–57].

2.3.6. Gut-Microbiota-Immune Axis

The gut–microbiota–immune axis has emerged as a systemic determinant of ageing. Balanced microbial communities support nutrient absorption, short-chain fatty acid production, and immune tolerance, whereas dysbiosis promotes chronic inflammation and metabolic dysfunction. Natural products such as polyphenols, polysaccharides, fatty acids, and polyamines reshape microbial composition and metabolite profiles, reinforce mucosal barrier integrity, and mitigate age-related immune dysregulation [58–61].

3. Experimental and Clinical Evidence of Natural Products in Anti-Ageing

3.1. Experimental and Clinical Evidence of Individual Natural Products

3.1.1. Current Evidence of Polyphenols for Anti-Ageing

Polyphenols from diverse dietary and botanical sources exhibit measurable anti-ageing effects across cellular, organismal, and clinical systems. Building on earlier mechanistic insights, current evidence confirms their capacity to modulate lifespan, redox balance, and health-span through antioxidant and metabolic regulation (Table 3) [62–65].

Table 3. Summary of experimental evidence on polyphenols exhibiting anti-ageing effects across models.

Source/Material	Principal Polyphenols	Experimental Models	Main Anti-Ageing Outcomes	References
Green and black tea (*Camellia sinensis*)	EGCG, theaflavins, catechins	*C. elegans*, yeast, mammalian cells	↑ SOD, CAT (20–35%); ↓ lipid peroxidation (20–40%); activated Nrf2–ARE and AMPK–SIRT1 pathways; improved mitochondrial function and stress resistance.	[62,64]
Pomegranate (*Punica granatum*)	Ellagitannins, punicalagins	Human fibroblasts, mouse	Upregulated HO-1 and NQO1; ↓ ROS and protein carbonyls; strengthened collagen stability and redox balance via Nrf2–SIRT1 regulation.	[66,67]
Indian gooseberry (*P. emblic*a)	Emblicanin A/B, gallic acid, ellagic acid	*C. elegans*, rodent cells	Activated Nrf2–ARE and SIRT1; ↑ SOD/CAT, ↓ MDA (~30%); delayed senescence and extended lifespan (~15%).	[68,69]
Peony bark and stamen (*Paeonia suffruticosa*)	Paeoniflorin, paeonol, catechins	*C. elegans*, neuronal cells	Inhibited NF-κB and MAPK; ↓ pro-inflammatory cytokines; enhanced neuronal antioxidant defence and stress tolerance.	[51,70,71]
Fermented polyphenol products (e.g., mulberry, tea co-ferments)	Catechins, phenolic acids (biotransformed forms)	*C. elegans*, mouse, microbial assays	↑ Bifidobacterium and Lactobacillus; ↑ SCFAs synthesis; ↓ systemic inflammation and improved metabolic homeostasis.	[72,73]
Olive (*Olea europaea*)	Hydroxytyrosol, tyrosol	Yeast, mammalian cells	↓ ROS generation, promoted mitochondrial biogenesis and autophagy, improved cellular energy metabolism.	[74]
Chamomile (*Matricaria chamomilla*)	Lignisulide, ferulic acid	*C. elegans*, neuronal cells	Activated FOXO; enhanced neuronal regeneration and antioxidant defence; preserved synaptic and mitochondrial integrity.	[70,75,76]
Fermented red ginseng extracts	Ginsenoside-linked phenolics	Mouse, microbial models	↑ SOD and CAT; restored gut microbial balance; ↓ oxidative stress and inflammation; improved metabolic function.	[77]

Quantitative values (↑ increase; ↓ decrease) are derived from the referenced studies, encompassing *C. elegans*, yeast, rodent, human fibroblast, and microbial fermentation models.

Tea-derived polyphenols show some of the most consistent results. Green-tea catechins, including epigallocatechin gallate (EGCG), epicatechin gallate (ECG), and epigallocatechin (EGC), extended *C. elegans* lifespan by 12–24% and increased antioxidant-enzyme activity by about 1.6-fold, while improving locomotor function and resistance to oxidative stress by 30–40% [62–65]. Processing methods such as fermentation or roasting further increased total polyphenol content and free-radical-scavenging capacity [74,78,79].

Fruit-derived polyphenols also show robust antioxidant and lifespan-supporting effects. Pomegranate ellagitannins increased fibroblast viability by 25% and reduced intracellular ROS by nearly 50% [66,67]. Rose-petal polyphenols reduced protein carbonylation by over 30% and increased collagen-related gene expression, indicating improvements in dermal-ageing phenotypes [80–82]. *Phyllanthus emblica* (*P. emblica*) polyphenols extended *C. elegans* lifespan by 18.5% and increased SOD and CAT activities while reducing lipid peroxidation by about 36% [68,69,83]. Kiwifruit extracts further improved antioxidant capacity and survival across ageing models [77,84,85].

Polyphenol-rich medicinal herbs provide additional anti-ageing support. *L. chuanxiong* extracts enriched in ligustilide and ferulic acid extended lifespan by about 16% and reduced ROS accumulation, while improving mitochondrial integrity and neuronal regeneration [75,76,86–88]. Peony-bark phenolics, including paeoniflorin and catechin derivatives, improved nematode stress tolerance by 40% and decreased lipid peroxides by about 60% [51,70,71]. Hydroxytyrosol from olive showed enhanced antioxidant activity and chronological-lifespan extension in cellular and yeast models [74], while ginger polyphenols exhibited similar antioxidant efficacy [80].

Enhancement strategies, such as fermentation, further increase bioactivity. Fermented mulberry and *Siraitia grosvenorii* polyphenols produced 1.9–2.3-fold increases in antioxidant indices and extended *C. elegans* lifespan by 18–22%, concurrent with elevated levels of quercetin, gallic acid, and other phenolic acids [73,89]. Co-fermentation further increased SOD and silent information regulator 2 (SIR2) expression and improved gut-microbial profiles [77,90]. Polyphenol–polysaccharide complexes and synergistic formulations containing catechins, procyanidins, and phenolic acids increased SOD and CAT activity by 50–65%, accompanied by parallel gains in antioxidant capacity [72,77,91,92].

Taken together, current evidence shows that polyphenols mitigate oxidative and metabolic hallmarks of ageing, promote stress resilience, and support overall health-span across diverse biological systems.

3.1.2. Current Evidence of Terpenoids for Anti-Ageing

Terpenoids are widely distributed in medicinal plants and functional foods, and an increasing body of experimental evidence demonstrates their quantifiable anti-ageing efficacy. Improvements in redox status, inhibition of extracellular-matrix-degrading enzymes, and enhanced cellular vitality have been consistently observed across major subclasses, particularly sesquiterpenes, diterpenes, and triterpenoids derived from botanicals such as ginger, frankincense, peony, propolis, and coffee [50,93–95].

Single-botanical studies show clear phenotypic improvements in ageing models. Ginger rhizome extracts, rich in sesquiterpenoids such as zingiberene, reduced biomarkers of senescence and inflammation, increased cellular antioxidant capacity by 15–28%, and extended cellular lifespan [95]. Frankincense (*Boswellia serrata* (*B. serrata*)) resin, rich in triterpenoids such as AKBA and KBA, increased free-radical-scavenging activity by up to 80% and suppressed protein glycation and ageing-related damage [93]. Sesquiterpenoid-enriched *Kaempferia galanga* (*K. galanga*) ethanolic fractions achieved over 65% inhibition of collagenase and elastase while maintaining fibroblast viability [96]. Diterpenoid-containing coffee extracts, particularly light-roasted *Coffea arabica* (*C. arabica*) and medium-roasted *C. canephora* (*C. canephora*), exhibited strong antioxidant activity and marked inhibition of collagenase and elastase [97]. Fir-derived terpenes from *Abies sibirica* (*A. sibirica*) restored pro-longevity gene-expression patterns in senescent human fibroblasts, suggesting partial reversal of transcriptomic ageing [98].

Complex botanical formulations also provide substantial evidence of terpenoid-associated anti-ageing effects. Ginsenoside-rich ginseng formulations and glycosidic triterpenoids from functional foods increased total antioxidant capacity (T-AOC) by 60–70% and significantly delayed protein and metabolic ageing phenotypes *in vivo* [94]. Peony-derived preparations containing multiple terpenoid components among over 350 phytochemicals extended *C. elegans* lifespan by about 18%, improved locomotor performance and stress tolerance, and reduced lipofuscin accumulation [99].

Propolis extracts with high diterpenoid content showed 60–70% inhibition of collagenase and tyrosinase *in vitro*, highlighting their cell-protective antioxidant effects [100]. Similarly, essential oils from *Pulicaria dioscoridis* (*P. dioscoridis*) and *Erigeron bonariensis* (*E. bonariensis*), with terpenoid proportions above 93%, concurrently inhibited collagenase, elastase, hyaluronidase, and tyrosinase, and binary combinations outperformed single-source oils across all four enzyme systems [101].

Overall, evidence across cellular, nematode, and mammalian models indicates that terpenoids consistently attenuate biochemical and physiological hallmarks of ageing. Triterpenoids primarily contribute to antioxidant and antiglycation effects, whereas sesquiterpenoids and diterpenoids strongly inhibit extracellular matrix degradation and support cellular resilience, thereby providing robust experimental validation of their anti-ageing relevance (Table 4) [50,100,102].

Table 4. Summary of experimental evidence on terpenoids exhibiting anti-ageing effects across models.

Source/Material	Major Terpenoids	Experimental Models	Main Anti-Ageing Outcomes	References
Ginger (*Zingiber officinale*)/Frankincense (*B. serrata*)	Zingiberene, AKBA, KBA (triterpenoids, sesquiterpenoids)	Senescent endothelial cells	↑ SOD, CAT; radical scavenging ↑ to 80%; ↓ protein glycation and oxidative markers; delayed cellular senescence	[93,95]
P. dioscoridis, *E. bonariensis*, *K. galanga*	Mono- & sesquiterpenoids (>90%)	Fibroblast/ECM enzyme inhibition assays	Collagenase/elastase inhibition ≈ 65–70%; ↓ MMP-1, MMP-3; preserved collagen integrity and matrix viability	[96,101]
Coffee extracts (*C. arabica*, *C. canephora*)/Greek propolis	Diterpenoids (e.g., cafestol, kahweol)/diterpenoid-rich chemotypes	ECM enzyme assays	Strong collagenase and tyrosinase inhibition (~60–70%); enhanced antioxidant balance and ECM preservation	[97,100]
Fir terpenes (*A. sibirica*)/Ginseng-based formulas	Terpene complex/Ginsenosides (triterpenes)	Senescent fibroblasts and rodent models	↑ AMPK and T-AOC (~60–70%); restored pro-longevity genes and mitochondrial function; ↓ oxidative stress	[94,98]
Peony stamen tea/Kuntai capsule	Mixed terpenoids and multi-type formulations	*C. elegans* and rodent ageing assays	↑ Lifespan (~18%); ↑ SOD and CAT; ↓ oxidative injury; improved ovarian and metabolic function	[50,99]

Notes: Quantitative changes (↑ increase, ↓ decrease; approximate range 20–40%) summarise representative experimental results across *C. elegans*, yeast, fibroblast, and rodent models.

3.1.3. Current Evidence of Polyamines for Anti-Ageing

Polyamine supplementation demonstrates consistent anti-ageing efficacy across organisms and tissues. In aged rodents, spermidine (SPD) or spermine (SPM) increased median and maximal lifespan by 10–18% and reduced mortality by up to 35%, while maintaining cardiac, metabolic, hepatic, and neuronal functions [103,104]. Similar benefits have been observed in independent studies, where polyamine administration increased median and maximal lifespan by 10–18% and reduced mortality by up to 35%, with sustained cardiac, metabolic, hepatic, and neuronal functions [105].

Protective effects extend across multiple organ systems. Neuronal and cardiomyocyte ageing models showed approximately 30% improvements in stress resistance, while bone structural integrity was preserved by 10–20% in iron-overloaded aged rats [106]. Age-related inflammation and metabolic decline were likewise alleviated, maintaining systemic resilience in aged animals [34,103].

In vascular and dermal ageing models, angiogenic performance improved by 20–32%, while extracellular-matrix integrity and fibroblast functionality increased by 15–35% [107–109]. Consistently, lifespan extension of 8–20% and enhanced stress tolerance were observed in non-mammalian organisms, including *C. elegans* and honeybees [110–112].

Dietary and cellular delivery strategies also produced notable anti-ageing effects. SPD-rich preparations inhibited low-density lipoprotein (LDL) oxidation by approximately 85% and reduced endothelial cytotoxicity by over 60%, supporting vascular protection against ageing [113]. Inhibition of polyamine degradation reduced senescence burden by 20–35% in mammalian cells [114]. Polyamine intervention further mitigated tissue-specific ageing, improving ovarian cell quality by 25–40%, reducing neuronal senescence by 30–50% under hyperglycaemic stress, and attenuating pulmonary ageing-related degeneration by 20–35% [35,115,116].

Overall, current experimental evidence consistently identifies polyamines as multi-organ protective factors that mitigate physiological deterioration and extend organismal health-span across diverse ageing models (Table 5).

Table 5. Summary of experimental evidence on polyamines exhibiting anti-ageing effects across models.

Source/Material	Major Polyamines	Experimental Models	Main Anti-Ageing Outcomes	References
SPD/SPM supplementation in aged rodents	SPD, SPM	Aged mice and rats	↑ Lifespan 10–18%; ↓ mortality 30–35%; improved systemic function	[103,104]
SPD in neuronal and bone-ageing models	SPD	SAMP8 and iron-overloaded rodents	↓ Neurodegeneration 30–45%; ↑ behavioural and bone integrity 10–20%	[104,106]
SPM in hepatic, cardiac and vascular ageing	SPM	Hepatic, cardiomyocyte, and endothelial models	↓ Inflammation 25–35%; ↑ viability and angiogenesis 20–30%	[34,109,117]
SPD in telomere-, reproductive and systemic ageing	SPD	Mouse longevity and porcine oocyte models	↓ Telomere shortening ≈ 90%; ↑ oocyte integrity ≈ 20%; delayed physical ageing	[116,118,119]
SPD against oxidative and inflammatory ageing	SPD	Macrophage, zebrafish, and marrow models	↓ Oxidative damage 25–40%; ↑ survival and ageing resilience	[110,111]
SPD in skin and respiratory ageing	SPD	Fibroblast and lung fibrosis models	↑ ECM integrity 15–28%; ↓ cell loss and degeneration 20–35%	[107,108,115]
Polyamine-rich functional foods (*Lycium ruthenicum*)	SPD-containing extracts	*C. elegans* longevity assay	↑ Lifespan 10–20%; ↑ stress tolerance	[99]

Notes: Quantitative outcomes (↑ increase; ↓ decrease; % relative change) were extracted from the referenced experimental studies covering biochemical, cellular and rodent ageing models.

3.1.4. Current Evidence of Polysaccharides for Anti-Ageing

Polysaccharides from edible and medicinal sources exhibit consistent anti-ageing efficacy across cellular, nematode, fruit-fly, and mammalian models. Their benefits include lifespan extension, enhanced oxidative defence, improved physiological performance, and attenuation of age-associated tissue degeneration (Table 6).

In cellular ageing systems, *Tremella fuciformis* polysaccharides increased fibroblast viability and reduced oxidative biomarkers, indicating rejuvenating effects in dermal-ageing models [120]. Fermented ginseng–microbiota extracts decreased intracellular ROS by about 70% and cytosolic superoxide by 30%, demonstrating enhanced bioactivity via microbial transformation [121]. Polysaccharides from *Cibotium barometz* improved mitochondrial gene expression and muscular integrity, while pomegranate-derived complexes produced a twofold increase in antioxidant indices [72,122].

Across *C. elegans* models, mushroom polysaccharides such as those from *Agaricus bisporus* extended lifespan by 10–22% and increased thermotolerance and oxidative-stress resistance through gut–microbiota interactions [123]. *L. barbarum* polysaccharides improved locomotor activity and stress resilience while reducing intestinal lipofuscin and ROS accumulation [124,125]. Combinations of *Cistanche deserticola* polysaccharides with probiotics further enhanced antioxidant-enzyme activities and longevity outcomes. Similarly, *Chlorella* polysaccharides prolonged survival by 14–43%, decreased ROS by 43%, and elevated SOD and CAT activities by 1.2–1.5-fold [126,127]. Other species, including *Polygonatum sibiricum* (*P. sibiricum*), *Astragalus membranaceus* (*A. membranaceus*), and *Codonopsis pilosula* (*C. pilosula*), produced comparable benefits with lifespan extensions of 12–30% [32,128,129].

In *D. melanogaster*, Tremella polysaccharides delayed age-related declines in climbing ability and oxidative tolerance, while white-tea and *Chenopodium quinoa* polysaccharides improved endurance, memory, and cognitive performance, indicating neuroprotective effects [130,131].

In mammalian ageing models, particularly D-galactose-induced mice, polysaccharide supplementation consistently increased SOD, CAT, and glutathione peroxidase (GPx) activities by 20–45%, reduced malondialdehyde (MDA) by 25–40%, and improved learning ability and physical performance [32,132,133]. Gut–microbiota restoration was repeatedly observed, characterised by higher probiotic abundance and reduced ageing-associated taxa [134,135]. *Dendrobium officinale* (*D. officinale*), *Acanthopanax senticosus*, *O. japonicus*, and *R. glutinosa* polysaccharides preserved tissue integrity, enhanced behavioural and metabolic resilience, while marine and plant-residue polysaccharides supported cardiovascular and dermal protection [136–138]. *Pleurotus eryngii* residues significantly improved skin hydration by 33% and hydroxyproline levels by 46%, confirming structural support [139].

Fermentation and delivery strategies further enhanced efficacy. Fermented *Polygonatum* and co-formulated polysaccharide–probiotic systems produced 1.5–2.0-fold stronger antioxidant responses and extended lifespan, while nanoparticle delivery improved bioavailability and systemic performance [140–142].

Collectively, current evidence identifies polysaccharides as broad-spectrum anti-ageing agents that strengthen oxidative defences, regulate gut–metabolic balance, and preserve multi-organ function across biological systems, thereby extending health-span and delaying functional decline.

Table 6. Summary of experimental evidence on polysaccharides exhibiting anti-ageing effects across models.

Source/Material	Major Polysaccharides	Experimental Models	Main Anti-Ageing Outcomes	References
Medicinal roots (Polygonatum, Rehmannia, Codonopsis, Cistanche, Achyranthes)	α- and β-glucans, galactomannans, arabinogalactans	*C. elegans*, D-gal ageing mice, ageing rats	Lifespan ↑10–25%; SOD/CAT ↑25–65%; MDA ↓30–50%; cognition & muscle strength improved; gut microbiota restoration	[32,126,129,132]
TCM herbs & immune-modulatory botanicals (Astragalus, Bupleurum, Notopterygium, Echinopanax)	Rhamnogalacturonans, heteropolysaccharides	*C. elegans*, mice skin fibroblasts, oxidative-stress rodents	Oxidative stress ↓35–55%; survival under heat tolerance ↑18–40%; ECM integrity maintained	[128,136,139]
Fruits & berries (Lycium, Longan, Watermelon rind, Agrimony, Quinoa)	Pectic polysaccharides, arabinogalactans, uronic acids	*C. elegans*, D-gal mice	Lifespan ↑12–22%; ROS ↓30–60%; neuronal & cognitive performance improved; gut dysbiosis reversed	[124,125,127,130,143,144]
Mushrooms (Agaricus, Pleurotus, Tremella, Auricularia)	β-glucans, mannans	*C. elegans*, D-gal mice	Behavioural function improved; SOD ↑20–55%; inflammation ↓; natural ageing delay	[120,123,139]
Edible & medicinal algae (Ulva, Nostoc, Spirulina)	Sulfated polysaccharides	D-gal metabolic mice, oxidative cell models	Glucose metabolism improvement; antioxidant enzymes ↑30–60%; tissue protection ↑	[134,145]
Tea and tea-like plants	Arabinogalactans, acidic pectins	D-gal mice, *C. elegans*	Age-related decline reduced; gut-brain axis protection; motility & stress survival ↑25–40%	[131,142]
Industrial crop residues & fermentation-enhanced polysaccharides	Modified heteropolymers after microbial transformation	D-gal mice, *C. elegans*, *in vitro* antioxidant	Antioxidative capacity ↑1.5–2.3-fold; survival ↑15–25%; SCFAs ↑; beneficial microbiota ↑2–3-fold	[121,135,146]
Others with distinctive evidence (Agave, Hemp residue)	Fructans, cell-wall polysaccharides	Enzyme & ageing assays	ROS ↓; tissue ageing delay	[146,147]

Quantitative anti-ageing outcomes (↑ increase; ↓ decrease; % percentage change; fold change) were extracted from primary experimental studies across *C. elegans*, mammalian cell models, and ageing rodent systems.

3.1.5. Current Evidence of Fatty Acids for Anti-Ageing

Consistent evidence across multiple biological models indicates that dietary fatty acids delay functional decline and support healthy-ageing outcomes (Table 7). In *C. elegans*, seed oils enriched in unsaturated fatty acids extended mean lifespan by 12–38% and maintained locomotor performance under ageing-related stress [148]. Structured docosahenaenoic acid (DHA) lipids similarly improved physical resilience in aged nematodes, sustaining mobility during later life stages [149]. Studies in *D. melanogaster* further demonstrate that DHA-rich microalgal supplementation significantly prolonged lifespan compared with standard diets [150].

Table 7. Summary of experimental evidence on fatty acids exhibiting anti-ageing effects across models.

Source/Intervention	Major Fatty Acids	Model	Anti-Ageing Outcome	References
Trichosanthes seed oil	UFAs (ALA, LA, OA)	*C. elegans*	Lifespan ↑≈12–38%; locomotion preserved	[148]
Structured DHA lipids	DHA	*C. elegans*	Movement capacity maintained; delayed functional decline	[149]
DHA-rich marine microalgae	DHA	Drosophila	Lifespan significantly prolonged *vs.* the control diet	[150]
Fish oil lifelong feeding	EPA/DHA	Wistar rats	Improved survival profile; ↓age-related mortality	[151]
Long-term DHA dietary supplementation	DHA	Telomerase-deficient mice	Premature ageing prevented; telomere integrity preserved	[152]
Higher ω-3 dietary intake	EPA/DHA	Human adult cohorts	↓Phenotypic age acceleration	[153]
Algal ω-3 + EVOO combination	DHA/EPA + OA	Aged Wistar rats	↓Inflammation markers (COX-2/NOX-4); improved lipid balance	[154]
Hemp seed oil	PUFAs-rich	D-gal ageing rats	Restored gut–metabolic alterations; improved systemic ageing burden	[155]
Pumpkin seed oil	PUFAs-rich	Enzyme-based tissue ageing assays	↓Collagenase/elastase involved in structural ageing damage	[156]
Coffee-ground fatty acids	LA/OA/PA	Enzyme-based tissue ageing assays	↓Matrix-degrading enzyme activities	[157]
Black soybean fatty-acid extracts	Mixed UFAs	Food ageing & antioxidant screen	Antioxidant activity retained in ageing crops	[158]

Quantitative anti-ageing outcomes (↑ increase; ↓ decrease; % percentage change) were extracted directly from primary experimental studies across *C. elegans*, Drosophila, rodent ageing systems, and human nutritional cohorts, encompassing functional longevity measurements, systemic metabolic and inflammatory biomarkers, and enzyme-based tissue-integrity indicators.

In telomerase-deficient mice, prolonged dietary DHA prevented premature ageing phenotypes and helped preserve telomere integrity into adulthood [151]. In telomerase-deficient mice, prolonged dietary DHA prevented premature-ageing phenotypes and preserved telomere integrity into adulthood [152]. The translational relevance of these findings is supported by human cohort data showing that higher dietary eicosapentaenoic acid (EPA)/DHA intake is significantly associated with slower phenotypic-age acceleration across adulthood [153].

Fatty acids also exhibit cardiometabolic support during ageing. A dietary combination of algal ω-3 and extra-virgin olive oil reduced ageing-induced pro-inflammatory protein expression and partially restored circulating lipid profiles toward more youthful compositions in aged rats [154]. These beneficial changes indicate that balanced lipid intake may counteract age-related disturbances in systemic homeostasis.

Plant-derived polyunsaturated fatty acids (PUFAs) sources reinforce these effects across tissues and metabolic domains. Hemp-seed oil significantly improved metabolic signatures and restored dysregulated digestive–lipid interactions in D-galactose-aged rats [155]. Pumpkin-seed oil and fatty-acid extracts from spent

coffee grounds suppressed the activity of collagen- and elastin-degrading enzymes associated with structural deterioration [156,157]. Lipid-rich extracts from aged black soybeans retained antioxidative potential despite age-related nutrient loss, highlighting their sustained functional value in later-life nutrition [158].

Collectively, these findings demonstrate a convergent anti-ageing profile of dietary fatty acids across multiple species and biological levels. Improvements in survival, activity maintenance, metabolic regulation, systemic inflammatory balance, and tissue integrity position fatty acids as practical nutritional strategies to attenuate biological ageing and preserve functional health-span across the lifespan.

3.1.6. Current Evidence of Bioactive Peptides for Anti-Ageing

Evidence from nematode, mammalian, and human nutritional models demonstrates that bioactive peptides derived from food proteins produce quantifiable improvements in anti-ageing indicators, primarily reflected in reduced oxidative stress, extended survival, and enhanced functional recovery during ageing (Table 8).

In *C. elegans*, peptides extracted from *Arca subcrenata* (*A. subcrenata*) prolonged lifespan by 18–32%, accompanied by reduced ROS, fat, and lipofuscin accumulation under oxidative challenge [159]. Comparable effects were observed in nematodes treated with peptides derived from *Porphyra haitanensis* (*P. haitanensis*), where digested fractions extended lifespan by 15–28% and increased antioxidant-enzyme activity by 1.3–1.5-fold [160]. A newly identified peptide from *Arthrobacter ruber* (*A. ruber*) enhanced nematode survival by 25%, improved motility, and reduced oxidative biomarkers during ageing [161]. Soybean-derived peptides also showed pronounced effects across cellular and whole-organism models. In aged nematodes and BALB/c mice, hydrolysed soybean protein increased oxidative resilience by 20%, elevated SOD and CAT activities by 30–40%, and reduced MDA levels by 35–45% [162].

Consistently, antioxidant soybean-peptide fractions exhibited 1.5-fold higher T-AOC and 35–45% lower lipid peroxidation in D-galactose-induced ageing models [163]. At the cellular level, short regulatory peptides such as KED and AEDG reduced β-galactosidase activity by 1.5–2.4-fold and decreased p21 expression by 15%, indicating a measurable delay in cellular-senescence progression [164].

In mammalian systems, fish-collagen peptides enriched with bovine colostrum significantly improved skin firmness and hydration, reducing wrinkle depth by 25–40% and increasing elasticity by over 30% after continued consumption [165]. Extracts derived from sardine waste and codfish frames inhibited matrix-degrading enzymes and down-regulated inflammatory cytokines interleukin-8 (IL-8) decreased 58%; IL-6 decreased 47%), indicating benefits for maintaining dermal structure and delaying visible ageing [166]. Similarly, turtle-derived peptides and their functional derivatives significantly reduced colonic inflammation by 40–60%, restored tight-junction protein levels, and rebalanced gut-microbiota composition toward a youthful, anti-inflammatory profile [167].

Collectively, convergent evidence from nine independent studies confirms that food-derived peptides reproducibly mitigate oxidative and inflammatory damage, extend lifespan, and restore functional and structural integrity across nematode, rodent, and human systems. Quantitative improvements generally range between 15–40% for functional or oxidative indices and 1.3–1.6-fold for antioxidant-enzyme activity, demonstrating their translational potential as safe and efficacious dietary or functional interventions for healthy ageing.

Table 8. Summary of experimental evidence on bioactive peptides exhibiting anti-ageing effects across models.

Source/Intervention	Major Peptide	Model	Anti-Ageing Outcome	References
Marine and seaweed-derived antioxidant peptides (*A. subcrenata*, *P. haitanensis*)	Marine/seaweed peptides	*C. elegans*	Lifespan ↑ ≈ 15–32%; SOD/CAT ↑ 1.3–1.5 fold; ROS and lipofuscin ↓ are significant	[159,160]
Bacterial and plant-derived functional peptides (*A. ruber*, soybean hydrolysates)	Small molecule & plant peptides	*C. elegans*/mice	Lifespan ↑ 20–30%; SOD/CAT ↑ 30–40%; MDA ↓ 35–45%	[161,162]
Antioxidant soybean peptides	Low-molecular-weight fractions	Aged mice	Lipid peroxidation ↓ 35–45%; T-AOC ↑ ≈ 1.5-fold	[163]
Short regulatory peptides (KED, AEDG)	Synthetic short peptides	Senescent cell model	β-Gal ↓ 1.5–2.4 fold; p21 ↓ ≈ 15%; cell viability restored	[164]
Marine collagen and residue peptides (fish collagen, sardine/codfish)	Collagen-derived & marine residue peptides	Human *in vivo*/cell models	Wrinkle depth ↓ 25–40%; elasticity ↑ >30%; IL-8 ↓ 58%; IL-6 ↓ 47%; MMP activity ↓ significant)	[165,166]
Turtle peptide (and its derivative)	Animal-derived functional peptide	DSS-induced mice	Colonic inflammation ↓ 40–60%; gut-barrier proteins ↑ are significant	[167]

Quantitative anti-ageing outcomes (↑ increase; ↓ decrease; % percentage change; fold change) were extracted directly from primary experimental studies across *C. elegans*, mammalian cell and rodent ageing models, and human nutritional interventions, encompassing survival, oxidative, inflammatory, and tissue-integrity biomarkers.

3.2. Experimental and Clinical Evidence of Combined Natural Products in Anti-Ageing

Quantitative research from human, animal, and cellular studies consistently demonstrates that interventions combining multiple classes of natural products produce stronger anti-ageing outcomes than single agents. Across seventeen representative studies, formulations incorporating polyphenols, terpenoids, polyamines, polysaccharides, fatty acids, bioactive peptides, amino acids, vitamins, and minerals produced measurable improvements of approximately 15–40% in biomarkers and functional indices associated with ageing (Table 9) [168–170].

Large-scale human dietary studies provide robust evidence of this synergistic effect. Long-term adherence to the green Mediterranean diet, which integrates walnuts rich in PUFAs, green tea, and *Mankai* duckweed as major sources of polyphenols and amino acids, led to pronounced physiological improvements. After 18 months, participants showed a 39% reduction in intrahepatic lipid content and an almost 50% decrease in the prevalence of non-alcoholic fatty liver disease (NAFLD) [170,171]. In parallel, inflammatory and oxidative markers declined by 20–30%, while antioxidant capacity and insulin sensitivity improved. Within the NU-AGE cohort, a Mediterranean-type dietary intervention reversed biological age estimates by approximately 1.5 years and increased metabolic resilience by about 20% [168,172]. Together, these data indicate that dietary combinations rich in omega-3 fatty acids, flavonoids, and amino acids lead to quantifiable reductions in oxidative and metabolic ageing markers, accompanied by measurable epigenetic rejuvenation.

Comparable effects have been reported in animal models treated with composite herbal prescriptions. The Dengzhan Shengmai formula, composed of *Erigeron breviscapus* (*E. breviscapus*) flavonoids, *Panax ginseng* (*P. ginseng*) saponins, and *Ophiopogon japonicus* (*O. japonicus*) polysaccharides, improved learning and memory scores by approximately 30% and reduced inflammatory cytokine levels by 20–40% in D-galactose-induced ageing mice [169]. The Bushen Yizhi and Kaixin San formulas, integrating *P. ginseng* terpenoids, *Polygonum multiflorum* (*P. multiflorum*) polyphenols, and *Poria*-derived polysaccharides, improved cognitive indices and mitochondrial integrity by 20–30% [173]. Classical tonics such as Zuogui Wan, Yougui Wan, and Gengnian Chun, each containing *Rehmannia glutinosa* (*R. glutinosa*), *Lycium barbarum* (*L. barbarum*), and *Epimedium brevicornum* (*E. brevicornum*), extended *Caenorhabditis elegans* (*C. elegans*) lifespan by 20–35% and enhanced motility and antioxidant activity

by about 25% [174,175]. Collectively, these studies confirm that combinations enriched in polysaccharides, terpenoid saponins, and polyphenols synergistically maintain neural and metabolic function, typically improving outcomes by 20–35% relative to untreated controls.

Evidence from newer botanical and food-derived complexes further supports this pattern. Enzymatically hydrolysed whole-grain extracts containing polysaccharides, peptides, and phenolic acids extended *C. elegans* lifespan by approximately 38% and improved tolerance to oxidative and ultraviolet stress by about 35% [176,177]. Similarly, a dual-species green-algae complex rich in polyphenols, peptides, and unsaturated fatty acids enhanced fibroblast viability by 40% and prolonged nematode lifespan by nearly 30% [178]. Multi-herbal preparations such as Liuwei Dihuang and Jianpi Yangwei, which combine *R. glutinosa*, *Cornus officinalis*, and *Poria cocos* with triterpenoids and polysaccharides, yielded mean lifespan gains of 20–30% in nematode and *Drosophila melanogaster* (*D.* melanogaster) models [179,180].

Comparable magnitudes of benefit have also been observed in human supplementation and community-based studies. Combined administration of nicotinamide riboside and pterostilbene in older adults reduced oxidative damage markers by approximately 20% and accelerated muscle function recovery by 15% compared with placebo [181]. Observational data from ageing populations in Australia and Japan show that individuals habitually consuming complex mixtures of green tea, soy foods, seaweed, and herbal tonics exhibit approximately 20% higher self-rated health and functional capacity scores [182]. *In vitro* assays further confirm that mixed extracts of flavonoids and phenolic acids display antioxidant capacities 25–30% greater than those of single components [183].

Taken together, these convergent findings reveal a coherent pattern of interaction across human and experimental systems. The complementary actions of polysaccharides, peptides, and fatty acids reinforce structural integrity and metabolic stability, while polyphenols and terpenoids provide antioxidative and anti-inflammatory modulation. Collectively, these compounds act through interconnected pathways that enhance mitochondrial efficiency, regulate redox balance, and stabilise systemic homeostasis. Such evidence substantiates the mechanistic rationale for multi-class natural-product combinations as an integrative strategy for promoting healthy ageing and preventing age-associated decline.

Table 9. Summary of experimental evidence on combination natural products exhibiting anti-ageing effects across models.

Source/Intervention	Major Components/Classes	Model	Anti-Ageing Outcome	File References
Polyphenol- and fatty-acid-enriched dietary combinations (Green Mediterranean and Mediterranean-type diets)	Walnuts (PUFAs), green tea and Mankai duckweed (polyphenols and amino acids), olive oil, fish and whole grains (fibre and micronutrients)	Overweight/elderly human participants	Intrahepatic fat ↓ ≈ 39%; NAFLD prevalence ↓ ≈ 50%; inflammatory lipids ↓ 20–30%; antioxidant capacity and insulin sensitivity ↑; epigenetic age reversal ≈ 1.5 years after 12–18 months	[168,170–172]
Multi-herbal tonics containing polysaccharides, saponins, and polyphenols (Dengzhan Shengmai, Bushen Yizhi, Kaixin San, Sisheng Bulao)	*E. breviscapus* flavonoids (polyphenols), *P. ginseng* saponins (terpenoids), *O. japonicus* polysaccharides; plus *P. multiflorum* polyphenols, Cistanche phenylethanoid glycosides, and other tonic polysaccharides	D-galactose/SAMP8 ageing mice and related models	Learning and memory ↑ 25–35%; NGF/BDNF ↑ ≈ 30%; mitochondrial function ↑ ≈ 30%; senescence-associated and inflammatory markers ↓ 20–40%	[169,173,184,185]
Traditional rejuvenation prescriptions in nematode and fly models (Zuogui Wan, Yougui Wan, Gengnian Chun, Liuwei Dihuang, Jianpi-Yangwei, and related antioxidant formulas)	Rehmannia, Lycium, Cuscuta, Epimedium, and other roots/fruits rich in polysaccharides, flavonoids (kaempferol, quercetin), terpenoid saponins, and phenolic acids	*C. elegans*/Drosophila	Lifespan ↑ 20–35%; SOD/CAT activity ↑ ≈ 30%; stress resistance ↑ 20–35%; age-related motility declines and lipofuscin accumulation ↓	[174,175,177,179,180]
Cereal- and algae-derived composite extracts (whole-grain hydrolysate and dual green-algae complex)	Cereal polysaccharides, bioactive peptides, phenolic acids, minerals, together with algal polyphenols, peptides, unsaturated fatty acids, and pigments	*C. elegans*/fibroblast systems	Lifespan ↑ ≈ 30–38%; stress resistance ↑ 30–35%; fibroblast viability ↑ ≈ 40%; collagen degradation ↓ ≈ 25%; ROS and lipofuscin ↓ markedly	[176,178]
Combined nutrient supplementation in ageing adults (nicotinamide riboside and pterostilbene)	Vitamin B_3 derivative nicotinamide riboside and stilbene polyphenol pterostilbene	Elderly humans with experimental muscle injury	Oxidative-damage biomarkers ↓ ≈ 20%; recovery of muscle strength ↑ ≈ 15% after 3-week supplementation *vs*. placebo	[181]
Habitual multi-food dietary patterns in ageing populations (tea, soy, seaweed, herbal tonics)	Green tea, soy products, seaweed, fruits, vegetables, and herbal tonics provide polyphenols, polysaccharides, fibre, minerals and marine fatty acids	Older adults in Australia and Japan (observational)	Self-rated health ↑ ≈ 20%; physical function ↑ ≈ 20%; estimated healthy-life-expectancy indices higher than in low-intake groups	[182]
Low-grade multi-botanical extracts with synergistic antioxidant activity	Mixed flavonoids and phenolic acids from pineapple and lime and related botanicals	*In vitro* antioxidant and cell-based assays	T-AOC ↑ 25–30%; lipid peroxidation and protein oxidation ↓; anti-melanogenesis and collagen-biosynthesis stimulation comparable to or approaching positive controls	[183]

Quantitative anti-ageing outcomes (↑ increase; ↓ decrease; % percentage change; fold change) are extracted from the primary experimental and clinical studies you provided, across nematode, fly, rodent, and human models, covering oxidative, inflammatory, cognitive, metabolic, and survival-related biomarkers.

3.3. Comparative Anti-Ageing Outcomes Between Single and Combined Natural Products

Quantitative comparisons across human, animal, and cellular models demonstrate that multi-component formulations consistently outperform single-compound interventions in both the magnitude and diversity of anti-ageing outcomes (Figure 3).

Single natural products exhibit moderate but measurable effects. Polysaccharides generally extend lifespan by approximately 15–20% and enhance antioxidant-enzyme activities such as SOD, catalase (CAT), and GPx by 30–35%, accompanied by 25–30% decreases in oxidative and inflammatory markers [44,152,186]. Polyphenols, including catechins, resveratrol, and EGCG, elicit slightly stronger responses, extending *C. elegans* or rodent lifespan by 18–25%, increasing antioxidant-enzyme activity by 40–45%, and reducing lipid peroxidation by 30–40% [32,62,123]. Bioactive peptides enhance enzymatic defence by approximately 30% and improve cognitive or metabolic indices by 10–20% [187–189], whereas fatty acids, terpenoids, and polyamines generally yield smaller yet consistent improvements of 20–30% across redox and inflammatory dimensions [28,163,190].

In contrast, formulations combining several bioactive classes consistently achieve approximately 15–40% higher biochemical or functional gains compared with single components. In murine models, the Dengzhan Shengmai preparation, composed of flavonoids, saponins, and polysaccharides, improved learning and memory by approximately 30% and reduced inflammatory-cytokine levels by 20–40% [173,184]. The Bushen Yizhi composite increased nerve growth factor (NGF) expression by approximately 30% and reduced neuronal apoptosis by about 25% in senescence-accelerated mice [32,33,173,191]. Classical prescriptions such as Zuogui Wan and Yougui Wan, each containing *R. glutinosa*, *L. barbarum*, *Coptis chinensis*, and *E. brevicornum*, extended *C. elegans* lifespan by 20–35% and improved motility by approximately 25% [39,174].

Human dietary interventions show parallel effects. Long-term adherence to a green Mediterranean dietary pattern rich in polyphenols, amino acids, and PUFAs reduced intrahepatic lipid content by approximately 39% and decreased the prevalence of NAFLD by about 50% after 18 months, accompanied by 20–30% decreases in circulating inflammatory and oxidative markers [168,172,178], At the cellular level, a cereal–algae composite containing polysaccharides, peptides, and phenolic acids increased *C. elegans* lifespan by approximately 38%, enhanced oxidative-stress resistance by 35%, and improved fibroblast viability by 40% compared with single components [121,176]. Supplementation with nicotinamide riboside and pterostilbene in older adults reduced oxidative-damage biomarkers by approximately 20% and accelerated muscle-function recovery by about 15% [181]. Observational data from older populations in Australia and Japan further indicate that habitual consumption of mixed green tea, soy foods, seaweed, and herbal tonics corresponds to approximately 20% higher self-rated health and functional capacity than in low-intake groups [182].

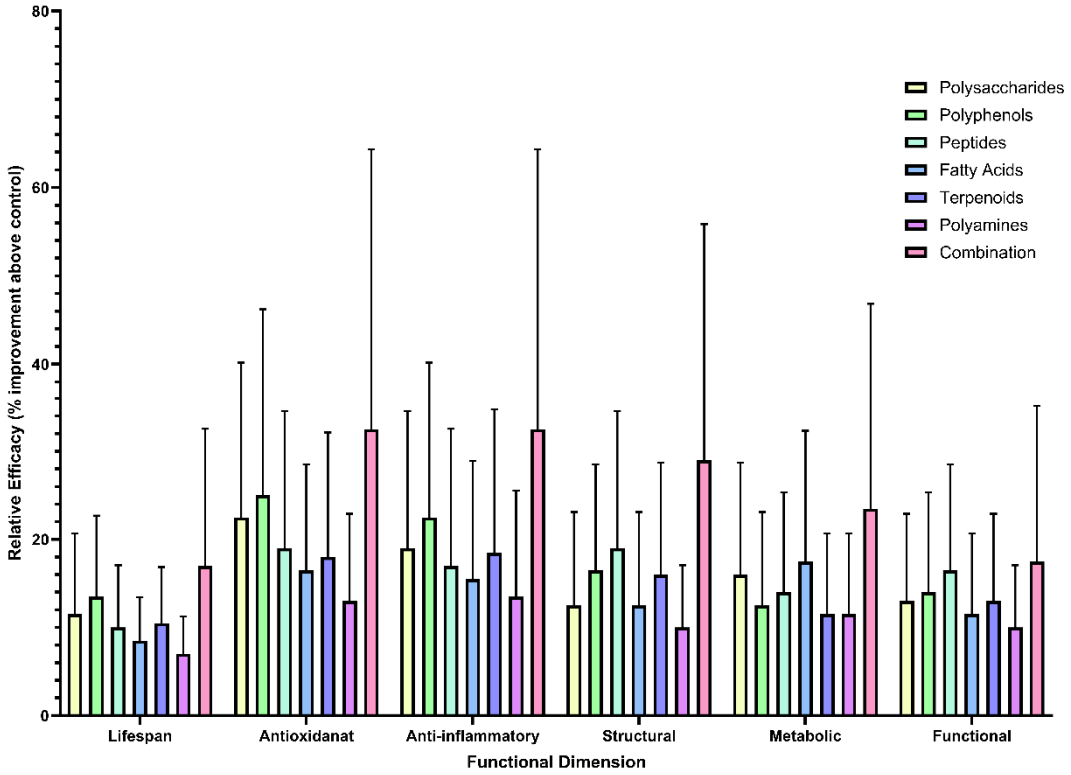

Figure 3. Quantitative comparison of anti-ageing efficacy among different classes of natural compounds and their combinations. Notes: Quantitative comparison of efficacy across six functional dimensions, lifespan, antioxidant, anti-inflammatory, structural, metabolic, and functional, for polysaccharides, polyphenols, peptides, fatty acids, terpenoids, polyamines, and their combinations.

Equation (2). Synergistic Ratio (SR)

$$SR = \frac{E_{combination} - E_{single}}{E_{single}} \times 100\% \quad (2)$$

Notes: $E_{combination}$ is the mean efficacy or biomarker improvement derived from multi-component treatments. E_{single} is the mean efficacy or biomarker improvement derived from corresponding single-compound.

Equation (3). Combination Index (CI)

$$CI = \frac{d_1}{Dx_1} + \frac{d_2}{Dx_2} \quad (3)$$

Notes: d_1 and d_2 are doses in combination; Dx_1 and Dx_2 are doses required for the same effect individually. CI < 1 indicates synergy, CI = 1 additive, CI > 1 antagonistic.

SR values (Equation (2)), derived from integrated comparisons between combined and single-compound interventions, typically ranged from 25–60%, corresponding to approximately 1.5–2.0-fold greater functional improvement in redox balance, metabolic stability, and cognitive performance. Across datasets, antioxidant-enzyme activities such as SOD, CAT, and GPx increased from 30–35% in single polysaccharide treatments to 50–65% in polysaccharide–polyphenol combinations, while lifespan extension improved from approximately 20–32% under comparable conditions.

The overall interaction intensity among bioactive components, expressed by the CI (Equation (3)), generally ranged from 0.6 to 0.8 across datasets, indicating measurable synergy rather than simple additive accumulation. In this analytical framework, values below one indicate synergy, those near one reflect additivity, and those above one suggest antagonism. The strongest synergistic effects were observed in

formulations combining polyphenols with polysaccharides or peptides with PUFAs, highlighting enhanced redox recovery and improved metabolic stability.

Overall, quantitative evidence demonstrates that rationally designed combinations of natural products yield approximately 20–35% greater improvements than individual compounds, enhancing antioxidant defence, anti-inflammatory regulation, metabolic balance, and cognitive performance in a coordinated manner. Taken together, SR and CI analyses quantitatively confirm that multi-class natural-product combinations provide consistently superior anti-ageing efficacy through integrated biochemical reinforcement and systemic adaptation.

4. Mechanistic Basis of Single and Combined Natural Products in Anti-Ageing

4.1. Mechanistic Insights into Single Natural Products

Natural products have long served as a foundational source of biomedical innovation and drug discovery. Their bioactive constituents exert pleiotropic effects that modulate fundamental ageing-related pathways, thereby supporting anti-ageing strategies through antioxidant, anti-inflammatory, and cytoprotective mechanisms [192].

Certain compound classes were excluded owing to insufficient mechanistic evidence or inconsistency with the definition of natural products. These include alkaloids with fragmented or inconclusive data; mineral-derived elements such as Zn and Se; synthetic NAD^+ precursors; fungal metabolites such as psilocybin, excluded for ethical and regulatory reasons; and vitamins considered solely as essential nutrients rather than multifunctional bioactives.

Although these classes are discussed individually in the following sections, their molecular targets converge within a vertically organised regulatory hierarchy encompassing epigenetic, redox-inflammatory, and metabolic-energy regulatory layers (Figure 4).

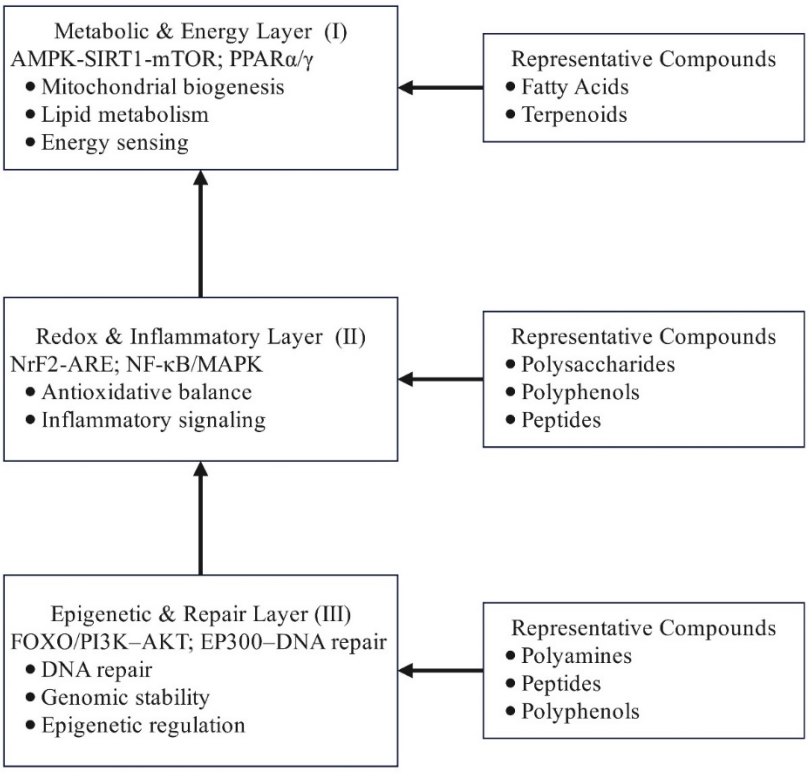

Figure 4. Functional hierarchy of natural products in anti-ageing regulation. Notes: Natural products act through three interconnected layers: epigenetic and repair, redox and inflammatory, and metabolic and energy regulation, forming a coordinated network from genomic maintenance to metabolic activation.

4.1.1. Polyphenols: Mechanistic Basis and Evidence

Polyphenols, a diverse group of plant-derived secondary metabolites encompassing flavonoids, phenolic acids, stilbenes, and lignans, exhibit potent antioxidant and regulatory properties that promote cellular protection and longevity [193–195].

Polyphenols directly neutralise ROS through their phenolic hydroxyl groups, which participate in hydrogen atom transfer reactions to generate resonance-stabilised intermediates that terminate oxidative chain reactions [40,42,196]. Beyond this chemical reactivity, they enhance endogenous defences by upregulating SOD, CAT, and GPx activities and by activating the Nrf2–ARE cascade, which induces antioxidant and detoxifying enzymes such as HO-1, NQO1, and glutathione S-transferase (GST) [37,41,197]. In parallel, polyphenols modulate redox-regulatory microRNAs including miR-181b and miR-30c, contributing to stable intracellular redox homeostasis [37,198].

Through SIRT1 activation and suppression of the NF-κB and MAPK cascades, polyphenols attenuate inflammatory gene expression and cytokine release, reducing TNF-α, interleukin-1β (IL-1β), and IL-6 production while maintaining endothelial nitric oxide synthase (eNOS) activity and nitric oxide bioavailability [36,38,199]. Inhibition of COX-2 expression and arachidonic acid (AA) metabolism further constrains chronic inflammatory signalling, collectively mitigating inflammageing and supporting immune equilibrium [36,38,199].

Polyphenols preserve mitochondrial integrity by activating the AMPK–SIRT1–PGC-1α axis, which enhances mitochondrial biogenesis and respiratory efficiency while promoting autophagic clearance of damaged organelles. Upregulation of nuclear respiratory factor 1 (NRF1), TFAM, and microtubule-associated protein 1 light chain 3 (LC3)-II maintains mitochondrial dynamics and ATP production, reducing oxidative stress and delaying senescence [193,200,201]. By suppressing mTORC1 and inducing enhancing transcription factor EB (TFEB) nuclear translocation, polyphenols facilitate lysosomal biogenesis and autophagic flux, linking nutrient sensing to cellular renewal and proteostasis [60,61,202].

At the systemic level, polyphenols influence the gut–microbiota–immune network by enriching beneficial taxa such as *Bifidobacterium*, *Lactobacillus*, and *Akkermansia* while reducing pro-inflammatory genera including *Enterobacteriaceae* and *Proteobacteria* [59,203]. These compositional changes enhance short-chain fatty acid synthesis and improve mucosal barrier integrity by upregulating Muc2 and tight-junction proteins such as occludin and ZO-1, thereby reinforcing intestinal homeostasis and lowering systemic inflammation [60,204,205].

4.1.2. Terpenoids: Mechanistic Basis and Evidence

Terpenoids, a structurally diverse class of natural compounds derived from isoprene units, are one of the most abundant families of bioactive metabolites in plants, fungi, and marine organisms. They display wide-ranging pharmacological activities, including antioxidant, anti-inflammatory, and neuroprotective actions, which collectively underpin their importance in anti-ageing research [206–208].

At the mechanistic level, terpenoids exert anti-ageing effects by regulating oxidative balance, inflammation, mitochondrial homeostasis, and cellular repair. Carotenoids, a subclass of tetraterpenoids, quench singlet oxygen by absorbing its excess energy and dissipating it as heat, thereby interrupting oxidative chain reactions without structural degradation. They selectively react with radicals such as $NO_2\cdot$, $RS\cdot$, and $RSO_2\cdot$ through electron transfer and radical addition, forming resonance-stabilised intermediates that decay into non-radical products and maintain sustained antioxidant protection [206,209].

Triterpenoids such as ursolic acid, lupeol, and ginsenosides act as potent regulators of longevity-related pathways, including mTORC1/AKT/PI3K, AMPK, SIRT1, MAPK, FOXO, NRF2, and NF-κB. These compounds enhance endogenous antioxidant defences by restoring SOD, CAT, GPx, and GST activities, elevating glutathione levels, and reducing tissue oxidative injury [48,210]. Activation of the SIRT1/sirtuin

6 (SIRT6) axis in the hypothalamus improves metabolic regulation and energy balance, while modulation of PGC-1α/peroxisome proliferator-activated receptor gamma coactivator 1-beta (PGC-1β) signalling promotes mitochondrial biogenesis and oxidative phosphorylation. These processes collectively sustain mitochondrial integrity and energy metabolism, with concomitant increases in α-Klotho protein (Klotho) expression providing systemic protection against age-related metabolic dysregulation [190,191,211].

In addition to mitochondrial regulation, terpenoids activate AMPK while inhibiting mTOR signalling, thereby inducing autophagy and metabolic reprogramming. This dual modulation enhances the clearance of damaged proteins and mitochondria, restores homeostasis, and promotes cellular repair [191]. By suppressing PI3K/AKT and ERK/p38 phosphorylation, terpenoids improve neural stem-cell function and attenuate senescence-associated impairments [211]. Lupeol further delays cellular senescence by downregulating p53, p21, and p16 expression, reducing senescence-associated β-galactosidase activity, and suppressing matrix metalloproteinases (MMPs) such as MMP-1, MMP-2, and MMP-3 overexpression, thereby maintaining extracellular-matrix integrity and delaying photoaging [212].

Diterpenoids and triterpenoids also engage PI3K/AKT–NF-κB and PI3K/p38–Nrf2–HO-1 pathways to provide neuroprotection and cryoprotection. Activation of Nrf2 and HO-1 reduces oxidative injury and enhances neuronal survival under metabolic or oxidative stress [212,213]. Concurrent suppression of NF-κB and modulation of MAPK/ERK/p38 signalling alleviate chronic inflammation, stabilise redox balance, and preserve tissue homeostasis [214].

Collectively, these findings identify terpenoids as multifunctional modulators of ageing-related signalling networks. Through integrated control of AMPK–SIRT1–mTORC1, Nrf2–ARE, and PI3K–AKT–NF-κB cascades, terpenoids coordinate antioxidant defence, autophagy, and energy metabolism, thereby promoting neuroprotection, tissue repair, and metabolic resilience. Their multitarget actions and cross-pathway regulation position terpenoids as key natural agents for mitigating ageing and age-associated degenerative disorders.

4.1.3. Polyamines: Mechanistic Basis and Evidence

Polyamines are small polycationic alkylamines containing two or more amino groups ($-NH_3^+$) and are primarily synthesised from *L*-ornithine via amino-acid decarboxylation. Their positive charges enable interactions with negatively charged biomolecules such as DNA, RNA, ATP, and phospholipids, thereby regulating nucleic acid conformation, ion balance, and protein synthesis [215,216]. Putrescine, SPD, and SPM are the principal forms, whereas non-canonical species such as cadaverine and norspermidine occur predominantly in prokaryotes. Post-synthetic acetylation and methylation influence intracellular localisation and metabolic stability [217,218]. Functionally, polyamines act as endogenous bioactive molecules with antioxidant, anti-inflammatory, and regulatory activities that preserve redox balance, immune stability, and gut barrier function. Elevated polyamine levels, particularly SPD, correlate with extended lifespan and improved physiological resilience across model organisms, and altered polyamine metabolism is consistently linked to neurodegenerative and cardiovascular ageing [219,220].

At the molecular level, polyamines exert antioxidant effects through metal chelation and membrane stabilisation. Their polycationic nature binds transition metals such as Fe^{2+} and Cu^{2+}, preventing hydroxyl radical generation and limiting propagation of lipid peroxidation [221,222]. SPD and SPM directly neutralise hydroxyl radicals and singlet oxygen, enhancing mitochondrial integrity and energy metabolism while lowering ROS accumulation [221,223]. SPM also protects lipid-soluble antioxidants such as α-tocopherol and carotenoids, prolonging vitamin E stability and preserving pigment integrity [224]. These actions collectively contribute to the maintenance of mitochondrial homeostasis and oxidative-stress defence, supporting cellular longevity and resilience.

Polyamines regulate autophagy and epigenetic signalling that underpin cellular renewal. SPD reduces excessive acetylation and stimulates autophagic flux through upregulation of LC3, Beclin-1, and p62, while

stabilising acetylated eIF5A to enable efficient translation of TFEB, a transcription factor governing lysosomal biogenesis and autophagy genes [225,226]. Depletion of polyamines impairs proteostasis and energy balance, whereas supplementation restores autophagic capacity across yeast, nematode, and mammalian models [221]. SPD also inhibits the histone acetyltransferase E1A-associated protein p300 (EP300), inducing chromatin hypoacetylation that stabilises gene expression and supports lifespan extension [225,226]. Regulation of transcription factors such as c-Myc, c-Fos, and c-Jun further maintains cell-cycle control and genomic integrity [227,228].

At the immune and inflammatory interface, polyamines suppress NF-κB p65 translocation and attenuate PI3K–AKT and MAPK activation, reducing inducible nitric oxide synthase (iNOS) and COX-2 expression and the subsequent production of NO, prostaglandin E_2 (PGE_2), and cytokines such as TNF-α, IL-1β, and IL-6 [229]. They increase interleukin-10 (IL-10) release and decrease leukocyte adhesion by downregulating LFA-1/CD11a on mononuclear cells [220,230,231]. These immuno-modulatory actions cooperate with their antioxidant activity to limit chronic inflammation and preserve cellular homeostasis.

Within the gut–microbiota axis, intestinal bacteria convert ornithine into putrescine and subsequently into SPD and SPM via aminopropyl transfer reactions [219,232]. These metabolites are absorbed by the intestinal epithelium and distributed systemically [233]. In the intestinal mucosa, polyamines stimulate epithelial renewal, enhance tight-junction protein expression, and strengthen barrier integrity [220,234]. They also promote the growth of beneficial microbes and optimise microbial communication through biofilm and vesicle signalling, thereby contributing to metabolic stability and health-span maintenance [232,235].

In summary, polyamines integrate antioxidant, autophagic, epigenetic, and anti-inflammatory mechanisms to sustain cellular and systemic homeostasis. Polyamines coordinate mitochondrial protection, chromatin remodelling, and gut–immune balance, functioning as versatile molecular mediators that collectively delay ageing and enhance physiological resilience.

4.1.4. Polysaccharides: Mechanistic Basis and Evidence

Polysaccharides are complex carbohydrate polymers composed of long chains of monosaccharides joined by glycosidic bonds, exhibiting remarkable structural and functional diversity that underpins their biological activities [236,237]. They may occur as homopolysaccharides containing identical sugar residues, or as heteropolysaccharides composed of mixed monosaccharides such as glucose, galactose, mannose, arabinose, and xylose, arranged in linear or branched configurations [238]. Depending on charge characteristics, they occur as anionic or cationic polymers [239]. The versatile molecular conformations and reactive hydroxyl, sulphate, and amino groups of polysaccharides confer broad biological functionality, allowing them to participate in immune regulation, cellular adhesion, wound repair, and metabolic homeostasis [240,241].

Bioactive polysaccharides from terrestrial and marine sources demonstrate broad anti-ageing potential through coordinated redox regulation, metabolic adaptation, and immune modulation. They enhance antioxidant defence by activating the Nrf2–ARE pathway, increasing SOD, CAT, GPx, and GST expression, and reducing free radical propagation [30,44,242]. Many preparations scavenge hydroxyl and superoxide radicals and inhibit NO overproduction by downregulating iNOS mRNA, thereby decreasing lipid peroxidation and preserving mitochondrial integrity [44,243].

At the metabolic level, polysaccharides adjust energy homeostasis through AMPK–SIRT1–PGC-1α signalling and suppress mTORC1/ribosomal protein S6 kinase (S6K) activity, thereby improving mitochondrial biogenesis, autophagy, and stress tolerance [28,30,39]. In parallel, they modulate the IIS–FOXO–p53 cascade to induce stress-response genes and upregulate DNA-repair enzymes such as 8-oxoguanine DNA glycosylase (OGG1), X-ray repair cross-complementing protein 1 (XRCC1), and poly (ADP-ribose) polymerase 1 (PARP1), thereby reducing phosphorylated H2A histone family member X

(γH2AX) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) accumulation and maintaining genomic stability [28,39]. Polysaccharides further promote autophagy and mitophagy via AMPK–SIRT1–Unc-51-like autophagy-activating kinase 1 (ULK1) and PTEN-induced putative kinase 1 (PINK1)/E3 ubiquitin-protein ligase Parkin (Parkin) pathways, supporting telomere maintenance by enhancing telomerase activity and limiting telomere-associated damage [30,244].

Beyond intracellular protection, polysaccharides exert pronounced immunomodulatory and microbiota-regulating effects. Their chain conformation and monosaccharide composition determine interaction with innate immune receptors such as toll-like receptor 2 (TLR2) and toll-like receptor 4 (TLR4) and dendritic cell-associated C-type lectin-1 (Dectin-1), leading to balanced activation of NF-κB and MAPK signalling that reduces IL-6, TNF-α, and IL-1β release while elevating IL-10 production [49].

In the gut, polysaccharides are fermented to short-chain fatty acids (SCFAs) (acetate, propionate, and butyrate) that bind G protein-coupled receptor 41 (GPR41), G protein-coupled receptor 43 (GPR43), and Hydroxycarboxylic acid receptor 2 (HCAR2), enhancing interleukin-18 (IL-18) secretion and reinforcing mucosal immunity [58,245]. They simultaneously strengthen the intestinal barrier by upregulating antimicrobial peptides, mucins, and tight-junction proteins while lowering lipopolysaccharide (LPS) production and epithelial permeability [246,247]. As fermentable substrates, polysaccharides selectively stimulate beneficial taxa such as *Akkermansia* and *Lactobacillus*, while suppressing pathogens and reshaping microbial metabolism toward increased SCFAs and reduced pro-inflammatory metabolites (trimethylamine N-oxide (TMAO), indoles), thereby supporting intestinal and systemic equilibrium [49,248].

Sulphated or uronic-acid-rich polysaccharides display strong anti-glycation activity by inhibiting advanced glycation-end-product (AGE) formation and associated oxidative stress [47,249]. Their sulphate and hydroxyl groups trap reactive carbonyl species (RCS) such as methylglyoxal and glyoxal, preventing protein cross-linking, while their intrinsic antioxidant capacity further suppresses AGE–receptor for advanced glycation end-products (RAGE)-mediated inflammation [250,251]. By lowering lipid peroxidation, improving SOD, CAT, and GSH-Px activities, and stabilising mitochondrial membranes, polysaccharides preserve extracellular matrix structure and cellular viability.

Collectively, these actions define polysaccharides as multifunctional macromolecules that integrate redox regulation, metabolic balance, immune synchronisation, and gut-microbiota symbiosis to mitigate oxidative, inflammatory, and glycation-related ageing processes, thereby maintaining systemic homeostasis and promoting longevity.

4.1.5. Fatty Acids: Mechanistic Basis and Evidence

Fatty acids constitute the fundamental structural units of complex lipids that support cellular energy storage, membrane organisation, and signalling regulation. Their structural diversity, defined by chain length and degree of unsaturation, determines their physicochemical properties and biological functions [53,252].

Among them, unsaturated fatty acids, particularly long-chain monounsaturated and polyunsaturated species, are essential for maintaining metabolic flexibility, mitochondrial efficiency, and redox balance. Humans rely on dietary intake of essential fatty acids such as linoleic (ω-6) and α-linolenic acids (ω-3), which serve as precursors for long-chain derivatives including AA, EPA, and DHA [54].

Functionally, fatty acids act as metabolic fuels, membrane constituents, and precursors of bioactive mediators such as eicosanoids. Unsaturated fatty acids, especially monounsaturated fatty acids (MUFAs) and PUFAs, modulate transcriptional programs through PPAR, SIRT1, and AMPK signalling, thereby promoting β-oxidation, mitochondrial biogenesis, and antioxidant defence. Long-chain ω-3 PUFAs such as EPA and DHA exert neuroprotective and cardioprotective effects, preserve telomere length, and correlate with improved longevity indices, whereas MUFAs enhance metabolic stability and membrane fluidity [52,53,57]. Collectively, these features position unsaturated fatty acids as central regulators of energy metabolism, oxidative homeostasis, and cellular lifespan.

Omega-3 fatty acids function as transcriptionally active ligands of PPARs, particularly PPAR-α and PPAR-γ, which regulate lipid oxidation, glucose utilisation, and inflammatory tone. Upon receptor binding, EPA and DHA form heterodimers with the retinoid X receptor (RXR) to activate peroxisome proliferator response elements (PPREs), enhancing fatty-acid oxidation and suppressing NF-κB- and activator protein-1 (AP-1)-mediated cytokine transcription. This signalling modulation increases the expression of antioxidant enzymes such as SOD and CAT, reduces lipid peroxidation, and stabilises cellular redox status. Concurrently, EPA and DHA serve as precursors to specialised pro-resolving mediators (SPMs), including resolvins, protectins, and maresins, which bind formyl peptide receptor 2 (FPR2)/lipoxin A4 receptor (ALX) and G protein-coupled receptor 120 (GPR120) to promote M2 macrophage (M2) polarisation, accelerate efferocytosis, and resolve inflammation [253,254]. Through this dual PPAR–SPM axis, omega-3s convert pro-inflammatory signalling into pro-resolving cascades, mitigating oxidative injury and chronic inflammation that drive cellular ageing [255,256].

Epigenetic and multi-omics studies reveal that ω-3 PUFAs influence DNA methylation and histone acetylation patterns, particularly in genes governing metabolic and immune regulation, such as TNF-α, Interferon alpha-13 (IFNA13), and ATPase phospholipid transporting 8B3 (ATP8B3), leading to reduced inflammatory transcription and improved insulin sensitivity [55]. These changes are tissue-specific yet consistently associated with enhanced metabolic resilience and lower frailty indices. Upregulation of antioxidant systems, including SOD, CAT, GPx, and glutathione, further reduces oxidative modification of proteins and lipids, preventing telomere attrition and genomic instability [254,257]. Diets with higher PUFAs and MUFAs content and a low n-6:n-3 ratio correlate with longer telomeres and slower physiological decline, whereas saturated-fat-rich diets are associated with elevated oxidative stress and frailty [253,258].

Beyond cellular and genomic regulation, ω-3 PUFAs maintain systemic homeostasis through the gut–mucosal–immune axis. Supplementation enhances microbial α-diversity, enriches *Bacteroidetes, Akkermansia*, and butyrate-producing *Lachnospiraceae*, and suppresses pro-inflammatory *Proteobacteria* and *Enterobacteriaceae* [259,260]. These compositional shifts elevate SCFAs such as butyrate and propionate, which activate G-protein-coupled receptors free fatty acid receptor 2 (FFAR2) and free fatty acid receptor 3 (FFAR3) and inhibit histone deacetylases, reducing pro-inflammatory cytokine expression. SCFAs also serve as energy substrates for colonocytes and promote tight-junction integrity via upregulation of occludin and claudin [258]. Additionally, omega-3s increase intestinal alkaline phosphatase activity, detoxifying LPS and lowering endotoxemia. Omega-3-derived SPMs further enhance mucosal repair and barrier stability, limiting microbial translocation and chronic low-grade inflammation [257,258].

Collectively, these effects reinforce epithelial and immune equilibrium, suppress NF-κB and NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) activation, and preserve mitochondrial function. Through these integrated mechanisms, omega-3 fatty acids sustain metabolic and inflammatory balance, supporting health-span and mitigating age-related decline.

4.1.6. Bioactive Peptides: Mechanistic Basis and Evidence

Bioactive peptides are short amino-acid fragments produced through enzymatic hydrolysis, microbial fermentation, or physiological digestion of proteins, functioning as regulatory molecules that support systemic homeostasis and delay ageing [187,261]. Their activity largely depends on sequence composition and the presence of hydrophobic, proline, lysine, or arginine residues, which influence structural stability and receptor affinity [262]. These peptides originate from diverse sources, including milk, eggs, marine organisms, plants, and microbial-fermentation systems, and exhibit multifunctional bioactivities such as antioxidant, anti-inflammatory, and immunomodulatory effects [261,263]. Peptides derived from marine and fermented sources are particularly notable for their strong metabolic and redox regulatory capacity, supporting cellular resilience and longevity-related pathways.

The anti-ageing actions of bioactive peptides arise from interconnected antioxidant, anti-inflammatory, antiglycation, and metabolic-regulatory mechanisms [187,264]. By scavenging reactive oxygen and nitrogen species and chelating transition metals such as Fe^{2+} and Cu^{2+}, peptides suppress Fenton-type oxidative reactions and limit lipid peroxidation [189,265]. This redox modulation decreases inhibitor of NF-κB α (IκBα) phosphorylation, blocks NF-κB nuclear translocation, and down-regulates MAPK cascades involving p38, JNK, and ERK [266]. Consequently, the expression of COX-2, iNOS, TNF-α, IL-1β, and IL-6 is attenuated, accompanied by reduced MMP and elastase activities that preserve extracellular-matrix integrity and tissue elasticity [265,267]. This integrated regulation of oxidative and inflammatory pathways enhances cytoprotective capacity, maintains redox equilibrium, and mitigates stress-induced cellular ageing.

At the transcriptional level, bioactive peptides activate the Nrf2–ARE signalling pathway by modifying cysteine residues on kelch-like ECH-associated protein 1 (Keap1), facilitating Nrf2 nuclear translocation and induction of antioxidant enzymes including HO-1, NQO1, and glutamate–cysteine ligase catalytic subunit (GCLC) [29,187]. The enhanced enzymatic capacity restores redox balance and indirectly suppresses pro-inflammatory transcription factors. Parallel modulation of the AMPK–SIRT1–PGC-1α axis promotes mitochondrial biogenesis, enhances β-oxidation, and maintains autophagic flux while repressing mTOR activity [264,268]. The interplay between Nrf2-mediated antioxidation and AMPK–SIRT1 metabolic control forms a coordinated defence circuit that supports mitochondrial integrity, energy efficiency, and proteostasis balance during ageing.

Peptides also prevent carbonyl stress and maintain protein functionality by reducing AGE accumulation. Carnosine and related dipeptides neutralise RCS such as methylglyoxal and MDA, disrupting the AGE–RAGE feedback loop that amplifies oxidative and inflammatory damage [269,270]. This antiglycation effect preserves enzymatic activity and prevents cross-linking of structural proteins, thereby contributing to tissue elasticity and metabolic stability [261]. Through regulation of the AMPK–mTORC1 pathway, peptides further stimulate autophagy and lysosomal degradation of damaged proteins, maintaining cellular-clearance mechanisms and promoting long-term viability [264,271]. These combined antioxidative, antiglycative, and proteostasis functions ensure the preservation of macromolecular integrity under chronic stress.

Beyond intracellular protection, bioactive peptides exert profound effects on immune and vascular systems. By inhibiting NF-κB and JAK/STAT signalling, they promote macrophage transition from the pro-inflammatory M1 macrophage (M1) phenotype to the reparative M2 macrophage (M2) state, reducing cytokine release and restoring immune equilibrium [189,272]. At the endothelial level, activation of the PI3K/AKT/eNOS and vascular endothelial growth factor (VEGF)/fibroblast growth factor (FGF) pathways enhances nitric-oxide synthesis and angiogenic signalling, improving microvascular circulation and oxygen delivery [261,266]. These vascular effects reinforce nutrient exchange and metabolic efficiency, counteracting age-related hypoxia and tissue decline.

Collectively, through integrated control of oxidative defence, autophagy, protein-quality maintenance, immune regulation, and vascular renewal, bioactive peptides establish a multifaceted molecular framework that preserves cellular homeostasis and extends health-span.

4.2. Integrated Mechanistic Framework of Combined Natural Products in Anti-Ageing

The synergistic anti-ageing efficacy of combined natural products arises from the integration of multiple regulatory cascades that collectively sustain oxidative defence, metabolic balance, and cellular repair. Rather than acting through a single dominant route, polyherbal and multi-nutrient formulations engage complementary molecular targets within interconnected pathways such as AMPK–SIRT1–mTORC1, Nrf2–ARE, NF-κB, and PI3K–AKT–MAPK, thereby reinforcing mitochondrial homeostasis, genomic stability, and stress adaptation [188,189,261,268].

4.2.1. Convergent Core Pathways and Shared Mechanistic Networks

The anti-ageing potential of diverse natural product classes arises from their interactions with conserved molecular networks that jointly regulate energy metabolism, redox balance, inflammation, and genomic maintenance. Despite their structural heterogeneity, polysaccharides, polyphenols, peptides, fatty acids, terpenoids, and polyamines converge on overlapping regulatory axes, including AMPK–SIRT1–mTORC1, Nrf2–ARE, NF-κB, FOXO, PPAR, and insulin-like growth factor (IGF)–IIS/PI3K–AKT–MAPK pathways, which together sustain cellular homeostasis and resilience under stress [28,44,188]. This convergence underscores a shared molecular infrastructure through which natural compounds influence longevity-related signalling and adaptive cellular responses [30,189].

At the metabolic level, the AMPK–SIRT1–mTORC1 cascade functions as a central rheostat linking nutrient status with mitochondrial bioenergetics and autophagic renewal. Activation of AMPK promotes SIRT1-mediated deacetylation of PGC-1α and mitochondrial transcription factor A (TFAM), enhancing mitochondrial biogenesis, β-oxidation, and autophagic flux while suppressing mTOR signalling [39,258]. Polyphenols and terpenoids modulate this network via AMPK phosphorylation and SIRT1 activation, whereas fatty acids and polyamines regulate energy metabolism through PPARα/γ–AMPK coupling [190,191].

Redox homeostasis represents a unifying target, primarily mediated through the Nrf2–ARE pathway. Polyphenols, terpenoids, and polysaccharides enhance Nrf2 translocation and transcription of antioxidant enzymes such as SOD, CAT, and HO-1, thereby reducing oxidative stress and lipid peroxidation [187,189]. Fatty acids and peptides contribute indirectly through PPARs- and SIRT1-dependent redox regulation, while polyamines stabilise oxidative–inflammatory equilibrium via reciprocal regulation of Nrf2 and NF-κB [44,273].

At the genomic level, FOXO transcription factors act as conserved effectors of stress resistance and longevity. SIRT1-dependent deacetylation of FOXO1/3a activates repair-related genes such as OGG1 and PARP1, maintaining genomic integrity [28]. Terpenoids and polyphenols modulate FOXO activity through MAPK/ERK-mediated phosphorylation and PI3K–AKT inhibition, thereby supporting autophagic capacity [210]. Concurrently, PPAR and MAPK signalling integrate lipid metabolism with immune regulation, while polyamines couple metabolic sensing with epigenetic stability [233].

Collectively, these mechanisms delineate a shared mechanistic foundation across natural-product categories. Through coordinated regulation of energy sensing, oxidative defence, and genomic stability, these compounds sustain cellular adaptability and stress tolerance. This convergence defines the molecular basis for their anti-ageing efficacy and establishes the platform upon which complementary mechanisms can further integrate [44,188].

4.2.2. Complementary and Parallel Mechanisms of Natural Product Classes

Across the six principal categories of natural products, anti-ageing efficacy is mediated through distinct yet interrelated molecular hierarchies. These include immunometabolism modulation, transcriptional reprogramming, and chromatin-level regulation that operate in complementary and parallel manners to sustain systemic homeostasis [28,33,44]. Each compound class contributes through its characteristic biochemical interface, engaging unique regulatory tiers while maintaining dynamic interactions within shared signalling networks [188,189].

Polysaccharides primarily operate along the immune–microbial axis, modulating the gut-associated lymphoid tissue and commensal microbiota to restore mucosal tolerance and barrier integrity. *Astragalus* and *Ganoderma lucidum* polysaccharides attenuate TLR2/4–myeloid differentiation primary response 88 (MyD88)–NF-κB activation in intestinal epithelial and myeloid cells, suppressing transcription of pro-inflammatory genes such as iNOS, COX-2, and TNF-α, while enhancing IL-10 and transforming growth factor-β (TGF-β) expression via signal transducer and activator of transcription 3 (STAT3)-regulated anti-

inflammatory signalling [185,274]. Simultaneously, they promote secretory immunoglobulin A (IgA) and short-chain fatty acid production, reinforce epithelial tight-junction integrity, and mitigate microbial translocation. Sulphated marine polysaccharides such as fucoidan further stabilise intestinal epithelia, reduce LPS burden, and inhibit inflammasome activation, thereby attenuating systemic inflammation and metabolic stress [28,44]. Through these mechanisms, polysaccharides function as immunometabolism gatekeepers linking mucosal stability to organismal longevity.

Polyphenols exert broad transcriptional and epigenetic control over inflammatory and oxidative responses. Compounds such as curcumin, resveratrol, and catechins covalently modify Keap1 cysteine residues, releasing Nrf2 to upregulate HO-1, NQO1, and GCLC, while simultaneously suppressing IκB kinase β (IKKβ) and NF-κB p65 nuclear translocation. These effects collectively reduce the expression of IL-6, IL-1β, and monocyte chemoattractant protein-1 (MCP-1) in macrophages and senescent fibroblasts [7,275]. Polyphenols further reprogram histone acetylation through SIRT1 activation and regulate non-coding RNAs such as miR-146a and miR-21, which target TNF receptor–associated factor 6 (TRAF6) and IKKβ, thereby attenuating inflammatory feedback at both transcriptional and post-transcriptional levels [61]. Activation of the SIRT1–AMPK–PGC-1α cascade enhances mitochondrial biogenesis and ATP production, while Nrf2–p62 crosstalk strengthens antioxidant defence and autophagic recycling [188,275].

Bioactive peptides function as signalling modulators that intercept phosphorylation cascades and receptor-mediated cytokine release. Peptides derived from Spirulina platensis, soy, and milk hydrolysates suppress MAPK members, including p38, ERK1/2, and JNK, thereby reducing COX-2 expression and AP-1 activation in immune and stromal cells [187,261,262]. Certain food-derived peptides bind to TLR2 or ACE2 receptor sites, in animal models, peptide supplementation elevates SIRT1 and FOXO3a expression, enhances antioxidant-enzyme activities, and reduces cytokine release, demonstrating dual regulation of redox and inflammatory homeostasis. Additionally, antiglycation peptides neutralise RCS and inhibit MMPs, thereby preserving extracellular-matrix architecture and vascular elasticity [29,187,263].

Fatty acids primarily act through PPAR-centred transcriptional regulation and lipid-mediator resolution. Long-chain ω-3 PUFAs, including EPA and DHA, are enzymatically converted into SPMs that limit neutrophil infiltration, enhance macrophage efferocytosis, and promote M1 to M2 phenotypic transition. Activation of PPAR-α and PPAR-γ further suppresses NF-κB- and AP-1-driven cytokine transcription while promoting the resynthesis of IκBα, thereby maintaining a controlled inflammatory tone [255,256,260]. These fatty acids integrate into membrane phospholipids, alter receptor clustering and lipid-raft composition, and thereby modulate TLR4 signalling while improving redox–metabolic stability [52,259].

Terpenoids exhibit dual redox and metabolic regulation. Carotenoids, ginsenosides, and triterpenes activate Nrf2-dependent antioxidant enzymes while inhibiting IKKβ-mediated NF-κB translocation, thereby coupling oxidative defence with anti-inflammatory control [48,191,210]. They simultaneously modulate AMPK–mTORC1–ULK1 signalling to enhance autophagic flux and upregulate hypothalamic SIRT1–SIRT6–Klotho pathways that maintain nutrient sensing and neuroendocrine balance [190,212,214].

Polyamines, represented by SPD and SPM, act predominantly at the chromatin level. Their positive charge facilitates interaction with DNA and histones, neutralising promoter regions of inflammatory genes and regulating histone acetyltransferase and deacetylase activity [274,276]. SPD promotes autophagic flux via EP300 inhibition and stabilisation of acetylated Eukaryotic translation initiation factor 5A (eIF5A), while TFEB translation and lysosomal biogenesis. These actions suppress NLRP3 inflammasome activity and IL-1β maturation, thereby maintaining proteostasis and genomic stability [216,277].

Collectively, these complementary mechanisms form a stratified anti-ageing hierarchy: polysaccharides preserve immune and microbial balance; polyphenols and terpenoids modulate transcriptional and redox regulation; peptides and fatty acids coordinate cytoplasmic kinase and lipid-mediated signalling; and polyamines maintain chromatin and epigenetic stability. The interaction among

these regulatory strata sustains metabolic coordination, oxidative equilibrium, and transcriptional fidelity, providing the molecular foundation for synergistic anti-ageing outcomes [28,44,188].

4.2.3. Hierarchical Integration and Network-Level Synergistic Regulation

The anti-ageing potential of combined natural products arises not merely from additive actions but from the hierarchical coupling of regulatory networks that coordinate metabolic, redox, inflammatory, and genomic processes. This integration represents a systems-level organisation in which different compound classes interact through feedback and feed-forward loops that stabilise cellular homeostasis and enhance functional resilience under stress conditions [28,33,44].

At the core of this network, the AMPK–SIRT1–mTORC1 signalling module functions as the central metabolic rheostat that synchronises energy availability with autophagic and biosynthetic programmes. Polysaccharides and bioactive peptides enhance this metabolic sensing by activating AMPK and upregulating SIRT1–PGC-1α, which promote mitochondrial biogenesis and efficient ATP turnover. Concurrent inhibition of mTORC1 by terpenoids, fatty acids, and polyamines maintains autophagic clearance and proteostasis, forming a coordinated energy recycling loop that sustains long-term cellular viability [188,268,278]. This integrated metabolic control ensures that nutrient signals couple with redox balance and catabolic adaptation, preventing the metabolic rigidity characteristic of ageing tissues [32,189].

Redox regulation forms the second hierarchical tier of this coupling system. Activation of Nrf2 by polyphenols, terpenoids, and polysaccharides enhances transcription of antioxidant enzymes, including SOD, CAT, GPx, and HO-1, thereby reinforcing mitochondrial and cytosolic redox buffering. Simultaneously, suppression of NF-κB and MAPK signalling by peptides, fatty acids, and polyamines limits pro-inflammatory cytokine release and oxidative amplification. Reciprocal inhibition between the Nrf2 and NF-κB modules allows precise tuning of oxidative and inflammatory responses, stabilising the cellular environment and sustaining signalling fidelity across multiple tissues [187,188,274]

The third integration layer involves transcriptional and epigenetic coupling. Polyphenols, terpenoids, and polyamines remodel histone acetylation and DNA methylation via modulation of SIRT1, EP300, and TFEB, thereby linking metabolic sensing to chromatin dynamics. These epigenetic adjustments coordinate the expression of longevity-associated transcription factors such as FOXO, PPAR, and p53, ensuring balanced control of repair, apoptosis, and stem-cell renewal [48,261]. Fatty acids and peptides further contribute to this layer by modulating membrane fluidity, receptor clustering, and signal-transduction efficiency, thereby bridging transcriptional regulation with extracellular and cytoplasmic signalling continuity [216,226].

These interconnected layers operate as a dynamic adaptive network rather than isolated pathways. Metabolic sensors such as AMPK and SIRT1 integrate upstream nutrient and stress signals; redox regulators such as Nrf2 and NF-κB calibrate the antioxidant and inflammatory balance; and downstream effectors, including FOXO, mTORC1, and PPAR, translate these inputs into sustained cytoprotective gene expression. The mutual reinforcement among these axes ensures resilience against both intrinsic and extrinsic ageing stressors. When one pathway is weakened, compensatory circuits maintain energy flow, redox integrity, and proteostasis balance, achieving a form of network redundancy that underlies the durability of multi-compound interventions [30,44,185].

Collectively, these cross-connected regulatory hierarchies demonstrate that synergistic combinations of natural products function as coordinated network stabilisers rather than simple mixtures of active molecules. By engaging convergent and complementary mechanisms across metabolic, redox, and genomic dimensions, they promote cellular adaptation and longevity at both molecular and organismal levels [28,188,274].

5. Conclusions and Future Perspectives

Natural products represent a rapidly expanding frontier in anti-ageing research, bridging nutrition, pharmacology, and systems biology. Across major classes such as polysaccharides, polyphenols, peptides, fatty acids, terpenoids, and polyamines, extensive mechanistic and experimental evidence confirms their capacity to modulate oxidative stress, inflammation, mitochondrial dynamics, genomic maintenance, and autophagy regulation. Despite marked structural heterogeneity, these compounds converge upon a shared regulatory network centred on AMPK–SIRT1–mTORC1, Nrf2–ARE, NF-κB, PPAR, and FOXO cascades, collectively sustaining cellular homeostasis and longevity. Increasing evidence on combination formulations further reveals synergistic and complementary interactions that amplify these effects through integrated network pharmacology rather than single-target modulation. Nevertheless, several challenges persist. Translating preclinical discoveries into clinically validated outcomes remains constrained by variability in compound purity, bioavailability, dosage optimisation, and long-term safety evaluation. In addition, inter-individual variability in metabolic status, age-associated physiological differences, and gut microbiome composition may lead to heterogeneous responses to identical natural bioactive combinations, further complicating efficacy evaluation and translational generalisation. Moreover, uncertainties surrounding bioavailability and *in vivo* biotransformation remain a critical challenge, as circulating metabolites rather than parent compounds may ultimately mediate biological effects, particularly in multi-component formulations. The intrinsic complexity of multi-component interactions necessitates advanced analytical approaches such as multi-omics profiling, computational network modelling, and human-based systems biology to elucidate the precise contribution of each constituent within combination matrices. Moreover, harmonised regulatory frameworks and standardised manufacturing protocols are required to ensure product consistency and consumer safety across global markets.

Despite growing interest in multi-component natural bioactives, robust animal and clinical evidence evaluating well-defined combinations remains limited, largely due to the structural and compositional complexity of natural products. Many bioactives exist as heterogeneous mixtures in which subtle variations in derivative structures may differentially modulate the activity of relatively conserved core scaffolds, complicating mechanistic attribution and dose–effect interpretation. Source-dependent factors such as growth conditions, nutrient availability, harvest timing, and extraction procedures further introduce batch-to-batch variability, posing challenges for the qualitative and quantitative evaluation of anti-ageing efficacy. Moreover, the multi-target and network-level modes of action characteristic of natural products, while underpinning synergistic effects, may obscure causal relationships due to pathway crosstalk and regulatory feedback. Long-term clinical data assessing the safety, stability, and sustained efficacy of combined natural bioactives also remain scarce.

Looking ahead, integration of natural-product research with emerging technologies such as metabolomics, microbiome modulation, nanodelivery systems, and precision nutrition will accelerate the development of evidence-based, personalised anti-ageing interventions. In parallel, a key future direction will be the transition from empirically derived combinations to mechanism-informed, rationally designed natural bioactive formulations guided by systems-level insights. Advancing predictive frameworks that link compositional features with reproducible biological outcomes will further improve the robustness and translational reliability of multi-component anti-ageing strategies. Future investigations should prioritise translational validation through well-designed clinical trials, longitudinal biomarker monitoring, and cross-disciplinary collaboration among food scientists, clinicians, and regulatory experts. These advancements will refine the mechanistic understanding of ageing and facilitate the safe translation of natural bioactive combinations into next-generation functional foods and health-supplement therapeutics that support healthy longevity.

Statement of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

AI tool was used in polishing the first draft, and then the manuscript was edited by senior authors.

Author Contributions

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