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From Anti-Aging Supplements to Over-the-Counter Healthspan Pharmacology: Evidence Domains, Functional Architecture, and Practical Boundaries

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Abstract

Over-the-counter (OTC) supplements are widely used in anti-aging, longevity, performance, and biohacking contexts, yet they are often discussed as isolated products, consumer trends, or unsystematic stacks. This creates conceptual confusion because non-prescription compounds may serve different biological roles: substrate optimization, muscle-brain energy support, redox modulation, metabolic flexibility, neuroendocrine regulation, structural support, gut-liver support, immune modulation, cognitive support, pain resilience, or advanced cellular signaling.

This paper proposes a functional architecture of over-the-counter healthspan pharmacology. Its central claim is that anti-aging supplementation should be interpreted beyond minimum intake or deficiency prevention. Public-health reference intakes are useful for population-level sufficiency, whereas healthspan optimization concerns functional reserve within homeostatic limits. Functional reserve is operationalized here through measurable or observable domains such as muscle strength, lean mass, metabolic markers, cognitive performance, sleep quality, recovery capacity, inflammatory tone, gut-barrier function, pain resilience, immune resilience, and structural durability.

The model organizes supplements into four layers: substrate optimization, functional performance support, cellular signaling support, and advanced optimization compounds. It further integrates intake architecture, dose architecture, medication-context alignment, interaction logic, food-context bioavailability, formulation quality, biomarker-guided use, phenotype-specific selection, cyclic strategies, and sequenced optimization. Representative compounds include creatine, omega-3 fatty acids, glycine plus N-acetylcysteine (GlyNAC), urolithin A, palmitoylethanolamide (PEA), allulose, L-glutamine, functional mushrooms, Astragalus membranaceus, and selected botanical or formulation-specific compounds.

OTC supplements become scientifically meaningful when selected and organized according to biological role, evidence maturity, dose logic, timing, formulation, food context, medication context, biomarker response, phenotype, and functional goal. The central distinction is not supplement versus medication, but random accumulation versus organized biological optimization.

Keywords: over-the-counter supplements, healthspan optimization, nutraceuticals, anti-aging, dose architecture, supplement timing, creatine, glycine plus N-acetylcysteine, palmitoylethanolamide, allulose, functional mushrooms, gut barrier, biomarker monitoring

1. Introduction

Aging is increasingly understood as a multi-domain biological process involving genomic, telomeric, epigenetic, mitochondrial, inflammatory, metabolic, proteostatic, immune, stem-cell, and intercellular communication changes rather than a single linear decline [1]. Geroscience therefore shifts attention from disease absence alone toward preservation of function, resilience, and biological capacity across the life course [2]. This paper builds on a broader precision-healthspan pharmacology perspective in which anti-aging interventions are interpreted through evidence domains, monitoring requirements, practical boundaries, and functional endpoints [3]. The present manuscript narrows that broader question to over-the-counter (OTC) supplements and nutraceuticals.

OTC supplements have become central to contemporary anti-aging, longevity, performance, and biohacking practice. Omega-3 fatty acids, magnesium, creatine, cholecalciferol vitamin D3, menaquinone vitamin K2, coenzyme Q10 (CoQ10), nicotinamide adenine dinucleotide (NAD) precursors, curcumin, berberine, glycine, N-acetylcysteine (NAC), urolithin A, collagen peptides, phosphatidylserine, citicoline, ashwagandha, taurine, palmitoylethanolamide (PEA), allulose, L-glutamine, functional mushrooms, algae products, polyphenols, Astragalus membranaceus, and selected botanical compounds are commonly used to support energy, cognition, metabolic health, stress resilience, sleep, recovery, skin quality, physical performance, pain resilience, gut health, immune function, or long-term healthspan.

The scientific problem is not supplement use itself, but the lack of structure in how supplements are often interpreted. A multivitamin, creatine, berberine, red yeast rice, urolithin A, glycine, magnesium, allulose, PEA, fenugreek, Brahmi, Triphala, L-glutamine, functional mushrooms, Astragalus, and fisetin do not belong to the same functional category merely because they are available without prescription. They differ in mechanism, biological role, evidence maturity, timing requirements, food interactions, medication relevance, formulation dependence, and individual suitability.

Anti-aging supplementation is therefore best understood as structured biological optimization. The relevant question is not only whether intake prevents deficiency, but whether intake supports functional reserve: muscle strength, lean mass, metabolic flexibility, mitochondrial energy, cognitive performance, sleep quality, recovery capacity, inflammatory balance, gut-barrier integrity, immune resilience, pain resilience, structural durability, and long-term vitality.

2. Scope and Evidence-Selection Logic

This paper is a conceptual evidence-mapping review. It is not a systematic review, meta-analysis, or clinical guideline. Its purpose is to organize a heterogeneous field of OTC supplements into functional domains, evidence categories, intake principles, interaction logic, medication-context interpretation, and practical boundaries for healthspan optimization. The compounds discussed are representative examples for the proposed architecture, not an exhaustive supplement inventory. To avoid circularity and marketing-based inclusion, the model applies explicit inclusion criteria. A compound is included when it meets at least one of the criteria summarized in Table 1.

Table 1. Inclusion Criteria for OTC Healthspan-Relevant Compounds

Inclusion criterion	Meaning
Substrate relevance	The compound provides or supports a substrate required for physiological function.
Functional endpoint relevance	The compound affects a healthspan-relevant domain such as muscle, cognition, sleep, glucose metabolism, lipid metabolism, stress resilience, mitochondrial energy, redox balance, connective tissue, gut-liver function, intestinal barrier integrity, pain modulation, immune regulation, or neuroendocrine function.
Human evidence	The compound has human evidence for a relevant biomarker or functional endpoint.
Mechanistic plausibility	The compound has strong pathway relevance with translational logic, even where human outcome evidence is still emerging.
Context relevance	The compound is important because of food context, medication overlap, formulation sensitivity, timing, absorption, or interaction logic.

This inclusion logic prevents circularity. A compound is not healthspan-relevant because it is marketed for anti-aging; it is healthspan-relevant when it maps onto a defined mechanism, biomarker, functional endpoint, or optimization context. Human evidence, biomarker evidence, mechanistic plausibility, and translational hypotheses are therefore treated as distinct evidentiary levels.

3. Functional Reserve Beyond Minimum Intake

Public-health reference intakes are designed primarily to prevent deficiency in broad populations. Healthspan optimization has a different objective: preserving and expanding biological capacity.

A nutrient intake may prevent classical deficiency while still being suboptimal for older adults, athletes, individuals under chronic stress, people with high training load, medication-associated depletion, gastrointestinal burden, or increased metabolic demand. Protein intake sufficient for basic nitrogen balance may not be optimal for aging adults facing anabolic resistance; expert recommendations for older adults emphasize higher protein targets to preserve muscle function and physical capacity [4]. Magnesium is involved in energy metabolism, neuromuscular function, glucose regulation, and cardiovascular physiology, making magnesium status relevant beyond classical deficiency states [5]. Creatine supports phosphocreatine-dependent energy buffering in muscle and brain, with extensive evidence for performance-related outcomes and emerging evidence for cognitive support under energetic stress [6,7]. L-glutamine can function as a conditional gut-barrier and immune substrate in high-demand states, with meta-analytic evidence suggesting effects on intestinal permeability in selected contexts [8]. Omega-3 fatty acids influence membrane biology, inflammatory signaling, vascular function, and, in randomized data, DNA-methylation measures of biological aging when combined with vitamin D and exercise [9].

Functional reserve is not unlimited biological amplification. Healthspan optimization operates within homeostatic boundaries. Many nutrients, antioxidants, adaptogens, minerals, endocrine-adjacent

compounds, and signaling molecules follow non-linear dose-response patterns: insufficient exposure fails to correct a bottleneck, appropriate exposure improves function, and excessive exposure may trigger counter-regulation, receptor desensitization, transport competition, reductive stress, gastrointestinal intolerance, or metabolic burden [10].

This distinction separates true reserve expansion from temporary pathway forcing. True reserve expansion improves adaptive capacity, recovery, structural integrity, metabolic flexibility, or stress tolerance within physiological feedback systems. Temporary pathway forcing produces short-term stimulation, biochemical saturation, or symptom masking without durable functional gain. Dose architecture therefore aims at the optimal biological window, not maximal intake.

4. The OTC Healthspan Architecture Model

The proposed architecture organizes OTC supplements by biological role rather than by consumer category, popularity, or legal status. As shown in Table 2, the model distinguishes substrate optimization, functional performance support, cellular signaling support, and advanced individualized optimization.

Table 2. Four-Layer OTC Healthspan Architecture Model

Layer	Function	Representative examples
Substrate Optimization Layer	Biological substrates required for high-level function	Protein, essential amino acids, leucine, L-glutamine, omega-3 fatty acids, magnesium, vitamin D3, vitamin K2, B vitamins, zinc, selenium, iodine, copper, electrolytes, trace elements
Functional Performance Layer	Muscle, brain, sleep, stress tolerance, training adaptation, recovery	Creatine, glycine, taurine, L-theanine, collagen peptides, medium-chain triglyceride (MCT) oil, citicoline, alpha-glycerophosphocholine (Alpha-GPC), phosphatidylserine, electrolytes
Cellular Signaling Layer	Mitochondria, redox, inflammation, glucose handling, vascular function, gut-metabolic signaling, immune modulation, mushroom-derived signaling, adaptive stress responses	CoQ10, NAC, glycine plus N-acetylcysteine (GlyNAC), urolithin A, berberine, curcumin, resveratrol, oligomeric proanthocyanidins (OPC), quercetin, astaxanthin, sulforaphane, alpha-lipoic acid, spermidine, PEA, allulose, fenugreek, Jiaogulan, Triphala, Lion's Mane, Reishi, Cordyceps, Turkey Tail, Shiitake, Maitake, Chaga, Tremella fuciformis, Poria cocos

Layer	Function	Representative examples
Advanced Optimization Layer	More specific, individualized, cyclic, formulation-dependent, pharmacologically overlapping, or pathway-dependent use	Ashwagandha, tongkat ali, low-dose lithium, red yeast rice, shilajit, diindolylmethane (DIM), fisetin, NAD precursors, tauroursodeoxycholic acid (TUDCA), Brahmi, Astragalus membranaceus, Astragalus-based telomere-related preparations, formulation-specific liver-support products exemplified by Liv.52-like preparations

Advanced optimization indicates greater context dependence, pathway specificity, formulation relevance, cyclic logic, narrow homeostatic window, pharmacological overlap, or need for biomarker interpretation. It is not a lower category; it is a more individualized category.

5. Evidence Maturity and Mechanism-to-Endpoint Logic

Because OTC compounds differ in evidence maturity, the model separates foundational support, domain-specific human evidence, emerging healthspan evidence, and advanced individualized optimization. Table 3 provides the evidence classification used in this paper. A supplement should be evaluated by the connection between mechanism, evidence, biomarker, and functional endpoint. Strong mechanistic plausibility and strong human evidence are not the same. Some compounds have robust human evidence in specific domains, while others have strong translational rationale but limited direct healthspan outcome evidence.

Table 3. Evidence Maturity Classes for OTC Healthspan Compounds

Evidence class	Meaning	Examples
Class I: Foundational human-relevant support	Broad physiological relevance and established human-domain evidence	Protein, omega-3 fatty acids, magnesium, vitamin D when needed, creatine
Class II: Domain-specific human evidence	Human evidence within a narrower functional domain	Berberine, CoQ10, collagen peptides, psyllium, ashwagandha, GlyNAC, PEA, fenugreek for glucose-related outcomes, Bacopa monnieri for cognition
Class III: Emerging healthspan evidence	Mechanistic or early human evidence with limited direct healthspan outcomes	Urolithin A, NAD precursors, spermidine, sulforaphane, pyrroloquinoline quinone (PQQ), magnesium L-threonate, allulose, Gynostemma pentaphyllum, Triphala, L-glutamine in gut-barrier contexts, functional mushrooms

Evidence class	Meaning	Examples
Class IV: Advanced individualized optimization	Context-specific use requiring phenotype, formulation, biomarker, medication-context, or cyclic interpretation	Fisetin, low-dose lithium, tongkat ali, red yeast rice, shilajit, DIM, Astragalus-based telomere-related preparations, formulation-specific liver-support products

These evidence classes describe maturity, domain specificity, and interpretive context, not biological value. They also prevent category inflation. A secondary domain should be assigned only when supported by human endpoint evidence, a measurable biomarker pathway, or a clearly defined mechanistic bridge. Pathway activation alone is not sufficient to claim a broad functional endpoint. This is especially important for functional mushrooms, adaptogens, polyphenols, senolytic-oriented compounds, and metabolic botanicals.

The mechanism-to-endpoint logic is operationalized in Table 4. The table links representative compounds to primary mechanisms, possible biomarkers, and functional endpoints, thereby connecting supplementation to measurable healthspan-relevant domains.

Table 4. Mechanism-to-Endpoint Mapping of Representative OTC Compounds

Compound	Primary mechanism	Possible marker	Functional endpoint
Creatine	Phosphocreatine energy buffering	Lean mass, strength, cognitive performance under stress	Muscle-brain energetic reserve
GlyNAC	Glutathione precursor support	Glutathione, oxidative stress, inflammation	Fatigue, recovery, metabolic resilience
L-glutamine	Enterocyte fuel, immune-cell substrate, gut-barrier support	Gastrointestinal symptoms, intestinal permeability markers, recovery indicators	Gut-barrier integrity, immune resilience
Urolithin A	Mitophagy and mitochondrial quality control	Mitochondrial biomarkers	Muscle endurance, energy resilience
Berberine	Glucose and lipid pathway modulation	Fasting glucose, glycated hemoglobin A1c (HbA1c), triglycerides	Metabolic flexibility
Omega-3 fatty acids	Membrane and inflammatory signaling	Omega-3 index, high-sensitivity C-reactive protein (hs-CRP), lipids	Vascular, inflammatory, cognitive support
PEA	Neuroimmune and low-grade inflammatory modulation	Pain scores, inflammatory markers, recovery indicators	Pain resilience, mobility, recovery
Allulose	Postprandial glucose and endogenous incretin-related effects	Postprandial glucose, insulin, glucagon-like peptide-1 (GLP-1), peptide YY (PYY) where studied	Diet adherence, metabolic flexibility, weight-loss support

Compound	Primary mechanism	Possible marker	Functional endpoint
Fenugreek	Glucose, insulin, lipid, and androgen-adjacent signaling	Fasting glucose, HbA1c, insulin, lipids, testosterone where relevant	Metabolic flexibility, vitality, body-composition support
Jiaogulan	Adenosine monophosphate-activated protein kinase (AMPK)-linked metabolic and adaptogenic signaling	Glucose, lipids, body composition, exercise-related outcomes	Metabolic resilience, exercise adaptation
Triphala	Gut-polyphenol and microbiome-related signaling	Bowel function, microbiome markers, oxidative/metabolic markers	Gut-metabolic resilience
Bacopa monnieri	Neurocognitive and antioxidant botanical signaling	Memory tasks, attention, cognitive scales	Learning, memory, cognitive resilience
Functional mushrooms	Beta-glucans, polysaccharides, triterpenoids, phenolics, ergothioneine, and species-specific metabolites	Immune markers, gut symptoms, recovery markers, cognitive measures depending on species	Immunometabolic, neurocognitive, gut-immune, antioxidant, and recovery support
Astragalus membranaceus	Immunomodulatory, antioxidant, mitochondrial, and telomere-related botanical signaling	Immune markers, inflammatory markers, telomere-related markers where studied	Immune-aging and adaptogenic support
Formulation-specific liver-support products	Multi-herb hepatoprotective support	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), appetite, liver-function indicators	Liver-related functional support
Collagen plus vitamin C	Collagen substrate and synthesis support	Skin, joint, tendon, connective-tissue markers	Structural durability
Ashwagandha	Stress and neuroendocrine modulation	Cortisol, sleep, perceived stress	Stress resilience and recovery

GlyNAC is included because clinical studies in older adults suggest that combining glycine and NAC can increase glutathione availability and influence oxidative stress, mitochondrial function, inflammation, and age-associated functional domains [11]. Urolithin A is included because randomized human data in older adults suggest effects on muscle endurance and mitochondrial-related biomarkers [12]. Berberine is

included because systematic reviews and meta-analyses report effects on glucose and lipid metabolism, especially in metabolic syndrome and type 2 diabetes contexts [13]. Allulose is included as a diet-architecture compound because evidence supports postprandial glucose attenuation and incretin-adjacent metabolic effects [14,15]. PEA is included as a neuroimmune and pain-resilience compound because systematic reviews and meta-analyses support its relevance in pain and inflammatory symptom contexts [16,17]. Fenugreek is included because clinical meta-analyses support glucose-related effects, while androgen-adjacent outcomes require narrower interpretation [18,19]. Gynostemma pentaphyllum is included because randomized-trial reviews suggest lipid and metabolic relevance [20]. Triphala and Bacopa monnieri are included as formulation-sensitive botanicals with gut-metabolic and neurocognitive relevance [21-24]. Collagen peptides and vitamin C are included because collagen supplementation has been reviewed in relation to joint, tendon, connective-tissue, and exercise-recovery outcomes [25,26]. Ashwagandha is included because evidence summaries support stress, anxiety, sleep, and cortisol-related outcomes [27].

6. Primary and Secondary Domain Assignment

Because several compounds affect more than one biological domain, primary and secondary domain assignment is required to prevent category inflation. Table 5 applies this distinction by assigning each compound to a primary domain and a conditional secondary domain.

Table 5. Primary and Secondary Domain Assignment

Compound	Primary domain	Secondary domain
Creatine	Muscle-brain energy	Strength, cognition, performance, aging-related muscle preservation
L-glutamine	Gut-barrier and immune substrate	Recovery, training stress, catabolic burden
Omega-3 fatty acids	Membrane and inflammatory signaling	Vascular function, cognition, lipid signaling
Magnesium	Electrolyte and neuromuscular substrate	Sleep, glucose regulation, stress physiology
Berberine	Metabolic flexibility	Glucose, lipids, gut-metabolic signaling
PEA	Neuroimmune inflammation	Pain resilience, mobility, recovery
Allulose	Diet architecture	Postprandial glucose, appetite, weight-loss support
Fenugreek	Metabolic regulation	Appetite, lipids, androgen-adjacent vitality
Bacopa monnieri	Neurocognition	Antioxidant and neuroinflammatory modulation
Triphala	Gut-metabolic polyphenol support	Microbiome interaction, oxidative balance
Jiaogulan	Metabolic-adaptogenic signaling	AMPK-linked exercise and weight-management hypotheses
Functional mushrooms	Species-specific immunometabolic signaling	Cognition, gut-immune support, exercise recovery, skin and structural aging depending on species

Compound	Primary domain	Secondary domain
Astragalus membranaceus	Immune-aging and adaptogenic botanical	Oxidative stress, mitochondrial protection, telomere-related hypotheses
Red yeast rice	Lipid-modifying nutraceutical	Pharmacological overlap with statin-like pathways
TUDCA	Liver, bile, and endoplasmic-reticulum stress support	Mitochondrial and metabolic-liver contexts
Formulation-specific liver-support products	Liver-function support	Appetite, liver enzymes, metabolic-liver contexts

This table clarifies the primary reason for inclusion while allowing secondary roles without turning multi-pathway compounds into nonspecific panaceas. A compound may have human evidence in one domain, mechanistic plausibility in another, and only theoretical relevance in a third. These levels should remain separate.

7. Intake, Dose, and Interaction Architecture

Supplement effects depend on timing, meal context, absorption conditions, dose logic, and functional purpose, such as creatine, citicoline, Alpha-GPC, B vitamins, CoQ10, MCT oil, and selected NAD precursor strategies. Evening use may fit compounds aligned with recovery, sleep quality, autonomic regulation, or stress downshifting, such as magnesium, glycine, taurine, L-theanine, gamma-aminobutyric acid (GABA), and ashwagandha in selected individuals.

Food context matters. Fat-soluble compounds such as vitamin D, vitamin K2, omega-3 fatty acids, CoQ10, astaxanthin, and some polyphenols are often better aligned with fat-containing meals. Berberine, allulose, fenugreek, fiber, and. Morning or daytime use may fit compounds that support energy, cognition, metabolism, or training performance psyllium are often interpreted in relation to meals because of postprandial glucose, appetite, and metabolic effects.

Dose should be interpreted as a dynamic biological variable rather than a fixed consumer instruction. Table 6 summarizes the main dosing logics used in this model, ranging from deficiency correction to cyclic and situational use.

Table 6. Dose and Intake Logic in OTC Healthspan Optimization

Dosing logic	Meaning	Examples
Deficiency correction	Correction of documented insufficiency	Vitamin D, cobalamin vitamin B12, iron, iodine, magnesium
Maintenance support	Sustained physiological sufficiency	Omega-3 fatty acids, protein, minerals, vitamins
Functional optimization	Performance, cognition, recovery, resilience	Creatine, glycine, CoQ10, magnesium

Dosing logic	Meaning	Examples
Targeted domain use	Specific pathway or biomarker target	Berberine, red yeast rice, TUDCA, pyridoxal-5-phosphate (P-5-P), PEA, fenugreek
Gut-barrier and immune-substrate use	Conditional substrate support under gastrointestinal, immune, or catabolic demand	L-glutamine, zinc, omega-3 fatty acids, vitamin D
Diet-architecture use	Diet adherence, glucose handling, appetite context	Allulose, fiber, psyllium, protein
Botanical and mushroom domain use	Multi-pathway support of metabolism, stress, cognition, gut, immune function, or liver function	Ashwagandha, Brahmi, Triphala, Jiaogulan, Lion's Mane, Reishi, Cordyceps, Astragalus, formulation-specific liver-support products
Cyclic use	Defined periods followed by pauses	Fisetin, quercetin, berberine, selected adaptogens, intensive NAD strategies
Situational use	Context-dependent use	Electrolytes during heat or training, L-theanine for stress, glycine for sleep

Interaction logic is part of optimization. Glycine and NAC support glutathione synthesis through complementary substrate supply. Vitamin D, vitamin K2, and magnesium form a cofactor logic in calcium metabolism, bone function, muscle function, and endocrine physiology. Vitamin B12, folate, pyridoxal-5-phosphate (P-5-P), and trimethylglycine (TMG) intersect with methylation and homocysteine metabolism.

Mineral timing requires kinetic interpretation. Divalent ions such as calcium, magnesium, iron, and zinc can compete for intestinal absorption through overlapping transporter systems and luminal binding dynamics. Non-heme iron uptake is strongly linked to divalent metal transporter 1 (DMT1), and calcium can inhibit iron absorption in a dose-dependent manner. High-dose mineral protocols should therefore be sequenced when the target is iron repletion, magnesium repletion, zinc correction, thyroid-medication timing, or avoidance of absorption interference [28].

Fiber may alter absorption of medications or other compounds if taken simultaneously. Glucose-modulating compounds such as berberine, alpha-lipoic acid, fiber, allulose, fenugreek, and cinnamon may overlap in metabolic effects. The central question is whether combinations are intentional, interpretable, and endpoint-aligned.

8. Medication Context and Pharmacological Alignment

Medication use changes supplement strategy. A supplement may be supportive, compensatory, timing-dependent, interaction-sensitive, or pharmacologically overlapping.

Metformin use has been associated with vitamin B12 depletion in long-term follow-up studies, making B12 monitoring relevant in this medication context [29]. Proton-pump inhibitors and diuretics are common examples of medication contexts in which magnesium or electrolyte status may require closer interpretation. Berberine, alpha-lipoic acid, fiber, allulose, fenugreek, and other glucose-modulating

compounds require different interpretation in people using antidiabetic medication. Beetroot nitrate, citrulline, magnesium, taurine, and CoQ10 may influence vascular tone and should be interpreted differently in people using antihypertensive therapy. Red yeast rice is a lipid-modifying nutraceutical with statin-like pharmacological overlap. Minerals such as calcium, magnesium, iron, and zinc may require timing separation from thyroid medication, selected antibiotics, and bisphosphonates. Multi-herb formulas should be interpreted through the tested formulation rather than assumed equivalent across products.

Medication context does not negate OTC healthspan optimization; it individualizes it. Some supplements become more relevant because medication use creates depletion, while others require timing separation, biomarker monitoring, or avoidance of pharmacological duplication.

9. Formulation, Purity, and Bioavailability

A supplement is not defined only by its name. Table 7 summarizes the formulation, purity, standardization, bioavailability, and contaminant-control variables that determine whether a product can be meaningfully interpreted as a biological intervention.

Table 7. Formulation, Purity, and Bioavailability Variables

Compound or category	Formulation variable
Magnesium	Form differs by tolerability and target use, including glycinate, citrate, oxide, malate, and L-threonate.
Curcumin	Bioavailability depends on formulation, including phytosome, liposomal, piperine-enhanced, or other delivery systems.
CoQ10	Form and delivery system may differ, including ubiquinone and ubiquinol preparations.
Collagen peptides	Hydrolysis, peptide profile, and dosing form influence interpretation.
Bacopa monnieri	Standardization to bacosides is relevant for comparing studies and products.
Ashwagandha	Standardization to withanolides and extract type influence interpretation.
Fenugreek	Extract standardization may involve saponins, protodioscin-related fractions, or 4-hydroxyisoleucine-related metabolic activity.
Red yeast rice	Monacolin K content, statin-like pharmacological overlap, batch variability, citrinin contamination, and contaminant testing are central. Citrinin is a nephrotoxic mycotoxin and a decisive quality-control variable.
Shilajit	Purification and standardization of humic and fulvic acid fractions are essential.
Functional mushrooms	Species identity, fruiting body versus mycelium, beta-glucan content, polysaccharide standardization, triterpenoid profile, extraction method, molecular weight, solubility, bioavailability, and contaminant testing determine interpretation.
Astragalus membranaceus	Root extract quality, astragaloside IV, cycloastragenol content, polysaccharide fraction, and whether evidence refers to a single-herb extract, TA-65-like compound, or multi-ingredient formula are central.

Compound or category	Formulation variable
Algae products	Heavy-metal and contaminant testing is essential for spirulina and chlorella products.
Formulation-specific liver-support products	Evidence applies to the tested formula, not automatically to all products with similar herbal labels.

The real intervention is not the marketing name, but the compound, dose, purity, formulation, bioavailability, and biological exposure. Red yeast rice illustrates this point because monacolin K content, statin-like pharmacological overlap, and citrinin contamination can vary across products. Citrinin is a nephrotoxic mycotoxin produced during some Monascus fermentation processes and should be treated as a central purity marker in red yeast rice quality assessment [30-32]. Shilajit illustrates formulation dependence because heavy-metal profiles and purification status are central to interpreting biological exposure [33]. Functional mushrooms require species identity, fruiting-body versus mycelium source, beta-glucan content, polysaccharide structure, extraction method, and contaminant testing [34-38]. Astragalus membranaceus requires distinction between whole-root extract, astragaloside-containing extract, cycloastragenol-containing preparations, TA-65-like preparations, and multi-ingredient formulas [39-41].

10. Substrate and Functional Performance Optimization

Substrate optimization includes compounds that support biological capacity beyond deficiency prevention. Protein and essential amino acids support muscle protein synthesis, tissue repair, immune function, enzyme systems, recovery, and healthy aging. Leucine is especially relevant in aging-related anabolic resistance. Beta-hydroxy-beta-methylbutyrate (HMB) may be considered in muscle-preservation contexts, especially where frailty, catabolic burden, or low protein intake is present [4].

L-glutamine belongs to gut-barrier and immune-substrate support. Its relevance is not vague “gut support,” but epithelial energy metabolism and barrier maintenance. Glutamine is a major oxidative fuel for rapidly renewing intestinal epithelial cells, including enterocytes and colonocytes under high-demand conditions. It supports mucosal repair, immune-cell metabolism, and tight-junction integrity, including regulation of barrier proteins such as claudin-1, occludin, and zonula occludens proteins. Its strongest use is targeted: high training load, gastrointestinal stress, catabolic burden, immune demand, inflammatory mucosal stress, or impaired recovery [8,42].

Omega-3 fatty acids support membrane biology, inflammatory balance, lipid signaling, vascular function, and possibly brain health. The DO-HEALTH analysis of older adults reported a small protective effect of omega-3 supplementation on DNA-methylation clocks over three years, with additive effects when combined with vitamin D and exercise [9]. Magnesium is central to neuromuscular function, energy metabolism, sleep, glucose regulation, blood pressure, stress response, and exercise recovery [5]. Vitamin D3, vitamin K2, zinc, selenium, iodine, copper, B vitamins, electrolytes, and trace elements influence bone, thyroid function, immune function, methylation, endocrine physiology, and cellular metabolism.

Creatine is best classified as a muscle-brain bioenergetic compound. It supports phosphocreatine-dependent energy buffering in skeletal muscle and brain, with relevance to strength, power, lean mass,

training adaptation, fatigue resistance, muscle preservation, cognitive stress resilience, and sleep-deprivation-related performance [6,7].

Glycine supports sleep quality, collagen synthesis, glutathione pathways, methylation balance, and inhibitory neurotransmission. Taurine intersects osmoregulation, mitochondrial function, cardiovascular balance, inhibitory signaling, and stress resilience. L-theanine supports calm focus and autonomic regulation. Collagen peptides support connective tissue, tendons, skin, joints, and structural durability [25,26]. Citicoline, Alpha-GPC, and phosphatidylserine support cholinergic, membrane, and stress-related cognitive domains.

11. Cellular Signaling, Metabolic Flexibility, and Inflammation

The cellular signaling layer includes compounds that influence mitochondrial quality, redox balance, inflammation, glucose handling, lipid signaling, vascular function, gut-metabolic signaling, immune modulation, and adaptive stress responses.

Urolithin A is relevant to mitophagy and mitochondrial quality control. In older adults, urolithin A supplementation was associated with improved muscle endurance and mitochondrial-related biomarkers [12]. CoQ10 supports mitochondrial electron transport and cellular energy. PQQ is discussed in relation to mitochondrial biogenesis and redox signaling. NAD precursors such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) influence NAD metabolism, while TMG may support methylation demands related to NAD precursor strategies. Trials generally support increases in NAD-related biomarkers, while clinical outcome evidence remains less mature than biomarker evidence [43,44].

NAC and glycine support glutathione synthesis through complementary substrate logic. NAC supplies cysteine, the frequently limiting intracellular substrate for the first enzymatic step, in which glutamate and cysteine form gamma-glutamylcysteine through gamma-glutamylcysteine synthetase. Glycine supports the second step, in which glutathione synthetase adds glycine to gamma-glutamylcysteine to form reduced glutathione. GlyNAC is therefore a kinetic substrate strategy, not merely an antioxidant stack. Clinical work in older adults suggests improvements in glutathione status, oxidative stress, mitochondrial function, inflammation, and physical function [11,45].

Vitamin C, astaxanthin, alpha-lipoic acid, quercetin, resveratrol, OPC, curcumin, Triphala, and sulforaphane intersect redox and inflammatory signaling. Curcumin has been reviewed in relation to oxidative and inflammatory conditions, metabolic syndrome, arthritis, and lipid-related outcomes [46]. Sulforaphane is relevant through nuclear factor erythroid 2-related factor 2 (Nrf2)-linked cytoprotective and inflammatory-response pathways [47,48]. Spermidine is included as an autophagy-linked compound because experimental and translational studies connect spermidine availability with fasting-related autophagy and healthspan mechanisms [49,50].

Berberine supports metabolic flexibility through glucose, lipid, gut, and insulin-related pathways. A recent systematic review and meta-analysis of randomized placebo-controlled trials found significant improvements in glucose and lipid metabolism components of metabolic syndrome [13]. Psyllium and prebiotic fibers support glucose regulation, lipid balance, microbiome function, and gut barrier integrity.

Subclinical low-grade inflammation, sometimes described as silent inflammation, may impair recovery, pain threshold, sleep quality, vascular function, mobility, and metabolic resilience before overt inflammatory disease is diagnosed. PEA belongs to neuroimmune and low-grade inflammation support through inflammatory tone, pain sensitivity, recovery capacity, and functional limitation [16,17].

Allulose belongs to metabolic diet architecture. It is a rare sugar with relevance to sugar reduction, postprandial glucose control, satiety-related gut hormone responses, and weight-loss diet support. Evidence supports postprandial glucose attenuation and incretin-adjacent metabolic effects [14,15].

Fenugreek belongs to metabolic and neuroendocrine optimization. Its strongest relevance lies in glucose handling, insulin sensitivity, lipid-related metabolic support, appetite regulation, and body-composition contexts. In men, selected extracts may also be discussed as androgen-adjacent botanicals with possible relevance to libido, free testosterone interpretation, training response, and vitality [18,19].

Jiaogulan, or Gynostemma pentaphyllum, belongs to metabolic-flexibility and adaptogenic-signaling discussion through gypenoside-related AMPK, glucose, lipid, exercise, and weight-management hypotheses [20].

12. Functional Mushrooms and Astragalus as Classification Examples

Functional mushrooms illustrate why OTC supplements require species-level and formulation-level classification rather than generic product naming. Medicinal mushrooms contain bioactive compounds such as beta-glucans, polysaccharides, triterpenoids, phenolics, ergothioneine, and species-specific metabolites with immunometabolic, antioxidant, neurocognitive, gut-immune, and recovery-related relevance [34-38].

Lion’s Mane, or Hericium erinaceus, is best placed in the neurocognitive domain because of its relevance to cognition, mood, stress resilience, and nerve-growth-factor-related hypotheses [35]. Reishi, or Ganoderma lucidum, belongs primarily to immune-adaptogenic and inflammatory-balance contexts. Cordyceps militaris and Cordyceps sinensis are better placed in the energy, exercise-performance, metabolic, and recovery domains [36]. Turkey Tail, or Trametes versicolor, Shiitake, or Lentinula edodes, Maitake, or Grifola frondosa, and Agaricus blazei or Agaricus subrufescens belong mainly to beta-glucan and immune-modulation contexts [37]. Chaga, or Inonotus obliquus, is best interpreted as an antioxidant and inflammation-oriented mushroom, while Tremella fuciformis may be discussed in skin, hydration, and structural-aging contexts. Poria cocos may be included in gut, fluid-balance, and traditional metabolic-liver contexts.

This mushroom category includes neurocognitive, immunometabolic, antioxidant, gut-immune, structural-aging, and exercise-recovery subdomains. Evidence strength differs by species, extract, preparation, and endpoint. Therefore, mushroom products require species-level naming, fruiting-body versus mycelium distinction, extraction-method description, beta-glucan standardization, and contaminant control.

Astragalus membranaceus belongs to the advanced botanical immune-aging category, but preparation matters. Whole-root extracts are best interpreted through polysaccharide, saponin, flavonoid, immunomodulatory, antioxidant, mitochondrial, and nuclear factor erythroid 2-related factor 2 (Nrf2)-

linked mechanisms. Astragaloside IV is a more specific saponin fraction. Cycloastragenol and TA-65-like preparations belong to a narrower telomerase- and telomere-related category. These are not interchangeable interventions. Astragalus should therefore be interpreted by extract type, astragaloside IV content, cycloastragenol content, polysaccharide fraction, dose, pharmacokinetics, and whether the evidence refers to a single-herb extract, purified compound, TA-65-like compound, or multi-ingredient formula [39-41].

13. Neurocognitive and Stress-Resilience Optimization

Nootropics should be interpreted through brain energy, membrane integrity, cholinergic support, stress regulation, visual cognition, sleep quality, and neuroplasticity support rather than stimulation alone.

Citicoline and Alpha-GPC belong to cholinergic and membrane-support categories. Phosphatidylserine is relevant to neuronal membranes, stress physiology, and cognitive function. Creatine supports brain-energy buffering, particularly where cognitive performance is constrained by sleep deprivation or high energetic demand [7]. Magnesium L-threonate is discussed in relation to brain magnesium and cognition. Lion's Mane belongs to nerve-growth-factor-related and cognitive-support hypotheses [35]. Lutein and zeaxanthin belong to the brain-eye axis, visual processing, and cognitive aging. MCT oil and ketone strategies may support alternative brain-energy metabolism in selected contexts.

Brahmi, or Bacopa monnieri, belongs to neurocognitive optimization through memory, learning, attention, cognitive resilience, antioxidant neuroprotection, and possible neuroinflammatory modulation. Meta-analytic and review literature supports cognitive relevance, with effects influenced by extract, dose, duration, and population [23,24].

Stress resilience is part of healthspan optimization because chronic stress influences sleep, glucose regulation, inflammation, appetite, recovery, immune function, mood, testosterone, thyroid interpretation, and long-term behavior. Ashwagandha belongs to stress-resilience and neuroendocrine optimization. Evidence summaries support effects on perceived stress, anxiety, sleep, and cortisol-related measures [27]. L-theanine supports calm focus and relaxation. Glycine supports sleep and glutathione synthesis. Taurine intersects inhibitory signaling, osmoregulation, mitochondrial function, and cardiovascular balance. Magnesium supports neuromuscular relaxation, sleep, stress response, and energy metabolism. Phosphatidylserine may be relevant to stress-response modulation. Fenugreek, tongkat ali, Astragalus, and selected adaptogenic botanicals may be discussed in vitality-related or androgen-adjacent contexts.
The target is improved adaptive capacity, recovery, clarity, and functional vitality.

14. Structural Aging, Gut-Liver Function, and Endogenous Clearance

Structural aging includes connective tissue, joint resilience, tendon function, ligament integrity, bone density, skin barrier, fascia, muscle attachment, and musculoskeletal durability. Collagen peptides, vitamin C, silica, boron, vitamin D, vitamin K2, magnesium, creatine, omega-3 fatty acids, astaxanthin, hyaluronic acid, and Tremella fuciformis may support this domain. PEA may also be relevant where pain sensitivity, joint discomfort, or neuroimmune burden limits function.

Gut and liver support should be framed through endogenous hepatic, renal, gastrointestinal, bile-acid, microbiome, and barrier systems rather than vague cleansing language. Fiber, psyllium, prebiotics, and

probiotics support gut function, microbiome ecology, stool regularity, lipid metabolism, glucose control, and gut barrier integrity. L-glutamine supports enterocyte energy, mucosal resilience, and immune-cell substrate availability [8,42]. Triphala is a gut-metabolic polyphenol compound with relevance to gastrointestinal function, microbiome interaction, oxidative-stress modulation, metabolic balance, and endogenous clearance support [21,22]. Poria cocos may be considered in traditional gut, fluid-balance, and metabolic-liver contexts, while mushroom beta-glucans may contribute to gut-immune and microbiome-related signaling [37,38].

TUDCA belongs to bile-acid, liver, endoplasmic-reticulum stress, and mitochondrial discussions. NAC and glycine support glutathione-related pathways. Choline supports hepatic lipid handling and methylation-related metabolism. Sulforaphane supports adaptive stress-response and detoxification-enzyme pathways [47,48]. Spirulina and chlorella may be discussed in nutrient-density and environmental-burden contexts. Formulation-specific liver-support products, exemplified by Liv.52-like preparations, should be discussed as tested multi-herb formulations rather than generic herbal categories. This domain matters because supplement response depends on absorption, bile flow, microbiome signaling, hepatic metabolism, intestinal barrier integrity, and inflammatory load.

15. Advanced and Phenotype-Specific Optimization

Advanced optimization compounds are defined by specificity, context dependence, pathway relevance, cyclic use, formulation sensitivity, pharmacological overlap, biomarker dependence, or narrow homeostatic window. Tongkat ali may be discussed in relation to male vitality, libido, stress, and androgen-adjacent outcomes. DIM may be discussed in relation to estrogen metabolism. Low-dose or trace lithium belongs to neuroprotective and mood-stability hypotheses, distinct from pharmaceutical lithium therapy. Red yeast rice is a lipid-modifying nutraceutical with statin-like pharmacological overlap and must be interpreted through lipid markers, monacolin K exposure, citrinin control, medication context, muscle symptoms, liver enzymes, and kidney-function context [30-32]. Shilajit is discussed in relation to mitochondrial and mineral-humic substances, with sourcing and purification as central variables [33]. Fisetin and quercetin may be discussed as senomorphic or senolytic-oriented compounds, more logically as cyclic strategies than continuous background exposure. Spermidine belongs to autophagy and cellular renewal [49,50]. NAD precursors belong to cellular energy and NAD metabolism [43,44]. TUDCA belongs to liver, bile, mitochondrial, and endoplasmic-reticulum stress contexts. Astragalus-based compounds belong to botanical immune-aging and telomere-related hypotheses, with interpretation dependent on preparation, pharmacokinetics, and outcome [39-41].

Supplement needs differ by phenotype. Older adults may require greater attention to protein, essential amino acids, creatine, vitamin D, omega-3 fatty acids, urolithin A, collagen, magnesium, L-glutamine, and muscle-preservation strategies. Vegan or vegetarian individuals may require attention to vitamin B12, creatine, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), iron, zinc, iodine, and protein quality. Athletes may require creatine, electrolytes, magnesium, protein, collagen with vitamin C, taurine, nitrate strategies, L-glutamine, Cordyceps, and recovery compounds. Individuals with metabolic burden may benefit from fiber, allulose, berberine, fenugreek, magnesium, omega-3 fatty acids, alpha-lipoic acid, and polyphenol strategies. Individuals with stress or sleep vulnerability may require magnesium, glycine, taurine, L-theanine, ashwagandha, Reishi, Astragalus, and phosphatidylserine. Individuals with cognitive-performance goals may focus on creatine, citicoline, phosphatidylserine, Bacopa monnieri, Lion’s Mane,

lutein, zeaxanthin, MCT oil, and magnesium L-threonate. Individuals with pain or low-grade inflammatory burden may benefit from PEA, omega-3 fatty acids, curcumin, magnesium, collagen, and recovery-oriented strategies. Individuals with gut, liver, bile, or immune concerns may require attention to fiber, L-glutamine, Triphala, TUDCA, NAC, glycine, choline, sulforaphane, beta-glucans, Turkey Tail, Shiitake, Maitake, Poria cocos, and formulation-specific liver-support compounds.

Phenotype-specific supplementation means that selection should follow the dominant biological bottleneck: substrate deficit, metabolic burden, stress load, gut-barrier demand, cognitive demand, inflammatory tone, tissue durability, medication context, or recovery need.

16. Biomarker-Guided and Sequenced Optimization

Supplements should be evaluated through biomarkers and functional endpoints where appropriate. Biomarkers do not replace function, but they help determine whether supplementation is correcting a gap, supporting a domain, or creating unnecessary biological noise.

Relevant markers may include fasting glucose, fasting insulin, HbA1c, homeostatic model assessment of insulin resistance (HOMA-IR), C-peptide, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, apolipoprotein B (ApoB), lipoprotein(a) [Lp(a)], hs-CRP, ferritin, homocysteine, vitamin B12, folate, methylmalonic acid, magnesium, zinc, selenium, copper, iodine status where relevant, ALT, AST, GGT, bilirubin, creatinine, estimated glomerular filtration rate (eGFR), cystatin C, vitamin D, calcium, parathyroid hormone, testosterone, free testosterone, sex hormone-binding globulin (SHBG), estradiol, dehydroepiandrosterone sulfate (DHEA-S), cortisol, sleep quality, fatigue, reaction time, mood, executive function, pain scores, gastrointestinal symptoms, grip strength, lean mass, and bone density.

Random stacking produces biological noise; sequenced optimization produces interpretable results. A rational sequence begins with substrate optimization: protein, essential fatty acids, minerals, vitamins, electrolytes, sleep, sunlight, resistance training, and dietary quality. The next step is functional support: creatine, glycine, magnesium, collagen, omega-3 fatty acids, L-glutamine where gut-barrier or immune demand is relevant, and compounds aligned with muscle, brain, sleep, recovery, and stress resilience. Metabolic, inflammatory, mitochondrial, gut-liver, mushroom/botanical, and redox compounds can then be added according to specific need. Advanced compounds should be added when the biological target is clear.

The goal is maximal biological coherence, not maximal supplement count.

17. Foundations, Limitations, and Conclusion

Supplements are optimization tools, not substitutes for the physiological foundations of healthspan. Omega-3 fatty acids do not replace dietary quality. Creatine does not replace resistance training. Magnesium does not replace sleep discipline. Collagen does not replace adequate protein intake. L-glutamine does not replace microbiome and gut-health foundations. Berberine, allulose, and fenugreek do not replace metabolic nutrition. Ashwagandha, Reishi, and Astragalus do not replace stress regulation and recovery. NAD precursors do not replace exercise-driven mitochondrial adaptation. Vitamin D does not

fully replace sunlight exposure, circadian rhythm, and outdoor activity. Nootropics do not replace purpose, meaningful work, cognitive challenge, and psychological stability.

This paper is a conceptual evidence-mapping review and does not provide fixed dosing protocols. A central limitation of this model is that it organizes evidence across heterogeneous compounds, mechanisms, and endpoints rather than testing a single intervention. Evidence strength differs substantially between nutrients, botanicals, mushroom extracts, metabolic compounds, and advanced optimization agents. Some compounds are supported by human endpoint data, while others rely mainly on biomarker evidence, mechanistic plausibility, or formulation-specific studies. The model therefore should be interpreted as a classification and decision-architecture tool, not as proof that every included compound produces durable healthspan extension. Its value lies in separating substrate support, functional performance, cellular signaling, formulation quality, dose logic, and phenotype-specific use into a coherent structure for future research and individualized interpretation.

OTC supplements should therefore be organized as functional tools within over-the-counter healthspan pharmacology. The model proposed here classifies supplements into substrate optimization, functional performance support, cellular signaling support, and advanced individualized optimization. Supplement use should be interpreted through timing, dose logic, food context, interaction architecture, medication context, formulation quality, cyclic use, biomarker response, phenotype, and functional outcomes.

The anti-aging question is not whether intake is sufficient to avoid deficiency. The deeper question is whether supplementation, nutrition, training, recovery, sunlight, sleep, and lifestyle together support superior functional reserve. The central distinction is not between natural and pharmaceutical, nor between supplement and medication, but between unstructured consumption and scientifically organized optimization.

18. Conflict of Interest

The author declares no conflict of interest.

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