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From Anti-Aging Medicine to Precision Healthspan Pharmacology: Evidence Domains, Monitoring Requirements, and Practical Boundaries

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Abstract

Pharmacological anti-aging is a rapidly expanding and heterogeneous field. It includes approved drugs used beyond their original indications, repurposed medications, metabolic therapies, hormone optimization, neuroactive compounds, psychedelics, peptides, anabolic agents, nutraceuticals with medication-like effects, and selected experimental compounds. These interventions differ substantially in indication, mechanism, evidence strength, regulatory status, monitoring burden, interaction potential, and long-term risk.

This paper presents a conceptual evidence-mapping review that reframes anti-aging medicine as precision healthspan pharmacology. It argues that anti-aging should not be reduced to disease treatment, survival medicine, or passive acceptance of age-related decline. Its central aim is to exceed age-imposed biological constraints by preserving and expanding functional reserve. Pharmacological intervention should therefore be organized into functional domains: metabolic healthspan, nutrient and electrolyte correction, environmental burden, female and male hormone optimization, neuroendocrine and circadian adjuncts, neuroimmune modulation, vascular support, muscle and skeletal preservation, neurofunctional and neuroenergetic activation, psychedelic neuroplasticity, neuropeptide research, experimental longevity peptides, repair peptides, nutraceutical-pharmacological overlap, and mechanistically heterogeneous experimental compounds.

The central criterion is not whether a compound is marketed as anti-aging, but whether it plausibly supports a defined healthspan domain and whether its evidence maturity, monitoring burden, interaction profile, and safety profile justify its classification. The paper also emphasizes that pharmacology cannot replace the foundations of human physiology and psychosocial health: adequate nutrition, sufficient protein and essential amino acids, essential fatty acids, micronutrients, fiber, minerals, sunlight, movement, resistance training, deep sleep, recovery, structured stress reduction, meaningful social contact, personally significant goals, purpose and meaning in life, and the reduction of avoidable metabolic, toxicological, and inflammatory stressors. These foundations are especially important because modern environments differ substantially from earlier human environments: food is quantitatively abundant but not always nutrient-dense, air pollution is widespread, water and air may contain microplastics, and

animal-derived foods may carry contaminant burdens such as veterinary drug residues, hormonal growth-promoter residues, or heavy metals in fish. The conclusion is that precision healthspan pharmacology should be organized around functional domains, evidence maturity, sex-specific evaluation, biomarker monitoring, nutrient and electrolyte status, environmental burden, protocol-level risk, psychosocial meaning, and long-term safety.

Keywords: precision healthspan pharmacology, anti-aging medicine, healthspan optimization, functional aging, metabolic healthspan, hormone optimization, neurofunctional activation, neuroenergetics, neuroplasticity, peptides, nutraceutical-pharmacological overlap, biomarker monitoring, environmental burden, purpose in life, longevity medicine, off-label pharmacology

1. Introduction: From Anti-Aging Medicine to Precision Healthspan Pharmacology

Anti-aging medicine has entered a pharmacological phase. Earlier anti-aging discourse was often dominated by cosmetic interventions, vitamins, antioxidants, lifestyle advice, and generalized wellness claims. Contemporary anti-aging pharmacology is broader and more complex. It now includes metabolic drugs, hormone optimization, anabolic compounds, neuroactive agents, psychedelics, peptides, mitochondrial compounds, immune modulators, nutraceuticals with medication-like effects, and selected experimental compounds.

This expansion creates opportunity and conceptual confusion. Several age-related processes are pharmacologically modifiable. Obesity, insulin resistance, visceral adiposity, fatty liver, menopause-related hormone decline, male endocrine decline, sarcopenia, chronic inflammation, endothelial dysfunction, fatigue, depression, cognitive impairment, psychological rigidity, and functional decline all interact with aging. However, not every drug that changes a biomarker belongs to the same category. A compound may reduce disease risk, optimize function, support resilience, modulate symptoms, or remain primarily experimental.

The central problem is classificatory. Pharmacological anti-aging requires a model that distinguishes disease treatment, prevention, nutrient correction, hormone optimization, healthspan-oriented risk reduction, functional support, experimental intervention, nutraceutical overlap, and research-boundary use. Without these distinctions, anti-aging pharmacology becomes a list of unrelated substances rather than a coherent scientific field.

This paper presents a conceptual evidence-mapping review. Its purpose is to classify major substance domains, identify plausible mechanisms, separate stronger from weaker evidence categories, and define practical boundaries. The organizing criterion is functional healthspan, defined here as the preservation and expansion of metabolic resilience, muscle, mobility, cognition, psychological flexibility, hormonal vitality, recovery capacity, vascular performance, and quality of life.

Anti-aging medicine should not be reduced to disease treatment, survival medicine, or passive acceptance of age-related decline. Its central aim is to exceed age-imposed biological constraints by preserving and expanding functional reserve. In this sense, anti-aging is not merely restoration to an average age-matched baseline, because age-matched baselines may themselves reflect decline. The relevant goal is optimized healthspan: metabolic resilience, endocrine vitality, muscle and skeletal integrity, cognitive function,

vascular performance, recovery capacity, sleep quality, psychological flexibility, meaningful purpose, and long-term functional strength.

2. Definitions and Conceptual Boundaries

The term anti-aging is often used imprecisely. In popular contexts, it may refer to skin appearance, weight loss, sexual function, energy, mood, cognitive performance, hormone optimization, or lifespan extension. Scientific use requires greater precision.

In this paper, anti-aging refers to interventions intended to reduce, delay, or counteract age-related decline while preserving or expanding functional reserve. Healthspan refers to the preservation and optimization of function, mobility, cognition, metabolic health, hormonal vitality, body composition, psychological resilience, recovery capacity, meaningful purpose, and quality of life. Longevity refers to lifespan extension. A drug may improve healthspan without proving lifespan extension.

Optimization refers to the monitored attempt to exceed age-depressed baselines, preserve youthful functional reserve, and improve performance-relevant healthspan markers beyond mere disease avoidance. It does not mean accepting population averages as optimal simply because they are common. In aging biology, the average often reflects accumulated decline. Precision healthspan pharmacology therefore aims to shift function upward: toward stronger metabolic resilience, endocrine vitality, muscle integrity, recovery capacity, cognitive function, vascular performance, sleep quality, adaptive reserve, and psychosocial vitality.

This must be distinguished from unmonitored high-risk escalation. The problem is not optimization itself, but intervention without biomarkers, functional endpoints, risk stratification, interaction assessment, or stopping criteria.

Off-label use refers to the use of an approved medication outside its approved indication. A repurposed drug is an established medication investigated for a new therapeutic purpose or mechanism. Hormone optimization refers to correction, restoration, or functional improvement of endocrine status in relation to symptoms, biomarkers, body composition, recovery, sexual function, mood, and long-term healthspan. A neuroendocrine adjunct is a compound that influences adrenal, steroidogenic, neurosteroid, mitochondrial, circadian, or cognitive pathways without functioning as primary hormone replacement. Neurofunctional activation refers to support of wakefulness, task initiation, effort tolerance, fatigue resistance, executive function, and the transition from intention to action. Neuroenergetic adjuncts refer to interventions that may support brain-energy metabolism or mitochondrial signaling. A psychoplastogen is a compound that may promote structural or functional neural plasticity. A nutraceutical-pharmacological overlap compound is a supplement-like substance with medication-like mechanisms or biomarker effects. A research-boundary compound is a substance whose discussion is primarily mechanistic, preclinical, or exploratory rather than clinically established. A multi-compound concept is a combined protocol or stack that lacks independent validation as a defined therapy.

These distinctions matter because each category requires a different evidentiary threshold. A postmenopausal hormone therapy used to address ovarian hormone decline cannot be evaluated like an experimental peptide. A metabolic drug used for obesity or diabetes has a different evidentiary position

than a compound used for hypothetical neurogenesis. A psychedelic studied for depression or trauma belongs to plasticity and psychological flexibility rather than direct lifespan extension. A nutraceutical with medication-like activity should not be treated as harmless merely because it is sold outside prescription channels.

3. Scope and Methodological Approach

This paper uses a conceptual scoping evidence-mapping framework. It is designed as a narrative conceptual review and map, not as a formal systematic review, meta-analysis, Joanna Briggs Institute scoping review, Arksey-and-O'Malley scoping review, or Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-based evidence synthesis. Its purpose is to organize a heterogeneous field into pharmacological domains, evidence maturity categories, monitoring requirements, environmental context, psychosocial foundations, protocol-level interaction risks, and practical boundaries. Sources were selected according to their relevance for conceptual classification, mechanistic plausibility, evidence maturity, monitoring requirements, and practical boundary-setting.

The paper does not provide a dosing protocol, prescribing guide, or consumer-use manual. Interventions are classified by biological domain, proposed healthspan relevance, evidence maturity, monitoring requirements, risk profile, and practical boundary between treatment, optimization, prevention, nutraceutical support, and research-boundary use.

A substance is included only when it can be linked to a defined functional domain such as metabolic resilience, endocrine optimization, skeletal integrity, cognition, neuroplasticity, tissue repair, inflammatory burden, nutrient status, recovery capacity, psychosocial function, environmental burden, or functional performance. Human evidence, translational animal evidence, cellular evidence, and mechanistic plausibility are kept conceptually separate.

4. Healthspan Domains and Pharmacological Classification

Pharmacological healthspan intervention can be organized into functional domains. The following classification map prevents unrelated interventions from being grouped under one vague anti-aging label.

Table 1. Functional Domains of Precision Healthspan Pharmacology

Domain	Examples	Functional logic	Paper position
Metabolic healthspan	Retatrutide, tirzepatide, semaglutide, metformin, sodium-glucose cotransporter 2 (SGLT2) inhibitors, acarbose	Obesity, insulin resistance, visceral fat, fatty liver, inflammation, mobility	Central category
Nutrient, electrolyte, and acid-base management	Vitamin B12, magnesium, bicarbonate correction where indicated	Drug-induced depletion, electrolyte shifts, metabolic acidosis	Monitoring and correction category
Environmental burden	Air pollution, microplastics, heavy	Toxicological load, inflammation, oxidative	Foundational context

Domain	Examples	Functional logic	Paper position
	metals, food contaminants, veterinary drug residues	stress, endocrine disruption, metabolic stress	
Psychosocial foundations	Social contact, goals, purpose, meaning, stress-reduction practices	Resilience, mortality risk, emotional stability, adherence, adaptive capacity	Foundational context
Female hormone optimization	Estradiol, progesterone	Menopause, bone, sleep, urogenital health, mood, connective tissue, body composition	Central sex-specific category
Male hormone optimization	Testosterone, human chorionic gonadotropin (hCG), selected axis-preserving approaches	Libido, muscle, mood, energy, body composition, recovery, fertility-related axis preservation	Functional endocrine category
Hormone-management adjuncts	Aromatase-inhibitor alternatives, topical hair-loss adjuncts	Estradiol balance, dihydrotestosterone (DHT)-related scalp sensitivity, side-effect management	Supportive category
Neuroendocrine-cognitive adjuncts	Pregnenolone, dehydroepiandrosterone (DHEA), 7-keto-dehydroepiandrosterone (7-keto-DHEA), melatonin	Neurosteroids, cognition, mood, adrenal aging, circadian and mitochondrial regulation	Adjunct category
Immune and inflammatory modulation	Low-dose naltrexone	Neuroimmune modulation, chronic pain, fatigue, inflammatory burden	Functional support category
Vascular and endothelial function	Tadalafil	Endothelial function, nitric oxide signaling, urogenital function	Secondary healthspan category
human growth hormone (HGH) / insulin-like growth factor 1 (IGF-1) axis	HGH, secretagogues, IGF-1-related approaches	Somatotropic decline, recovery, tissue resilience, body composition	High-monitoring category
Muscle, skeletal, and frailty preservation	Resistance training, protein, selected anabolic agents	Muscle, strength, bone, joints, mobility, frailty prevention	Functional endpoint category

Domain	Examples	Functional logic	Paper position
Neurofunctional and neuroenergetic aging	Very-low-dose methylphenidate, modafinil, methylene blue, exogenous ketones	Task initiation, fatigue resistance, wakefulness, brain-energy metabolism	Functional capacity category
Psychedelic neuroplasticity	Psilocybin, lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), ayahuasca, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), ketamine	Plasticity, emotional relearning, psychological flexibility	Research domain
Neuropeptide adjuncts	Semax, Selank, Cerebrolysin-like approaches	Cognition, neurotrophic signaling, stress regulation	Experimental or regionally validated
Experimental longevity peptides	Epitalon, MOTS-c, SS-31, Pinealon	Telomere, pineal, circadian, mitochondrial hypotheses	Experimental category
Repair and recovery peptides	body protection compound 157 (BPC-157), thymosin beta-4-related TB-500 (TB-500), glycyl-L-histidyl-L-lysine copper complex (GHK-Cu), lysine-proline-valine peptide (KPV)	Tissue repair, inflammation, skin, hair, gut barrier, recovery	Mechanistic / limited human evidence
Nutraceutical-pharmacological overlap	Red yeast rice, palmitoylethanolamide (PEA), pyridoxal-5-phosphate (P-5-P), alpha-glycerophosphocholine (Alpha-GPC)	Medication-like mechanisms, pain, lipids, prolactin, cholinergic cognition	Boundary category
Experimental compounds	ISRIB, NSI-189, Dihexa	Proteostasis, integrated stress response, neurogenesis, synaptogenesis	Research-boundary category
Multi-compound concepts	Repair-peptide, neuroendocrine, metabolic, and nutraceutical combinations	Combined exposure, possible interaction burden	Protocol-risk category

4.1 Physiological, Environmental, and Psychosocial Foundations That Pharmacology Cannot Replace

Pharmacological anti-aging should be understood as an adjunct to the foundations of human physiology and psychosocial health. Adequate nutrition, hydration, protein and essential amino acids, essential fatty acids, fiber, vitamins, minerals, trace elements, sunlight exposure, movement, resistance training, deep sleep, recovery, structured stress reduction, meaningful social contact, personally significant goals, and purpose and meaning in life remain essential for metabolic health, muscle preservation, immune resilience, hormone regulation, cognition, tissue repair, emotional stability, adaptive capacity, and long-term functional reserve [1–11].

Stress reduction should not be treated as a vague wellness phrase. In a healthspan model, it includes structured practices such as meditation, relaxation exercises, breathing exercises, restorative time in nature, and, where appropriate, technology-assisted relaxation tools such as binaural beats or audio-visual entrainment devices. These methods differ in evidence strength and should not be treated as interchangeable: meditation, breathwork, and nature exposure have broader clinical and psychological evidence, whereas binaural beats and mind-machine-like audio-visual entrainment approaches are best framed as adjunctive and emerging relaxation tools rather than core healthspan foundations [7-11].

The modern environment changes the meaning of anti-aging. Human physiology did not evolve in the current mixture of abundant calories, reduced nutrient density, environmental pollutants, artificial light exposure, sedentary work, chronic psychosocial stress, indoor living, sleep disruption, and widespread chemical exposure. Food is more available than ever in many societies, but quantity does not guarantee quality. Historical food-composition analyses suggest that selected fruits and vegetables may contain lower concentrations of some minerals and vitamins than decades ago, partly because high-yield agricultural selection can dilute nutrient density [12]. Therefore, modern healthspan optimization requires attention to nutrient density, protein quality, essential fatty acids, mineral status, micronutrients, fiber, and food-source quality.

The same foundational logic also requires reducing exposures that accelerate functional decline. Regular alcohol intake, tobacco smoking, highly processed foods, industrial trans fats, and chronically high sugar consumption can undermine metabolic health, vascular function, inflammatory balance, mitochondrial resilience, body composition, sleep quality, and long-term functional capacity [13-17].

Environmental load also matters. Fine particulate air pollution is associated with cardiovascular, respiratory, metabolic, and inflammatory burden [18]. Microplastics have been detected in drinking water, table salt, and air, making chronic exposure a relevant modern healthspan variable even though long-term causal effects remain under investigation [19]. Animal-derived foods may carry contaminant concerns. Meat may contain residues of veterinary drugs, antibiotics, or hormonal growth promoters depending on region, production method, regulation, and enforcement [20,21]. Fish remains nutritionally valuable because of protein, iodine, selenium, and omega-3 fatty acids, but some species accumulate methylmercury and other contaminants, especially higher-trophic predatory fish [22].

This does not mean that all modern food is harmful or that all animal foods should be avoided. It means that anti-aging medicine must be adapted to the modern exposure environment. Precision healthspan

pharmacology should consider not only hormones, drugs, and biomarkers, but also food quality, contaminant burden, water quality, air quality, sleep environment, sunlight, movement, stress regulation, social context, goals, and meaning.

Pharmacological interventions may modify selected pathways, correct defined deficiencies, or reduce specific risk factors, but they cannot compensate for chronically poor nutrition, inadequate essential amino acid or essential fatty acid intake, inactivity, insufficient sleep, lack of sunlight, persistent stress overload, social isolation, lack of purpose, or repeated exposure to avoidable metabolic, toxicological, and inflammatory stressors. Precision healthspan pharmacology should therefore be built on physiological, environmental, and psychosocial foundations rather than treated as their replacement.

5. Metabolic Interventions as Drivers of Functional Healthspan

Metabolic healthspan is one of the strongest current domains in precision healthspan pharmacology. Metabolic dysfunction accelerates functional decline through obesity, insulin resistance, visceral adiposity, hepatic steatosis, chronic inflammation, hypertension, sleep apnea, osteoarthritis-related immobility, and impaired glucose regulation.

5.1 Retatrutide and the Triple-Agonist Shift in Metabolic Healthspan

Retatrutide represents a next-generation triple-agonist metabolic intervention acting through glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and glucagon receptor pathways [23]. Its healthspan relevance lies in the possibility of modifying several metabolic drivers of functional aging at once: obesity, visceral fat, insulin resistance, fatty liver, cardiometabolic burden, sleep-apnea-related stress, inflammatory load, mobility impairment, and obesity-associated decline in quality of life.

The potency of retatrutide also creates specific monitoring requirements. Strong weight-loss therapy must be evaluated together with lean-mass preservation, resistance training, protein intake, bone density, gastrointestinal tolerability, nutritional adequacy, durability of benefit, and rebound after discontinuation. Weight reduction is most relevant to healthspan when it preserves or improves functional reserve.

5.2 Semaglutide and Tirzepatide as Established Incretin-Based Risk Modifiers

Semaglutide and tirzepatide are clinically important metabolic agents with healthspan relevance. They may improve obesity, glycemic control, visceral adiposity, and cardiometabolic stress [24,25]. Their strongest classification is metabolic healthspan support in individuals with defined obesity or metabolic disease risk.

5.3 Lean-Mass Preservation During Pharmacological or Diet-Induced Weight Loss

Metabolic healthspan cannot be reduced to scale weight. Strong weight loss, whether produced by severe caloric restriction, intensive dieting, glucagon-like peptide-1 (GLP-1) receptor agonists, dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) agonists, or triple-agonist metabolic drugs, may reduce not only fat mass but also lean body mass and skeletal muscle mass [26]. This is especially important in older adults, physically active individuals, and anyone at risk for sarcopenia, frailty, low protein intake, or insufficient resistance training.

Loss of skeletal muscle is not a cosmetic issue. It can reduce strength, mobility, glucose disposal, resting metabolic rate, joint stability, fall resistance, recovery capacity, training tolerance, and long-term

functional reserve. Therefore, a weight-loss intervention that improves body weight while significantly reducing skeletal muscle may partly undermine its own healthspan benefit.

A healthspan-oriented metabolic protocol should distinguish fat mass from lean mass. Body-composition monitoring, preferably by dual-energy X-ray absorptiometry or comparable methods, should be combined with resistance training, adequate protein intake, sufficient essential amino acids, and attention to total energy intake. Resistance training can substantially reduce muscle loss during caloric restriction in older adults [27]. In selected high-risk or medically supervised contexts, anabolic support may be considered as part of a muscle-preservation strategy, but it should not replace protein intake, resistance training, and body-composition monitoring.

Changes in metabolic status may also alter endocrine interpretation. In particular, reductions in fasting insulin during strong weight loss or incretin-based therapy can increase sex hormone-binding globulin (SHBG), thereby altering the ratio of total to bioavailable free hormones independently of primary gonadal output [28].

The relevant endpoint is not maximal weight loss, but improved metabolic health with preserved or improved muscle function. Pharmacological weight loss should therefore be judged by body composition, strength, mobility, metabolic markers, endocrine interpretation, and functional reserve rather than by body weight alone.

5.4 Metformin as a Repurposed Metabolic Aging Candidate

Metformin remains a classic repurposed geroscience candidate. Its relevance lies in insulin sensitivity, mitochondrial stress signaling, inflammation, cancer-risk hypotheses, and age-related disease prevention research [29]. Its appropriate classification is a plausible repurposed metabolic candidate with context-dependent healthspan relevance.

5.5 SGLT2 Inhibitors as Cardiorenal and Organ-Fat Risk Modifiers

Sodium-glucose cotransporter 2 inhibitors belong to cardiometabolic, renal, and metabolic-healthspan pharmacology. Their primary relevance lies in type 2 diabetes, kidney protection, heart failure, and cardiovascular-risk reduction in indicated populations [30,31]. In a healthspan framework, they may also be relevant because they can modestly influence body weight, visceral and ectopic fat, blood pressure, glucose burden, and fatty-liver-related metabolic stress. Their role is best described as organ-protective metabolic risk modification rather than primary weight-loss pharmacology.

5.6 Acarbose, Postprandial Glucose, and Translational Geroscience

Acarbose is relevant because of postprandial glucose control, gut-microbiome effects, and translational geroscience interest [32]. Human relevance should be distinguished from animal longevity findings; in this paper, acarbose is discussed primarily as a postprandial glucose and metabolic-risk modifier.

5.7 Nutrient, Electrolyte, and Acid-Base Effects of Metabolic Drugs

Metabolic pharmacology should include monitoring for drug-induced nutrient depletion, electrolyte shifts, and acid-base disturbances. Metformin is the clearest example because long-term use may reduce vitamin

B12 status; therefore, vitamin B12 should be monitored and repleted when deficient, especially when fatigue, neuropathy, anemia, cognitive symptoms, or long-term exposure are present [33,34].
Magnesium status may become relevant in selected medication or healthspan contexts, especially with proton-pump inhibitors, diuretics, high sweat loss, muscle cramps, arrhythmia tendency, fatigue, or increased training load. Magnesium should be treated as a common electrolyte variable that may need monitoring and correction.

Acid-base balance is relevant in selected contexts. SGLT2 inhibitors may rarely contribute to ketoacidosis, while kidney dysfunction or chronic metabolic acidosis may require bicarbonate-based correction. Oral bicarbonate preparations should be understood as targeted correction for documented metabolic acidosis rather than as a general anti-aging adjunct.

6. Female Hormone Optimization After Menopause

Female hormone optimization is a central healthspan domain. After menopause, ovarian estradiol and progesterone decline affects multiple domains of aging biology and function. Menopause is not merely a symptom state; it is a major endocrine transition [35].

6.1 Female Hormone Optimization After Menopause

Estradiol is central to female healthspan after menopause. Its decline is associated with vasomotor symptoms, sleep disruption, mood changes, bone loss, urogenital atrophy, sexual function changes, skin and connective-tissue changes, body-composition shifts, and altered cardiometabolic risk patterns. Systemic hormone therapy requires individualization according to route, dose, age, timing, menopause stage, clotting risk, breast and gynecological risk, liver considerations, and monitoring.

6.2 Progesterone, Endometrial Protection, Sleep, and Neurosteroid Balance

Progesterone must be discussed together with estradiol. In women with an intact uterus, progesterone or a progestogen is generally required when systemic estrogen is used to protect the endometrium. Progesterone also has independent relevance for sleep, mood, neurosteroid signaling, and endocrine balance. Postmenopausal female hormone optimization may require individualized consideration of estradiol and progesterone according to anatomy, symptoms, risk profile, timing, route, and monitoring.

6.3 Restoration and Optimization in Female Hormone Therapy

Female hormone therapy should be understood through the distinction between restoration, optimization, and unmonitored high-risk escalation. In menopause or premature ovarian insufficiency, hormone therapy may address a defined endocrine transition. In broader healthspan contexts, the relevant goal is not maximal hormone exposure, but endocrine support for bone, sleep, urogenital health, mood, connective tissue, body composition, and long-term function.
This distinction avoids both extremes: passive acceptance of avoidable endocrine decline as normal simply because it is common, and excessive hormone exposure that exceeds functional need or safety monitoring.

7. Male Hormone Optimization and Endocrine Axis Management

Male hormone optimization should be discussed separately from female hormone restoration. Male and female endocrine aging are not mirror images. In men, testosterone status is relevant to libido, sexual

function, mood, motivation, energy, muscle mass, strength, bone density, erythropoiesis, body composition, metabolic function, recovery capacity, and overall vitality.

A precision healthspan model should not define endocrine success as mere survival within a broad population reference range. Population averages may reflect age-related decline, obesity, poor sleep, metabolic dysfunction, environmental exposures, medication effects, chronic stress, and secular changes in male testosterone levels. Therefore, the relevant question is not whether a man is barely within a statistical reference interval, but whether his endocrine profile supports optimal functional capacity, body composition, mood, recovery, sexual health, bone integrity, training response, and long-term metabolic resilience.

7.1 Testosterone Optimization Beyond Age-Depressed Baselines

Testosterone therapy or testosterone-supportive intervention should be framed as functional endocrine optimization when the aim is to maintain, restore, or approximate youthful androgen-supported function. Bioavailable testosterone tends to decline with age, and population-level data suggest that testosterone concentrations have also declined across recent decades independently of chronological aging [36,37]. Contemporary low-normal values should therefore not automatically be interpreted as optimal male physiology.

The appropriate goal is not passive adaptation to age-depressed endocrine status, but individualized optimization guided by symptoms, function, biomarkers, body composition, recovery, mood, libido, training response, and safety markers. Evaluation should include total testosterone, free testosterone, sex hormone-binding globulin, luteinizing hormone, follicle-stimulating hormone, estradiol, hematocrit, prostate-specific antigen where appropriate, fertility goals, blood pressure, sleep apnea risk, cardiometabolic status, body composition, libido, mood, training response, recovery, and adverse effects [38].

In selected testosterone protocols, low-dose aspirin may be considered as an antiplatelet adjunct when cardiovascular risk, hematological markers, and bleeding risk justify it, but it should not be presented as a direct substitute for managing testosterone-induced erythrocytosis through dose adjustment, formulation change, sleep-apnea evaluation, or therapeutic phlebotomy where indicated.

This model rejects two errors at once: accepting endocrine decline as optimal merely because it is common, and using androgens without adequate monitoring, functional targets, or risk control.

7.2 Axis-Preserving Approaches in Male Hormone Management

Axis-preserving approaches may be relevant where fertility, testicular function, or endogenous hormonal signaling should be maintained. These approaches should be positioned as individualized options in selected contexts rather than as universal alternatives.

7.3 Estradiol Balance and the Limits of Routine Aromatase Inhibition

Testosterone optimization should not automatically be combined with aromatase inhibitors. Estradiol contributes to bone integrity, sexual function, mood, connective tissue, vascular biology, and general endocrine balance in men. Excessive suppression of estradiol may therefore create its own healthspan costs [39]. When estradiol-related symptoms or excessive aromatization occur, first-line considerations

may include dose adjustment, injection-frequency modification, route selection, body-composition improvement, reduction of excessive adiposity, or avoidance of unnecessarily high androgen exposure.

7.4 Human Chorionic Gonadotropin for Testicular Function and Fertility Preservation During Testosterone Replacement Therapy

Human chorionic gonadotropin (hCG) may be relevant in selected men receiving testosterone replacement therapy (TRT) or optimization therapy, especially when fertility, testicular function, testicular volume, or intratesticular testosterone preservation matters. Exogenous testosterone can suppress luteinizing hormone and follicle-stimulating hormone, thereby reducing intratesticular testosterone and spermatogenesis. Human chorionic gonadotropin can partially substitute luteinizing-hormone-like stimulation of the testes and may help preserve testicular activity during testosterone therapy [40].

7.5 Hair Preservation During Testosterone Optimization

Testosterone optimization may accelerate androgenetic hair loss in genetically susceptible men through increased dihydrotestosterone activity. If scalp hair preservation is relevant, scalp-directed options such as topical finasteride or dutasteride, minoxidil, alfatradiol, and low-level red-light or laser therapy may be considered as hair-preservation adjuncts [41,42]. These approaches should be distinguished from anti-aging therapy itself and should aim to support local scalp management while minimizing unnecessary systemic endocrine disruption.

8. Neuroendocrine and Circadian Adjuncts in Cognitive Aging

Pregnenolone, dehydroepiandrosterone, 7-keto-dehydroepiandrosterone, and melatonin should be separated from primary hormone replacement. Their relevance is neuroendocrine, cognitive, adrenal, circadian, mitochondrial, and metabolic.

8.1 Pregnenolone and Neurosteroid-Based Cognitive Resilience

Pregnenolone is a neurosteroid and steroid precursor. Its healthspan relevance is mainly cognitive and neuroendocrine. Potential domains include memory, mood, stress resilience, sleep architecture, neurosteroid balance, adrenal steroidogenesis, and brain-aging hypotheses [43]. Because pregnenolone may enter downstream steroidogenic pathways, interpretation should include sex-specific endocrine monitoring.

8.2 DHEA, Keto-DHEA, and Age-Related Adrenal Steroid Decline

Dehydroepiandrosterone (DHEA) is an adrenal steroid that declines with age and is discussed in relation to energy, mood, immune function, libido, and body composition [44]. It should be monitored as a steroid precursor rather than treated as a simple adrenal supplement, because downstream conversion varies by sex, adiposity, aromatase activity, enzyme expression, and individual metabolism. In women, DHEA may produce androgenic effects such as acne, hirsutism, hair loss, or voice changes; in men, conversion into estradiol may become relevant in individuals with high aromatase activity or higher adiposity.

7-keto-dehydroepiandrosterone (7-keto-DHEA) belongs to the same adrenal-aging category but has a stronger metabolic emphasis. Unlike standard DHEA, it is not primarily used as a sex-hormone precursor.

Its relevance lies in metabolic rate, thermogenesis, body composition, energy metabolism, and the overlap between adrenal aging and cognitive energy [45].

8.3 High-Dose Melatonin Beyond Sleep: Circadian, Mitochondrial, and Metabolic Boundaries

Melatonin should not be reduced to a sleep aid. In a healthspan context, it may also be discussed as a neuroendocrine, circadian, mitochondrial, antioxidant, anti-inflammatory, and immune-modulatory molecule [46]. Higher-dose melatonin belongs to a research-oriented adjunct category because its proposed relevance extends beyond sleep timing into oxidative stress, mitochondrial function, inflammatory regulation, neuroprotection, and cellular resilience.

The metabolic interpretation depends strongly on timing. High-dose melatonin is typically used at night, ideally separated from food intake and during the sleep-fast period. The main metabolic concern is not nighttime use itself, but elevated melatonin signaling combined with late eating, impaired glucose tolerance, diabetes risk, or melatonin receptor 1B gene (MTNR1B)-related susceptibility [47]. High-dose melatonin should therefore be evaluated by timing, meal proximity, glucose status, insulin dynamics, genotype where available, daytime sedation, and long-term metabolic outcomes.

9. Neuroimmune and Inflammatory Modulation as Functional Support

Chronic inflammation and neuroimmune signaling are important in aging. The relevant question is whether modulation improves defined healthspan endpoints such as pain, fatigue, mobility, mood, sleep, metabolic risk, or neurocognitive function.

9.1 Low-Dose Naltrexone and Neuroimmune Symptom Burden

Low-dose naltrexone (LDN) should be framed as an off-label neuroimmune and inflammatory-modulation candidate. It is relevant to chronic pain, fibromyalgia-like symptom clusters, neuroinflammation hypotheses, immune modulation, and fatigue-related states [48]. Its healthspan relevance is indirect but functional: if chronic pain, inflammation, or neuroimmune dysregulation impairs function, modulation may support healthspan.

9.2 Inflammation as a Functional Endpoint

Inflammation-targeted interventions should be evaluated by functional outcomes rather than inflammatory terminology alone. In this model, anti-inflammatory mechanisms matter when they translate into improved pain, recovery, metabolic resilience, sleep, cognition, or mobility.

10. Vascular and Urogenital Healthspan

Vascular aging contributes to functional decline. Tadalafil may be included as a secondary vascular and endothelial-function candidate.

10.1 Tadalafil, Endothelial Function, and Urogenital Aging

Tadalafil is a phosphodiesterase type 5 inhibitor used for erectile dysfunction and benign prostatic hyperplasia. Its mechanism involves nitric-oxide and cyclic guanosine monophosphate signaling. In a healthspan context, tadalafil may be relevant to endothelial function, vascular responsiveness, urogenital function, sexual health, and cardiometabolic overlap [49].

11. Human Growth Hormone and Insulin-Like Growth Factor 1: Somatotropic Decline, Functional Reserve, and High-Monitoring Optimization

Human growth hormone (HGH) and insulin-like growth factor 1 (IGF-1) are frequently discussed in anti-aging contexts because the somatotropic axis declines with age and influences body composition, recovery, connective tissue, bone, exercise capacity, lipid metabolism, glucose regulation, sleep quality, and general vitality [50,51].

A precision healthspan model should not frame this domain only as deficiency replacement. The more accurate distinction is between documented deficiency, age-related decline, functional optimization, and unmonitored high-risk escalation. The goal is not to accept age-related loss of recovery and tissue resilience as inevitable, but to evaluate whether somatotropic status supports functional reserve, body composition, recovery, bone integrity, exercise tolerance, and metabolic health.

This domain requires stricter monitoring than many other healthspan interventions. Potential risks include edema, carpal tunnel symptoms, insulin resistance, increased fasting glucose, joint pain, possible sleep apnea worsening, and unresolved concerns related to excessive growth signaling. Therefore, HGH and IGF-1-related strategies belong to a high-monitoring category and should be evaluated through IGF-1, fasting glucose, fasting insulin, HbA1c, edema, joint symptoms, sleep apnea risk, body composition, recovery response, and long-term safety.

12. Muscle, Skeletal Integrity, Joint Function, and Frailty Prevention

Muscle and skeletal preservation are central to healthspan because functional aging is shaped by strength, mobility, joint comfort, balance, bone density, recovery, glucose disposal, and independence. This domain must be distinguished from cosmetic muscle gain or unmonitored anabolic escalation.

12.1 Muscle and Bone as Functional Healthspan Endpoints

The foundation of muscle and skeletal preservation is resistance training, adequate protein, sufficient essential amino acids, sleep, recovery, body-composition monitoring, joint function, and prevention of excessive weight-loss-related lean-mass decline. This is especially relevant during strong weight-loss interventions, where reduced appetite and reduced total food intake may unintentionally lower protein intake and accelerate skeletal muscle loss unless resistance training, amino acid sufficiency, and body-composition monitoring are deliberately maintained.

12.2 Nandrolone Decanoate in Muscle, Bone, Pain, and Frailty Contexts

Nandrolone decanoate should be discussed as a muscle-, bone-, pain-, and frailty-oriented compound rather than as an unmonitored bodybuilding agent. Its relevance is based on historical and clinical links to postmenopausal osteoporosis, bone-mineral preservation, pain reduction, anemia, wasting, lean mass, and age-related musculoskeletal decline [52]. This does not imply superiority over other anabolic agents, such as oxandrolone in selected catabolic contexts, but reflects nandrolone's specific connection to musculoskeletal and frailty-related endpoints.

In women, nandrolone requires sex-specific caution because androgenic effects may include acne, hirsutism, hair loss, menstrual disruption, clitoral enlargement, and voice deepening. Some virilizing

effects, especially voice changes and clitoral enlargement, may be only partially reversible or irreversible. Female use therefore belongs in a high-monitoring, indication-dependent category.

12.3 SARMs as Experimental Anabolic Compounds

Selective androgen receptor modulators should be classified as experimental or gray-market anabolic compounds. They are often marketed ahead of long-term safety evidence and should not be treated as established healthspan medicine.

13. Neurofunctional Activation, Neuroenergetics, and Behavioral Capacity

Neurofunctional aging refers to the ability to remain awake, initiate tasks, tolerate effort, resist fatigue, organize behavior, and convert intention into action. These functions are not identical to intelligence. A person may retain cognitive capacity but fail to initiate or sustain meaningful action because of fatigue, apathy, depression, poor sleep, or executive dysfunction.

13.1 Very-Low-Dose Methylphenidate and the Intention-to-Action Transition

Very-low-dose methylphenidate should be classified as a neurofunctional activation candidate. Its relevance lies in task initiation, effort valuation, fatigue resistance, behavioral scaffolding, and the intention-to-action transition [53]. Such a model is relevant to functional aging because aging often involves reduced initiation, fatigue, lower behavioral flexibility, and difficulty sustaining goal-directed routines.

Relevant risks include cardiovascular load, sleep disruption, appetite suppression, reinforcement, learned reliance, stimulant stacking, and misuse. Therefore, neurofunctional activation requires a strict distinction between monitored functional optimization, medical treatment, controlled research, and unmonitored escalation.

13.2 Modafinil and Armodafinil as Wakefulness and Fatigue-Resistance Tools

Modafinil and armodafinil belong to wakefulness, vigilance, fatigue resistance, and sleep-pressure reduction. Their relevance is functional: maintaining alertness and cognitive endurance under specific conditions [54].

13.3 Methylene Blue and Neuroenergetic Aging Hypotheses

Methylene blue belongs to mitochondrial and neuroenergetic discussion. It is mechanistically interesting because of mitochondrial electron-transfer hypotheses and neurodegenerative research interest [55]. Its classification is neuroenergetic and experimental in the broader healthspan context.

13.4 Exogenous Ketones and Beta-Hydroxybutyrate

Exogenous ketones, including beta-hydroxybutyrate salts such as magnesium beta-hydroxybutyrate, belong to the neuroenergetic adjunct category. Their relevance lies in transiently increasing ketone availability as an alternative cerebral fuel and signaling metabolite, with possible relevance for cognitive fatigue, metabolic flexibility, mitochondrial stress, and neurodegenerative vulnerability [56,57].

They should be evaluated by formulation, tolerability, electrolyte and mineral load, renal function, glucose status, acid-base balance, and long-term outcome data.

14. Psychedelic Neuroplasticity and Adaptive Relearning

Psychedelics should be positioned within neuroplasticity, psychological flexibility, emotional relearning, depression research, trauma processing, habit change, and existential reorientation. Their relevance to healthspan is psychobehavioral rather than direct cellular rejuvenation.

This section also builds on prior work distinguishing low-dose psychoactive use from full-dose psychedelic intervention and emphasizing that microdosing is not one uniform category, but a substance-specific field requiring attention to pharmacology, dose range, receptor profile, tolerance, adverse effects, and behavioral context [58].

14.1 Classical Psychedelics and Psychological Flexibility

Classical psychedelics include psilocybin, lysergic acid diethylamide, dimethyltryptamine, ayahuasca, 5-methoxy-dimethyltryptamine, and mescaline. Their mechanisms are often discussed through 5-hydroxytryptamine 2A (5-HT2A) receptor signaling, altered salience, network-level reorganization, emotional processing, psychological flexibility, and dendritic or synaptic plasticity hypotheses [59,60]. Psychedelic research may therefore belong to neurocognitive and psychobehavioral healthspan.

14.2 Ketamine, Glutamatergic Plasticity, and Rapid Antidepressant Effects

Ketamine is not a classical serotonergic psychedelic, but it belongs in this chapter because of rapid antidepressant effects and plasticity-related mechanisms involving glutamatergic signaling, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) pathways, brain-derived neurotrophic factor, and downstream plasticity-related cascades [61,62]. In this paper, ketamine is treated as a plasticity-related psychiatric intervention.

14.3 Psychoplastogens and the Future of Plasticity-Based Intervention

Emerging psychoplastogens may include non-hallucinogenic compounds intended to promote neural plasticity. This is a promising research direction, but neuroplasticity is context-dependent. Plasticity can support adaptive change, but it can also reinforce maladaptive patterns when context, psychological screening, emotional state, sleep, and integration are poor.

15. Neuropeptide Adjuncts for Cognition, Stress, and Neuroprotection

Neuropeptides should be separated from repair peptides and longevity peptides by primary domain rather than by absolute pathway exclusivity. Their relevance lies in cognition, neurotrophic signaling, stress regulation, emotional stability, and neuroprotection.

15.1 Semax and Neurotrophic Cognitive Support

Semax belongs to the neuropeptide and cognitive-adjunct category. It is discussed in relation to cognition, attention, neurotrophic signaling, stroke-related research, and possible neuroprotection [63].

15.2 Selank and Stress-Regulation Pathways

Selank belongs to stress regulation, anxiety modulation, emotional stability, and possible indirect cognitive support through reduction of anxiety burden [64]. Its relevance to healthspan is neuropsychological resilience.

15.3 Cerebrolysin-Like Approaches as Disease-Oriented Neurotrophic Interventions

Cerebrolysin-like peptide mixtures may be discussed as disease-oriented neurotrophic interventions, especially in neurodegenerative or post-stroke contexts [65,66]. Their position is disease-oriented neurorepair rather than broad healthy optimization.

16. Experimental Longevity Peptides and Cellular Aging Hypotheses

Experimental longevity peptides are compounds discussed in relation to cellular aging, circadian regulation, mitochondrial signaling, telomere biology, pineal-aging hypotheses, and long-term organismal function.

16.1 Epitalon, Telomere Biology, and Pineal-Aging Models

Epitalon belongs to experimental longevity peptides. Its main proposed relevance lies in pineal aging, circadian regulation, melatonin output, sleep-wake rhythm, and telomere or telomerase hypotheses [67,68]. Human reports on Epitalon and related pineal peptides suggest normalization of daily melatonin rhythm in older individuals, including assessment through urinary 6-sulfatoxymelatonin, a major melatonin metabolite [68].

Telomere-related claims require caution. Longer telomeres or telomerase activation are not automatically beneficial or harmful; their relationship to regeneration, senescence, genomic stability, and cancer risk is context-dependent. Epitalon is therefore best classified as an experimental longevity peptide with pineal, melatonin-related, and telomere-related hypotheses, not as an established human healthspan therapy.

16.2 Mitochondrial-Derived Peptide MOTS-c and Mitochondrial Stress-Signaling Research

The mitochondrial-derived peptide MOTS-c belongs to mitochondrial and metabolic peptide research. Its proposed relevance lies in mitochondrial signaling, metabolic regulation, stress resistance, and exercise-related pathways [69].

16.3 SS-31 / Elamipretide and Mitochondrial Medicine

Szeto-Schiller peptide 31 (SS-31), also known as elamipretide, belongs to mitochondrial medicine and disease-specific mitochondrial research. It should be evaluated through mitochondrial function, disease-specific outcomes, and potential extension into broader healthspan domains [70].

16.4 Pinealon and Experimental Pineal-Neuroendocrine Concepts

Pinealon and related peptides belong to experimental neuroendocrine or pineal-aging hypotheses. Their inclusion is justified as part of the broader research landscape of peptide-based aging concepts.

17. Repair and Recovery Peptides

Repair and recovery peptides are discussed in relation to tissue repair, inflammation, wound healing, gut-barrier integrity, skin aging, hair support, and recovery. Their relevance to healthspan lies in repair capacity and regenerative signaling rather than direct lifespan extension. This paper evaluates peptides as compounds and mechanistic categories; it does not focus on vendor quality or product purity.

17.1 BPC-157 and Tissue-Repair Hypotheses

Body protection compound 157 (BPC-157) should be discussed as a repair-oriented peptide candidate. Proposed domains include tissue repair, tendon and ligament models, gastrointestinal protection, inflammation modulation, and wound-healing hypotheses [71]. Its relevance is repair biology and recovery.

17.2 TB-500 and Thymosin Beta-4-Related Remodeling Pathways

TB-500 and thymosin beta-4-related approaches belong to repair and recovery peptide research. Their proposed relevance lies in tissue remodeling, injury recovery, angiogenesis-related mechanisms, and cellular migration [72]. Because these pathways can overlap with growth and remodeling biology, discussion should remain mechanistic and evidence-based.

17.3 GHK-Cu for Skin, Hair, Connective Tissue, and Repair Biology

Glycyl-L-histidyl-L-lysine copper complex (GHK-Cu) belongs to copper-peptide biology, skin, connective tissue, wound healing, tissue repair, and hair-support discussions. It may be relevant to visible aging, scalp health, hair-density support, and repair biology, while remaining distinct from broad systemic longevity claims [73].

17.4 KPV and Barrier-Inflammation Signaling

Lysine-proline-valine peptide (KPV) belongs to anti-inflammatory and barrier-function peptide discussions. Its relevance lies in inflammatory signaling, gut and skin barrier hypotheses, and immune-modulatory research [74]. It should be treated as a targeted repair and inflammation peptide.

18. Multi-Compound Concepts, Stacking, and Protocol-Level Risk

Multi-compound concepts are common in healthspan communities, but it rarely makes sense to use all or most discussed interventions at the same time. The interventions reviewed in this paper belong to different biological domains, and simultaneous use may create pharmacodynamic, pharmacokinetic, endocrine, metabolic, renal, hepatic, electrolyte, acid-base, cardiovascular, sleep-related, or neuropsychiatric interactions.

The relevant unit of evaluation is therefore not only the individual compound, but the combined exposure. A protocol combining a lower-risk, established intervention with a higher-risk or experimental compound should be classified according to the highest-risk component and the most interaction-sensitive pathway. In practical terms, a Class I intervention combined with a Class IV compound should not remain a Class I protocol. The overall protocol should be upgraded in risk classification and downgraded in evidence maturity unless the combination itself has human safety and outcome data.

Stacking introduces risks that are not visible when substances are evaluated individually. These include overlapping effects on inflammation, glucose metabolism, blood pressure, sleep, appetite, endocrine signaling, angiogenesis, tissue remodeling, renal handling, hepatic metabolism, electrolyte balance, acid-base physiology, and neuropsychiatric state. Therefore, multi-compound protocols should be evaluated as combined exposures rather than as isolated ingredients.

19. Experimental Compounds and Mechanistically Heterogeneous Research Chemicals

Experimental compounds should not be treated as a single category merely because they are discussed in cognitive enhancement or healthspan communities. The integrated stress response inhibitor ISRIB, NSI-189, and Dihexa are included only as illustrative examples of mechanistically distinct research-boundary compounds.

ISRIB represents integrated stress response modulation and proteostasis-related signaling [75]. NSI-189 represents experimental neurogenesis and neuropsychiatric research [76]. Dihexa represents synaptogenesis, hepatocyte growth factor/c-Met signaling, and cognitive-repair hypotheses [77]. These compounds mark different edges of the research-boundary zone: proteostatic modulation, neurogenic hypotheses, and synaptogenic repair signaling. Preclinical plausibility must be connected to human safety, functional outcomes, dose-response data, and long-term tolerability before practical healthspan classification is justified.

20. Nutraceutical-Pharmacological Overlap

Some supplements occupy a boundary zone between nutrition, nutraceutical support, and medication-like effects. They should not be presented as simple drug replacements, but as compounds that may partially overlap with pharmacological mechanisms in selected contexts.

Red yeast rice requires special clarification. Its active monacolin K component is chemically identical to lovastatin and works through the same 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition pathway [78]. Therefore, red yeast rice is not included because its pharmacological logic differs from statins. It is included only as a nutraceutical-pharmacological overlap example showing how supplement status can obscure medication-like activity, dose variability, lipid-lowering effects, and interaction risk. The underlying logic remains cardiovascular risk modification rather than core rejuvenation.

Palmitoylethanolamide (PEA) may be relevant as a pain, neuroinflammatory, and recovery-support adjunct [79]. Pyridoxal-5-phosphate (P-5-P) may be discussed in relation to prolactin regulation and neuroendocrine balance [80]. Alpha-glycerophosphocholine (Alpha-GPC) belongs to the cholinergic cognitive-support boundary because it may influence acetylcholine-related signaling and has been studied mainly in cognitive impairment and dementia-related contexts [81].

This category is important because healthspan pharmacology does not end at prescription drugs. However, supplement-like status should not lower the evidentiary threshold. These compounds should be evaluated by mechanism, effect size, biomarker response, dose variability, safety, interaction potential, and whether their supplement framing masks medication-like effects.

21. Evidence Maturity Classes and Protocol-Level Downgrading

A responsible healthspan pharmacology requires evidence classification, but a rigid multi-level hierarchy can create artificial precision. This paper therefore uses four evidence maturity classes rather than a numerical ranking of all interventions.

Table 2. Evidence Maturity Classes in Precision Healthspan Pharmacology

Evidence class	Description	Examples of domains
Class I: Established clinical-domain evidence	Approved therapies or guideline-supported interventions with strong evidence in defined medical populations and clear monitoring standards	Incretin-based metabolic therapy, SGLT2 inhibitors in indicated populations, hormone therapy in defined endocrine contexts
Class II: Repurposed or domain-specific human evidence	Interventions with plausible healthspan relevance supported by human data, but not established as general anti-aging therapy	Metformin, acarbose, tadalafil, low-dose naltrexone, selected nutrient and electrolyte corrections
Class III: Emerging translational or limited human evidence	Interventions supported by early human data, mechanistic plausibility, or translational evidence, requiring stronger outcome studies	Exogenous ketones, methylene blue, selected peptides, neuroendocrine adjuncts, psychedelic plasticity research
Class IV: Experimental or research-boundary evidence	Compounds mainly supported by preclinical, mechanistic, or early exploratory evidence without sufficient long-term human outcome data	ISRIB, NSI-189, Dihexa, experimental longevity peptides, multi-compound combinations

These classes identify evidence maturity and monitoring burden. A Class I intervention may still be inappropriate outside its indicated population, while a Class III or IV intervention may be scientifically relevant but requires stronger protocol-level safety and outcome data before broad healthspan classification.

For combined protocols, evidence maturity should be assigned at the protocol level. If interventions from different classes are combined, the total protocol should generally be classified according to the least mature evidence class and the highest-risk interaction pathway unless the combination itself has been studied. This prevents a high-risk or experimental addition from being normalized by the presence of an otherwise established intervention.

22. Risk Stratification by Domain, Not by Hype or Legal Status

Risk must be classified by biological domain rather than generalized labels. Metabolic drugs require monitoring for gastrointestinal tolerance, rebound, body-composition changes, lean-mass loss, nutritional adequacy, and long-term adherence. Metabolic and renal-risk stratification should also include nutrient depletion and acid-base status. In particular, metformin requires attention to vitamin B12 status, while SGLT2 inhibitors and kidney-related interventions require awareness of ketones, bicarbonate, electrolytes, renal function, hydration status, and metabolic acidosis risk where clinically relevant.

Hormone therapy requires sex-specific monitoring, cancer-risk assessment, clotting-risk assessment, hematocrit, fertility considerations, endometrial protection, and symptom response. Testosterone protocols require attention not only to serum testosterone but also estradiol balance, aromatization, fertility

goals, testicular function, hematocrit, DHT-related effects, and hair-loss susceptibility. HGH and IGF-1 interventions require glucose, insulin, edema, sleep apnea, joint symptoms, and IGF-1 monitoring.

Neurofunctional agents require sleep, cardiovascular, dependence, anxiety, appetite, and learned-reliance monitoring. Psychedelics require psychiatric screening, context control, integration, sleep, emotional stability, and post-acute support. Melatonin and neuroendocrine adjuncts require attention to dose, timing, meal proximity, sedation, endocrine context, interaction potential, and long-term uncertainty. Peptides require mechanism-specific risk assessment: telomerase-related peptides require cancer-biology caution; tissue-remodeling peptides require growth and repair pathway caution; neuropeptides require neuropsychiatric and evidence-level caution. Nutraceuticals with medication-like effects require attention to dose, biomarker response, interactions, and whether their pharmacological overlap is underestimated because they are sold as supplements. Multi-compound protocols require evaluation as combined exposures.

Environmental risk should also be recognized. Air pollution, microplastics, veterinary drug residues, heavy metals, food processing, alcohol, smoking, high sugar intake, and industrial trans fats are not pharmacological interventions, but they influence inflammation, endocrine signaling, oxidative stress, vascular health, metabolic resilience, and recovery. A pharmacological healthspan model that ignores environmental load may overestimate drug effects while underestimating background stressors that drive functional decline. Within this framework, identifying a high environmental toxicological burden does not automatically warrant unvalidated detoxifying chelators, but commands strict exposure reduction and the optimization of endogenous hepatic, renal, gastrointestinal, and barrier clearance mechanisms before initiating complex compound stacks.

23. Biomarker and Monitoring Model

A pharmacological healthspan model requires monitoring rather than isolated intervention. Because many interventions discussed in this paper affect metabolism, hormones, body composition, cardiovascular function, inflammatory signaling, sleep, cognition, or tissue remodeling, baseline and follow-up testing should be treated as part of the model itself.

The earlier phase of intervention requires closer monitoring than the stable maintenance phase. For potent metabolic, hormonal, renal, anabolic, or neuroactive interventions, laboratory reassessment is often more appropriate within approximately 4-6 weeks after initiation, dose escalation, or meaningful protocol change. This early interval is especially relevant for hematocrit changes during testosterone therapy, renal function and electrolyte changes with metabolic or renal-active drugs, glucose and insulin changes during metabolic interventions, nutritional compromise during strong weight-loss therapy, and direct ketone assessment when SGLT2 inhibitor-related ketoacidosis is clinically relevant [82-85].

The twice-yearly comprehensive blood-test rhythm should therefore be understood as a stable-maintenance principle, not as an initiation-phase rule. More frequent monitoring may be required during initiation, dose escalation, drug changes, adverse symptoms, high-risk hormonal interventions, strong weight-loss therapy, anabolic compounds, HGH/IGF-1-related interventions, SGLT2 inhibitor use, complex multi-compound protocols, or any evidence of renal, hepatic, hematological, endocrine, electrolyte, ketone-related, or acid-base instability.

Clinical trigger points should be stated where established. For example, metformin is generally avoided or discontinued when estimated glomerular filtration rate falls below 30 mL/min/1.73 m², and initiation is commonly not recommended when estimated glomerular filtration rate is between 30 and 45 mL/min/1.73 m² [82]. SGLT2 inhibitor use depends on indication and guideline context, but kidney and cardiometabolic guidelines increasingly define lower estimated glomerular filtration rate thresholds for indicated populations [83]. SGLT2 inhibitor-associated euglycemic ketoacidosis may occur without marked hyperglycemia, making direct blood or urinary ketone monitoring, particularly beta-hydroxybutyrate where available, more informative than glucose alone when symptoms or risk conditions are present [84,85]. Testosterone therapy requires hematocrit monitoring, and hematocrit above approximately 54% should prompt intervention such as dose reduction, temporary discontinuation, formulation change, evaluation for hypoxia or sleep apnea, and clinical reassessment [38]. If antiplatelet therapy such as low-dose aspirin is considered in a testosterone protocol, it should be evaluated separately through cardiovascular risk, gastrointestinal bleeding risk, intracranial bleeding risk, platelet-related indications, concomitant anticoagulants or nonsteroidal anti-inflammatory drugs, and the underlying hematocrit-management strategy.

Table 3. Biomarker and Monitoring Domains for Precision Healthspan Pharmacology

Domain	**Suggested markers**
Metabolic	Fasting glucose, fasting insulin, HbA1c, homeostatic model assessment of insulin resistance (HOMA-IR), C-peptide
Nutrient, electrolyte, and acid-base status	Vitamin B12, methylmalonic acid or homocysteine where relevant, magnesium, bicarbonate/carbon dioxide (CO2), electrolytes, anion gap, direct blood or urinary ketone monitoring, specifically beta-hydroxybutyrate where indicated, renal function
Body composition	Dual-energy X-ray absorptiometry, lean mass, fat mass, visceral fat, bone density
Inflammation	High-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor alpha where available
Kidney	Creatinine, estimated glomerular filtration rate, cystatin C, urine albumin/creatinine
Liver and fatty liver	alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), ultrasound or magnetic resonance imaging-proton density fat fraction (MRI-PDFF) where available
Male hormones	Total testosterone, free testosterone, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, dihydrotestosterone (DHT) where relevant, prostate-specific antigen (PSA) where relevant, hematocrit, fertility goals
Female hormones	Estradiol, progesterone context, FSH/LH, menopause status, endometrial and breast-risk assessment
Neuroendocrine	dehydroepiandrosterone sulfate (DHEA-S), pregnenolone where available, prolactin where relevant, cortisol rhythm where relevant, melatonin timing or sleep-wake profile
Growth hormone / IGF axis	IGF-1, fasting glucose, fasting insulin, edema, sleep-apnea risk

Domain	Suggested markers
Environmental burden	Lead, mercury, arsenic, cadmium, persistent organic pollutants where clinically indicated, occupational or geographic exposure history
Psychosocial function	Sleep quality, perceived stress, mood, social connection, purpose, goals, adherence capacity
Neurocognitive	Sleep, mood, fatigue scales, reaction time, executive function
Nutraceutical-pharmacological overlap	Lipids for red yeast rice, prolactin for P-5-P contexts, pain and inflammatory markers where relevant
Safety	Complete blood count, liver enzymes, renal markers, blood pressure, electrocardiogram where indicated

Biomarkers are supportive indicators. The central endpoint is functional healthspan.

24. Limitations and Interpretive Boundaries

This paper is a conceptual evidence-mapping review based on narrative scoping evidence organization, not a systematic review or meta-analysis. It does not claim exhaustive retrieval of all available studies, formal risk-of-bias scoring, protocol registration, structured database screening, or pooled effect-size estimation. Its contribution lies in classification, conceptual clarification, evidence-domain separation, monitoring logic, environmental context, psychosocial foundations, and boundary setting.

Because healthspan pharmacology spans approved drugs, off-label use, hormone optimization, nutraceutical-pharmacological overlap, peptides, environmental burden, psychosocial factors, and experimental compounds, no single evidentiary standard applies equally to all categories. Established domains can be evaluated through clinical outcomes, guideline-based use, and established monitoring. Emerging domains require more emphasis on mechanism, translational plausibility, safety signals, and future human outcome data.

Animal, cellular, and mechanistic findings are treated as hypothesis-generating unless supported by human outcome data. This distinction is especially important for translational geroscience compounds such as acarbose, Epitalon, mitochondrial peptides, myostatin-pathway interventions, and experimental neuroplasticity compounds. A mouse-lifespan signal, cellular mechanism, or biomarker change is therefore not presented as equivalent to demonstrated human healthspan benefit.

Environmental burden is included as a conceptual healthspan modifier, not as a claim that all environmental exposures can be individually quantified or eliminated. Air pollution, microplastics, food contaminants, veterinary drug residues, and heavy metals differ in dose, geography, regulation, measurement reliability, and clinical relevance. Their inclusion reflects the modern exposure context in which anti-aging medicine operates.

Psychosocial factors such as purpose, goals, social connection, and stress reduction are included because they influence resilience, behavior, adherence, emotional stability, and long-term health. However, they should not be treated as interchangeable with pharmacological mechanisms. They form part of the healthspan foundation on which pharmacology operates.

Biomarkers are useful for monitoring but do not fully capture functional resilience, cognition, recovery capacity, quality of life, social functioning, purpose, or frailty risk. The framework should be understood as a classification and monitoring model for precision healthspan pharmacology, not as proof that any single intervention extends lifespan.

25. Future Outlook: Precision Monitoring and Adaptive Dosing

Future healthspan pharmacology will likely become more individualized through better monitoring and adaptive dosing. Wearables, continuous glucose monitors, blood-pressure tracking, sleep data, body-composition tools, digital cognitive tests, imaging, environmental exposure assessment, psychosocial monitoring, and advanced blood panels may help adjust interventions more accurately to metabolic status, hormone profile, organ function, exposure burden, stress burden, side effects, and functional goals.

This may allow healthspan pharmacology to move away from fixed generic protocols toward a more precise model: the right intervention, at the right intensity, for the right person, with regular monitoring, environmental awareness, psychosocial support, and clear stopping criteria.

26. Exclusion and Boundary Criteria

The paper excludes or marginalizes interventions when one or more of the following applies: the intervention is primarily disease-risk management rather than healthspan optimization; the intervention conflicts with core healthspan goals such as muscle growth, recovery, or immune resilience; the human evidence is too weak for practical healthspan classification; the pathway is biologically important but clinically unsafe to generalize; the compound has unresolved tumor-biology concerns; or the compound is mainly research-boundary use without adequate human safety data.

Statins are not treated as core anti-aging drugs because lipid-lowering is primarily cardiovascular risk management. Red yeast rice does not represent a mechanistic exception to this exclusion, because monacolin K is lovastatin-like in mechanism. Its inclusion in the nutraceutical-pharmacological overlap category serves a different conceptual purpose: it illustrates how supplement status can obscure medication-like pharmacology, lipid-lowering activity, dose variability, and interaction risk.

Colchicine is also excluded from the core structure. Although it is a potent anti-inflammatory drug with clinically relevant uses, its functional spectrum is too narrow for broad healthspan classification, and its interaction burden is substantial [86,87]. Food, supplement, and medication factors affecting cytochrome P450 3A4 (CYP3A4) or P-glycoprotein pathways may significantly alter colchicine exposure, making it poorly suited for generalized healthspan protocols.

Myostatin and follistatin approaches are excluded from the practical structure because increased muscle signaling does not automatically produce function, safety, or long-term benefit [88,89]. The relevant endpoint is not pathway activation alone, but strength, mobility, recovery, frailty reduction, and long-term safety.

Rapamycin requires a more prominent boundary explanation than simple exclusion. It is one of the most important translational geroscience compounds because mechanistic target of rapamycin (mTOR) signaling connects nutrient sensing, autophagy, immune function, growth, and aging biology [90].

However, the functional healthspan model used in this paper prioritizes muscle preservation, recovery capacity, immune resilience, and anabolic reserve. This creates a central tension: cellular maintenance and autophagy-oriented geroscience may conflict with muscle-anabolic and recovery-oriented healthspan goals when mTOR inhibition is excessive, mistimed, or poorly monitored.

Rapamycin is therefore not dismissed as irrelevant. It is excluded from the practical core of this paper because it represents a different geroscience paradigm: modulation of cellular growth and autophagy rather than direct support of functional performance, muscle preservation, recovery, or endocrine optimization. This conflict should be treated as a major future research question rather than as a resolved practical recommendation.

27. Conclusion

Healthspan pharmacology should not be organized around hype, isolated biomarkers, or single molecular pathways. It should be organized around functional domains: metabolism, muscle, skeletal integrity, hormones, cognition, psychological flexibility, recovery, nutrient status, environmental burden, psychosocial meaning, social functioning, and long-term safety.

All interventions discussed in this paper are adjuncts to, not replacements for, physiological and psychosocial foundations: nutrition, hydration, protein and essential amino acids, essential fatty acids, micronutrients, fiber, minerals, sunlight, movement, resistance training, sleep, recovery, structured stress reduction, meaningful social contact, personally significant goals, purpose and meaning in life, and the reduction of avoidable metabolic, toxicological, and inflammatory stressors.

The strongest current domain is metabolic healthspan, especially incretin-based and emerging multi-agonist therapies. However, strong weight loss should not be treated as automatically healthspan-positive. Severe dieting and pharmacological weight loss can reduce lean mass and skeletal muscle when protein intake, resistance training, and muscle-preserving strategies are insufficient. Changes in fasting insulin and sex hormone-binding globulin may also alter the interpretation of total versus free sex hormones. The relevant goal is not maximal weight reduction, but fat-loss-dominant metabolic improvement with preserved muscle, strength, mobility, endocrine interpretability, and functional reserve.

Hormone optimization is another central domain. Estradiol and progesterone deserve particular attention after menopause, while male hormone optimization should be understood as functional endocrine support rather than mere disease rescue. Testosterone-related protocols require attention to total and free testosterone, sex hormone-binding globulin, estradiol balance, fertility preservation, hematocrit, prostate-related monitoring where appropriate, and dihydrotestosterone-related hair-loss management.

Other categories require stricter boundary-setting. Low-dose naltrexone, tadalafil, pregnenolone, dehydroepiandrosterone, 7-keto-dehydroepiandrosterone, melatonin, very-low-dose methylphenidate, modafinil, methylene blue, exogenous ketones, psychedelics, neuropeptides, repair peptides, longevity peptides, and nutraceutical-pharmacological overlap compounds may all have domain-specific relevance, but they should not be collapsed into a single anti-aging category. Each requires classification by mechanism, evidence maturity, monitoring burden, interaction risk, and functional endpoint.

This paper does not reject anti-aging medicine. It reframes it as precision healthspan optimization. A responsible model should not define success as mere survival, minimal disease control, or remaining within age-depressed population averages. Its goal is to exceed age-imposed biological decline by preserving and expanding functional reserve, metabolic resilience, endocrine vitality, cognition, mobility, recovery capacity, vascular performance, sleep quality, purpose, and long-term health.

Anti-aging is therefore not simply treatment of disease. It is the monitored optimization of biological function against the downward pressure of aging and the modern burden of environmental and psychosocial stressors. The essential distinction is not between "natural" decline and "enhancement," but between intelligent healthspan optimization and unmonitored high-risk escalation.

28. Conflict of Interest

The author declares no conflict of interest.

29. Acknowledgement

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