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Urolithin A, Spermidine, and NAD+ Precursors in Human Healthy Aging: A Comparative Narrative Review of Recent Clinical Evidence

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Abstract

Background: Nutritional geroscience has increasingly focused on compounds that target conserved cellular maintenance pathways implicated in aging. Urolithin A, spermidine, and NAD+ precursors, particularly nicotinamide riboside and nicotinamide mononucleotide, are frequently grouped as "longevity supplements," although they differ substantially in mechanism, clinical evidence, and translational maturity. **Methods:** This focused narrative review evaluated peer-reviewed evidence published between January 2016 and April 2026, prioritizing systematic reviews, meta-analyses, and human randomized controlled trials. Outcomes of interest included muscle performance, cognitive function, cardiometabolic markers, inflammation, immune aging, mitochondrial biomarkers, quality of life, and safety. **Results:** Urolithin A: 1 peer-reviewed systematic review and 10 human randomized studies were identified, including 9 placebo-controlled efficacy/safety trials with approximately 392 randomized participants; 1 randomized bioavailability crossover study increased the total to approximately 492 participants. Spermidine: 0 full peer-reviewed systematic reviews/meta-analyses, 1 structured mini-review, and 6 unique peer-reviewed randomized trials were identified, involving approximately 360 - 370 participants. Oral NAD+ precursors: 6 peer-reviewed systematic reviews/meta-analyses and 25 unique peer-reviewed randomized NR/NMN trials were identified, involving approximately 1,070 randomized participants. **Conclusion:** Current human evidence does not support treating urolithin A, spermidine, and NAD+ precursors as equivalent longevity interventions. Urolithin A currently shows the most coherent translational profile, with aligned mechanistic, biomarker, and early functional evidence, particularly for mitochondrial health, muscle endurance, and immune aging. Spermidine remains biologically plausible but clinically unvalidated. Oral NR/NMN reliably increases NAD+-related biomarkers and exhibits robust

pharmacodynamic activity, but current evidence for broad anti-aging efficacy remains promising yet inconsistent across clinical outcomes. Longer, adequately powered, head-to-head trials using standardized geroscience outcomes are needed.

Keywords

Healthy Aging, Urolithin A, Spermidine, Nicotinamide Riboside, Nicotinamide Mononucleotide, NAD^+, Autophagy, Mitophagy, Geroscience

1. Introduction

A central premise of geroscience is that interventions targeting conserved biological mechanisms of aging may delay functional decline and reduce the burden of age-related disease. Among the nutritional compounds now positioned within this framework, urolithin A, spermidine, and NAD^+ precursors have attracted particular attention because each is linked to cellular maintenance pathways rather than to conventional symptomatic treatment. However, these interventions are often grouped together in commercial and popular discourse despite important differences in mechanism, evidence quality, and clinical maturity.

Urolithin A is a gut microbiome-derived metabolite of ellagitannins that has been studied primarily as a mitophagy-promoting compound with relevance to mitochondrial quality control, muscle aging, and, more recently, immune aging [1] [2]. Spermidine is a naturally occurring polyamine commonly framed as an autophagy enhancer with potential roles in proteostasis, cardiovascular aging, and cognition [3]. NR and NMN, by contrast, are precursors designed to augment NAD^+ availability, thereby affecting cellular energetics, stress resistance, and DNA repair pathways [4]. Although these three intervention classes converge at the level of cellular resilience, they are not mechanistically interchangeable.

The present review compares these compounds on the basis of the most recent scientific evidence, with particular attention to human intervention data. The aim is not to determine whether any of these agents "extends lifespan" in humans, a claim for which no convincing clinical evidence presently exists, but rather to evaluate which compound currently shows the strongest translational case for improving aging-relevant physiology and function.

2. Methods

This article was designed as a focused narrative review. Recent literature available between January 2016 and April 2026 was considered, with priority given to human randomized controlled trials, systematic reviews, and meta-analyses. The comparison centered on studies evaluating outcomes relevant to healthy aging, including muscle performance, cognition, cardiometabolic markers, inflammatory and immune phenotypes, mitochondrial biomarkers, quality of life, and safety.

For interpretive consistency, evidence was weighted according to translational relevance: first, systematic reviews and meta-analyses; second, placebo-controlled randomized trials; and third, smaller proof-of-concept and safety studies.

3. Results

Between January 2016 and April 2026, the search identified one peer-reviewed systematic review [5] and ten human randomized studies evaluating direct Urolithin A supplementation [6]-[15]. Of the ten randomized human studies, nine were placebo-controlled efficacy or safety trials, while one was an open-label randomized crossover bioavailability study comparing direct Urolithin A supplementation with pomegranate juice [7]. Therefore, the core clinical efficacy/safety evidence comprised nine randomized controlled trials involving approximately 392 randomized participants; when the bioavailability crossover study was included, the randomized human evidence base increased to ten studies and approximately 492 participants. For spermidine, the search identified no full peer-reviewed systematic review or meta-analysis focused specifically on human randomized trials of spermidine supplementation. One structured mini-review using a systematic search strategy was identified [16], which included three randomized controlled trials of spermidine supplementation for cognitive outcomes. The primary human randomized evidence base comprised six unique peer-reviewed randomized trials of spermidine or spermidine-rich supplementation [17]-[22]. These trials included approximately 360 - 370 participants, depending on whether randomized or analyzed samples are counted. Additionally, the search identified six peer-reviewed systematic reviews/meta-analyses relevant to oral NAD^+ precursor supplementation with nicotinamide riboside and/or nicotinamide mononucleotide [4] [23]-[27]. While the peer-reviewed human randomized evidence base comprised 25 unique oral NR/NMN randomized controlled studies, approximately 1070 participants were randomized [28]-[33].

4. Discussion

4.1. Comparative Biological Rationale

Although all three interventions are discussed within the longevity field, they occupy different positions within the biology of aging. Urolithin A is most closely linked to mitophagy, making it particularly relevant where mitochondrial turnover and bioenergetic efficiency are central, such as skeletal muscle and immune-cell metabolism [2] [12] [13]. Spermidine is more strongly associated with autophagy, polyamine metabolism, and cellular housekeeping, with much of the human literature concentrated on brain aging and cognition [16]. NR and NMN primarily act as substrate-based NAD^+ boosters, a broader systems-level strategy that may influence metabolism, vascular function, inflammation, and brain health, but whose clinical translation depends on whether oral increases in circulating NAD^+ meaningfully improve tissue function. Recent reviews have also cautioned that age-related NAD^+ decline in humans is biologically plausible but not as uniformly

demonstrated across tissues and studies as often implied in marketing narratives [34].

4.2. Urolithin A: The Strongest Current Translational Profile

Among the three classes reviewed, urolithin A presently shows the most coherent alignment between mechanism, biomarker response, and early functional benefit in humans. A 2024 systematic review identified five human studies including 250 participants, with doses ranging from 10 to 1000 mg/day over 28 days to 4 months; across these studies, urolithin A showed dose-related anti-inflammatory effects and upregulation of markers linked to mitochondrial biology, autophagy, and fatty-acid oxidation [2]. The clinical signal is strongest in muscle aging. In a randomized clinical trial in older adults published in JAMA Network Open, urolithin A supplementation was safe and well-tolerated and was associated with benefits in muscle endurance and mitochondrial health [8]. Complementary trial reports in middle-aged adults similarly described improvements in muscle strength, exercise performance, and biomarkers of mitochondrial health, reinforcing the interpretation that the compound engages a biologically coherent target in humans.

More recent evidence extends this profile into immune aging. A 2025 randomized, double-blind, placebo-controlled proof-of-concept trial in 50 healthy middle-aged adults administered 1000 mg/day for 4 weeks and examined T-cell subpopulations together with mitochondrial activity in $CD3^+$ cells as primary endpoints. This study suggests that urolithin A may affect immune-cell composition and immune mitochondrial biology, broadening its relevance beyond musculoskeletal aging. Although the trial was short and not powered for clinical endpoints, it materially strengthens the translational case for urolithin A by demonstrating target engagement in another aging-sensitive system [13].

Urolithin A shows promising but preliminary human evidence as a mitochondrial-health and healthy-aging compound. Randomized trials suggest good short-term tolerability and possible benefits for muscle endurance, selected strength outcomes, inflammatory biomarkers, immune-aging profiles, and exercise recovery. However, evidence remains limited by small sample sizes, short intervention periods, heterogeneous populations, variable endpoints, and inconsistent effects on major functional outcomes such as 6-minute walk distance, peak power, cardiovascular function, and clinical disease markers.

4.3. Spermidine: Compelling Biology, But Heterogeneous Human Efficacy

Spermidine remains an important candidate because of its strong mechanistic relationship with autophagy and its long-standing association with healthy aging in observational and experimental work [16]. However, the human intervention evidence remains less mature than that for urolithin A and is dominated by cognition-oriented studies [18]. The most important trial to date is the randomized clinical

trial in older adults with subjective cognitive decline, in which longer-term spermidine supplementation did not significantly improve memory or other major biomarkers relative to placebo [20]. This negative primary result substantially tempers enthusiasm regarding the current level of clinical proof. At the same time, the totality of spermidine evidence is not uniformly negative. A 2025 synthesis of observational and interventional studies reported that among four interventional trials, three showed positive cognitive signals , but emphasized that the literature remains heterogeneous, relatively small, and centered on cognition rather than on broader geroscience outcomes such as physical function, frailty, multimorbidity, or immune aging [3]. Small studies in older adults with dementia have also reported improvements in memory performance, but these findings remain difficult to generalize because of sample size, population specificity, and limited replication [18]. Safety data for purified spermidine are improving. In 2024, an exploratory randomized trial found that 40 mg/day of high-purity spermidine for 28 days in older men was safe and well tolerated, with minimal effects on circulating polyamine levels [22]. This is valuable for formulation and tolerability questions, but it does not resolve the central efficacy problem: the field still lacks robust, replicated trials showing clinically meaningful improvements in generalized healthy-aging outcomes.

4.4. NAD⁺ Precursors (NR/NMN): Robust Biomarker Engagement and Emerging Clinical Promise

NR and NMN are the most widely discussed of the three categories, but their clinical evidence is also the most vulnerable to overstatement. The broadest recent synthesis, a 2026 PRISMA-guided systematic review in Ageing Research Reviews [27], identified 113 eligible studies, including 33 human intervention studies and 28 randomized trials, and concluded that NAD^+ augmentation shows clear biological activity but that clinical effectiveness for anti-aging or wellness outcomes remains inconclusive. When the count was restricted to placebo-controlled clinical efficacy or safety trials and excluded primarily pharmacokinetic, acute biomarker, preprint, and duplicate secondary analyses, 25 unique randomized controlled trials remained.

The distinction between target engagement and functional benefit is also evident in specific trials. In older adults with mild cognitive impairment, NR significantly increased blood NAD^+ concentrations but did not alter cognition, underscoring the recurrent pattern in which biochemical improvement is not matched by clear clinical gain [35]. Similarly, a 2025 pilot randomized trial testing NR combined with exercise in hypertensive middle-aged and older adults tested a biologically plausible hypothesis that NAD^+ repletion may augment exercise-induced vascular benefits [36]. Although NR plus exercise was not superior to placebo plus exercise in reducing blood pressure, exploratory findings suggested a trend toward greater nighttime blood pressure reduction, particularly among participants not receiving anti-hypertensive medication [36]. More encouraging evidence comes

from a randomized controlled trial in patients with Friedreich's ataxia [37], where NR combined with individualized aerobic and resistance training produced the strongest efficacy signal. The combination group showed a significant improvement in cardiopulmonary fitness, measured by peak VO_2, compared with the control group. This suggests that NR may support exercise-related metabolic adaptation in conditions characterized by impaired mitochondrial function and low cardiopulmonary capacity. Recent meta-analyses further constrain interpretation. A 2025 systematic review and meta-analysis concluded that current evidence does not support NMN or NR supplementation for preserving muscle mass and function in adults with a mean age above 60 years [26].

Separate syntheses of NMN trials have found that supplementation is generally well tolerated and may improve some intermediate measures, but effects on physical performance and metabolic health are either small, inconsistent, or non-significant overall [33] [38]. Recent randomized controlled human trials show that NAD^+ precursor supplementation, particularly oral nicotinamide riboside and nicotinamide mononucleotide, reliably increases circulating NAD^+ or NAD-related metabolites in a dose-dependent manner [39]. Current data support NAD^+ precursors as biologically active and generally well tolerated [40], but not yet as universally effective anti-aging or disease-modifying therapies. Longer, adequately powered trials with standardized NAD^+ assays and clinically relevant endpoints are required. On the other hand, current human evidence suggests that direct intravenous NAD^+ is biologically active, although its clinical value remains uncertain. IV NAD^+ can alter NAD-related metabolites; however, it may be rapidly metabolized or taken up by tissues, limiting sustained increases in circulating NAD^+. In a recent 2026 retrospective study comparing IV NAD^+ versus IV NR [35], IV NR was administered more rapidly and was better tolerated than IV NAD^+. Participants receiving IV NAD^+ more frequently reported adverse infusion-related symptoms, including abdominal cramping, nausea, vomiting, throat or chest pressure, and increased heart rate, whereas IV NR was associated with milder symptoms. The mean infusion time was also substantially shorter for IV NR than for IV NAD^+, approximately 37 minutes versus 97 minutes, respectively. Emerging evidence also exists for other parenteral NAD^+-related approaches. Intravenous NMN appeared to be well tolerated in a small study of 10 healthy volunteers, with no major changes in ECG, pulse, blood pressure, or organ-function markers, and with a reported reduction in triglycerides [41]. In addition, a 7-day course of NAD^+ injections in patients with heart failure was associated with improvements in cardiac function, oxidative stress, and markers of endothelial injury compared with saline control [42]. Collectively, these findings suggest that parenteral NAD^+ and NAD^+ precursors may have biological and potential therapeutic effects, but the current evidence remains preliminary. Larger, well-controlled clinical trials are required to determine optimal formulation, route of administration, dosing, tolerability, effects on circulating and tissue NAD^+, and clinically meaningful outcomes.

4.5. Overall Comparison and Interpretation

Taken together, the evidence supports a provisional hierarchy. Urolithin A currently has the strongest translational profile because it combines a clear mechanistic target, reproducible biomarker effects, and early but reasonably consistent human functional signals, particularly in muscle and potentially immune aging. Spermidine remains biologically attractive, but its human intervention literature is narrower, more heterogeneous, and not yet persuasive at the level required for broad healthy-aging recommendations. NR/NMN have the best evidence for biomarker engagement and the largest volume of trials, but not for consistent improvements in clinically meaningful aging outcomes.

Several limitations cut across all three literatures. First, trials are generally short, often weeks to months rather than years. Second, samples are modest and frequently restricted to narrow populations, such as healthy middle-aged adults, older adults with subjective cognitive decline, or selected metabolic phenotypes. Third, outcomes are highly heterogeneous and often surrogate-heavy, making cross-study comparison difficult. Fourth, none of the compounds has been tested in adequately powered head-to-head trials using shared geroscience endpoints. For that reason, the present comparison should be interpreted as an evidence ranking, not as definitive comparative proof.

5. Conclusion

Current human evidence does not justify treating urolithin A, spermidine, and NAD^+ precursors as equivalent "longevity supplements." Urolithin A presently appears to be the strongest candidate among the three, because its mechanistic promise is supported by the most coherent pattern of clinical and translational findings. Spermidine is promising but still insufficiently validated in humans, while NR and NMN reliably shift biomarkers without yet demonstrating broad or durable anti-aging efficacy. The next generation of trials should use longer follow-up, standardized outcome frameworks, biologically stratified enrollment, and direct comparator designs to determine whether these compounds are genuinely distinct gerotherapeutic options or merely partially overlapping metabolic interventions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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