The NAD+ stack, optimized: A multi-target strategy to support healthy aging

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Research has identified key mechanisms driving aging and actionable targets for promoting longevity. A promising strategy is to preserve the cell's ability to produce energy, repair DNA, and stress resilience, with nicotinamide adenine dinucleotide (NAD+) playing a central role. Here, Dr. Rebecca Crews presents a multi-target approach to support healthy aging

Decades of research have uncovered key mechanisms driving the aging process, identifying actionable targets to support longevity. One of the most promising strategies is preserving the cell's capacity for energy production, DNA repair, and stress resilience. Central to all of these processes is nicotinamide adenine dinucleotide (NAD+), a coenzyme that fuels hundreds of metabolic reactions, including mitochondrial ATP production and sirtuin-mediated cellular maintenance.

It is known that NAD+ levels significantly diminish with age. This decline is tightly linked to the hallmarks of aging, contributing to mitochondrial dysfunction, impaired repair, cellular senescence, and age-related damage. Restoring NAD+ levels closer to youthful norms has, therefore, become a major focus within longevity science.

However, simply boosting NAD+ with precursors addresses only one aspect of a complex issue. A truly effective strategy tackles the root causes of NAD+ decline and maximizes outcomes. Therefore, a thoughtful strategy involves a multi-pronged approach: slowing NAD+ degradation, supporting its synthesis, and improving how NAD+-dependent pathways function (Sharma et al., 2023).

The foundation: NAD+ precursors

The most straightforward way to boost NAD+ levels is by supplying the body with its molecular precursors.

The two most widely used options are:

> Nicotinamide Riboside (NR) or Nicotinamide Mononucleotide (NMN): Both convert efficiently into NAD+ via the salvage pathway. Human trials consistently report 40–60% increases in blood NAD+ at daily doses of 250–1,000 mg (Conlon & Ford, 2022).

Choosing between NR, NMN, or using both typically depends on individual goals and cost. Consistent, daily dosing is key to maintaining elevated NAD+ levels.

Enhancing efficiency: Sirtuin activators

Many of NAD+'s health benefits stem from its role in fueling sirtuins, a family of NAD+-dependent enzymes that drive DNA repair, metabolic balance, stress resilience, and inflammation control. Sirtuin Activating Compounds (STACs) amplify these protective functions:

- Resveratrol:
  A grape polyphenol that directly stimulates SIRT1. Its poor bioavailability is improved when taken with dietary fat or via advanced delivery systems (e.g., liposomal encapsulation, and solid-lipid nanoparticles).
- Pterostilbene:
  A blueberry-derived analog of resveratrol that achieves higher plasma levels and may exert stronger SIRT1 activation.

Combining NAD+ precursors with STACs ensures both ample substrate and maximized sirtuin function (Sharma et al., 2023).

Protecting the pool: CD38 Inhibitors

CD38 is a major NADase whose activity increases with age and chronic inflammation, accelerating NAD+ depletion. Inhibiting CD38 conserves existing NAD+, keeping it available for beneficial pathways like sirtuin mediated repair.

Natural flavonoids have emerged as promising CD38 inhibitors:

- Apigenin:
  Abundant in chamomile, parsley, and celery, apigenin blocks CD38 in preclinical models, elevating NAD+ and downstream sirtuin activity. It also delivers anti-inflammatory and antioxidant benefits (Kramer & Johnson, 2024).
- Quercetin:
  A common flavonoid found in onions, apples, and berries, quercetin inhibits CD38 and offers potent antioxidant, anti-inflammatory, and senolytic benefits (Chini et al., 2018).

Flavonoid CD38 inhibitors offer multiple benefits: they simultaneously preserve NAD+, reduce oxidative stress, and curb inflammatory signaling.

Clearing the way: Senolytics

Senescent cells accumulate with age, acting as cellular "zombies" that resist death while secreting pro-inflammatory factors (SASP). This SASP, in turn, boosts CD38 in nearby cells, leading to faster NAD+ depletion.

Key senolytics (compounds that selectively eliminate these "zombie" cells) include:

- Fisetin: Found in strawberries and apples, this flavonoid has demonstrated the ability to reduce senescent cell burden, enhance health span, and extend lifespan in aged mice (Yousefzadeh et al., 2018).
- Spermidine: This polyamine, present in fermented foods and legumes, induces autophagy and may support the clearance of senescent cells. It's associated with improved cardiovascular health and lifespan in mice (Hofer et al., 2022).

Calming the storm: Anti-inflammatory support

Chronic inflammation, a hallmark of aging, further depletes NAD+ by increasing CD38 activity. Resolving this inflammation is key to preserving the NAD+ pool and creating a healthier cellular environment:

- Curcumin: The active compound in turmeric, suppresses NF-κB and COX-2 signaling and may indirectly support sirtuins. Due to poor absorption, high-bioavailability formulations are essential (Hegde et al., 2023).
- Omega-3 Fatty Acids (EPA & DHA): These fish oil–derived fats integrate into cell membranes to reduce inflammatory signals and serve as building blocks for specialized pro resolving mediators (SPMs) that actively shut down inflammation (Kavani et al., 2022).

Synergistic anti-inflammatory effects have been observed when curcumin and omega-3 fatty acids are administered together (Saw et al., 2010).

Integrating the stack: Synergy and practical considerations

This multi-component stack represents a strategic and comprehensive approach to NAD+ metabolism. NAD+ precursors ensure ample substrate supply, STACs optimize its efficient use, CD38 inhibitors protect against its premature breakdown, senolytics reduce the detrimental burden of senescent 'zombie' cells, and targeted anti-inflammatory compounds re- establish cellular homeostasis. The goal is a synergistic effect that promotes overall cellular resilience.

However, implementation requires attention:

- Lifestyle first: Supplements cannot replace a foundation of a healthy diet, regular exercise, quality sleep, social connection, and stress management.
- Gradual introduction: Start supplements one by one ("start low, go slow") to gauge individual tolerance.
- Quality is key: Opt for reputable brands that provide third-party testing for purity and potency.
- Personalization: Monitor biomarkers and subjective well being.

Conclusion: A balanced perspective on NAD+ optimization

Supporting NAD+ levels is a promising strategy in the effort to maintain cellular function and health with age. The approach outlined here – boosting NAD+ production, reducing its breakdown, improving how it's used, and supporting the broader cellular environment – reflects the current understanding of NAD+ as a dynamic and interconnected system.

NAD+ boosting strategies should be seen as a flexible starting point, not a one-size-fits-all solution. As research advances, more personalized strategies will likely become available, guided by individual health data and deeper insights into NAD+ biology.

Importantly, NAD+support works best as part of a bigger picture. Lasting health and longevity depend just as much on diet, exercise, sleep, stress management, and social connection. Keeping these foundations strong while staying informed about new science is the most practical way to approach NAD+ optimization today.

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