

Urolithin A: A Novel Geroprotectant Capable of Stimulating Mitophagy

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Abstract

The quest for longevity and improved quality of life in the aging population has fueled extensive research into the biological mechanisms underlying aging and the discovery of novel geroprotective agents. Among the promising candidates emerging from this research is urolithin A, a metabolite derived from ellagitannins found in certain fruits and nuts, which has shown significant potential in modulating cellular and molecular pathways associated with aging. In particular, its effects on mitochondrial health and mitophagy have garnered attention for their implications in age-related diseases and overall cellular senescence.

Stem cells, renowned for their self-renewal and differentiation capabilities, play a crucial role in tissue regeneration and repair. However, the aging process adversely impacts stem cell function, leading to diminished regenerative capacity and increased susceptibility to age-related pathologies. The intersection of stem cell biology and anti-aging research thus presents a unique opportunity to explore therapeutic strategies aimed at preserving stem cell functionality and enhancing tissue homeostasis in the elderly.

Recent studies have highlighted the potential of urolithin A as a geroprotector, capable of improving mitochondrial function and inducing mitophagy, a selective form of autophagy targeting damaged mitochondria. The ability of urolithin A to enhance mitophagy and mitigate mitochondrial dysfunction suggests a promising avenue for bolstering stem cell health and delaying the onset of age-associated decline.

In this article, we explore the dual role of urolithin A as both a geroprotective agent and a molecule with significant anti-aging properties by investigating the molecular mechanisms through which it exerts its effects. The article highlights the extraordinary pleiotropic effects this molecule has shown in experimental and human studies and its possible clinical applications.

By elucidating these pathways, we aim to provide a comprehensive understanding of how urolithin A can be harnessed to promote healthy aging and enhance stem cell-mediated tissue regeneration, ultimately contributing to improved health span and longevity.

Keywords

Mitophagy; Urolithin A; Longevity; Geroprotector agent; Pleiotropic molecule.

Abbreviations

Urolithin A: UA

Introduction

Urolithin A is a natural metabolite produced by gut bacteria from ellagic acid, a polyphenol found in various plant-based foods such as berries, nuts and pomegranates. In the gut, ellagic acid is converted by the gut microbiota into metabolites called urolithins (Figure 1).

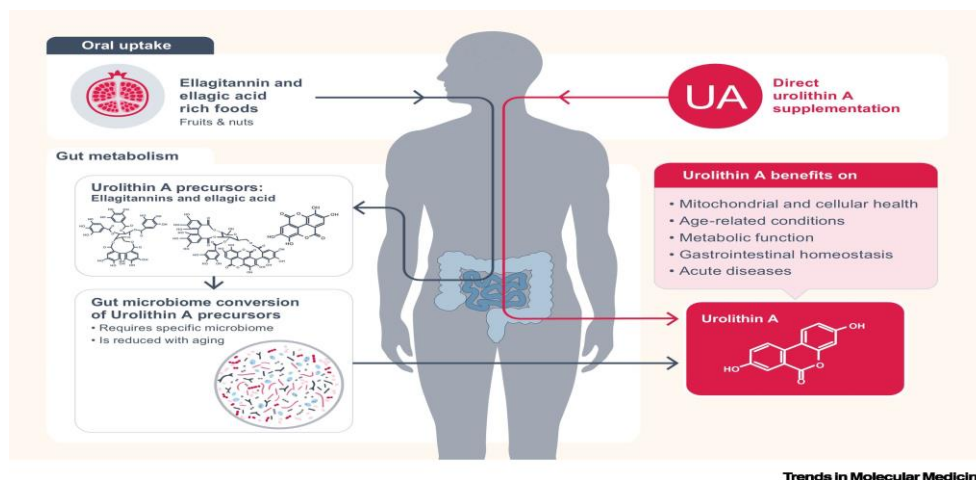


Figure 1: UA belongs to the urolithin family, which consists of compounds produced by the gut microbiome's conversion of natural polyphenols present in foods like pomegranates, strawberries, raspberries, and nuts. UA can provide benefits for mitochondrial health, aging-related diseases, metabolism, skeletal muscle, brain function, cardiovascular health, and gastrointestinal homeostasis [9].

Three main urolithin 'metatypes' have been identified: metatype A (urolithin A producers), metatype B (urolithin B producers) and metatype O. Urolithin A is the one with the most healthy properties.

Urolithin production depends on the individual's gut microbiota, called the metatype, which defines the individual's ability to produce specific metabolites from food precursors based on the metabolic profile of the gut microbiota. So, after eating foods rich in precursors such as ellagic acid, only a portion of the population is able to efficiently convert these compounds into active urolithin A and those who do have better metabolic health parameters and microbiota composition the others.

Direct supplementation with Urolithin A by passes the need for gut microbial conversion.

But why take urolithin A as a supplement? We might consider directly manipulating the endogenous gut microbiota. Really, the microorganism or microbial group responsible for the conversion of ellagic acid and ellagitannins to urolithin A in the human gut has not yet been isolated with certainty. Recent studies demonstrated that more than 30% of the discriminating genera between UM-A and UM-B belonged to the Gordonibacter and Ellagibacter family.

The Authors report a new bacterium isolated from the feces of a healthy woman, named *Enterocloster bolteae* CEBAS, capable of producing the final metabolites Uro-A and Uro-B from Uro-C and IsoUro-A, respectively. It has also been hypothesised that transplantation of faecal microbiota from donors with high endogenous production of urolithin A (metatype A) may favour this conversion in recipients with low/absent production. However, experimental confirmation is currently needed.

There are currently no probiotics specifically indicated to promote endogenous production of urolithin A from its dietary precursors, although this is an area that is being investigated. What has been proven is that UA significantly enhances gut barrier function and attenuates inflammatory bowel disease in preclinical models.

The capacity to produce UA decreases with age, from 61% in 20 to 50-year-olds to only 39% in those over 60. The positive effect on aging mediated by mitophagy is present from worms through to mammals. It extends lifespan and also improves health span parameters such as muscle function.

Methods and Discussions

The mechanisms of action of Urolithin A are multiple, even if activation of mitophagy is the main one. Mitophagy, the selective autophagy of mitochondria, is a critical cellular process that ensures the removal of damaged or dysfunctional mitochondria, thereby maintaining mitochondrial quality control. This process is essential for cellular homeostasis, as mitochondria play a pivotal role in energy production, regulation of metabolic pathways, and apoptosis. As organisms age, the efficiency of mitophagy declines, leading to the accumulation of damaged mitochondria, which in turn contributes to increased oxidative stress, cellular dysfunction, and the onset of age-related diseases.

The impairment of mitophagy is increasingly recognized as a significant factor in the aging process. Therefore, enhancing mitophagy has emerged as a potential therapeutic strategy to mitigate the detrimental effects of aging.

Urolithin A has been identified as a potent inducer of mitophagy.

In this scenario, mitophagy is mediated by two main pathways: a PINK1/Parkin-dependent pathway and a PINK1/Parkin-independent pathway.

The PINK1/Parkin-dependent pathway is based on phosphorylation of Parkin by PINK1, a protein kinase that accumulates on the outer mitochondrial membrane of damaged mitochondria, leading to the elimination of these mitochondria. UA is able to increase the levels of these two key proteins, thus promoting the turnover of dysfunctional mitochondria.

The PINK1/Parkin-independent pathway involves mitochondrial receptors that directly bind LC3 and trigger mitophagy.

There are also other mechanisms of action of UA.

Urolithin A activates AMPK, inhibits mTOR, the physiological inhibitor of mitophagy, increases PGC-1 α levels and thus improves mitochondrial biogenesis.

It activates sirtuins and FOXO, with antioxidant and anti-inflammatory effects.

It reduces inflammation by inhibiting NF- κ B, pro-inflammatory cytokines and activating Nrf2 in several animal models. It has the ability to modulate oxidative stress, either by enhancing endogenous antioxidant defenses or by inhibiting the production of ROS.

Research has shown its capacity to enhance mitophagy by activating the expression of glutathione S-transferases. Urolithin A stimulates the Nrf2 signaling pathway, subsequently upregulating the expression of GSTs, thereby enhancing cellular autophagy and mitochondrial quality control.

At the same time of this stimulation of mitochondrial 'cleanliness', it also improves key functional such as respiratory capacity, leading to an overall improvement in mitochondrial function.

The positive effect on aging mediated by mitophagy is present from worms through to mammals.

It extends lifespan and also improves health span parameters such as muscle function.

By promoting the removal of damaged mitochondria and facilitating the generation of new, functional mitochondria, urolithin A helps maintain mitochondrial integrity and function. This enhancement of mitochondrial turnover is crucial for sustaining cellular energy levels and reducing oxidative stress.

The mechanistic action of urolithin A in inducing mitophagy not only enhances mitochondrial health but also extends its pleiotropic effects across various physiological systems. These effects, which will be elaborated upon in subsequent sections, include improved muscle function, reduced oxidative stress, and enhanced cellular homeostasis, ultimately contributing to overall health and longevity.

Animal Studies

UA is negatively correlated with total and LDL cholesterol, meta inflammation and BMI and has a positive potential on cardiometabolic health.

UA significantly reduced triglyceride accumulation and increased fatty acid oxidation in cultured human adipocytes and hepatocytes.

It prevents damage and reduces ischemic damage and atherosclerosis in animal models.

It improves insulin sensitivity, acting mainly on mitochondrial function in skeletal muscle.

Urolithin A exerts ant obesity effects through enhancing adipose tissue thermogenesis in mice. UA treatment increases energy expenditure by enhancing thermogenesis in brown adipose tissue and inducing browning of white adipose tissue. Increased thermogenesis is favored by an elevation of the thyroid hormone triiodothyronine (T3) levels in brown adipose tissue. Consistent with this mechanism, UA loses its beneficial effects on activation of brown adipose tissue and metabolism, when thyroid hormone production is blocked by an inhibitor, such as propylthiouracil. Conversely, administration of exogenous thyroid hormone tetraiodothyronine (T4) to PTU-treated mice restores UA-induced activation of brown adipose tissue.

UA supplementation has also shown promise as a treatment of senile osteoporosis.

It significantly reduced the expression of osteoclast-related genes and bone resorption.

In an experimental model of aging, UA reduced bone loss in the proximal femur, spine and tibia of aging mice.

It even develops positive effects on intervertebral disc degeneration and osteoarthritis. It also alleviates neuropathic pain by the same mitophagy mechanism.

An exciting study published by Sarah Livingston of Arizona University shows how Urolithin A and Vitamin D cooperate to amplify serotonin gene expression in neuroendocrine cells. Urolithin A enhances the ability of vitamin D to induce the serotonergic enzyme in tryptophan metabolism to serotonin, namely TPH2 and function as a booster of the action of 1,25D to stimulate gene expression via VDR VDRE. Leptin normally inhibits synthesis and release of brain-derived serotonin, favoring bone mass accrual, appetite, and energy metabolism. Vitamin D represses adipocyte leptin and induces TPH2 to enhance serotonin relay signaling in the cerebral cortex. So, a combination of Vitamin D and urolithin A is an attractive potential to raise serotonin in the central nervous system and perhaps improve mood.

Research shows that UA significantly increases type I collagen expression, reduces matrix metalloproteinase-1 expression, and reduces intracellular ROS in senescent human skin fibroblasts.

It exerts protective effects against UVA-induced photoaging and prevented various morphologic changes typically observed after UVA exposure through NRF2 activation and mitophagy.

UA exerts remarkable effects on neurodegenerative diseases (Figure 2).

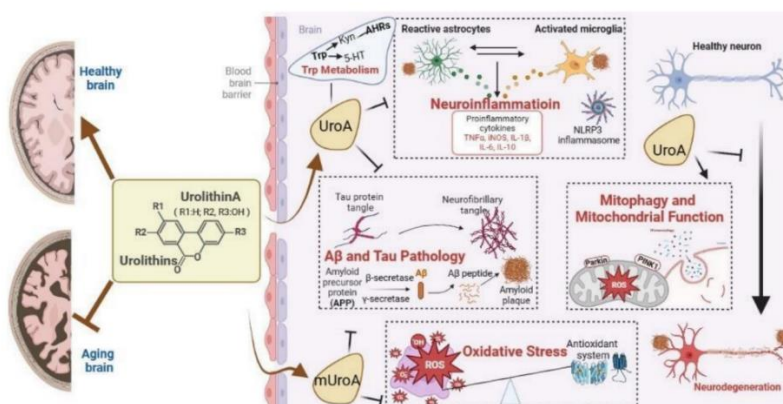


Figure 2: Overview of UA's Effects on Brain Aging: Mechanisms and Actions. The mechanisms by which UroA mitigates brain aging include promoting mitophagy, enhancing mitochondrial function, and reducing neuroinflammation. Other significant actions are the reduction of oxidative stress, inhibition of A β and tau pathology, and regulation of tryptophan metabolism. UA also activates key anti-aging pathways such as AMPK and SIRT, while inhibiting mTOR [35].

In the neurons of patients with Alzheimer's disease, mitophagy is deficient, leading to the accumulation of malfunctioning mitochondria.

Urolithin A reduces levels of beta-amyloid and hyperphosphorylated tau protein by inducing mitophagy.

It mitigates neuroinflammation, oxidative stress and neuronal damage and prevents cognitive decline.

The beneficial effects of UA on brain function during aging are associated with multitarget actions that include promoting mitophagy and mitochondrial function, attenuation of chronic oxidative stress and inflammation, inhibiting amyloid- β and tau protein, and regulating tryptophan metabolism thereby counteracting the pathogenesis of Alzheimer's disease.

Urolithin A attenuates auditory cell and prevents premature senescence in auditory cells. The activation of mitophagy using UA can be a potential preventive strategy for patients with age-related hearing loss.

Urolithin A is also known for its anti-cancer properties. A trial investigated the impact of UA in colorectal cancer cells. The investigators conclude that UA decreases cancer cell proliferation, delays cell migration, and potentially prevents metastasis in a dose-dependent manner.

Urolithin A is mainly known for its positive impact on muscle mass and its potential to counteract sarcopenia.

Skeletal muscle aging is associated with progressive muscle mass and strength decline. Reducing muscle function below critical thresholds results in a clinical condition known as sarcopenia, significantly impacting quality of life by reducing the ability to perform daily tasks. It is now well known that mitochondria play a central role in the deterioration of skeletal muscle during aging. The loss of strength and muscle mass in both old animals and older adults has been associated with impaired mitochondrial energy and increased mitochondrial-mediated cell death by apoptosis. One cause of the loss of mitochondrial homeostasis during aging is the accumulation of dysfunctional mitochondria. This, in turn, results from the reduced ability of cells to remove defective organelles via mitophagy.

Many findings establish a solid scientific foundation for the application of Urolithin A in improving muscle health, promoting muscle growth, and enhancing exercise performance.

Urolithin A may offer benefits in the treatment of muscular atrophy in pathological conditions but also sarcopenia or extended periods of immobility.

It can stimulate muscle protein synthesis while inhibiting protein degradation pathways, helping to preserve muscle mass and mitigate muscle wasting.

Urolithin A can stimulate muscle protein synthesis, contributing to muscle growth and maintenance. This effect is especially advantageous for individuals aiming to enhance and maintain muscle mass, including athletes and fitness enthusiasts.

Urolithin A shows promise in delaying the onset of muscle fatigue during prolonged or high-intensity exercise.

By enhancing mitochondrial function in muscle cells, it provides sustained energy support, allowing individuals to engage in longer and more intense training sessions.

By suppressing the inflammatory response, Urolithin A contributes to the mitigation of muscle pain and inflammation and promotes muscle repair and recovery.

Urolithin A has been demonstrated to enhance muscle health and performance by activating AMPK, inhibiting NF- κ B, and upregulating the expression and activation of PGC-1 α .

This regulation results in improved muscle protein synthesis and reduced degradation through the suppression of FoxO activation, inhibition of the ubiquitin-proteasome system, and modulation of mTORC1 activity and the expression of Atrogin-1/MuRF.

Human Studies

The first human trial with UA administration was a randomized, double-blind study conducted over 4 weeks in healthy elderly men and women aged 61 to 85 years.

UA showed a favorable safety profile, with no observed side effects, both after a single oral dose up to 2000 mg and after multiple doses up to 1000 mg, with good oral bioavailability at all doses tested.

The most famous study on urolithin A, conducted by Singh et al. and published in 2022 in *Cell Reports Medicine*, is a randomized, double-blind, placebo-controlled clinical trial (Figure 3).

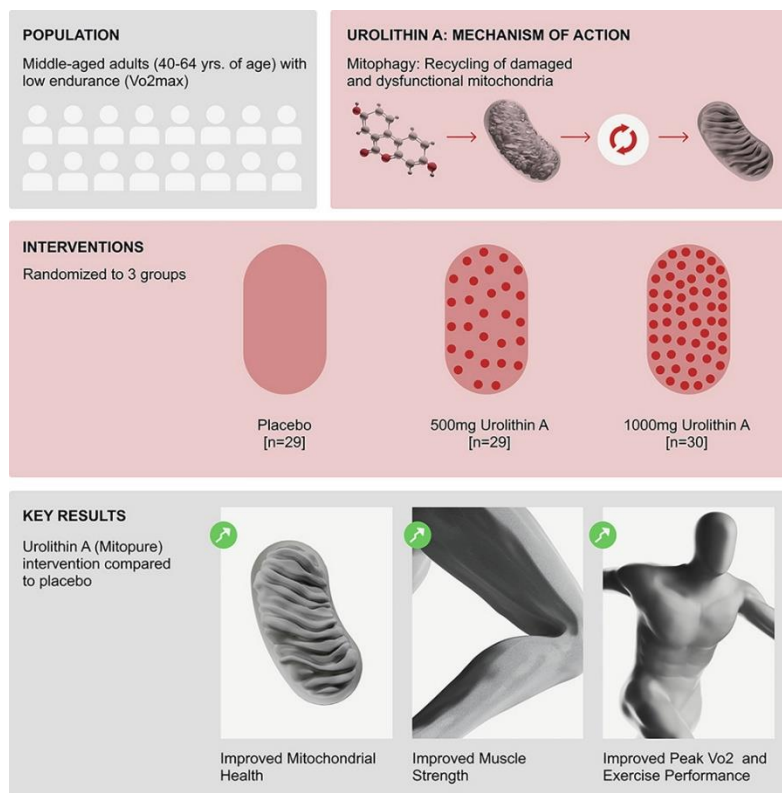


Figure 3: The figure illustrates the structure of the human trial. Oral supplementation with Urolithin A improved mitochondrial health, muscle strength, and exercise performance [42].

The study involved 88 middle-aged (40-65 years) overweight and sedentary adults who were divided into three groups: a placebo group, a group that received 500 mg of urolithin A, and a group that received 1000 mg of urolithin A, all for a period of four months.

Urolithin A at both dosages significantly improved lower limb muscle strength. And it clearly showed the involvement of all the pathways we discussed earlier.

Muscle proteomic analysis revealed the activation of pathways linked to mitochondrial metabolism and mitophagy.

- Increased levels of the active phosphorylated form of Parkin.
- Increased mtDNA/nDNA ratio as an indicator of mitochondrial content.
- Increased respiratory chain protein in skeletal muscle.
- Significant reduction in plasma C-reactive protein.

In another randomized, double-blind, placebo-controlled clinical trial conducted by Liu S and published in JAMA, it was demonstrated that urolithin A significantly improved the endurance of both hand and leg skeletal muscles in older adults. Hence, of muscles that anatomically and functionally are different.

Summary and Conclusions

Urolithin A has emerged as a multifunctional molecule targeting etiopathogenetic factors common to multiple age-related diseases and aging. Recent evidence shows that it is an extraordinary pleiotropic molecule capable of developing multiple beneficial effects on a variety of organs and pathologies.

It acts on multiple metabolic pathways positively correlated with longevity, although mitophagy is the main one. It showed positive effects on cardiovascular, neurodegenerative, osteoarticular diseases, on cancer but also on osteoporosis, vitamin D, osteoarthritis, skin aging, insulin resistance and metabolism. Exciting human studies have highlighted its potential in improving muscle health, with good oral bioavailability and a high safety profile.

Urolithin A can be used alone or in combination with other mitophagy activators, such as Spermidine, Resveratrol and NAD or NAD activators, with a synergistic effect in addition, of course, to physical activity and intermittent fasting.

It has limited adverse side effects, and this greatly augments its applications as a potential nutraceutical tool for therapies to counteract age associated disease and favored successful aging.

While further research is necessary to solidify the current evidence, the results thus far are highly promising.

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