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Review

Impact of the Natural Compound Urolithin A on Health, Disease, and Aging

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Urolithin A (UA) is a natural compound produced by gut bacteria from ingested ellagitannins (ETs) and ellagic acid (EA), complex polyphenols abundant in foods such as pomegranate, berries, and nuts. UA was discovered 40 years ago, but only recently has its impact on aging and disease been explored. UA enhances cellular health by increasing mitophagy and mitochondrial function and reducing detrimental inflammation. Several preclinical studies show how UA protects against aging and age-related conditions affecting muscle, brain, joints, and other organs. In humans, benefits of UA supplementation in the muscle are supported by recent clinical trials in elderly people. Here, we review the state of the art of UA's biology and its translational potential as a nutritional intervention in humans.

Highlights

Urolithin A (UA) is a gut microbiome-derived natural compound that only 40% of people can naturally convert from dietary precursors at meaningful levels.

Positive effects of direct UA administration in health, aging, and age-related conditions have been identified in several recent studies.

Experimental models consistently show that UA increases mitophagy and mitochondrial function and blunts excessive inflammatory responses.

UA increased biomarkers of mitochondrial function in preclinical models of aging and in healthy elderly people.

UA is a promising strategy to target health and disease conditions of aging, especially those linked to mitochondrial and muscle dysfunction.

Urolithin A: A Natural Gut Microbiome-Derived Metabolite

UA belongs to the family of urolithins, characterized by a chemical structure containing an α-benzo-coumarin scaffold (Figure 1). Urolithins are produced in the colon following the microbiome-mediated transformation of the natural polyphenols ETs and EA, which are contained in dietary products, such as pomegranates, strawberries, raspberries, and walnuts [1–3]. (Figure 1 and Box 1).

First identified as an EA metabolite in rats in 1980 [4], similar **gut microbiome** (see Glossary) conversion of ETs to UA was later demonstrated across many species, including flies and mice [1] . A pioneering study also showed the production of UA from ETs by the human gut microbiota [5], making UA the most common urolithin species produced in nature. Two clinical studies then measured UA in human plasma after consumption of pomegranate [6], berries, and nuts [7]. Interestingly, the conversion of dietary precursors to UA does not occur in all individuals. The process is variable [8] and takes place in only approximately 40% of the human elderly population [9]. Being a 'UA producer' requires an appropriate gut microbiome and varies with age, health status, and dietary intake [10].

Backed by growing interest in nutritional interventions to address the ever-increasing health problems of an aging population [11,12], several research groups started to study the role and relevance of direct supplementation with UA instead of with UA precursors.

This review outlines the most relevant *in vivo* preclinical studies that show positive impacts of UA on health conditions due to natural aging and on progressive diseases linked to aging. It describes the molecular mechanisms that explain how UA can counter the hallmarks of aging. Finally, this review explores the translational relevance and potential applications of UA as a nutritional intervention in humans.

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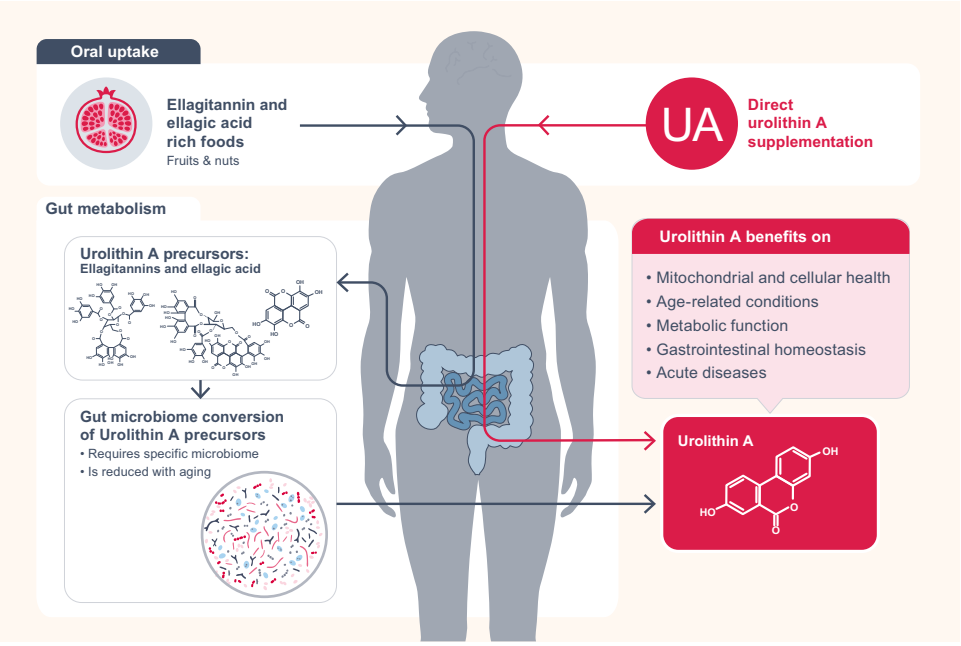

Figure 1. Urolithin A (UA) Is a Gut Microbiome-Derived Compound with Health Benefits for Aging and Diseases. Several dietary products contain the natural polyphenols ellagitannins (ETs) and ellagic acid (EA). Upon ingestion of such foods, ETs and EA are metabolized into UA by the microflora in the large intestine. This conversion occurs only in the presence of the appropriate microbiome and declines with aging. Direct supplementation with UA bypasses the need of a microbiome-mediated conversion of UA precursors. Once absorbed, UA positively impacts mitochondrial and cellular health in age-related conditions and diseases.

UA Mechanisms of Action

Mitophagy and Mitochondrial Function

The most consistent effect of UA across species is the improvement of mitochondrial health, an effect observed in cells, worms, mice, and humans. This benefit is driven by the clearing and recycling of dysfunctional mitochondria, a selective autophagy process called mitophagy [13]. Mitophagy is impaired with increased age and in several age-related diseases [13,69]. Restoring correct levels of mitophagy is a promising strategy to counteract age-related decline of organ function [14,16].

Box 1. Conversion of Ellagitannins and Metabolism of UA

The complex natural polyphenols ETs and EA are present in a variety of plant products and foods and are the main dietary precursors of UA. ETs have a very low bioavailability and are either directly eliminated in the stool or converted into more bioavailable derivates [2]. ETs are hydrolyzed into EA by gut bacterial enzymes called tannases. Further enzymatic reactions transform EA into UA and other urolithins (Figure 1) [2]. UA and urolithin B (UB) are the most abundant final products, and UA is the most conserved and widely studied urolithin across species [2].

Ingesting ET-rich foods is not always enough to expose people to UA, as its formation depends on having the appropriate gut microbiome [10]. Of note, several efforts have been made to identify the bacterium, or bacteria, responsible for UA conversion. Although some species have been proposed based on *ex vivo* studies in feces [60,61], the UA-producing bacteria in the human gut are still unknown [10].

After its production and absorption into the blood circulation, UA undergoes phase 2 metabolism to form UA conjugates, mainly UA-glucuronide and UA-sulfate. UA-glucuronide is the most abundant form of UA detected in the human plasma [2]. The biological role of UA conjugates *in vivo* is still not clear. *In vitro* experiments suggest that UA conjugates have lower or no biological activity compared with UA [2,70].

Glossary

APP/PS1 mouse model: transgenic mouse model of Alzheimer's disease (AD) expressing genes encoding for the humanized amyloid precursor protein (APP) and human presenilin-1 (PSEN1), both directed to the CNS. Both *APP* and *PSEN1* genes contain mutations that are associated with early-onset AD. These mice develop amyloid beta (Aβ) plaques in the hippocampus and cortex and have deficits in synaptic plasticity and cognitive functions.

Cytokines: small proteins (such as interleukins) secreted by immune cells that modulate immune and inflammatory responses.

Gut microbiome: the pool of microorganisms, bacteria, viruses, protozoa, and fungi residing in the gastrointestinal tract.

Mitochondrial respiratory capacity: the efficiency by which mitochondria perform metabolic reactions to convert the energy stored in macronutrients to ATP, the primary energy carrier in cells. The process, named oxidative phosphorylation, takes place in the inner mitochondrial membrane through enzymes forming the electron transport chain (ETC). Electrons are transported in a series of redox reactions to generate a proton gradient, which is then used to generate ATP.

***mdx* mouse models of Duchenne muscle dystrophy (DMD):** models used for studying DMD, a genetic disease associated with progressive muscle weakness caused by mutations in the gene encoding for dystrophin. The *mdx* mouse strain is a commonly used DMD model, which has a spontaneous mutation in the dystrophin gene and therefore lacks a functional dystrophin protein. The *mdx/Utr*$^{-/-}$ double *knockout* (DKO) strain is another model in which genes encoding for both dystrophin and utrophin (*Utr*) are lacking. Compared with *mdx* mice, DKO mice exhibit more severe muscle dysfunctions and have a shorter lifespan, similar to that observed in human DMD patients.

PINK1 (PTEN-induced kinase 1): a mitochondrial serine/threonine-protein kinase that triggers the removal of damaged mitochondria though the PINK1/Parkin-mediated mitophagy pathway. In healthy mitochondria, PINK1 is constantly cleaved and degraded. In damaged mitochondria, PINK1 degradation stops, leading to PINK1 stabilization on the outer mitochondrial membrane (OMM). PINK1

Mitophagy occurs when mitochondria are damaged or following exposure to external mitophagy inducers (Figure 2). The process proceeds via several pathways that UA can activate. PTEN-induced kinase 1 (**PINK1**)/Parkin-dependent mitophagy starts with the stabilization of the kinase PINK1, which recruits and phosphorylates the ubiquitin-conjugating protein Parkin. Parkin in turn promotes **ubiquitination** of mitochondrial proteins, which are phosphorylated by PINK1 and serve as docking sites for adaptor proteins, such as the microtubule-associated protein LC3, and phagosome membranes. Once mitochondria are engulfed by the phagophore membrane, they merge with lysosomes for organelle clearance (Figure 2) [13]. Other PINK1–Parkin-independent mitophagy pathways activate mitochondrial proteins, such as BNIP3, NIX, and FUNDC1, which directly recruit LC3 to promote autophagosome formation (Figure 2) [13].

In the nematode *Caenorhabditis elegans*, UA increased the expression of mitophagy genes *lgg-1* [14], *pink-1*, and *pdr-1* [15], worm homologs of mammalian genes encoding for LC-3B, PINK1, and Parkin and autophagosome vesicle formation. The ablation of *pink-1* and *dct-1*, the *C. elegans* ortholog of mammalian *BNIP3*, abolished the beneficial effects of UA on mitophagy [16] and lifespan [14].

PINK1 and phospho-ubiquitin accumulation was prominent in C2C12 mouse muscle myoblasts treated with UA. *In vivo*, higher levels of ubiquitinated and phospho-ubiquitinated mitochondrial proteins were observed in muscle tissues after administering UA in wild-type rodents [14] and in the ***mdx* mouse model of Duchenne muscular dystrophy (DMD)** [15]. PINK1 stabilization by UA was reported in human neuroblastoma SH-SY5Y cells and hippocampal neurons of an Alzheimer's disease (AD) mouse model [16]. Consistently, mitophagy events were increased in AD mouse brains. PINK1/Parkin mitophagy activation was also reported in pancreatic cells of diabetic mice [17] and in mouse nucleus pulposus cells *in vitro* [18]. PINK1/Parkin independent mitophagy is less explored in mammals; however, some data show activation of *Bnip3* mRNA levels and mild accumulation of mitochondrial BNIP3 in the muscle of UA-treated *mdx* mice [15].

Mitophagy improves the quality of the cellular mitochondria pool and is tightly linked to the generation of new organelles, leading to improved **mitochondrial respiratory capacity** [19].

Mitochondrial abundance is reduced upon short-term treatment with UA in worms and C2C12 mouse muscle cells [14]. Conversely, muscle mitochondrial content is unchanged [14] or mildly increased in muscle [15] and increased in the liver [20] in mice after longer UA exposure. This suggests that UA, at first, activates mitophagy and thereafter favors mitochondrial biogenesis. Consistent with this, UA induced mitochondrial oxidative phosphorylation (OXPHOS) proteins in muscle cells and tissue [14,15] and in the kidney of mice subjected to acute kidney injury [21]. Mitochondrial gene sets were also among the most upregulated in transcriptomic data of UA-treated HT29 colon cells [22].

Mitochondrial functional readouts were measured in skeletal muscle, where UA elevated mitochondrial respiratory capacity in C2C12 cells [14] and Complex I- and II-mediated respiration in muscle tissues from *mdx* mice [15]. In humans, UA was shown to regulate mitochondrial function systemically and in skeletal muscle. Data from the first-in-human Phase I trial with UA administration showed a decrease in several plasma acylcarnitines [23], markers that reflect the efficacy of mitochondrial fatty acid oxidation at the level of the entire body [24], and an increase in the expression of mitochondrial gene sets in the muscle [23].

thereby recruits and phosphorylates the ubiquitin ligase Parkin. PINK1 also phosphorylates ubiquitin moieties added by Parkin on OMM proteins, thereby allowing the formation of phospho-ubiquitin chains.

Ubiquitination (or ubiquitylation): a post-translational modification occurring when the small protein ubiquitin is covalently attached to a lysine residue of a target protein. This occurs by the action of ubiquitin-conjugating enzymes (or ubiquitin ligases). Conjugation of multiple ubiquitin molecules leads to protein poly-ubiquitination. Poly-ubiquitinated proteins are recognized by the 26S proteasome system for degradation. In the mitochondria, ubiquitin moieties are phosphorylated by PINK1. Phospho-ubiquitinated proteins serve as a signal to promote the removal of the mitochondria through mitophagy.

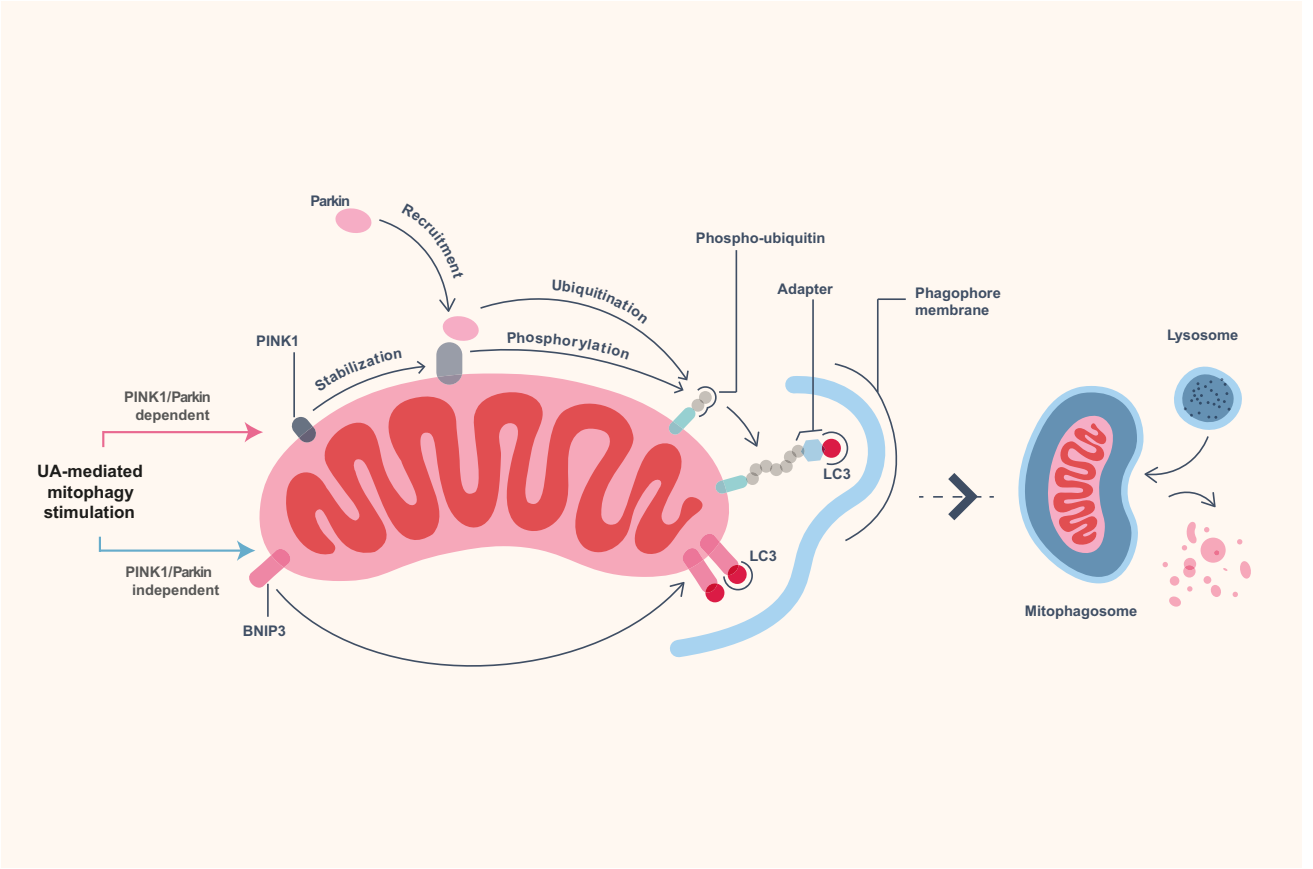

Figure 2. Schematic Representation of Mitophagy Pathways Activated by Urolithin A (UA). UA activates PINK1–Parkin-mediated mitophagy (pink arrow) by stabilizing the kinase PINK1. Parkin is then recruited to PINK1 and ubiquitinates mitochondrial proteins. Ubiquitin chains are in turn phosphorylated by PINK1, leading to accumulation of phospho-ubiquitinated mitochondrial proteins. These serve as docking sites for adapter proteins, such as optineurin and p62, which then bind LC3. UA also activates a PINK1–Parkin-independent pathway (blue arrow) by increasing mitochondrial BNIP3 levels. BNIP3 recruits LC3 independently of Parkin and other docking proteins. For both mitophagy pathways, LC3 allows the formation of a phagosome membrane around the mitochondria. The deriving mitophagosome fuses with lysosomes. Low pH and hydrolytic enzymes from lysosomes finally breakdown the mitochondria.

Inflammation

A common effect shared between preclinical models exposed to UA is the attenuation of detrimental inflammatory responses. This is particularly clinically relevant because aging and most age-related diseases are associated with chronic, low-grade inflammation. This process, recently named inflamm-aging [25], contributes to age-related decline in cellular and organismal function.

The anti-inflammatory effect of UA was reported for the first time as a decrease in mRNA and protein levels of the inflammatory marker cyclooxygenase 2 (COX2) in the colon of a dextran sulphate sodium (DSS)-induced rat model of acute colitis [26]. Further studies showed a consistent reduction in plasma of proinflammatory **cytokines** interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNFα) in both acute, trinitrobenzenesulfonic acid (TNBS)-induced and chronic, DSS-induced mouse models of colitis [22]. The same cytokines were reduced in the plasma of UA-treated streptozotocin-induced diabetic mice [17], where an increase in anti-inflammatory IL-10, was also noted [17]. IL-1β was reduced by UA in the livers of high-fat diet (HFD)-fed obese mice [20] and in the kidneys of mice subjected to cisplatin-induced nephrotoxic injury [27]. Lower levels of fractalkine, a proinflammatory cytokine that influences myocardial

function [28], were measured in a streptozotocin-induced rat model of diabetic cardiomyopathy (DCM) after treatment with UA [29].

In neuronal tissues, UA treatment reduced levels of IL-1β, IL-6, and TNFα in the brains of the amyloid precursor protein/presenilin 1 (**APP/PS1**) **mouse model** of AD [16,30]. These studies suggested that promotion of the phagocytic activity of microglia, cells that are crucial to clean up cellular debris from the central nervous system (CNS) and to control inflammatory responses, contributes to UA's protection against neuroinflammation [16,30]. Notably, knockdown of *Pink1* in microglia ablated UA-mediated reduction of TNFα and increased IL-10 secretion, indicating that UA reduces neuroinflammation via the induction of mitophagy [16]. A reduction in inflammatory cell infiltration was recently reported when analyzing white matter tissue in a mouse model of inflammatory experimental autoimmune encephalomyelitis (EAE) treated with UA [31].

Upstream mediators of UA's anti-inflammatory effects were studied mostly *in vitro*. They include NF-κB, which is required for the transcription of several inflammatory markers and whose activity is inhibited by UA in macrophages [32,33] and chondrocytes [34]. Furthermore, blocking the aryl hydrocarbon receptor (AhR)– nuclear factor erythroid 2-related factor 2 (Nrf2) (Ahr–Nrf2) pathway, which regulates gene expression through the antioxidant response element (ARE), blunted UA's anti-inflammatory effect in the colon [22] and in T helper (Th)17 immune cells [31]. UA's mechanism of action in the context of inflammation seems to vary between tissues and conditions, and its understanding merits further *in vivo* investigation.

Biological Effects of Urolithin A in Aging and Diseases

This section describes how UA impacts aging and age-related diseases, with a particular focus on diseases of the muscle, brain, joints, kidney, and metabolic systems. Table 1 provides a comprehensive description of *in vivo* experimental conditions in which UA has been tested.

Lifespan

One of the first publications to study the direct effects of UA *in vivo* was in the context of aging [14]. A comparison of different pomegranate metabolites testing their impact on worm longevity showed that UA extends lifespan by 45%, while its precursor EA has no effect [14]. After these studies in wild-type worms, the anti-aging effects of UA were also confirmed in the *wrn-1* worm model of Werner syndrome, a premature aging disease [35]. In mice, UA treatment significantly increased the survival rate of the ***mdx/Utr*$^{-/-}$ double knockout (DKO) mouse model of DMD** that shows premature death similar to human DMD patients [15].

Skeletal Muscle Function

UA was shown to increase markers of health span and skeletal muscle function in different species and experimental settings. In *C. elegans*, UA prevented age-related muscle decline [14], as indicated by improved integrity of muscle fibers, increased mobility, and higher rates of pharyngeal pumping in old, UA-treated worms [14].

Positive impacts of UA on muscle health during aging are conserved in mammals. UA was administered in the diet in a prevention study in middle-age C57BL/6 mice for 34 weeks and in an intervention study in old mice for 6 weeks. Mice showed enhanced skeletal muscle strength in the prevention study and better aerobic performance in both prevention and intervention mode [14]. Endurance, grip strength, and *ex vivo* tetanic force were promoted by UA in *mdx* and *mdx/Utr*$^{-/-}$ DKO dystrophic mice [15]. Supplementation with UA also increased running activity in young rodents, including C57BL/6J mice [36] and Wistar rats [14].

Table 1. Health Conditions and Diseases, Experimental Settings, and Main Biological Effects of UA in *In Vivo* Preclinical Studies[a]

	Condition	Animal model	Route of administration (formulation)	Dosing regimen	UA effects	Refs
Aging	Natural aging	*Caenorhabditis elegans*	Oral admin (bacterial solution in agar plate)	50 μM daily from egg stage until death	Lifespan extension mediated by mitophagy	[14]
	Werner syndrome			100 μM daily from L4 stage until death		[35]
	Duchenne muscular dystrophy	5-wo *mdx/Utr*$^{-/-}$ mice	Oral admin	50 mpk	Increased survival	[15]
Muscle dysfunctions	Natural aging	N2 WT *C. elegans*	Oral admin (bacterial solution in agar plate)	50 μM daily from egg stage until death	Better muscle fiber morphology, increased mobility and pharyngeal pumping rate	[14]
		23-mo C57BL/6J mice	Oral admin	50 mpk daily for 6 wk	Increased muscle strength and aerobic performance	
		16-mo C57BL/6J mice	Oral admin in HFD	50 mpk daily for 34 wk		
		5.5-wo Wistar rats	Oral admin	25 mpk daily for 6 wk	Increased running activity	
		12-mo C57BL/6J mice	Oral gavage (DMSO diluted in corn oil)	10 mpk daily for 16 wk	Increased ATP and NAD^+ levels and muscle angiogenesis	[37]
	Duchenne muscular dystrophy	5-wo *mdx* mice	Oral admin	50 mpk for 10 wk	Increased grip strength, tetanic force, and running ability	[15]
Cardiovascular diseases	Diabetic cardiomyopathy	12–14-wk STZ-induced diabetic Wistar rats	I.P. (DMSO-saline)	2.5 mpk daily 2 d after STZ injection for 3 wk	Prevention of diabetes-associated cardiac dysfunctions	[29]
	Myocardial ischemia	C57BL/6J mice subjected to myocardial ischemia/reperfusion injury (age NS)	I.P. (DMSO)	1 mg/kg 24 h and 1 h before surgery	Prevention of myocardial infarct size and cell death	[39]
	Atherosclerosis	Wistar rats (age NS), high-cholesterol diet + vitamin D3 with balloon injury of the aorta	Oral admin or gavage (NS)	3 or 30 mpk daily 3 d before surgery, then 3 wk or 12 wk (inconsistencies in text)	Decreased plasma lipids and angiotensin II levels; improvement of aortic lesions	[40]
Brain diseases	Alzheimer's disease	6-mo APP/PS1 mice	Oral gavage (NS)	200 mpk daily for 2 months	Improved cognition, reduced amyloid plaques and neuroinflammation	[16]
		13-mo 3×TgAD mice	Oral gavage (NS)	200 mpk daily for 1 month	Improved cognition and reduced tau phosphorylation	
		7-mo APP/PS1 mice	Oral gavage (0.5% CMC)	300 mpk daily for 14 d	Improved cognition, decreased neuronal loss and neuroinflammation	[30]
	Ischemic neuronal injury	C57BL/6 mice with middle cerebral artery occlusion	I.P. (DMSO-saline)	2.5–5 mpk daily 24 h and 1 h before surgery	Reduced brain infarct volume and neurological deficit score	[42]
	Multiple sclerosis	8–12-wo C57BL/6 with EAE	Oral admin	25 mpk daily for 15–30 d	Reduced development and severity of encephalomyelitis	[31]
IBD	Acute colitis	DSS-fed Fisher rats	Oral admin	15 mpk daily for 25 d	Reduced colon injury severity and improved mucosal integrity	[26]
		7–8-wo mice with TNBS-induced colitis	I.P. (0.25% sodium-CMC)	4 mpk 12 h after TNBS and every 12 h up to 72 h	Reduced colon inflammation, increased colon length, and improved intestinal permeability	[22]
				20 mpk daily for 1 wk before TNBS		

Table 1. (continued)

	Condition	Animal model	Route of administration (formulation)	Dosing regimen	UA effects	Refs
		7–8-wo DSS-fed mice	Oral gavage (0.25% sodium-CMC)	20 mpk on fourth and sixth day of DSS treatment		
	Chronic colitis	7–8-wo DSS-fed mice (4 DSS cycles)	Oral gavage (0.25% sodium-CMC)	20 mpk on fourth and sixth day of each of the four DSS cycles		
Joint and spine diseases	Intervertebral disc degeneration	12-wo Sprague Dawley rats; needle-punctured tail model	Oral admin	25 mpk daily for 4 wk	Attenuated intervertebral disc degeneration	[44]
	Knee osteoarthritis	10-wo C57BL/6J mice undergoing destabilization of the medial meniscus	Oral gavage (0.5% CMC)	20 mpk daily for 8 wk	Diminished cartilage degeneration and knee inflammation	[34]
Metabolic dysfunctions	Obesity	C57BL/6 mice fed with HFD	I.P. (DMSO-saline)	20 μg/day for 12 wk	Decreased liver triglyceride and adipocyte hypertrophy and improved insulin sensitivity	[20]
		8-wo C57BL/6 mice fed with HFD	Oral gavage (NS)	30 mpk daily for 6–10 wk	Antiobesity effect, improved insulin sensitivity. Reduced systemic inflammation and fatty liver	[36]
		6-wo *ob/ob* mice	Oral gavage (NS)	30 mpk daily for 6 wk		
		5–6-wo DBA/2J mice (HFHS diet)	Oral admin	0.1% for 8 wk		[48]
	Diabetes	10-wo C57BL/6 /type 2 diabetic (HFD and STZ)	Oral gavage (water solution)	50 mpk daily for 8 wk	Improved autophagic flow and decreased apoptosis and pancreatic damage	[17]
Acute kidney injury	Acute kidney injury	SD rats injected with cisplatin	Oral gavage (0.5% CMC)	50 mpk daily for 6 d	Reduced tubular damage, plasma creatinine, and inflammatory cytokines in kidney	[27]
		C57BL/6 mice injected with cisplatin	I.P. (DMSO-saline)	100 mpk for 1 or 2 d before and 3 d after cisplatin	Protection against nephrotoxicity	[47]
		Male 8–10-wo AKI mice, C57BL/6 mice, and Sprague Dawley rats	Oral gavage (NS)	50 mg/kg, three times/wk up to 19 d (mice)/single dose, 50 mg (rats)	Increased mouse survival	[21]
Cancer	Pancreatic ductal adenocarcinoma	Ptf1aCre/+; LSL-KrasG12D/+; Tgfbr2flox/flox (PKT) C56BL/6J mice	Oral gavage (NS)	20 mpk five times per wk for 3 wk	Reduced tumor progression and increased survival. Reduction of infiltrating macrophages and regulatory T cells	[55]

[a]Abbreviations: admin, administration; AKI, acute kidney injury; CMC, carboxymethyl cellulose; DSS, dextran sulfate sodium; EAE, experimental autoimmune encephalomyelitis; HFD, high fat diet; HFHS, high fat high sucrose diet; IBD, inflammatory bowel disease; I.P., intraperitoneal; mo, month-old; mpk, milligrams of compound per kilogram; NS, not specified; STZ, streptozotocin; TNBS, trinitrobenzenesulfonic acid; wk, week(s); wo, week-old; WT, wildtype.

When administered intragastrically to middle-aged mice for 16 weeks, UA increased markers of angiogenesis in the skeletal muscle [37]. Although no functional data were provided, this is a relevant observation, as impaired neovascularization plays an important role in muscle aging diseases [38].

Cardiovascular Diseases

The potential benefit of UA on cardiovascular disease (CVD) has been evaluated in preclinical models of cardiac ischemia, atherosclerosis, and DCM.

The effects of UA on cardiac ischemia were studied in a mouse model of ischemia reperfusion injury (IRI). Animals pretreated with UA showed a reduced infarct size and a partial preservation of the ejection fraction compared with controls [39]. This was accompanied by a reduction in IRI markers, such as circulating creatine kinase and lactate dehydrogenase levels, and by fewer apoptotic cells in the heart [39]. In a separate investigation, UA protected rats from atherosclerosis, reducing plasma lipid levels and aortic lesions [40]. Finally, better myocardial contractility was reported following UA treatment in a streptozotocin-induced rat model of DCM [29]. Although data from these studies are encouraging, lack of details calls for a reproduction of the results with more animals per group and better reporting of methods.

Neurodegeneration and Diseases of the CNS

Tests across species and conditions show that UA is neuroprotective. The molecule shows benefit in various animal models of AD. UA improved associative memory in response to aversive stimuli in worms that overexpress amyloid beta ($A\beta_{1-42}$), a cleavage product of APP that forms toxic aggregates in neurons [16]. Increased learning, memory retention, neuronal survival, and neurogenesis in the hippocampus was achieved with UA administration in the APP/PS1 mouse model of AD [16,30]. At the cellular level, UA lowered both insoluble $A\beta_{1-42}$ plaques and phosphorylated tau levels, currently the most relevant markers linked to AD development, progression, and severity [16].

Neuronal death and neurological impairment can also ensue after ischemic stroke, when brain cells receive insufficient oxygen because of restricted blood flow [41]. UA was protective in an *in vivo* model of ischemic stroke induced by cerebral artery occlusion through reducing infarct volume and the consequent neurological deficits [42].

Recently, UA was shown to have neuroprotective effects in the EAE mouse model of multiple sclerosis (MS) [31]. UA administration both at early and late stages reduced MS incidence and severity [31], accompanied by decreases in dendritic cells (DCs), macrophages, and pathogenic Th17 cells as well as reduced inflammation and white matter demyelination [31].

Spine and Joint Disorders

Aging is the main risk factor for intervertebral disc degeneration (IDD), a spine disorder characterized by progressive damage to intervertebral discs [43]. Tested in a rat needle-punctured tail IDD model, UA alleviated disc destruction and intervertebral space disc narrowing. It also increased the production of proteoglycan and collagen, key molecules of the extracellular matrix [44]. In another study, it was shown that the protection against IDD was associated with increased mitophagy and reduced apoptosis in nucleus pulposus cells [18].

In a model of osteoarthritis, an age-related and disabling joint disease caused by a slow degeneration of cartilage, UA improved knee joint cartilage morphology and reduced the narrowing of the intra-articular space [34].

Inflammatory Bowel Diseases

Ulcerative colitis and Crohn's disease are the two main types of inflammatory bowel disease (IBD). IBD is generally caused by a dysfunctional immune system, which leads to chronic inflammation of the digestive tract and to microbial dysbiosis [45].

UA has protective effects against a chronic DSS-induced model of IBD, leading to reduced levels of colon inflammation markers and to better mucosal integrity. These data are in line with the

results of studies supplementing UA in a rat model of DSS-induced acute colitis [26] and a mouse model of TNBS-induced acute colitis [22].

These findings support the use of UA to treat other conditions involving barrier dysfunction, such as irritable bowel syndrome, colon cancer, and celiac disease.

Acute Kidney Injury

Acute kidney injury (AKI) is a transient episode of kidney failure or damage that can require dialysis; a nonnegligible fraction of patients with AKI go on to develop chronic kidney disease [46].

The impact of UA, given either orally or intraperitoneally, was tested in three different studies involving mice or rats in which AKI was induced by cisplatin (Table 1) [21,27,47]. Despite slight differences in protocols and low numbers of animals per group, UA consistently reduced tubular damage induced by cisplatin, as shown by histopathology and by a reduction in circulating markers of kidney damage (creatinine) [21,27,47]. UA administration decreased the number of apoptotic tubular cells [21,27] or the expression of markers of apoptosis in the kidney (caspase-3 activity) [47]. When administered as nanoparticles to increase its bioavailability, UA even improved the survival of mice that received a lethal dose of cisplatin [21].

Metabolic Dysfunctions

Several *in vivo* experiments studied the role of UA on metabolic tissues and documented its protective effect against metabolic dysfunction, such as dyslipidemia, obesity, and glucose intolerance.

In a mouse model of HFD-induced obesity, daily intraperitoneal administration of UA attenuated triglyceride (TG) accumulation in the liver and reduced total cholesterol, low density lipoprotein (LDL), and adiponectin plasma levels [20]. No effects were observed on body weight and fat mass [20]. In a separate publication using the HFD model, UA treatment by oral gavage reduced adipocytes and decreased fat mass and body weight [36]. These data were reproduced in the leptin-deficient, *ob*/*ob* genetic model of obesity [36]. The inconsistent results of UA on body weight in obese mice could be explained by the use of different doses and administration routes (Table 1). Further studies are warranted to address this point.

In addition to lipid-related metabolic dysfunctions, UA improved systemic insulin sensitivity, measured by the glucose tolerance test and plasma insulin levels, in mouse models of obesity [20,36,48] and type 2 diabetes [17].

UA shows potential for the management of obesity and glucose intolerance. Additional studies are required to clarify the most appropriate route and dose of administration.

UA in Clinical Studies

UA has been investigated in two types of clinical studies: (i) association studies, where subjects received a food source of ETs and were subsequently assessed for their urolithin production profile (Box 2), and (ii) intervention clinical trials, where subjects directly received UA by oral administration.

As to intervention trials, UA was administered directly to humans for the first time in the context of a randomized, double-blind, placebo-controlled Phase I clinical trial (ClinicalTrials.gov: NCT02655393, https://clinicaltrials.gov/ct2/show/NCT02655393) [23]. Subjects enrolled included healthy elderly males and females (aged 61 to 85 years). UA showed a favorable safety

Clinician's Corner

Aging disrupts multiple cellular and systemic processes and leads to a progressive physiological decline in body functions. Aging is also a leading risk factor for several debilitating disorders, such as neurogenerative disease, osteoarthritis, and metabolic disorders.

A defining physiological feature of aging is mitochondrial dysfunction, which especially impacts organs with a high metabolic demand, such as skeletal muscle, the heart, kidneys, and brain. There is an ongoing search for pharmacological interventions that can support mitochondrial activity to reverse or delay age-related diseases. In addition, dietary supplements are playing a growing role in managing daily health in individuals in the absence of disease and represent a complementary approach to pharmaceuticals.

Urolithin A (UA) is a gut microflora-derived metabolite that is derived from dietary precursors and has recently shown promise in experimental models of aging and age-related conditions by improving mitochondrial health. A first-in-human clinical study showed safety and high bioavailability of UA in healthy elderly individuals at all doses tested. Further analyses revealed that UA reduced acylcarnitines in the plasma and enhanced mitochondrial gene sets in the skeletal muscle of elderly individuals. These biomarkers provide evidence that UA promotes better mitochondrial and muscle health. This is clinically relevant as about 20% of elderly individuals across the world suffer age-associated decline in muscle function, which contributes to sarcopenia, frailty, and other conditions. Notably, the molecular signature activated by UA resembled that observed as a consequence of physical exercise regimens.

Data from preclinical models to humans support UA's potential to promote both mitochondrial health and muscle health during aging. UA's impact on conditions and diseases associated with a decline in mitochondrial function merits further investigation.

Box 2. Urolithin Metabotypes and Association Studies

The profile of urolithins in plasma or urine of subjects following the consumption of foods rich in either ETs or EA may be classified according to the production (or not) of different urolithin metabolites by the gut microbiome. Distinct urolithin metabolite profiles (or metabotypes) have been described after the analysis of plasma and urine in participants consuming ET-rich foods in several clinical trials [8]. Individuals producing only UA and its conjugates became classified as 'metabotype A' or 'UM-A' [8]. Subjects producing only urolithin B (UB) or subjects not able to produce any form of urolithin were classified as metabotype B (UM-B) or metabotype 0 (UM-0), respectively [8].

In these clinical studies, metabotype A individuals had a body mass index (BMI) in the normal range (19–25 kg/m^2) and better gut health [63,64] compared with other urolithin profiles or metabotypes that did not contain elevated UA levels. These UA producers also had low-risk baseline values of serum CVD biomarkers, which did not change following pomegranate extract (PE) consumption for 2 days. Conversely, UM-B subjects had moderately high risk values at baseline and low risk values after PE consumption [65]. Future clinical studies using UA precursors to assess CVD risk factors should include longer administration time points and take into account subject variability in urolithin conversion ability.

Higher plasma UA levels were also positively associated with improved endothelial function [66] and were observed in individuals who consumed a Mediterranean diet [67], a plant-based diet high in unsaturated fat [68]. Conversely, the proportion of metabotype A profiles declined with age in subjects from 20 to 50 years of age [9].

These associations need to be reproduced in larger cohorts and cannot directly identify UA's health benefits in humans; but, they indicate that UA is the key metabolite of ETs and EA and that the ability to produce it is a sign of general health. The fact that UA levels decline with age is a concern that must be investigated further.

Outstanding Questions

Which gut bacteria allow the conversion of UA from its dietary precursors?

Why can the majority of the human population not produce UA? Does this further decline with age?

What is the relationship between the biological processes regulated by UA, such as mitochondrial function, mitophagy, and inflammation?

What precisely are the molecular mediators of UA's biological effects in various conditions and tissues?

Does the administration route of UA influence its effects in different health and disease settings?

profile, with no observed side effects following either single oral administration of UA up to 2000 mg or multiple oral dosing (28 days) of UA up to 1000 mg daily. UA also had a favorable pharmacokinetic profile, was bioavailable at all tested doses, and did not accumulate over time. It showed a relatively long-half life ($t_{1/2}$ = 17–22 hours), most likely due to an active enterohepatic recirculation. UA was present in plasma, both as the parent UA and its glucuronide and sulfonated conjugated forms, and in skeletal muscle tissue, primarily in its parent form [23]. Subjects supplemented with UA showed increased markers of mitochondrial health. The expression of mitochondrial gene sets was increased in skeletal muscle tissue biopsies [23]. Notably, the same gene sets were lower in the muscle of pre-frail elderly individuals compared with healthy elderly individuals [49]. Better systemic mitochondrial efficacy was indicated by the decrease in plasma levels of several acylcarnitines [23]. In summary, this first clinical study demonstrated that UA is safe, bioavailable, and positively impacts mitochondria, reproducing findings observed in the preclinical models discussed previously (see Clinician's Corner).

Concluding Remarks

This review outlines the health benefits of the food-derived compound UA on a broad spectrum of *in vivo* models of health decline linked to both aging and chronic diseases (Figure 3). Importantly, UA safeguards against physiological decline, as illustrated by improved muscle function in young animals and the prevention of age-related muscle decline in old mice, illustrating UA's benefits in a healthy setting (Figure 3).

The heightened interest in using UA nutritional supplementation to promote healthy aging is supported by two key factors. First, age might reduce the natural ability to produce UA from its precursors [9]. Second, people need a specific gut microbiome composition to carry out the conversion, a process that is variable [8] and takes place in only approximately 40% of the human elderly population [9]. Notably, gut dysbiosis is a common feature of several age-related conditions [50–52], and this could contribute to impaired UA production in the gut with age.

Mechanistically, UA's effect in aging and age-related diseases is mediated by the activation of mitophagy, improvement of mitochondrial function, and reduction of inflammation, which is most likely also linked with its impact on mitochondrial function [53,54]. Other mechanisms of

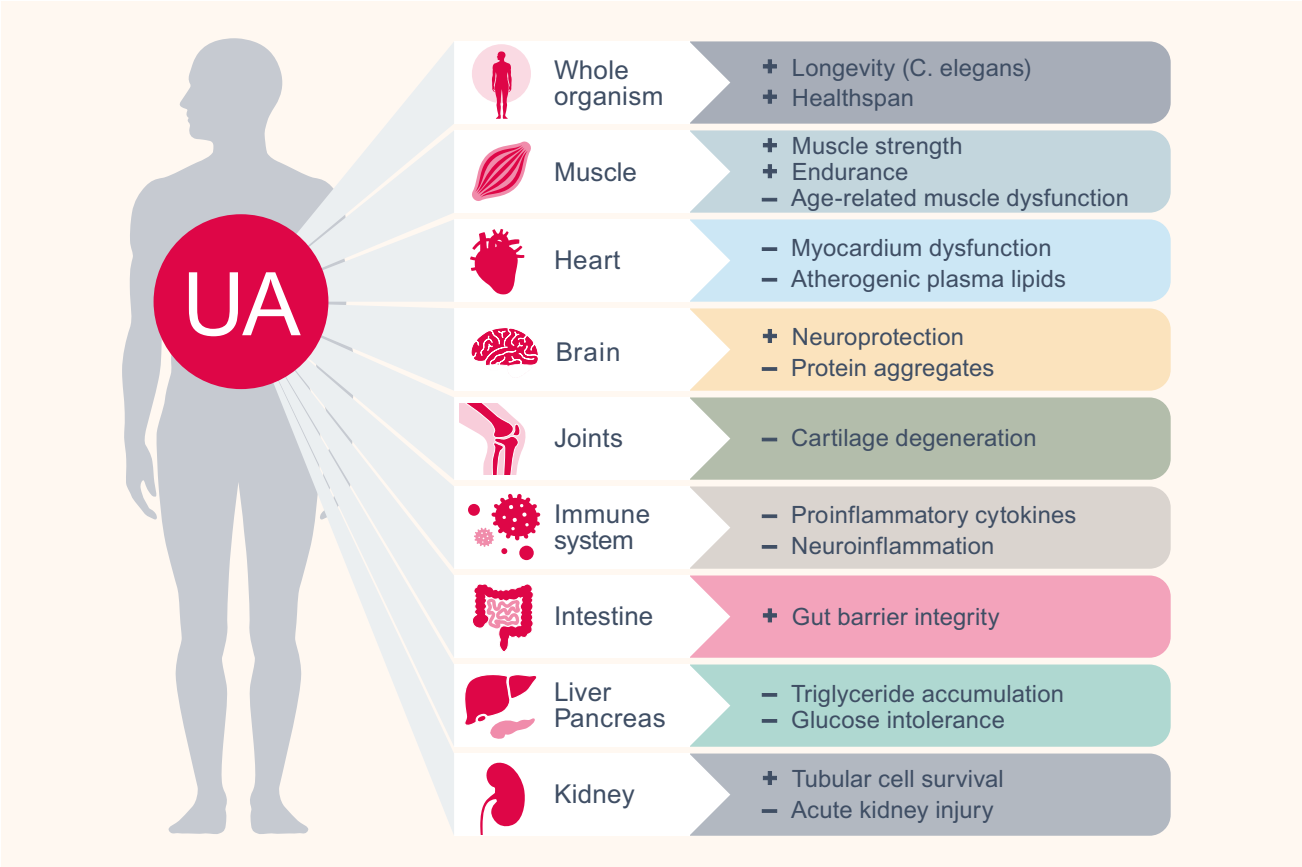

Figure 3. Health Effects of Urolithin A (UA). Summary of key biological effects of UA in different tissues and organs from *in vivo* preclinical studies and clinical trial data. UA promotes (+) several physiological functions that decline with aging and reduces the occurrence (–) of many age-associated pathological conditions. Abbreviation: *C. elegans, Caenorhabditis elegans.*

action have been proposed for UA, such as the activation of the Ahr/Nrf2 pathway and its downstream antioxidative stress response [22] and the inhibition of regulators of cancer cell proliferation [55]. The contribution of these mechanisms to the positive impact of UA in aging needs further study (see Outstanding Questions).

Current publications focus mostly on tissue- or disease-specific targets (Table 1), and it is plausible that UA affects different pathways depending on the organ and conditions analyzed. In addition, experiments described in this review often use different dosing regimens and administration routes (Table 1). Planning future studies on UA must account for this variability. Additional *in vivo* experiments should investigate the most suitable experimental settings to target different organs and conditions (see Outstanding Questions).

From a translational point of view, UA has only been investigated in humans for its benefits on mitochondrial and muscle health. A Phase I clinical study confirmed the activation of mitochondrial biomarkers in muscle and plasma, as previously shown in cells and *in vivo* in model organisms. Based on these findings, there is a strong rationale to study the effects of UA in conditions linked to both mitochondrial and muscle dysfunction. These include age-related conditions

with a strong mitochondrial component, such as muscle wasting and cognitive decline, and disease conditions, including mitochondrial diseases and muscle dystrophies [56].

UA has a beneficial role in many tissues and is tightly linked to our 'hidden' organ system, the gut microbiome [57]. Gut microbiome composition regulates the ability to produce UA from its precursors. A recent report also showed an impact of direct UA supplementation on gut microflora in obese rats [58]. Future research should shed light on the bacterial species responsible for the UA conversion (Box 1) and investigate the crosstalk between UA and gut microflora. This could help to better understand the role of the microbiome–mitochondria axis and its health benefits [59] (see Outstanding Questions).

A growing body of literature is elucidating the beneficial impact of UA, a natural compound with proven biosafety, on promoting healthy aging. These findings support the use of UA supplementation as a nutritional intervention in humans to improve mitochondrial function and organism health during aging. These findings also call for further studies to discover the therapeutic potential of UA in other health and disease conditions.

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Declaration of Interests

The authors declare the following competing interests: D.A, P.A.A., P.V., and A.S. are employees of Amazentis, C.R. is CEO and a board member of Amazentis, and J.A. is a member of the Scientific Advisory Board of Amazentis.

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