

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Urolithin A

Evidence Summary

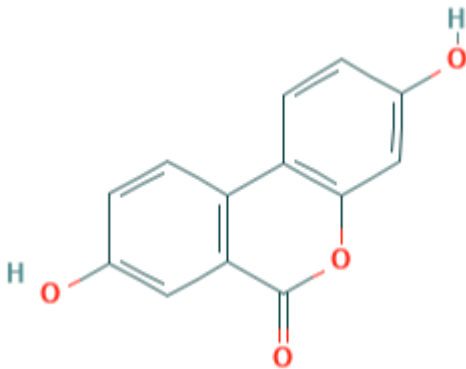
The autophagy/mitophagy effects of Urolithin A make it a promising longevity molecule.

Neuroprotective Benefit: Evidence suggests that pomegranate may be beneficial in Alzheimer's animal models; however, the potential of Urolithin A to promote autophagy and mitophagy is potentially more interesting.

Aging and related health concerns: Animal studies show benefits, but results for pomegranate in humans are mixed. Potential for Urolithin A in humans remains to be seen.

Safety: Long-term safety for supplementation of Urolithin A and pomegranate is not known, though short-term treatment with pomegranate extract is safe.



Availability: Urolithin A is currently in development and is not available; pomegranate extract available at vitamin stores	Dose: 250-2000mg in phase 1 study from Amazentis found Urolithin A to be safe over 28 days	Chemical formula: C ₁₃ H ₈ O ₄ MW: 228.2g/mol Source: Pubchem 
Half life: Urolithin A is present in urine up to 48 hours after pomegranate juice consumption	BBB: Possibly penetrant	
Clinical trials: 1 ongoing for muscle and mitochondrial function using Urolithin A; 1 for sarcopenia using pomegranate juice	Observational studies: ○	

What is it?

Pomegranates contain natural polyphenols including ellagitannins which are hydrolyzed to ellagic acid. Ellagic acid is transformed by the gut microbiota into urolithins. Although studies have looked at urolithin's antioxidant effects, more interesting from an aging perspective is that Urolithin A was recently reported to induce autophagy and mitophagy.

Since Urolithin A is still early in development, this report will also consider studies using pomegranate extract. Individuals metabolize pomegranate differently. [Espin and colleagues](#) identified three different urolithin metabolotypes (UMs): UM-B (subjects that produce isourolithin A and/or urolithin B as well as urolithin A), UM-A (only produce urolithin A), and UM-o (urolithin non-producers). In a study of overweight individuals, [Gonzalez-Sarrias et al \(2017\)](#) found that UM-B individuals had higher cardiovascular risk biomarkers (LDL-c, apoB, oxLDL-c, etc.) than those with UM-A and UM-o, and only those individuals with UM-B showed improvements in those biomarkers when consuming pomegranate extract for three weeks. It is not clear whether this is due to the UM, per se, or whether it is because UM-B individuals had worse CVD biomarkers at baseline.



In a another study, [Cortes-Martin et al \(2018\)](#) found that age was the major determinate of urolithin metabotype (not gender or BMI), where the UM-A metabotype was greatest at younger ages and UM-B increased over time. They suggest that interindividual differences in urolithin metabotype could explain the failures of pomegranate extract human trials. Due to this, the plasma levels of urolithins after consumption of pomagranate extract may be variable between individuals.

One study reported that human subjects taking 180ml of pomegranate juice (25mg of egallic acid, 318mg of ellagitannins) had 31.9ng/ml of ellagic acid in plasma 1 hour post-ingestion which was eliminated by 4 hours ([Seeram et al, 2004](#)).

Therefore, two caveats of studies using pomegranate extract or juice are 1) individuals may metabolize pomegranate differently, and 2) pomegranate juice contains many other compounds (e.g. other polyphenols).

A bioavailable form of Urolithin A is currently in development from [Amazentis](#).

Neuroprotective Benefit: Evidence suggests that pomegranate may be beneficial in Alzheimer's animal models; however, the potential of Urolithin A to promote autophagy and mitophagy is potentially more interesting.

Types of evidence:

- 7 preclinical studies using pomegranate extract

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

None

Human research to suggest benefits to patients with dementia:

None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

[Yuan et al \(2016\)](#) conducted an in silico computational study to evaluate the potential of different pomegranate extract constituents and urolithins to cross the BBB. No pomegranate constituents were predicted to cross the BBB; however, Urolithin A and B (and their methyl derivative) were all predicted



to penetrate the BBB. Urolithin A also reduced A β fibrillization *in vitro* and improved survival in a worm model of Alzheimer's disease.

Pomegranate extract (PE): Short-term treatment (3 weeks) in old Alzheimer's mice reduced A β ₄₂ but did not alter cognition ([Ahmed et al, 2014](#)). Longer treatment in young or old Alzheimer's mice decreased amyloid plaques, oxidative stress, inflammation (TNF α and other cytokines, microgliosis, but not astrogliosis) and increased synaptic density, BDNF, autophagy and improved cognitive performance ([Hartman et al, 2006](#); [Choi et al, 2011](#); [Rojanathammanee et al, 2013](#); [Subash et al, 2014](#); [Essa et al, 2015](#); [Braidy et al, 2016](#)).

APOE₄

None

Aging and related health concerns: Animal studies show benefits, but results for pomegranate in humans are mixed. Potential for Urolithin A in humans remains to be seen.

Types of evidence:

- One human safety study for Urolithin A
- One aging and three CVD studies for Urolithins in model organisms
- Four meta-analyses for pomegranate in humans
- One RCT in prostate cancer
- One lifespan study for pomegranate in model organisms
- Three CVD and one neuropathy study in rodents

Lifespan

In a phase 1 study in elderly adults, 28-day consumption of Urolithin A (250-2000mg/day) upregulated autophagy, improved mitochondrial function, and improved fatty acid oxidation in human skeletal muscles (from Amazentis conference presentation).

Urolithin A increased the lifespan of worms by 45%, though no effects were seen with ellagic acid. It increased worm activity (e.g. pharyngeal pumping) and improved muscle fiber organization. Life extension was dependent on mitochondrial function and mitophagy. Interestingly, Urolithin A decreased mitochondrial content in young worms while maintaining the maximal respiratory capacity and increased mitochondrial number in old worms. In two mammalian cell lines (muscle and intestine), Urolithin A also induced autophagy. 6-week treatment in old mice increased running endurance by 42%



while treatment in young mice increased running capacity by 65%. Lean muscle mass did not increase, suggesting that these benefits were due to muscle efficiency ([Ryu et al, 2016](#)).

Pomegranate supplementation to fruit fly food increased male and female lifespan by 18% and 8%, respectively ([Balasubramani et al, 2014](#)).

In vitro studies suggest that Urolithin A prevented the activation of macrophages which required autophagy ([Boakye et al, 2018](#)).

Cardiovascular

In a meta-analysis of 8 RCTs, [Sahebkar et al \(2017\)](#) reported that consumption of pomegranate juice (doses between 50 and 300ml/day) reduced systolic blood pressure (-5mmHg) and diastolic blood pressure (-2mmHg) regardless of the length of the study (> or < 12 weeks) or dose (systolic reductions were significant, diastolic reductions were slightly non-significant at high and low doses). [Sahebkar and colleagues \(2016\)](#) reported in another meta-analysis of 12 RCTs that pomegranate juice did not change LDLc or HDLc but did lower triglycerides. Two caveats to the aforementioned studies mentioned above are that pomegranate juice contains many other compounds and individuals metabolize ellagic acid differently and the studies may not be relevant to Urolithin A, per se. These mixed results may also be reflected in two meta-analyses showing no benefit with pomegranate juice on glucose management or CRP levels ([Sahebkar et al, 2016](#); [Huang et al, 2017](#)).

Urolithin: In a rat model of aortic injury on a high cholesterol diet, 12-week treatment with Urolithin A decreased LDLc, decreased angiotensin II levels, increased Nrf2 activity, and improved aortic wall morphology ([Cui et al, 2018](#)). In a rat model of streptozotocin (STZ)-induced type 1 diabetes, 3-week treatment with Urolithin A and B improved cardiac function (maximal rate of ventricular pressure, reduced contraction time, cardiomyocyte contractility, etc.) ([Savi et al, 2017](#)). In an ischemia/reperfusion model, Urolithin A reduced cell death and infarct size, improved cardiac function, and reduced levels of ROS. These effects were mediated through the PI3K/Akt pathway ([Tang et al, 2017](#)).

Pomegranate Extract: In a multiple mouse models of atherosclerosis, PE reduced atherosclerotic plaque size up to 44% and the proportion of occlusive coronary artery plaques. It also reduced levels of oxidative stress, ox-LDLc, MCP-1 (which recruits macrophages in to plaques), lipid accumulation,

macrophage infiltration, and fibrosis in the myocardium and increased macrophage cholesterol efflux ([Al-Jaralah et al, 2013](#); [Kaplan et al, 2001](#); [Aviram et al, 2000](#)).

In vitro studies suggest that a combination of Urolithin A and Urolithin B increase nitrite/nitrate levels and eNOS levels, but had no effect individually ([Spigoni et al, 2016](#)). In human artery endothelial cells exposed to ox-LDLc, Urolithin A improved cell survival, increased the expression of NO and eNOS, and decreased the expression of inflammatory proteins ([Han et al, 2016](#)).

Neuropathy

24-day treatment of a rat model of tibial and sural nerve transection with pomegranate extract attenuated neuropathic pain, reduced levels of TNF α , and increased levels of glutathione and nitrite ([Jain et al, 2013](#)).

Prostate Cancer

Pomegranate has also been tested in clinical studies for prostate cancer. In a trial of 183 subjects after primary therapy for prostate cancer, pomegranate extract (dose not specified) did not increase PSA doubling time. However, in a subset of patients with a manganese superoxide dismutase (*MnSOD*) AA genotype (which could indicate a low antioxidant status), PSA doubling time increased 12 months in the pomegranate group compared to 1.8 months in the placebo group. However, the number of *MnSOD* AA patients was small ([Pantuck et al, 2015](#)).

Safety: Long-term safety for supplementation of Urolithin A and pomegranate is not known, though short-term treatment with pomegranate extract is safe.

Types of evidence:

- One short study for Urolithin A
- Multiple meta-analyses for pomegranate

One short phase 1 study of a proprietary Urolithin A drug reported no adverse effects over 28 days (conference presentation). Long-term studies have not been conducted.

In clinical studies, pomegranate extract is safe. High doses (3000mg/day over 28 days) increased diarrhea. However, large-scale, long-term studies have not been conducted ([Vlachojannis et al, 2015](#)). Given this information, Urolithin A is probably safe, though future studies would need to confirm this.

Drug interactions:

No information on drug interactions with Urolithin A. However, pomegranate juice interacts with cytochrome P450 and thus may interact with other drugs ([Vlachojannis et al, 2015](#)).

Sources and dosing:

Urolithin A is currently unavailable, though it is being tested at doses of 250-2000mg/day. Most studies with pomegranate juice have used 250-500ml/day (or 500-1000mg/day of pomegranate extract).

Research underway:

A phase 2 study from Amazentis is reportedly going to take place soon. One study is ongoing looking at the effects of pomegranate juice on sarcopenia ([link](#)). Some other studies are ongoing for cancer and inflammatory bowel disease.

Search terms:

Pubmed:

urolithin, ellagic, pomegranate + alzheimer
urolithin + cardiovascular, autophagy
pomegranate + cardiovascular [meta-analysis], orthostatic, neuropathy, lifespan, [meta-analysis],
apoe, cancer [clinical trial]

Websites visited for Urolithin A:

- Clinicaltrials.gov (pomegranate and urolithin)
- Examine.com (punicalagins)
- DrugAge (o)
- Geroprotectors (o)
- Drugs.com (o)
- WebMD.com (o)
- PubChem
- DrugBank.ca
- Labdoor.com (o)



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