Whole Body Health

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Urolithin-A

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Not intended as Medical Advice

- This lecture is informational only and not intended to diagnose or suggest treatments to any individual listening to this lecture.
- We advise you to seek medical direction with your licensed primary care provider.

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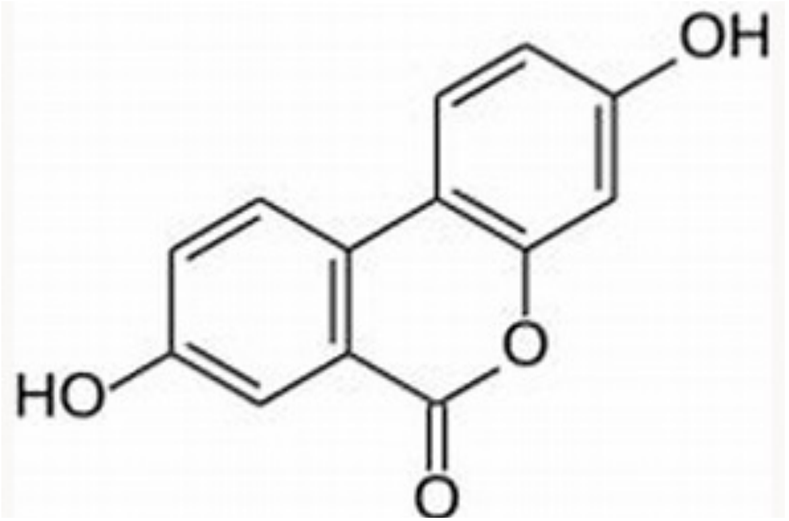
The Urolithin-A compound

1. Definition
2. What it does
3. How to incorporate



Urolithin-A what is it exactly?

1. Urolithin-A is a natural breakdown product by gut microbes metabolizing polyphenols in our food. This would be considered a postbiotic by definition.
2. Urolithins are not directly found in food. The polyphenols that they are created from are abundant in many vegetables, fruits and nuts. One example is certain species of gut microbes convert ellagic acid and ellagitannins into urolithins.
3. There are many urolithins but urolithin A and B are know in humans and urolithin-A is the most widely studied. Scientists are actively researching other urolithins for human benefits.

What is Urolithin A's role in human health?

Urolithin A is found in many tissues of humans and other organisms.

A growing amount of data supports the fact that urolithin-A aids and promotes mitophagy.

Mitochondrial dysfunction is a result of aging and many chronic diseases. Urolithin-A can mitigate or reverse this process by affecting mitophagy.

As humans age they convert fewer precursors to urolithin-A and this is also affected by inflammation and reactive oxygen species (ROS)

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What is Urolithin A's role in human health?

Urolithin-A is found to increase lifespan by 45% in some animal models

Urolithin-A supplemented group had a 57% increase in spontaneous exercise and a 9% increase in grip strength. There was a 42% increase in endurance. Running capacity increased by 65%.

In a cancer study higher doses of urolithin-A reduced numbers and size of colon-cancer stem cells and inhibited aldehyde dehydrogenases a marker of chemoresistance.

It appears to be neuroprotective and fights $\mathcal{B}$-amyloid fibrillation (anti-AD)

Nunez-Sanchez MA, Karmokar A, Gonzalez-Sarrias A, et al. In vivo relevant mixed urolithins and ellagic acid inhibit phenotypic and molecular colon cancer stem cell features: A new potentiality for ellagitannin metabolites against cancer. *Food Chem Toxicol.* 2016; 92:8-16.

Yuan T, Ma H, Liu W, et al. Pomegranate's Neuroprotective Effects against Alzheimer's Disease Are Mediated by Urolithins, Its Ellagitannin-Gut Microbial Derived Metabolites. *ACS Chem Neurosci.* 2016;7(1):26-33.

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Mitophagy

"A 2016 study showed that urolithin-A improved muscle function in aged mice and extended lifespan in worms. These promising results led to the same research group conducting human research studies.

There are also concerns about low dietary production of urolithin-A, which is dependent on health status, gut health, and age."

-Tovah Wolf PhD/RDN

Ryu, D., Mouchiroud, L., Andreux, P. A., Katsyuba, E., Moullan, N., Nicolet-Dit-Félix, A. A., ... Auwerx, J. (2016). Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. Nature Medicine, 22(8).

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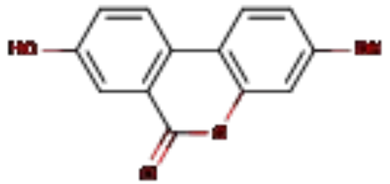
Where are the precursors found?

Currently the largest amounts of precursors for urolithin-A are found in:

- Pomegranates
- Strawberries
- Blackberries
- Camu-Camu
- Walnuts & Pecans
- Chestnuts
- Pistachios
- Brewed tea, aged wines and spirits ages in oak barrels
- Spirits containing ellagitannins or ellagic acid



Despite eating high precursor foods gut microbes are the weakest link in conversion and many folks suffer from lack of certain microbes discovered in fecal samples that make the ‘’conversion’’.

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Urolithin-A in supplement form

While precursors are available in foods it is in limited quantities.

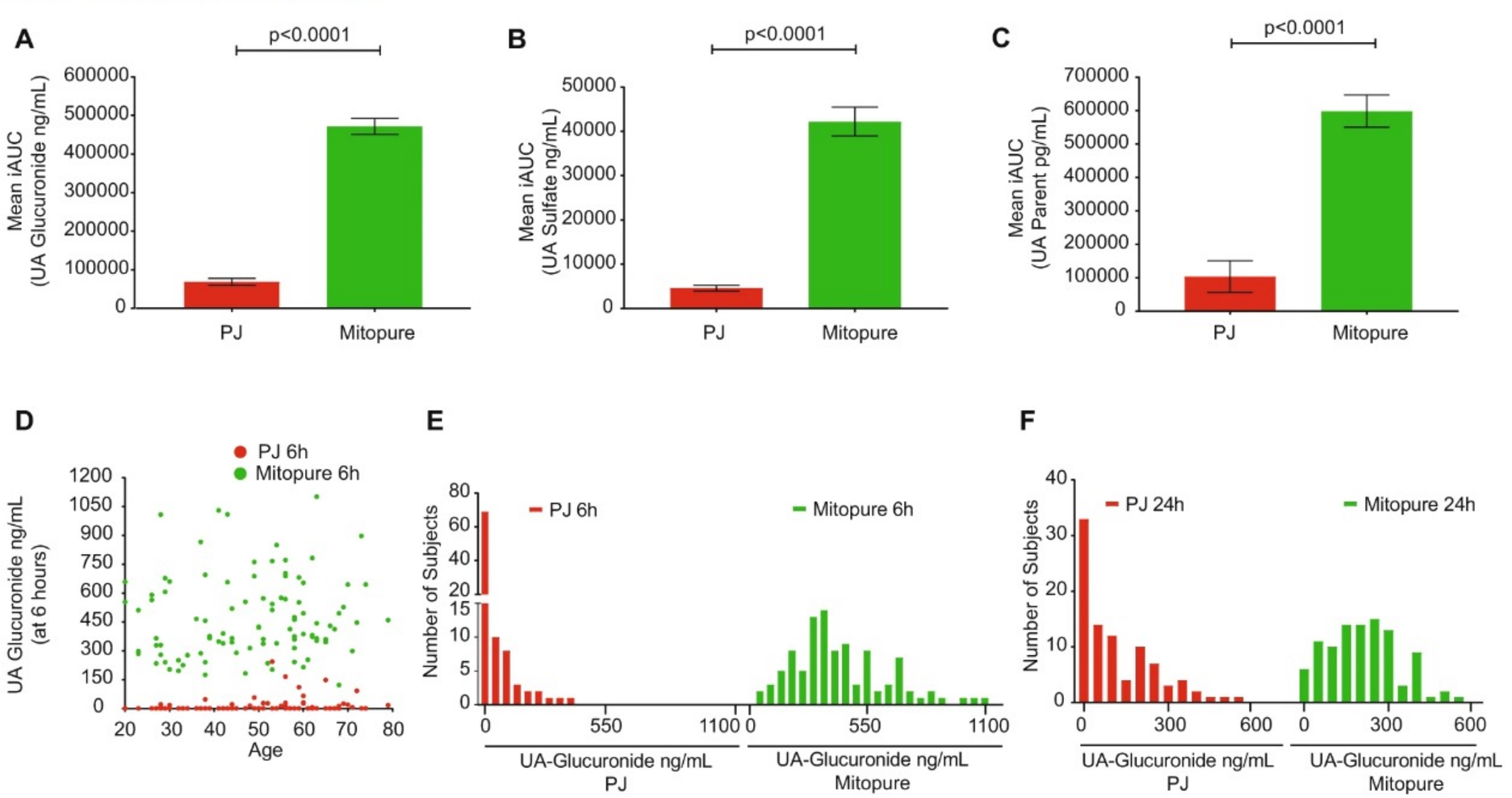
Dietary supplements contain much higher concentrations of DIRECT Urolithin-A not needing metabolism.

Studies show that oral supplementation with urolithin-A is much more effective than even the highest-precursor fruit (POM)

There are those who cannot convert precursor to urolithin-A and in one study only 12% of participants had detectable levels at the onset; 33% were unable to convert POM to urolithin-A and those taking oral urolithin-A had six-time higher levels than the POM group.

Cortés-Martín, Adrián, Selma, M. V., Tomás-Barberán, F. A., González-Sarrías, A., & Espín, J. C. (2020). Where to Look into the Puzzle of Polyphenols and Health? The Postbiotics and Gut Microbiota Associated with Human Metabotypes. Molecular Nutrition and Food Research, Vol. 64.

Singh, Anurag, D'Amico, D., Andreux, P. A., Dunngalvin, G., Kern, T., Blanco-Bose, W., … Rinsch, C. (2021). Direct supplementation with Urolithin A overcomes limitations of dietary exposure and gut microbiome variability in healthy adults to achieve consistent levels across the population. European Journal of Clinical Nutrition.



Mitopure supplementation delivers >6-fold levels of UA compared to PJ; UA-urolithin-A; PJ-Pom. Juice source: www.nature.com/articles/s41430-021-00950-1/figures/5

Singh, A., D'Amico, D., Andreux, P.A. *et al.* Direct supplementation with Urolithin A overcomes limitations of dietary exposure and gut microbiome variability in healthy adults to achieve consistent levels across the population. *Eur J Clin Nutr* **76**, 297–308 (2022).

Mediterranean Diet *vs* Western (SAD) Diet and urolithin-A

A study in 2020 showed a group of subjects in the Med. Diet cohort had higher urolithin-A in urine samples (attributed to higher walnut intake) than the 2nd cohort placed on the SAD.

Med. Diet produces more urolithin A, B, C and glucuronides and was also associated with lower hs-CRP, TGs, urine carnitine, lower BMI and body weight. Also, lipids and lipoproteins were more favorable. It appears in this study that the intake of POM and berries was no different. Microbiome evaluation showed differences in diversity between the two diets.

Meslier, V., Laiola, M., Roager, H. M., De Filippis, F., Roume, H., Quinquis, B., … Ercolini, D. (2020). Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. Gut, 69(7).

Singh, Amrit, Shannon, C. P., Gautier, B., Rohart, F., Vacher, M., Tebbutt, S. J., & Cao, K. A. L. (2019). DIABLO: An integrative approach for identifying key molecular drivers from multi-omics assays. Bioinformatics, 35(17).

Side Effects:

To date there are no observed side effects of urolithin-A.

Conclusion:

Studies to date show that pure urolithin-A supplementation increases plasma levels and has a wider impact on mitophagy and ultimately human aging and health.

Intake of precursor fruits and veggies is OK, but it is a low-yield proposition.

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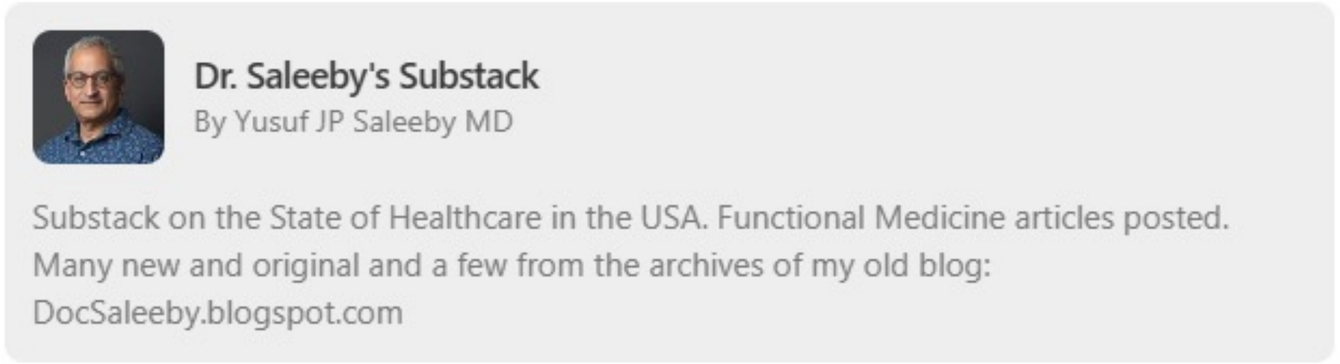

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