Enhanced Metabolism of Water Soluble Ellagate & Natural Urolithin Production

A Review

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Polyphenols are a broad class of phytochemicals produced by plants that have well established health benefits. Reported benefits include antioxidant activity, anti-aging, anti-tumor, anti-obesity, antibacterial, anti-lipid accumulation, inhibition of advanced glycation end-products (AGEs), insulin sensitivity and mitochondrial and muscle improvement. Well know polyphenols include the widely studied catechins found in green tea and resveratrol found in pomegranate. Similar compounds are also found in other foods, including berries, nuts, fruits and finished agricultural products including wine. A class of tannins, known as ellagitannins and ellagic acid are present in pomegranates, berries (raspberry, blackberry, strawberry cloudberry, and arctic bramble), tea, walnuts and some other nuts, oak-aged wines, and muscadine grapes.

While polyphenols are associated with a variety of health benefits, one common problem is their low solubility and bioavailability, that often requires a lifetime of consumption to provide sustainable-beneficial concentrations in the body. For example, intestinal absorption of ellagitannins and ellagic acid is low, (.004mg/mL), but these compounds can also be metabolized by intestinal bacteria to smaller urolithins, which have improved solubility and bioavailability [1–3]. Urolithins can reach higher micromolar solubility in the intestines and are absorbed across the colonic mucosa as well as systemic tissues, including the prostate, breast, brain, etc. In the last decade, urolithins have gained more attention because of the health implication of these microbial metabolites as potential anti-inflammatory, antioxidant, cardioprotective, neuroprotective and cancer preventive compounds [3,4]. However, both the health benefits associated with ellagitannin consumption and the ability to produce urolithins differ considerably among individuals. It is reported that not all individuals can produce urolithins [3,5–7], as this depends on the intestinal flora or microbiome of each person. Intestinal biomes have been categorized into three ellagitannin-metabolizing phenotypes, i.e. 'urolithin metabotypes', depending on the type of the urolithins formed. Thus, metabotype A is distinguished by the production of urolithin A, metabotype B individuals produce isourolithin A and/or urolithin B besides urolithin A, and those with metabotype 0 do not produce these final urolithins. Remarkably, individuals with metabotype 0 or non-producers represent 10-30% of population [7–9].

The clinical safety of urolithins has been demonstrated recently [10] and urolithins are considered as safe products (GRAS: Generally Recognized as Safe) by the FDA (12-20-2018. GRAS Notice No. GRN 000791). In this clinical study, it was shown that urolithin A intake may also modulate mitochondrial function and muscle markers, promising its use to promote muscle and mitochondrial health in the aging process [11] and was reported to preserve the integrity of the intestinal barrier in vivo [5,12, 16]. In addition, Zhao et al., (2019)[13] showed that urolithin B may also be used in the prevention of atherosclerosis in humans.

The research group on Quality, Safety and Bioactivity of Plant Foods (CEBAS-CSIC, Spain) is the premier group describing urolithin production and function in humans and has been studying ellagic acid metabolism and biological activity for the last two decades. Recently, this research group has identified several bacterial strains isolated from the human gut of healthy volunteers as urolithin producers [14,15] patent PCT/ES2014/070207. However, the *in vitro* production of urolithins is limited because of the low solubility of the precursor, ellagic acid.

Halo Life Science LLC. (USA) has developed an ellagic acid formulation called Naturalin®, which is over 40,000X, (187mg/mL) more soluble than free ellagic acid. This improved solubility creates a proportional increase in ellagic acid availability for downstream uptake, chemical reactions, or microbial metabolism. The coupling of this formulation with the necessary conditions and microbial organisms for ellagic acid catabolism, can increase urolithin production by several orders of magnitude. Initial study data demonstrates a 1,000-fold increase in urolithin production (Fig. 1), which, for the first time, shows a path to commercial-scale production of naturally occurring urolithins.

The collaboration established between CSIC and Halo Life Science has allowed the development of a procedure for the biotechnological production of different urolithins using natural occurring bacteria. The human health benefits of urolithins and improved solubility provided by Naturalin® is expected to impact today's food, nutraceuticals, and cosmeceuticals and tomorrow's synthetic pharmaceutical derivations. The proposed utility of these products is growing and the development of novel postbiotics, symbiotics, functional foods, and food complements eminent. These applications are particularly relevant in those individuals with metabotype 0, who are not able to produce bioactive urolithins and may thereby derive the greatest and previously untapped benefit of Naturalin®.

Efficiency of transformation of ellagic acid into urolithins from Naturalin versus EA alone

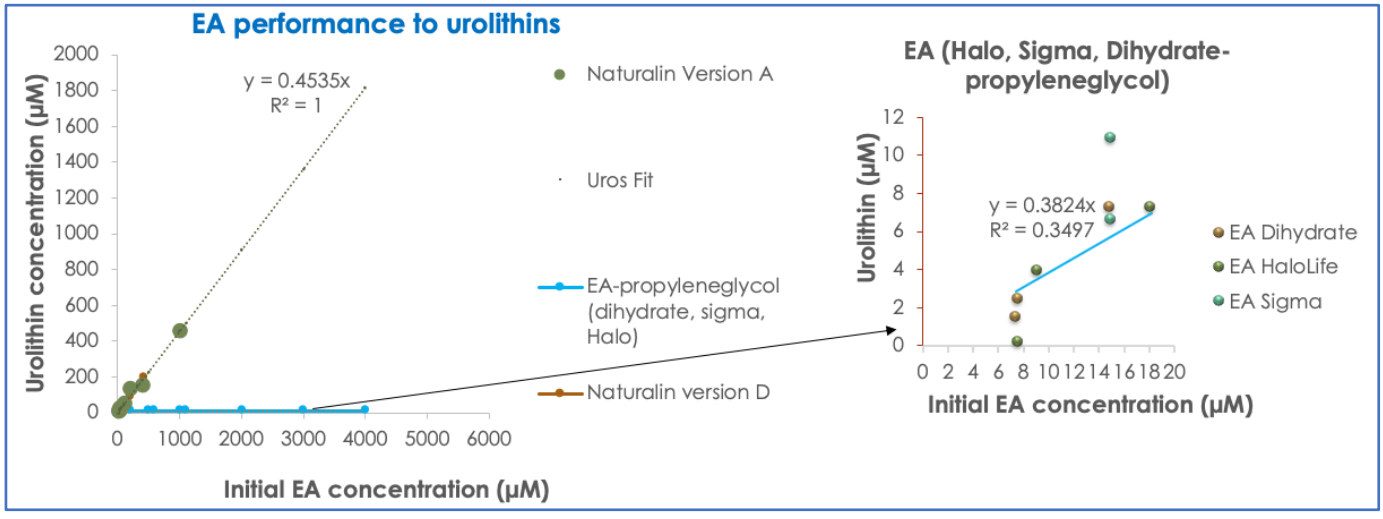

Fig. 1 - Ellagic acid or ellagic acid dihydrate is quite less soluble, even dissolved in propyleneglycol, resulting in less transformation into urolithins. High soluble, Naturalin, resulted in greater urolithin production.

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