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Pomegranate's Neuroprotective Effects against Alzheimer's Disease Are Mediated by Urolithins, Its Ellagitannin-Gut Microbial Derived Metabolites

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Abstract

Pomegranate shows neuroprotective effects against Alzheimer's disease (AD) in several reported animal studies. However, whether its constituent ellagitannins and/or their physiologically relevant gut microbiota-derived metabolites, namely, urolithins (6H-dibenzo[b,d]pyran-6-one derivatives), are the responsible bioactive constituents is unknown. Therefore, from a pomegranate extract (PE), previously reported by our group to have anti-AD effects in vivo, 21 constituents, which were primarily ellagitannins, were isolated and identified (by HPLC, NMR, and HRESIMS). In silico computational studies, used to predict blood-brain barrier permeability, revealed that none of the PE constituents, but the urolithins, fulfilled criteria required for penetration. Urolithins prevented β-amyloid fibrillation in vitro and methyl-urolithin B (3-methoxy-6H-dibenzo[b,d]pyran-6-one), but not PE or its predominant ellagitannins, had a protective effect in Caenorhabditis elegans post induction of amyloid β(1-42) induced neurotoxicity and paralysis. Therefore, urolithins are the possible brain absorbable compounds which contribute to pomegranate's anti-AD effects warranting further in vivo studies on these compounds.

Keywords: Alzheimer's disease; Pomegranate; blood-brain barrier; ellagitannins; microbial metabolites; urolithins.