CONFLICT OF INTEREST DISCLOSURE

I have no potential conflict of interest to report
mechanistic actions for potential neuroprotective effect of polyphenols

certainly not by a direct antioxidant effect as ROS scavengers !!!!!
absorption, relatively poor bioavailability, numerous metabolites with unknown biological activities

![Graph showing concentration of vitamins C and E in plasma, urine, and cells](image)

absorption and bioavailability
ability to cross the blood – brain barrier?

Polyphenols beyond barrier s: a glimpse into the brain. (Figueira et al. Curr Neuropharmacol, 2017)
Pomegranate’s Neuroprotective Effects against Alzheimer’s Disease Are Mediated by Urolithins, Its Ellagitannin-Gut Microbial Derived Metabolites

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Supporting Information

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: Pomegranate, Alzheimer’s disease, microbial metabolites, ellagitannins, urolithins, blood-brain barrier
C. Elegans model of AD

Punicalagin (PA)

not able to cross the BBB

Hydrolysis

Gut microflora

Urolithin A (UA)
Urolithin B (UB)

Methyl-UA (mUA)
Methyl-UB (mUB)

Ellagic acid (EA)

not able to cross the BBB

able to cross the BBB
potential neuroprotective action of berries polyphenols: why does it work?

The biological activity of polyphenols is linked to a moderate pro-oxidant effect and not to direct antioxidant activity.

(auto-oxidation of phenol groups leading to moderate ROS production)
potential neuroprotective action of berries polyphenols: why does it work?

1) hormetic effect*
activation of Keap1/NrF2/Antioxidant Response Element (ARE)
leading to the expression of genes coding for antioxidant and protective enzymes

• adaptation of cells to small amount of toxic products including ROS (mithridatisation effect)

potential neuroprotective action of berries polyphenols: why does it work?

1) hormetic effect
activation of Keap1/NrF2/Antioxidant Response Element leading to expression of genes coding for antioxidant and protective enzymes

2) redox signalling
(primordial importance)
2) redox signalling control

(Poly)phenols

moderate production of ROS

Inhibition
JNK, p38, ASK1
↓
iNOS, COX-2

Activation
ERK, Akt
CREB, FOXO
↓
Neurotrophins
i.e BDNF

mTOR, VEGF-β
TGF-β

(Neuro)inflammation
Suppression of activated microglia
Reduction in NO production
Cytokine reduction

Neuronal morphology
Synaptic plasticity
Improved neuronal communication
Spine density

Vascular effects
Increased blood flow
Angiogenesis
New nerve cell growth
Berry fruits enhances beneficial signaling in the brain (*Miller and Shukitt-Hale, J Agri Food Chem 2012*)

strawberry  Concord grape  blueberry

These performance improvements were associated with attenuated levels of a variety of signaling molecules involved in stress, survival, and neural plasticity in the hippocampus, including increased levels of phosphorylated CREB, ERK1/2, protein kinase B, and MAPK-activated protein kinase 1b as well as increased levels of brain-derived neurotrophic factor (BDNF), proBDNF, and activity-regulated cytoskeleton associated protein relative to age-matched controls that showed decreased signaling.
potential neuroprotective action of berries polyphenols: why does it work?

the biological activity of polyphenols is linked to a moderate pro-oxidant effect
(autooxidation of phenol groups leading to ROS production)

- 1) hormetic effect

- 2) redox signalling

- 3) improvement of endothelial function
3) Impaired neurovascular coupling in aging and Alzheimer's disease: Contribution of astrocyte dysfunction and endothelial impairment to cognitive decline

*(Tarantini et al. Experimental Gerontology 2017)*

Vascular dysfunction in the pathogenesis of Alzheimer's disease — A review of endothelium-mediated mechanisms and ensuing vicious circles

*(YuriDiMarco et al. Neurobiology of Disease 2015)*
the regulation of arterial blood pressure by polyphenols through adequate endothelial function

- BH$_4$ deficiency, smoking, hypercholesterolemia
- non-functional e-NOS
- ROS production
- hypertension
- functional eNOS
- NO (nitric oxide)
- normal blood pressure through vasorelaxation activity of NO
Vascular risk factor exposure accelerates structural brain aging and cognitive decline. (Debette et al. Neurology. 2011)
the regulation of arterial blood pressure by polyphenols through adequate endothelial function

Dietary polyphenols regulate endothelial function and prevent cardiovascular disease. (Yamagata K et al, Nutrition. 2015)
conclusions

1° oxidative stress (alteration in redox balance) has been well identified in human cognitive decline

2° epidemiological studies suggest that food rich in antioxidants but not classical synthetic antioxidants (vitamins C and E, carotenoids) supplementation may prevent human cognitive decline

3° promising role of dietary polyphenols (as food or extracts) in preventive human cognitive decline

4° biological activity of polyphenols through metabolites but also moderate pro-oxidant activities (hormesis, redox signalling and endothelial function)