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Ammar A, Trabelsi K, Boukhris O, Bouaziz B, Müller P, M Glenn J, Bott NT, Müller N, Chtourou H, Driss T, Hökelmann A. Effects of Polyphenol-Rich Interventions on Cognition and Brain Health in Healthy Young and Middle-Aged Adults: Systematic Review and Meta-Analysis. J Clin Med. 2020 May 25;9(5):1598.

What We Know, Think We Know, or Are Starting to Know

Research into the health effects of (poly)phenols has gathered momentum in recent years, as the mechanistic understanding of their acute and chronic effects has translated into intervention studies across a range of lifestage groups. Termed "lifespan essential" by antioxidant researchers Brigit Holst and Gary Williamson, this concept refers to the fact that, although these compounds are not required for life in the way vitamins are, they are critical to healthy functioning over the course of the lifespan [(1)].

The major source of (poly)phenols in the human diet are flavonoids, a structurally diverse group of compounds primarily consumed from fruits, vegetables, fruit juices, tea, red wine, coffee, and chocolate [(2)]. In an early cohort to examine flavonoid intake and brain health, flavonoid intake of up to 360mg/d was associated with significant protection against cognitive decline over a 10yr period [(3)]. In the US Nurses Health Study, the effect of high flavonoid intake delayed cognitive ageing by 2.5yrs, i.e., people aged 75yo scored similar to 73yo [(4)]. These long-term cohort studies suggested chronic effects of flavonoids, however, there was one snag: at the time many flavonoids were believed to remain in circulation only for about 90mins [(5)].

How could (poly)phenols add up to chronic effects if they were metabolised and excreted so quickly? Recent mechanistic studies have elucidated greater insight into the metabolism of these compounds, showing that may have a bioavailability of up to 48-hours post-ingestion* [(5,6)].

A number of interventions using flavonoid-rich drinks or foods have found improved cognitive function and/or memory performance [(7-11)]. With a diverse array of (poly)phenol compounds showing evidence of benefit in human intervention studies, the present study conducted a systematic review and meta-analysis of (poly)phenol supplement trials examining their effects on cognitive function.

*Geek Box: (Poly)phenol Metabolites

The metabolism of (poly)phenols has been of particular interest in trying to link their purported health benefits to biological plausibility. For the brain, this became even more puzzling when it was recognised that flavonoids do not cross the blood-brain barrier in significant quantities. There was also the fact that the parent compound, i.e., the form of the compound ingested whole through the diet, may have peak concentrations of only between 1-6hrs. However, there is now a greater understanding of the metabolism and bioavailability of (poly)phenolic compounds. Some (poly)phenols may be absorbed directly to the liver from the small intestine, where they undergo metabolism in the liver through a process known as 'first pass metabolism', similar to what drugs undergo. Remember: because these compounds are not recognised as nutrients by the body, they are treated as xenobiotic agents and are metabolised through the liver in the same way drugs would be. This is, in fact, critical to their benefits, because this process produces a diverse array of metabolites which are then released from the liver back into the circulation. (Poly) phenols also pass to the colon and, like fibre, undergo degradation by gut bacteria into phenolic metabolites, which are in turn absorbed in quantities far exceeded the levels absorbed from the small intestine. These metabolite compounds absorbed from the colon also pass through the liver, undergoing more extensive metabolism. Finally, enterohepatic circulation [the recycling of compounds between the liver and digestive tract via the hepatic portal vein] is another route of (poly)phenol metabolite circulation, as certain metabolites may be recycled up to 20 times! An enormous array of metabolites have been identified, for example up to 62 anthocyanin metabolites have been identified to date. These metabolites may be up to 100-fold greater in concentration than the parent compounds, and have significantly higher bioavailability. The fact that their continued metabolism and recycling means a bioavailability of up to 48hrs provides a plausible mechanistic explanation for chronic benefits observed in long-term cohort studies. For the brain and cognition, this has been a particularly important finding, because rather than cross the BBB in large quantities it was recognised that low physiological concentrations of their metabolites may act through signalling pathways in the brain.

The Study

The investigators conducted a systematic review and meta-analysis of studies up to July 2019, with the following inclusion criteria:

- Primary research published in English before 2019.
- Healthy human participants under 55yrs of age.
- Investigating the effect of (poly)phenols supplementation on brain health.

'Brain health' was defined as a range of cognitive functions, with outcomes including overall cognition, psychomotor performance, executive function, processing speed, attention, language, verbal memory and visual memory, and brain health measures like cerebrovascular blood flow [CBF] and brain-derived neurotropic factor [BDNF].

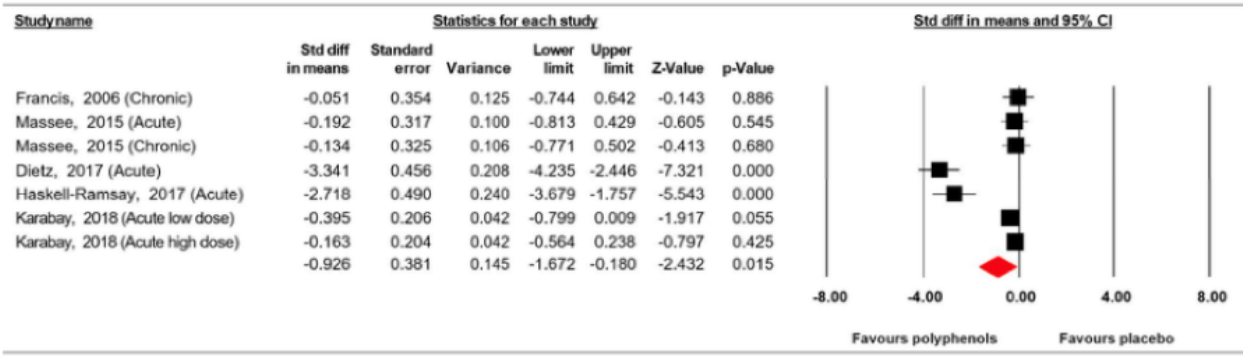
Due to substantial differences in the outcomes in included studies, however, only the cognitive tests of reaction time [RT], rapid visual information processing [RVIP], 7s serial subtraction [SS-7s], and mental fatigue [MF], and the brain health outcome BDNF, were sufficiently comparable between studies and included in the meta-analysis.

Results: 16 studies were included in the systematic review, of which 10 investigated acute effects of supplementation [i.e., over 6hrs] and 4 investigated chronic effects [5-days to 10-weeks], while 2 investigated both acute and chronic effects. The number of participants in the trials ranged from 12 to 60, with a total of 408 participants across all studies. All studies employed a randomised design, and 11/16 used a double-blind, placebo-controlled design.

3 studies used resveratrol as the intervention; 4 used cocoa flavonols, 3 used green tea epigallocatechin gallate [EGCG], and the 6 remaining studies used different interventions including soy extract, wine, orange juice citrus flavonoids, and purple grape anthocyanins. The doses varied from study to study.

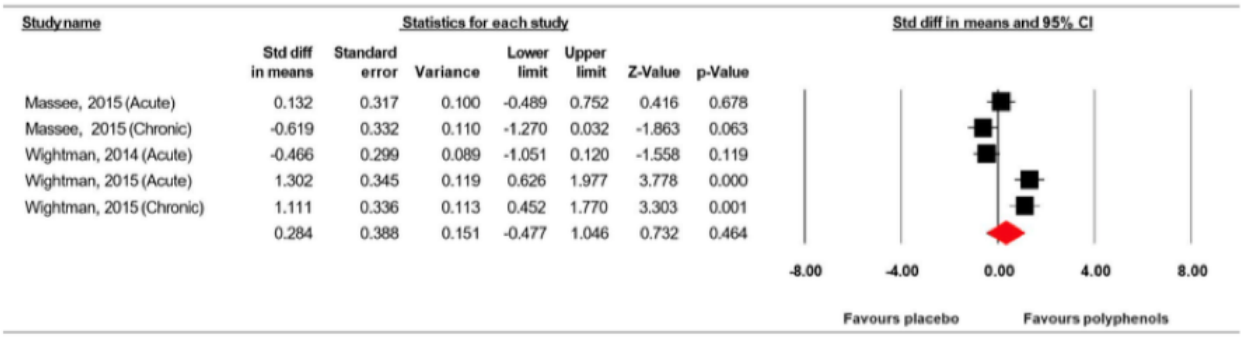
Meta-Analysis:

- **Simple Reaction Time:** From 5 studies included in this meta-analysis, (poly)phenol supplementation showed a moderate effect on reduced reaction time, an outcome that was influenced primarily by two acute studies. The two studies that had the largest effect used matcha tea [Dietz et al.] and anthocyanin-rich grape juice [Haskell-Ramsay et al.].



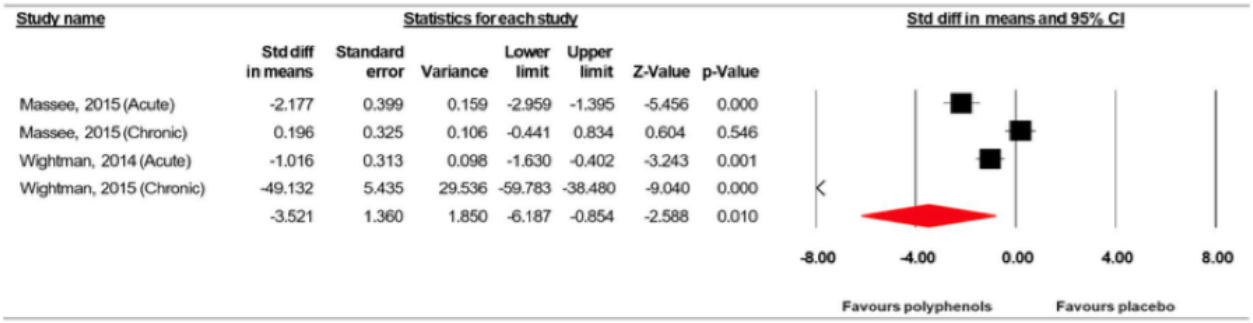
Forest plot *from the paper illustrating the effect of (poly)phenol supplementation on reaction time, i.e., where reduced reaction time indicates a benefit to the supplement.*

- **Rapid Visual Information Processing:** Data from 3 studies, but with 5 different effect sizes as two studies used different doses and durations of supplementation, indicated that (poly)phenol supplementation had a small effect on visual information processing. The study which provided two different measures of effect [acute and chronic], with the main effect, used resveratrol at a supplemental dose of 500mg/d [Wrightman et al.]



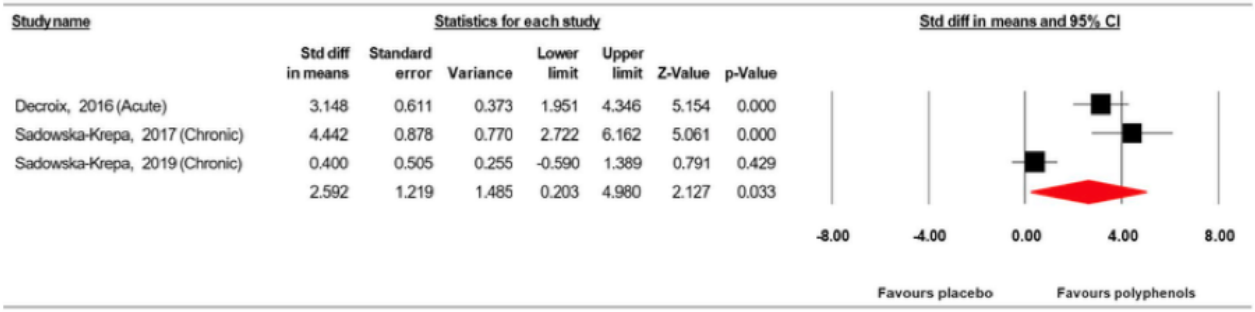
Forest plot *from the paper illustrating the effect of (poly)phenol supplementation on visual information processing, i.e., where the percentage of correctly answered visual stimuli indicates a benefit to supplementation.*

- **Mental Fatigue:** Data from 2 studies, each with both acute and chronic phases, i.e., 4 total data points, were included in the meta-analysis. (Poly)phenol supplementation had a large effect on reducing mental fatigue. The studies used cocoa flavonols [Massee et al.] and resveratrol [Wrightman et al.].



Forest plot *from the paper illustrating the effect of (poly)phenol supplementation on mental fatigue, i.e., where reduced mistakes on sustained performance tasks indicates a benefit to supplementation.*

- **Brain-derived Neurotropic Factor [BDNF]:** Data from 3 studies were included in the meta-analysis. (Poly)phenol supplementation had a very large effect on increasing BDNF. The studies which showed a significant increase in BDNF used gingko biloba [Sadowska-Krepa et al., 2017] and cocoa flavonols [Decroix et al.].



Forest plot *from the paper illustrating the effect of (poly)phenol supplementation on BDNF, which was measured using biochemical analysis.*

The Critical Breakdown

Pros: The overall methodological quality of the included studies was quite high, and study quality was assessed using a criteria checklist [Physiotherapy Evidence Database (PEDro) scale] more amenable to nutrition intervention studies in considering factors like blinding. The systematic review was conducted according the PRISMA guidelines, and the included studies thoroughly detailed in their design, intervention and control, and outcomes. Given the inherent difficulties facing meta-analysis of nutritional exposures, the investigators appeared to do their best to confine the meta-analysis to outcomes which had comparable methods across the included studies.

Cons: As would be expected from these types of intervention trials in nutrition, the included studies were mostly small and the overall numbers in the meta-analysis meant that it was not very well powered. You will also be familiar with the challenge inherent to meta-analysis in nutrition, that of 'distortive lumping' of compounds which may not necessarily be comparable. However, for (poly)phenols this may be more forgivable due to the broadly similar mechanisms of action on the brain. The authors state that they conducted sensitivity analyses and 'confirmed' the findings, but don't provide any detail in relation to these analyses, which would have been useful given the wide array of (poly)phenol interventions. I'll always include the 'limited to English language' only as a potential *Con*, however, given everything is published in English I'm starting to waver on how legit a critique this really is.

Key Characteristic

The challenge of meta-analysis with exposures like (poly)phenols, and with different durations of exposure, is all on display in this study. For example, it was useful to include studies of both acute and chronic supplementation, which could allow for differences in the duration of exposure to be detected. In the reaction time outcome, for example, the effect was driven by acute studies. But this may be a misnomer; the nature of these cognitive tests that are used is that they are acute response tests. Because chronic supplementation had no effect on an acute battery of cognitive tests does not mean that protective long-term effects on the brain are not happening [more under ***Interesting Finding***, below].

And because (poly)phenols may have a broadly similar mechanism of action on the brain [the finer details of which signalling pathways they act through is where things get complex and differ], the general criticism of lumping different exposures into a meta-analysis may be somewhat forgiven. For example, both cocoa flavonols and resveratrol reduced mental fatigue, and this effect may relate to the fact that both compounds improve cerebrovascular blood flow. These factors are all relevant: the exact (poly)phenol supplement used, the dose, the duration of exposure, and the type of outcome measure. It makes for challenges not easily solved for meta-analysis. The present study appears to have done the best it could, and there is sufficient detail to tease out some meaningful conclusions.

Interesting Finding

Without doubt the most interesting finding is the increase in BDNF. As alluded to above, the cognitive tests used in these brain health interventions are acute tests and may reflect more immediate effects of factors like blood flow to the brain [12]. However, it has been speculated that enhanced BDNF may provide an explanation for more chronic benefits to the brain over time. Flavonoids have been shown to increase and maintain BDNF levels [5,12]. However, enhanced cerebrovascular blood flow also may increase BDNF [5]. It is possible that the increases in cerebrovascular blood flow from flavonoids may be one mechanism through which BDNF is increased [5,12]. And BDNF is unlikely to be an outcome with any acute effect, as the pathway through which BDNF activation occurs does not appear to be an acute response pathway [5,12]. Thus, it is more likely that sustained activation of this pathway and maintained elevated BDNF levels may explain the long-term protective effect of (poly)phenols against neurodegenerative disease.

Relevance

There has been a proliferation of intervention studies with different (poly)phenol supplements as the exposure of interest. Despite the wide array of (poly)phenol supplements in this meta-analysis, the compounds that emerged as driving a particular effect is consistent with the wider literature.

Anthocyanins from blueberries or concord grapes have been shown to improve cognitive function across the lifespan, from children, to healthy young adults, to elderly adults with mild cognitive impairement [7-11]. Citrus flavonols, in particular hesperidin and narirutin, have been shown to result in increases in global cognitive function [13], including increases in assessments of executive function [14] that were not observed in trials using anthocyanins [7,8].

Cocoa flavanols have been shown to increase visual acuity and visual-spatial working memory [15]. Cocoa flavanols also led to reduced subjective mental fatigue across different time points, where cognitive test batteries were performed 2-minutes apart [16]. In fact, if we look through the outcomes in the present meta-analysis, cocoa flavonols repeatedly showed up, and again this provides consistency with the wider research.

An important feature from the present meta-analysis is the fact that participants were otherwise healthy and under 55yrs of age. Another important feature was the inclusion of biochemical measures, like BDNF, because it can sometimes be difficult to extrapolate the effects of acute cognitive tests beyond the circumstances in which they are conducted. Although the BDNF meta-analysis only included 3 studies, and the effect size driven entirely by 2 of those, it provides congruence with the wider mechanistic understanding of the potential chronic long-term effects of sustained brain activation pathways on cognitive function from adulthood into older age.

Application to Practice

It should be noted that certain of these compounds, like resveratrol, are used at doses that would not be replicable in the human diet. However, many other interventions are used at doses - blueberry anthocyanins, cocoa flavonols, citrus flavonols - which are obtainable at habitual levels of consumption. For example, many of the blueberry anthocyanin interventions equate to ~150-200g blueberries, the cocoa flavonol interventions to 20-40g of minimum 80% dark chocolate, and the citrus flavonol interventions to ~250ml orange juice. Factored into the even wider array of compounds in pigmented fruits and vegetables, and the "lifespan essential" nature of (poly)phenols, despite the supplemental nature of the interventions, a food-based approach to intake is entirely possible.

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