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## Coffee fruit extract – a nutritional stimulator of endogenous BDNF

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Dear Editor,

Brain-derived neurotrophic factor (BDNF) is a protein that plays a prominent role in the growth, maintenance and survival of neurons [1]. It also plays a key role in synaptic plasticity, the nervous system's ability to modify itself, and an important component of cognitive processes such as memory formation [2]. Common lifestyle-related health issues such as chronic stress, occupational burnout and insomnia have all been linked with reduced BDNF levels and are known to adversely affect cognitive function [3–5]. Lower levels of BDNF among older adults are also associated with more severe cognitive decline and brain atrophy [6,7]. In contrast, interventions that elevate BDNF levels appear to exert pro-cognitive effects [8,9]. This has led to a great deal of interest in the potential to enhance endogenous BDNF using nutritional interventions in an effort to maintain and optimise brain health.

The recently published review by Gravesteyn and colleagues is an important addition to this literature that summarised studies exploring the effect of various nutritional interventions on BDNF levels [10]. The authors concluded that there was evidence that polyphenols, particularly at high doses ( $\geq 1000$  mg), could have a positive effect on BDNF concentrations, though study results overall were inconsistent. Likewise, there was a lack of any clear efficacy demonstrated for many of the other supplements included in the review, including vitamins and minerals, long-chain omega-3 polyunsaturated fatty acids and probiotics.

However, we believe there is another important nutritional intervention that should also be considered in the context of this literature. Whole coffee fruit extract, a polyphenol-rich plant-based (*Coffea arabica*) extract, has been reported to be a potent stimulator of endogenous BDNF in a series of clinical trials. As detailed below (see also Table 1), ingestion of a single

100 mg dose of whole coffee fruit extract has been demonstrated to result in rapid increases in plasma BDNF levels and serum exosomal BDNF content in healthy young and middle-aged adults [11,12], as well as in older adults with subjective cognitive decline [13]. The magnitude of these increases has been reported to be significantly larger than those observed both in placebo and active control comparator conditions and, importantly, appears to be associated with pro-cognitive effects.

The first published evidence indicating that whole coffee fruit extract can significantly increase BDNF plasma levels came from a series of studies comparing its effects to placebo, chlorogenic acid and three other polyphenol-rich fruit extracts (grape seed extract powder, green coffee bean extract powder and green coffee caffeine powder) [11]. While ingestion of green coffee caffeine powder and grape seed extract powder increased BDNF levels in plasma by 42% and 30%, respectively, compared to baseline, these changes did not reach statistical significance. In contrast, ingestion of 100 mg of whole coffee fruit extract resulted in statistically significant increases in BDNF, producing an average increase in plasma BDNF levels of 143% in the hours following consumption. Based on these findings, the authors suggested that the stimulatory effect of whole coffee fruit extract on plasma BDNF levels is unlikely to be due to the amount of polyphenols or caffeine per dose, but potentially either the amount of procyanidins or to the unique coffee polyphenol profile of the whole coffee fruit extract material [11].

A subsequent placebo-controlled, within-subject crossover study conducted in 20 healthy adults reported that a single 100 mg dose of capsulated whole coffee fruit extract significantly increased plasma BDNF levels by 91% at 60 min and 66% at 120 min compared to

**Table 1.** Summary of studies examining the effect of whole coffee fruit extract on BDNF levels in human subjects.

Publication	Population	Trial design <sup>a</sup>	Comparator(s)	Summary of BDNF effects
Reyes-Izquierdo et al. [11]	Healthy subjects (aged 18–55 years) N = 40	Randomised, placebo-controlled, parallel groups trial	Placebo (silica oxide) Grape seed extract powder (100 mg) Green coffee bean extract powder (100 mg) Green coffee caffeine powder (100 mg) Placebo (water) Chlorogenic acid (50 mg) Placebo (empty gelatin capsule) Freshly brewed coffee (300 ml containing 130 ± 10 mg of caffeine)	In each of the included studies, those receiving whole coffee fruit extract were the only groups to exhibit statistically significant increases in plasma BDNF levels (both $p \leq 0.002$ ). When results were pooled across studies, ingestion of whole coffee fruit extract produced an average increase in plasma BDNF levels of 143% in the hours following consumption
Reyes-Izquierdo et al. [12]	Healthy subjects (aged 25–35 years) N = 20	Placebo-controlled, within-subject crossover trial		The study reported significant increases in participant's plasma BDNF levels both 60 and 120 min after consuming whole coffee fruit extract (by 91% and 66%, respectively, compared to baseline; $p < 0.001$ ) The increase in plasma BDNF levels at 60 min was significantly greater following consumption of whole coffee fruit extract than that observed during the placebo ( $p = 0.007$ ) and active control conditions ( $p = 0.02$ ). Exploratory analyses conducted in a randomly selected study participant indicated that after 60 min, whole coffee fruit extract also increased serum BDNF by 54% and exosomal BDNF by 206%. Serum and exosomal BDNF levels remained elevated at 120 min post-dose (32% and 39%, respectively, over baseline) The study reported a significant increase (41% compared to baseline) in participants exosomal BDNF levels within 90 min of consuming whole coffee fruit extract ( $p = 0.04$ ). Ingestion of the placebo resulted in a non-significant decline in exosomal BDNF levels over the equivalent 90-min period
Robinson et al. [13]	Older adults with subjective cognitive decline (mean age 60.75 ± 2.76 years) N = 8	Randomised, double-blind, placebo-controlled, within-subject crossover trial	Placebo (silica oxide)	

<sup>a</sup>Whole coffee fruit extract was administered as a single 100 mg dose in each of the listed trials, either using water as a vehicle [11] or in a capsule [12,13].

baseline [12]. This increase in plasma BDNF levels was significantly greater than that observed during both the placebo and active control (freshly brewed coffee) conditions. These results are consistent with the previous evidence that whole coffee fruit extract enhances BDNF levels in the blood, and to a greater extent than caffeine. Further exploratory analyses conducted in one of the study participants indicated that after 60 min, a single dose of whole coffee fruit extract also increased serum BDNF by 54% and exosomal BDNF by 206%. Serum and exosomal BDNF levels remained elevated, albeit reduced, at 120 min post-dose (32% and 39%, respectively, over baseline) [12]. A randomised, double-blind, placebo-controlled, within-subject crossover trial conducted in older adults with subjective cognitive decline has also recently reported a significant increase (41% compared to baseline) in exosomal BDNF levels within 90 min of consuming a single 100 mg dose of whole coffee fruit extract, but not after consuming placebo [13].

Importantly, in addition to elevating circulating BDNF levels, acute and longer-term dosing studies conducted in older adults have indicated that ingestion of whole coffee fruit extract can enhance cognitive performance and modulate brain activity [13,14]. A randomised, double-blind, placebo-controlled, crossover trial conducted in healthy young adults also reported that ingestion of beverages containing coffee fruit extract (100 or 300 mg) significantly attenuated participant-reported increases in mental fatigue and decreases in alertness during a series of cognitively demanding tasks compared to placebo [15].

Collectively, these results suggest that coffee fruit extract can have a marked effect on peripheral BDNF levels and a meaningful impact on cognitive function, even in healthy young adults. Interestingly, these effects were observed at a much lower dose (100 mg) than other BDNF-enhancing polyphenols identified in the recent systematic review by Gravesteyn and colleagues, most of which used doses  $\geq 1000$  mg [10]. While it cannot be discounted that the observed brain effects may, at least in part, also be due to other mechanisms, such as the antioxidant properties of this material [13], these results are promising and warrant further investigation. Further longer-term and larger studies will help to shed further light on coffee fruit extract, its associated mechanisms of action, as well as its potential beneficial effects across a wider range of cognitive functions.

## Disclosure statement

JC, NF and NS are employees of Reckitt Benckiser.

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