Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Coffee fruit

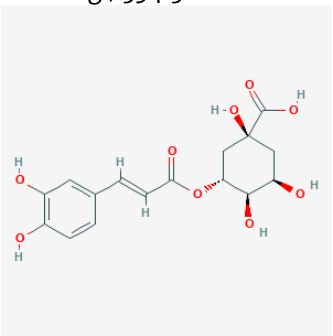
Evidence Summary

Only one small clinical study has been carried out and resulted in increased plasma levels of the neurotrophic factor BDNF.

Neuroprotective Benefit: Only one clinical study has tested the effect of acute whole coffee fruit extract and showed increased plasma BDNF levels, but larger clinical studies are needed to establish whether it has neuroprotective or cognitive benefits.

Aging and related health concerns: Preclinical studies suggest that coffee fruit extract may prevent tumor growth, but no studies have tested its benefit in clinical studies.

Safety: The NOAEL (no treatment-related adverse effects) in male and female rats was 3446 and 4087 mg/kg/day, respectively. No safety data exist in humans.

Availability: OTC, most studies have used the Coffeeberry® product from FutureCeuticals Inc.	**Dose**: 100 mg of whole coffee fruit concentrate powder increased plasma BDNF.	**Chemical formula:** e.g., $C_{16}H_{18}O_9$ **MW**: e.g., 354.311  Source: PubChem
Half life: unknown	**BBB**: chlorogenic acid and/or its metabolites appear to reach the brain in mice, but bioavailability data is conflicting	
Clinical trials: Only one clinical trial has been carried out, which included 25 healthy adults.	**Observational studies**: none	

What is it? Coffee fruits are often called coffee cherries or coffee berries. Coffee seeds (coffee beans) form inside of coffee fruits. Coffee fruits have long been recognized as having nutritional and health-enhancing potential including antioxidant capacity [1]. However, the cherry is highly perishable [2], and until recently, has been prone to rapidly develop extensive bacterial contamination and molds that generate toxic secondary metabolites known as mycotoxins. Consequently, the coffee fruit, other than its seed (coffee beans), has traditionally been considered waste material unsuitable for consumption, and has typically been discarded or used as fertilizer [3].

Neuroprotective Benefit: Only one clinical study has tested the effect of acute whole coffee fruit extract and showed increased plasma BDNF levels, but larger clinical studies are needed to establish whether it has neuroprotective or cognitive benefits.

Types of evidence:

- 1 clinical trial
- 1 laboratory study

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Only one clinical trial has tested the effects of coffee fruit extract [4]. This study, however, did not measure cognitive outcomes since it was an acute single-dose study. The study included 25 healthy adults, 5 subjects in each of the following groups: whole coffee fruit concentrate powder (WCFC; 100 mg), green coffee caffeine powder (N677; 100 mg), grape seed extract powder (N31; 100 mg), green coffee bean extract powder (N625, 100 mg), and placebo (silica oxide, 100 mg). Treatments with grape seed extract and green coffee caffeine powder increased levels of plasma BDNF by about 31% (neither was statistically significant), whereas treatment with whole coffee fruit extract increased it by 143% compared to control (p=0.001). It is important to note that a power analysis of the entire sample indicated that 40 subjects would be required to reach a power of 80%, so while grape seed and green coffee caffeine powders did not reach significance, a larger trial is needed to evaluate whether they can raise BDNF. One caveat to this study was that the treatment with placebo (silica oxide) resulted in a 34% reduction in BDNF blood levels, potentially magnifying the effects of other treatments.

Mechanisms of action are still not clearly defined—they tested several hypotheses (e.g., chlorogenic acid, polyphenols, caffeine, and trigonelline), but none of these panned out. For example, whole coffee fruit contains high amounts of chlorogenic acid, and it was hypothesized that this specific polyphenolic acid may cause an increase in blood level of BDNF. But the study showed that administration of 50 mg of chlorogenic acid did not increase blood levels of BDNF in a statistically significant manner, suggesting that this substance is not responsible for the ability of whole coffee fruit extract to increase BDNF. To explore the effects of polyphenols, they examined the effects of grape seed extract, which has relatively high polyphenol levels compared with the coffee fruit, but this extract failed to significantly increase plasma BDNF levels. Green coffee caffeine powder is mostly comprised of caffeine (72.8%), but caused only modest increases in plasma BDNF levels (and whole coffee fruit extract, which had the greatest magnitude of effect on BDNF has very little caffeine content—0.7% by weight). Trigonelline is a plant alkaloid thought to have health benefits, but both whole coffee fruit extract and green coffee bean extract had the highest levels, and only the whole coffee fruit extract was able to significantly elevate plasma BDNF levels.

These results suggest that the effects of whole coffee fruit extract on plasma BDNF levels is not associated with the amount of chlorogenic acid, polyphenols, caffeine, or trigonelline. Rather, the effect may be related to either the amount of procyanidins or to the unique coffee polyphenol profile of the whole coffee fruit extract. According to the present analyses, whole coffee fruit extract (WCFC) shows a significant amount of procyanidins in comparison to N677 (green coffee caffeine powder),

N625 (green coffee bean extract powder), and N31 (grape seed extract), suggesting that acute treatment with procyanidin-rich whole coffee fruit extracts (and possibly other procyanidin-rich extracts), may increase blood levels of BDNF in human subjects.

In order to confirm the results of the present pilot study, further clinical testing in a larger group is required. It is not known if this increase in blood levels of BDNF translates to increased levels in the brain or better cognitive functions.

Human research to suggest benefits to patients with dementia:
None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Potential mechanisms of action for coffee fruit extract include its ability to increase BDNF levels (described above, [4]) and its antioxidant capacity [5]. Of the different ways of processing coffee fruit extract, the multistep whole coffee fruit ethanol extracts displayed the highest chlorogenic acid content than single-step extracts, freeze-dried, or air-dried whole raw fruits [5]. In this study and in the BDNF study, all coffee samples were supplied by FutureCeuticals, Inc. (Momence, IL).

The multistep proprietary extraction (CFE1) produced significantly higher levels of chlorogenic acid than the single-step proprietary extraction (CFE2), air-dried whole coffee fruit powder (CFP1), and freeze-dried, powdered raw coffee fruits (CFP2). Specific chlorogenic acids, including 3-O-caffeoylquinic lactone, 4-O-caffeoylquinic lactone, the putative methyl-5-caffeoylquinic acid and dicaffeoylquinic lactone, were detected only in the multistep proprietary coffee fruit extracts (CFE-1). 3-O-Feruloylquinic acid was only detected in proprietary CFE-1 and CFE-2.

The antioxidant activity of whole coffee fruit extract was mainly attributable (>60%) to the hydroxyl scavenging capacity (as measured by the HORAC assay)[5]. Antioxidant capacities for HORAC, peroxynitrite scavenging capacity (measured by NORAC), superoxide anion scavenging (measured by SOAC), peroxyl radical scavenging (measured by ORAC), and total oxidant scavenging capacity (total ORAC) were between 7- and 25-fold higher in the multistep proprietary extraction (CFE-1) and single-step proprietary extraction (CFE-2) compared to air-dried whole coffee fruit powder (CFP1), and freeze-dried, powdered raw coffee fruits (CFP2). The total chlorogenic content of the extracts was strongly correlated ($p < 0.005$) with all of the antioxidant capacity measures except with SORAC.

APOE4 interactions: Unknown.

Aging and related health concerns: Preclinical studies suggest that coffee fruit extract may prevent tumor growth, but no studies have tested its benefit in clinical studies.

Types of evidence:

- Some laboratory studies

Cancer: POTENTIAL BENEFIT IN PRECLINICAL MODEL. In a mouse model of mammary tumor (SHN mice), coffee fruit extract (0.5% solution of hot water extract) for 10 days resulted in a marked inhibition of the tumor growth [6]. The percent changes of tumor sizes were +53.8% (+/- 11.7) and +13.8% (+/- 10.9) in the control and the experimental groups, respectively. Associated with this, thymidylate synthetase activity in the mammary tumors was significantly lower in the coffee fruit-treated group than in the control. Normal and preneoplastic mammary gland growth, body weight change, and weights and structures of endocrine organs were only slightly affected by the treatment. A subsequent study from the same group found that the same coffee fruit extract treatment for 60 days prevented the elevation of plasma and urine levels of liver enzymes (alanine amino-transferase and asparate aminotransferase), indicating that coffee fruit extract can protect against metabolic abnormality, which is thought to exacerbate mammary tumor susceptibility [7]. Coffee fruit extract treatment also resulted in an inhibition of the formation of precancerous mammary hyperplastic alveolar nodules. Neither food and water intake nor spontaneous motor activity was affected by this treatment.

Mechanisms of action were explored in the same mouse model by the same research group. They found that coffee fruit extract enhances the differentiation of thymocytes and the activation of peripheral T lymphocytes without affecting the natural killer activity of spleen cells [8]. Coffee fruit extract also enhanced B-lymphocyte response, and authors suggested that this immunopotentiation contributes to the anti-tumor actions of coffee fruit [9].

Blood pressure: UNKNOWN. No studies have examined the effects of coffee fruit extract on blood pressure. Chlorogenic acid is abundant in coffee fruit extract and is a polyphenol with antioxidative properties. In a placebo-controlled clinical trial of 28 mildly hypertensive subjects, chlorogenic acid from green coffee bean extract (140 mg/day) for 12 weeks resulted in significantly decreased blood pressure; from 145 ± 1 / 91 ± 1 mmHg at baseline to 142 ± 2 / 90 ± 1 mmHg at 2 weeks, 137 ± 2 / 84 ± 2 mmHg at 4 weeks, and 135 ± 2 / 84 ± 1 mmHg at 12 weeks (SBP $p < 0.001$, DBP $p < 0.05$)[10]. Systolic and diastolic blood pressures were significantly reduced in the chlorogenic acid treatment group compared

to the placebo group, while no significant change in blood pressure was observed in the placebo group. The hypotensive effect of chlorogenic acid might involve nitric oxide (NO)-mediated vasodilation.

Safety: The NOAEL (no treatment-related adverse effects) in male and female rats was 3446 and 4087 mg/kg/day, respectively. No safety data exist in humans.

Types of evidence:

- Only one rat toxicity study

The safety of CoffeeBerry® products (FutureCeuticals, Inc) was evaluated in three genotoxicity studies, three short-term oral toxicity studies, and a 90-day dietary toxicity study [11]. Bacterial mutagenicity studies and a micronucleus test using mouse peripheral cells demonstrated that none of the products showed mutagenic or genotoxic potential. In the short-term studies, despite palatability issues, female rats showed a tolerance for whole powder and ethanol extract at doses up to 8800 mg/kg/day. Male rats also exhibited palatability issues and tolerated lower doses of approximately 4000 mg/kg/day ethanol extract via gavage and approximately 2100 mg/kg/day whole powder or water extract in the diet. When fed in the diet to Sprague-Dawley rats for 90 days, ethanol extract showed no adverse effects at dietary concentrations of up to 5% (approximately 3446 and 4087 mg/kg/day for male and female rats, respectively). Human equivalent doses after taking into account the difference in body surface area are 555.8 mg/kg/day and 659.2 mg/kg/day for men and women, respectively. There was no mortality in any of the rat studies (7-day, 14-day, and 90-day treatment), and gross necropsy showed no abnormal findings other than incidental ones (none was accompanied by histopathological changes that would suggest toxicological relevancy to treatment with the test substance). Hematology, coagulation and clinical chemistry parameters revealed no adverse changes.

Drug interactions are unknown.

Sources and dosing: Most studies examining the efficacy of coffee fruit have used the Coffeeberry® product from FutureCeuticals, Inc. Dried whole coffee fruit powders as well as granules suitable for use in tea bags, custom roasted coffees, nutritional bars, snack chips, and desserts are available.

Coffee fruit extracts, standardized to levels of 600,000 and 1,500,000 oxygen radical absorbent capacity (ORAC) units/100 g, were designed to be used in beverages, capsule and tablet applications, or any application where high antioxidant capacity is desired [11]. In comparison, a US Department of Agriculture report on the phenolic content and ORAC (per 100 g) of selected foods (USDA, 2007) found

the highest ORACs in ground cloves (314,446), chocolate (49,926 in baking chocolate), and tree nuts (17,940 in pecans); other foods with relatively high ORACs included cranberries (9584), blueberries (6552), raw garlic (5346), and red table wine (3873) per 100 g. Coffee fruit extracts surpass these levels by several-fold.

Because of the low caffeine content, 1 gram of the multistep proprietary whole coffee fruit extract provides more than 10-fold the total chlorogenic acid content of a regular 200 mL cup of brewed roasted coffee (approximately 70 mg), and only 1.5% of the recommended maximum daily caffeine dose.

Coffeeberry® coffee fruit extracts are covered by pending US and foreign applications for the following patents: US 7,815,959, US 8,597,710, US 8,603,564, US 7,807,205, US 7,754,263 and US 8,603,563 (FutureCeuticals.com).

Research underway: There is one clinical trial registered on ClinicalTrials.gov that tested the effects of whole coffee fruit concentrate on cognition and mood in healthy adults (NCT01965795). This clinical trial posted on ClinicalTrials.gov a few months after the Reyes-Izquierdo study [4] came out in print (August 2013). The trial has completed enrollment as of January 2015, but results have not been posted or published. They enrolled 39 participants in a double-blind randomized controlled trial. Whole coffee fruit concentrate is in powder form and capsulated in gelatin capsules, and a dose of 100 mg was administered twice daily, once before breakfast and again before dinner. The primary outcome measure was plasma BDNF at 3 different time points within a 28 day period. Secondary outcome measures included tests of verbal memory, attention and inhibition, spatial short-term memory, working memory, executive function, and psychomotor speed. Other outcome measures included mood assessments.

Search terms:
Pubmed, Google:

- Coffee fruit(s), coffee berry(ies), coffee cherry(ies)

Websites visited for coffee fruit:

- Clinicaltrials.gov
- Examine.com (0)
- Treato.com (not accessible)
- DrugAge (0)

- Drugs.com (o)
- WebMD.com (o)
- Labdoor.com (o)
- ConsumerLab.com (o)

References:

1. Garciaa R, Aguilera A, Contreras-Esquivel JC *et al.* (2008) Extraction of condensed tannins from Mexican plant sources. *Z Naturforsch C* 63, 17-20.https://www.ncbi.nlm.nih.gov/pubmed/18386482

2. Bucheli P, Kanchanomai C, Meyer I *et al.* (2000) Development of ochratoxin A during robusta (Coffea canephora) coffee cherry drying. *J Agric Food Chem* 48, 1358-1362.https://www.ncbi.nlm.nih.gov/pubmed/10775397

3. Pandey A, Soccol CR, Nigam P *et al.* (2000) Biotechnological potential of coffee pulp and coffee husk for bioprocesses. *Biochem Eng J* 6, 153-162.https://www.ncbi.nlm.nih.gov/pubmed/10959086

4. Reyes-Izquierdo T, Nemzer B, Shu C *et al.* (2013) Modulatory effect of coffee fruit extract on plasma levels of brain-derived neurotrophic factor in healthy subjects. *Br J Nutr* 110, 420-425.https://www.ncbi.nlm.nih.gov/pubmed/23312069

5. Mullen W, Nemzer B, Ou B *et al.* (2011) The antioxidant and chlorogenic acid profiles of whole coffee fruits are influenced by the extraction procedures. *J Agric Food Chem* 59, 3754-3762.https://www.ncbi.nlm.nih.gov/pubmed/21401105

6. Nagasawa H, Yasuda M, Sakamoto S *et al.* (1996) Suppression by coffee cherry of the growth of spontaneous mammary tumours in SHN mice. *Anticancer Res* 16, 151-153.https://www.ncbi.nlm.nih.gov/pubmed/8615601

7. Nagasawa H, Yada E, Udagawa Y *et al.* (2001) Effects of coffee cherry, the residue left after removal of the beans from the coffee fruit, on mammary glands, automatic behavior and related parameters in mice. *Am J Chin Med* 29, 119-127.https://www.ncbi.nlm.nih.gov/pubmed/11321469

8. Kobayashi T, Yasuda M, Iijima K *et al.* (1996) Effects of coffee cherry on the immune system in SHN mice. *Anticancer Res* 16, 1827-1830.https://www.ncbi.nlm.nih.gov/pubmed/8712708

9. Kobayashi T, Yasuda M, Iijima K *et al.* (1997) Effects of coffee cherry on the activation of splenic lymphocytes in mice. *Anticancer Res* 17, 913-916.https://www.ncbi.nlm.nih.gov/pubmed/9137427

10. Watanabe T, Arai Y, Mitsui Y *et al.* (2006) The blood pressure-lowering effect and safety of chlorogenic acid from green coffee bean extract in essential hypertension. *Clin Exp Hypertens* 28, 439-449.https://www.ncbi.nlm.nih.gov/pubmed/16820341

11. Heimbach JT, Marone PA, Hunter JM *et al.* (2010) Safety studies on products from whole coffee fruit. *Food Chem Toxicol* 48, 2517-2525.https://www.ncbi.nlm.nih.gov/pubmed/20600539

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