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.

Cocoa

Evidence Summary

Likely to protect against some outcomes like cardiovascular disease, which might in turn be neuroprotective. Likely safe although long-term intake of high-dose cocoa flavanols is untested.

Neuroprotective Benefit: Small randomized trials suggest that cognitive benefits are possible but not extensive or consistent. A reasonably strong biological rationale suggests long-term protection might occur but 2 observational cohort studies give mixed results.

Aging and related health concerns: Observational studies suggest potential cardiovascular benefits, but in many studies involving chocolate intake the flavanol content is not known. May have anti-oxidant and anti-inflammatory effects.

Safety: Cocoa has been safely used for centuries, but excessive consumption of chocolate poses health risks due to high levels of sugar and fat in this form. The long-term safety of high dose flavanol supplements is unknown.

What are they? The cocoa bean, also called the cacao bean, is the processed seed of the Theobroma cacao tree. It is used to generate cocoa solids (e.g. cocoa powder) and cocoa butter, which are used in turn to create chocolate as well as other foods like mole sauce. Cocoa powder contains methylxanthines (caffeine and theobromine) and flavanols, a subclass of flavonoids that includes (-)-epicatechin and procyanidins.

Flavanols or Flavon-3-ols are often assumed to be the active ingredient in chocolate and cocoa for health, but cocoa is only a minor source of flavanols in our diet. For example, one recent study concluded that Europeans get most of their flavanols from tea, followed by pome fruits (e.g. apples, pears), then berries and small fruits, and finally cocoa beans and related products which comprise 3% of the dietary sources of flavanols (4). The flavanol content in cocoa-related foods varies substantially depending on the geographic source of the beans and as well as how they were processed and stored.

Neuroprotective Benefit: Small randomized trials suggest that cognitive benefits are possible but neither extensive nor consistent with flavanol-enriched cocoa. A reasonably strong biological rationale suggests long-term protection might occur but 2 observational cohort studies with chocolate give mixed results.

Types of evidence

- No meta-analyses. One 2013 systematic review (3) discusses small RCTs up to 6 weeks duration testing cognitive or mood but not specifically for aging or neurodegeneration.
- 3 trials in older people or those with cognitive impairment suggest benefit on some but not all cognitive tasks in older people (5-7). Another 2 trials report no benefit (8, 9). Similar mixed results reported from trials in younger people without cognitive impairment.
- 1 prospective 5-year study suggests no effects of chocolate (10) while 1 cross-sectional study suggests benefit but weaker than that of wine (11).
- Rationale for flavanol content of cocoa given from animal/cell culture studies.

Short clinical trials up to 8 weeks in duration have had mixed results but suggest that chocolate or cocoa might improve some but not most aspects of cognitive function. One trial in patients with mild cognitive impairment (MCI) reported that a high-dose flavanol cocoa had no overall effect on Mini Mental State Exam (MMSE) cognitive scores but improved scores on 2 of the cognitive tests. The treatment also improved a variety of markers of health related to insulin resistance, blood pressure, and oxidative

stress (the CoCoA study using 520-990mg/day cocoa flavanols) (5). Another recent trial reported that high-flavanol cocoa (900mg flavanols + 138 mg epicatechin/day) improved performance on a cognitive task vulnerable to brain aging but offered no benefit on a cognitive task vulnerable to early stages of Alzheimer's disease (6).). Other trials in elderly patients and younger people have been very mixed, per the conclusions of a systematic review, with short-term cognitive improvement sometimes but rarely seen along with increased cerebral blood flow (3).

Cocoa and chocolate products vary extensively in their flavanol content, which may account for the discrepancies between studies If the flavanols are the active ingredients, this variability might explain why the observational data is mixed from null (10) to benefit (11). However, clinical trials that compared high vs low flavanol cocoa drinks are also mixed. Two trials report benefit specifically from flavanol-enriched cocoa (5, 6) while another did not (9). Baseline health of the study participants might also affect the results.

Despite the mixed and limited evidence for cognitive benefit, a preclinical biological rationale suggests that long-term treatment might protect against cognitive decline and neurodegeneration through cardiovascular and metabolic health, inflammation, and oxidative stress (discussed in the aging section below).

ApoE4 interactions: There is no research for or against the idea that apolipoprotein E4 carriers will have a differential response to cocoa, chocolate, and related flavanols.

Aging and related health concerns: Observational studies suggest potential cardiovascular benefits, but in many studies involving chocolate intake the flavanol content is not known. May have anti-oxidant and anti-inflammatory effects.

Types of evidence

- *Aging/mortality:*
    - 1 prospective cohort in 470 elderly men reported that highest cocoa intake (quartiles) had lower risk all-cause mortality (Risk ratio (RR): 0.53, 95% CI 0.39-0.72), cardiovascular-related mortality (RR: 0.50, 0.32-0.78), and lower systolic & diastolic blood pressure, over 15 years follow-up(12).

  - 1 rat study reported increased lifespan with 12 months treatment of 24 mg/kg/day cocoa polyphenolic extract (Acticoa powder)(13). One fruit fly study reported increased lifespan but also indicated possible pro-oxidant effects in conditions of extreme oxidative stress(14)

- *Aging function*:One randomized trial combining group exercise, oral care, chocolate, and supplements in nursing home residents reported no effect on cognitive performance but protection from social and physical decline (15)

- *Cardiovascular benefits*: One meta-analysis of 42 small short duration RCTs suggests that chocolate or cocoa can reduce blood pressure (diastolic and arterial) and improve flow-mediated dilation (16). One meta-analysis of 10 trials of 2-12 weeks duration suggests dark chocolate/cocoa reduces LDL and total cholesterol but does not consistently affect HDL or triglyceride levels (17). RCTs have not been performed with long-term intake, but a 2011 meta-analysis concluded that 5 of 7 observational studies report a lower risk of cardiovascular disease (RR: 0.63, 95% CI 0.44-0.90) and stroke (RR: 0.71) when the highest intake of chocolate was compared to lowest intake (by quartiles). More recent cohort studies report decreased risk of cardiovascular endpoints including heart failure (18) and calcified atherosclerotic plaques (19), with the former specific to people with a body mass index (BMI) below 25 (i.e. not overweight).

- *Anti-oxidant*: Small RCTs suggest that cocoa flavanols can reduce oxidative damage ((5, 20) and others) although effects are not consistent (eg. (21)).

- *Insulin resistance*: A 2012 meta-analysis of short-term RCTs suggested decreased serum insulin but minimal effects on fasting glucose levels (16). A 2012 RCT in MCI patients reported that improved insulin resistance accounted for 40% of the variability in the observed benefits to cognitive function (5).

- *Inflammation:* Minimal evidence but one cohort study in healthy Italians (22) and one RCT in Iranian diabetic patients (23) reported decreased biomarkers of inflammation, like CRP, while a small RCT reported no benefit of cocoa versus green tea on CRP or IL-6 (20).

Safety: Cocoa has been safely used for centuries, but excessive consumption of chocolate poses health risks due to high levels of sugar and fat in this form. The long-term safety of high dose flavanol supplements is unknown.

The safety concerns of chocolate, cocoa, and cocoa flavanol supplements are few and mainly related to either the caffeine content or the sugars and saturated fat common to chocolate and related foods. On the other hand, the high-dose flavanol supplements in use today are new to our diets, with little long-term information collected either through long-term broad public use or through research.

Dosing and Sources: A recommended dose has not been established due to variation in clinical trials and observational studies. Clinical research hinting at benefits of high-flavanol cocoa products have used doses ranging from 520-990 mg/day flavanols, with epicatechin levels from 58-138 mg/day. In contrast, dietary intake of flavanols is far lower, particularly for cocoa-related flavanols. For example, dietary intake of flavanols in Europe was estimated at between 181 mg/day to 793 mg/day in European countries and 13.5 mg/d of epicatechin, and only 3% of those flavanols in European diets are derived from cocoa and related products. A 2002 review estimated that anti-oxidant benefits of flavonoid-rich chocolate would require doses of 38g for acute benefits and 125g for chronic benefits, a dose that is far higher than those measured in a prospective cohort study (median chocolate intake 2.1 g/day) that suggested reduced cardiovascular risk with higher chocolate intake (12).

The flavanol levels in chocolate and cocoa vary extensively. Milk chocolate has less cocoa than dark chocolate, so it has less flavanols as well. The presence of milk may also reduce its absorption, but that claim is controversial. Dark chocolate has substantially less flavanols if it has been "dutched" (i.e. processed with alkali), a common processing step to make cocoa darker and less acidic (24, 25).

Future research: Long-term studies are very needed, whether observational or RCT, that test different types of chocolates and particularly different doses of flavanol. A major flaw in the current research is that long-term intake of high-dose flavanols has not been proven safe and long-term studies have typically classified intake by "chocolate" or "cocoa" but these categories are extremely broad in actual content and may not even contain a significant amount of flavanols. No trials are reported underway for neurodegenerative diseases, although one trial is recruiting Parkinson's disease patients for a 1 week treatment (NCT02275884).

Search terms:

Pubmed:

- Cocoa, cognitive
- cocoa, alzheimer
- cocoa, aging
- cocoa, arterial with meta-analysis filter
- chocolate, aging
- cocoa, oxidative
- cohort, chocolate, cogn*
- cohort, cocoa, alzheimer
- cohort, cacao or cocoa, cogn*
- cocoa flavanol safety
- cohort, cocoa, cardiovascular
- cocoa, CRP
- cocoa, mortality

Embase:

- Cacao and cognition
- Cacao and aging

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