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**File: ■ Cocoa (*Theobroma cacao*, Malvaceae)**

■ Flavan-3-ols

■ Theobromine

■ Cardiometabolic Risk Factors

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**RE: Research Review Supports Cardioprotective Role of Cocoa**

Berends LM, van der Velpen V, Cassidy A. Flavan-3-ols, theobromine, and the effects of cocoa and chocolate on cardiometabolic risk factors. *Curr Opin Lipidol*. 2015;26(1):10-19.

Potential cardiovascular health benefits are attributed to cocoa (*Theobroma cacao*, Malvaceae) and chocolate through their bioactive constituents, including polyphenols, stearic acid, and methylxanthines. This review summarizes the recent research on the cardiometabolic effects of cocoa and chocolate and focuses on two key bioactive constituents: flavan-3-ols and theobromine. The main flavan-3-ols in chocolate are (–)-epicatechin, (+)-catechin, and some of their oligomers, known as procyanidins. Theobromine is another bioactive constituent of chocolate with potential beneficial health effects. The role of chocolate in cardiovascular disease (CVD) has been studied in both observational studies for cardiovascular endpoints and in randomized, controlled trials (RCTs) for cardiometabolic markers.

In a meta-analysis of six cohort studies and one cross-sectional study, a higher chocolate intake was associated with a reduced risk for cardiometabolic disorders.<sup>1</sup> The greatest reductions were seen for CVD (37%) and stroke (29%) in three studies. In one study, a reduction in diabetes was observed; no effects of chocolate intake on heart failure were observed. A meta-analysis of observational data showed an overall relative risk reduction of 19% for stroke when comparing the highest and lowest categories of chocolate intake.<sup>2</sup> Two other meta-analyses supported the association between chocolate intake and reduced risk for CVD.

Three meta-analyses of RCTs reviewed the impact of cocoa and chocolate consumption on cardiometabolic health from short-duration studies (≤18 weeks). One reported a 2.77 mmHg decrease in systolic blood pressure (SBP) and a 2.20 mmHg decrease in diastolic blood pressure (DBP) after cocoa intake.<sup>3</sup> Two of the meta-analyses reported improved levels of both high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) with cocoa consumption. In another study, daily cocoa

intake significantly improved HDL-C, glucose, and several inflammatory biomarkers, but did not affect blood pressure, LDL-C, or triglyceride concentrations.<sup>4</sup>

The authors conclude that data from available RCTs on cardiometabolic markers "largely support the findings on CVD outcomes in observational studies; the short duration studies support potentially clinically relevant effects of cocoa and chocolate on vascular function and insulin resistance." Additional longer-term trials are needed.

According to the authors, the most recent prospective cohort studies on flavan-3-ol intake and cardiovascular health report no association with coronary heart disease (CHD) mortality, CHD incidence, or stroke risk. One study of 98,469 men and women over seven years, however, reported that higher flavan-3-ol intake was associated with a 17% decrease in CVD mortality.<sup>5</sup> Another study of 1,063 women over five years reported a 66% decrease for atherosclerotic vascular disease mortality associated with flavanol intake.<sup>6</sup> A third study of 7,172 subjects followed for more than four years reported a 60% decrease in CVD events and mortality.<sup>7</sup>

Three systematic reviews sought to determine the effective dose of flavan-3-ols. In one, a nonlinear dose-response effect with a maximal effect was observed at a total polyphenol intake of 500 mg. In another, intakes of epicatechin > 50 mg resulted in greater effects on SBP and DBP; flow-mediated dilatation (FMD) improved at all levels of epicatechin intake.

The authors conclude that "flavan-3-ols may mediate the beneficial effects of cocoa and chocolate. However, in addition to elucidating the effective doses, it remains to be established whether the flavan-3-ol monomers, their phase-II-conjugated metabolites, the procyanidins or their gut metabolites are driving any cardiometabolic effects."

Theobromine may be responsible for mediating the observed beneficial effects of cocoa and chocolate on lipoprotein levels, suggests a short-term RCT in which daily consumption of theobromine (850 mg) for four weeks significantly increased HDL-C concentrations.<sup>8</sup> In another RCT, with a lower daily consumption of theobromine (476 mg daily for four weeks), no changes were reported in HDL-C levels.<sup>9</sup> In some studies, high-dose theobromine consumption was associated with gastrointestinal complaints, and acute stimulatory effects on heart rate were observed following consumption of 500-1000 mg theobromine.

The authors suggest further studies should investigate how theobromine affects HDL-C functionality and cardiovascular health, along with the effects at dietary-relevant levels, and its potential synergistic effects with other bioactive compounds in chocolate.

The authors conclude, "Evidence for a cardioprotective role of chocolate consumption is apparent from the population-based studies and short-term RCTs, and currently provides greater support for the flavan-3-ol content rather than theobromine. However, interpretation of findings is difficult because of considerable variability between studies and it is unclear whether they work individually or in synergy."

—*Shari Henson*

## References

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- <sup>6</sup>Ivey KL, Lewis JR, Prince RL, Hodgson JM. Tea and non-tea flavonol [sic] intakes in relation to atherosclerotic vascular disease mortality in older women. *Br J Nutr*. 2013;110(9):1648-1655.
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