

Cocoa Flavonoid Supplements and Cardio-metabolic Disease Prevention: A Promising Preventive Nutraceutical

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Flavonoids are a major group of antioxidants from various food sources. Excess oxidative load, which may rise from an inadequate supply of flavonoids, has been implicated in the pathogenesis of atherosclerosis, diabetes, and obesity [1,2]. Flavonoids have been shown to enhance cardio-metabolic health in many observational studies and randomized trials [3-5]. Therefore, nutrient supplies favoring pro-oxidant reactions have been considered as promising dietary interventions on cardio-metabolic diseases. As an important source of flavonoids, cocoa products are a potential tasty addition to the armamentarium of nutraceuticals.

Both observational studies and randomized trials of cocoa product consumption have consistently reported favorable effects on the intermediate cardio-metabolic biomarkers and the risk of cardio-metabolic diseases [6-8]. In addition, several reviews and meta-analyses have synthesized the evidence in support of the notion that cocoa products may enhance the profiles of cardio-metabolic health [9-14]. Ding *et al.* reported in a systematic review that cocoa consumption is likely protective against coronary heart disease mortality [12]. In a meta-analysis of prospective cohorts of men, Larsson *et al.* found that chocolate consumption may lower the risk of stroke (relative risk=0.83 comparing the highest and the lowest quartile of chocolate consumption) [14]. For intermediate cardio-metabolic biomarkers, a meta-analysis of twenty randomized trials reported that cocoa product consumption had a small but statistically significant effect in lowering blood pressure (-2.8 mm Hg systolic and -2.2 mm Hg diastolic) [15]. A more recent meta-analysis of randomized trials conducted by Hooper *et al.* showed that both flow-mediated dilation and homeostatic model assessment-insulin resistance (HOMA-IR) were also improved after chocolate consumption [10].

Despite that the protective effects of cocoa products against cardio-metabolic diseases have been consistently reported, the evidence for cocoa flavonoids, as the main active compounds in cocoa products, remains limited [16,17]. More importantly, fewer studies have directly evaluated specific biological parameters aside from those characterized by excess oxidative stress. Moreover, recent research has shifted its focus to other potential

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mechanisms underlying the protective effects of cocoa flavonoids on cardio-metabolic health, implicating that cocoa flavonoids may improve lipid profiles [18], insulin sensitivity [19], and endothelial function [20] and alleviate systemic inflammation [21] and thrombosis [22,23]. As yet, the exact mechanistic pathways responsible for the potential beneficial effects of cocoa remain to be elucidated.

Cardio-metabolic diseases have become a global epidemic that inflicts individual suffering, and the time has come to promote preventive strategies that emphasize healthy diets and adequate nutrient supplies. Although current literature is suggestive of the beneficial effects of cocoa products and cocoa flavonoids, the mechanistic pathways whereby these phytochemicals may exert

their effects on cardio-metabolic outcomes need to be confirmed in large long-term randomized trials. Comprehensive clinical studies should also be conducted to determine the optimal dose of cocoa flavonoids and other functionally active compounds in cocoa products.

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