



Cacao phytochemicals in the prevention of death from cardiovascular disease: commentary on the COSMOS study

Fitoquímicos del cacao en la prevención de muerte por enfermedad cardiovascular: comentario sobre el estudio COSMOS

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Cacao is a native fruit of America whose seed is the raw material to produce chocolate. Traditionally, pre-Hispanic cultures such as the Olmecs and Mayans cultivated this plant for various purposes. The value that these cultures gave to cacao is reflected in the fact that the drink prepared with the seeds was exclusive to the aristocracy and used in rituals of warriors and priests; in addition, the seeds were used as a form of currency.

More recently, scientific studies have shown the nutritional content of cacao to be high in fiber and proteins and in molecules such as theobromine and caffeine, which give it a slight stimulating effect.

In addition, phytochemicals have been isolated and characterized in the cocoa fruit, such as (-)-epicatechin (EC), a flavanol, which has been the subject of multiple investigations for its beneficial effects in recent years on cardiovascular health. Mexican scientists have been working for years to describe and characterize the molecular mechanisms by which EC exerts its effects, identifying trans-membrane receptors that are selectively activated and trigger specific cellular responses. Multiple *in silico* (computational systems), *in vitro* (test tube and cell cultures), and preclinical studies have shown EC's effects on modulating mitochondrial function, decreasing oxidative stress, and promoting mitochondrial biogenesis, demonstrating the reduction of myocardial

damage induced by ischemia/reperfusion by obstructing the coronary arteries in animals.¹

As a consequence of all the basic knowledge generated, small-scale clinical studies have been developed to contribute to the improvement of human health, mainly focused on chronic diseases of pandemic magnitude, among which are obesity, type 2 diabetes mellitus, and cardiovascular disease diseases (CVD). These clinical studies have verified the laboratory findings that the EC of cocoa is a molecule with potential pharmacological use for the primary and secondary prevention of CVD. With this arises the need to carry out large-scale studies with hundreds or thousands of patients.² However, the negligible economic support for science in Mexico makes it difficult to advance clinical studies for the development of new drugs. Fortunately for science, the sum of efforts among scientists worldwide allows multicenter and multidisciplinary studies to be carried out.

Recently, the COSMOS study: COcocoa Supplement and Multivitamin Outcomes Study (COSMOS) was published in the American Journal of Clinical Nutrition (2022) with the results of a randomized, double-blind study, controlled with placebo that included 21,442 participants older than 60 years. The intervention consisted of the consumption of cocoa extract containing 80 mg of (-)-epicatechin/day with a mean follow-up of 3.6 years. The results showed a decrease

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in CVD death (HR: 0.73; 95% CI: 0.54, 0.98) (Figure 1) and major cardiovascular events (HR: 0.84; 95% CI 0.71, 0.99).³

This means that supplementation with cocoa extracts rich in EC in older adults significantly reduces death from CVD by up to 27%. The significant reduction in death from CVD in the general population represents a phenomenon of great relevance, without precedent, since it is the supplementation with phytochemicals.

The systematic use of this type of supplementation would reduce CVD mortality and the economic impact that this pathology generates.

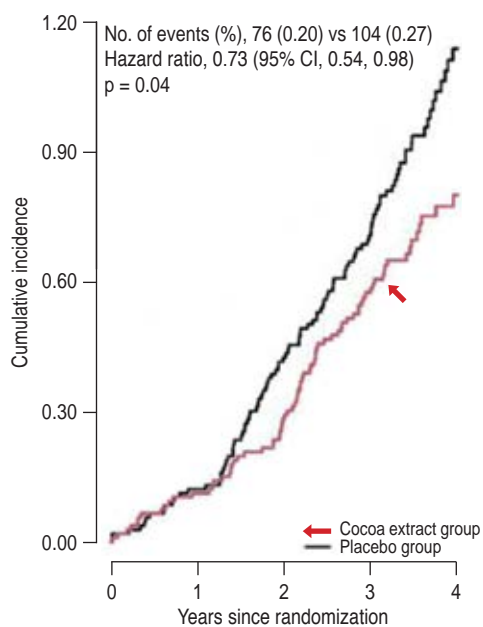
Finally, other benefits of cocoa phytochemical supplementation are that no adverse effects were found (only 6% reported nausea; HR: 1.06; 95% CI: 1.02, 1.11) and there was also a 5% decrease in symptoms associated with flu (both HRs: 0.95; 95% CI:

0.91, 0.99) and 15% reported a reduction in migraine (HR: 0.85; 95% CI: 0.78, 0.93).

This is how a randomized, double-blind, placebo-controlled clinical study with thousands of patients confirms the knowledge reported by basic studies.

It would suffice to say, to conclude, that this is a clear example of the urgent need for both the State and the pharmaceutical industry to invest financial resources into the development of these types of studies. The transferring of the knowledge generated in research laboratories, developed *in silico*, *in vivo*, or in animals, towards its application in humans will improve, of course, the health of Mexican patients, immersed, as we know, in a tangled skein of multiple risk factors that impact cardiovascular health such as sedentary lifestyle, obesity, diets rich in carbohydrates and fats, diabetes, etcetera.

In conclusion, current therapies based on statins reduce the risk of death from CVD by up to 24%.⁴ The results of the COSMOS study report a 27% reduction in mortality from CVD with the use of cocoa phytochemicals; therefore, the combined use of both therapies would synergistically favor the prognosis of patients in primary and secondary prevention.



Number at risk	0	1	2	3	4
Cocoa extract	10,719	10,569	10,408	9,846	3,462
Placebo	10,723	10,596	10,433	9,872	3,465

Modified from: Sesso HD et al.³

Figure 1: Cumulative incidence of death from cardiovascular disease according to the year of follow-up in the group treated with cocoa (arrow) and the placebo group.

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