

## Cocoa Flavanols, Nitric Oxide And Endothelial Function

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Diet patterns are widely recognized as contributors to hypertension. Widely studied potential contributors include intake of sodium, potassium, magnesium, calcium, soluble fiber, Omega-3 fatty acids, alcohol, protein, and calories. We add to that list the effect of dietary flavanols present in certain cocoas, which have sufficient activity on vascular nitric oxide to influence blood pressure control. Kuna Indians who live on islands near Panama have little age-related rise in blood pressure or hypertension. On migration to Panama City, blood pressure raises with age and the frequency of essential hypertension matches urban levels elsewhere. We have identified a specific food that probably makes an important contribution to cardiovascular status. Island-dwelling Kuna drink more than five cups of flavanol-rich cocoa per day and incorporate that cocoa into many recipes. Mainland Kuna ingest little cocoa and what they do take is commercially available and flavanol-poor. The flavanol-rich cocoa activates nitric oxide synthase in vitro and in intact humans in the doses that the Kuna employ. Island-dwelling Kuna have a 3-fold larger urinary nitrate: nitrite than do Mainland dwellers. As endothelial dysfunction is central to current thinking on cardiovascular pathophysiology, a food that enhances endothelial function could have broad implications. The list of candidate conditions that might be influenced is impressive, ranging from atherosclerosis and diabetes mellitus to hypertension and pre-eclampsia, to vascular dementias and end-stage renal disease. All share as a common feature endothelial dysfunction with loss of either production or action of nitric oxide.

If restoration of nitric oxide production can be achieved by ingestion of flavonoid-rich cocoa, as commonly it can, does this improve natural history? We reduced blood pressure with medications not to make the numbers nicer but because doing so reduces morbidity and mortality. The same logic applies to treatment of high blood cholesterol or a high blood sugar. Does restoration of nitric oxide production improve natural history in these conditions? Only a partial answer is available, but it is very promising. We are at the stage where epidemiology usually plays a crucial role. In the case of flavonoids, efforts to use epidemiology have been limited by the variability in the content of flavonoids in foods, largely representing processing or handling. Grapes grown in the same vineyard have a very different flavonoid content in different years, and so does the red wine produced from these grapes. When an individual eats applesauce or apple pie, he or she rarely knows whether the skin of the apple was included. Essentially all of the flavonoids in apples come from the skin. Flavonoid content in chocolate and cocoa is equally or even more variable. In the island-dwelling Kuna, conversely, cocoa intake is very high, and the cocoa is always rich in flavonoids. Thus, the indigenous Kuna provide an opportunity to address this issue. In data obtained from death certificates, mainland Panama residents who died had disease of the circulation as the most common cause and cancer as a close third. The frequency of these two problems was much lower in the San Blas where the indigenous Kuna live. Indeed, the relative risk of death from heart disease on the Panama mainland was 1,280% of that in the island, and a cancer death was 630%. Thus, the preliminary data available indicate that flavonoid-rich foods may provide an extraordinary benefit in the management of the two most common causes of death in today's world.