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Current Opinion in Food Science

Health beneficial effects of cocoa phenolic compounds: a mini-review

María Ángeles Martín and Sonia Ramos

Cocoa is a widely consumed food and a rich source of phenolic compounds, especially flavanols (a type of flavonoid). Different studies have shown that cocoa possesses health beneficial effects by contributing to prevent chronic diseases such as cancer, cardiovascular and neurodegenerative diseases, diabetes, obesity and ageing. However, contradictory results have been reported, which makes necessary to perform well-controlled clinical trials and mechanistic studies to fully understand the potential health beneficial effects of cocoa. This work reviews recent studies on the health benefits of cocoa flavanols related to the prevention of relevant chronic diseases, and discusses the potential molecular mechanisms of action.

Address
Department of Metabolism and Nutrition, Institute of Food Science and Technology and Nutrition (ICTAN), Consejo Superior de Investigaciones Científicas (CSIC), José Antonio Novais 10, Ciudad Universitaria, 28040, Madrid, Spain

Corresponding author: Ramos, Sonia (s.ramos@ictan.csic.es)

Current Opinion in Food Science 2017, **14**:20–25

This review comes from a themed issue on **Functional foods and nutrition**

Edited by **Cristina Delgado-Andrade**

For a complete overview see the Issue and the Editorial

Available online 29th December 2016

http://dx.doi.org/10.1016/j.cofs.2016.12.002

Introduction

Cocoa has been recognized as a rich source of phenolic compounds (10–12% by dry weight) [1]. However, the amount of polyphenols largely depends on the origin and the methods of processing of cacao beans to produce cocoa [1]. In general terms, the major polyphenols present in cocoa are monomeric flavanols such as (−)-epicatechin (EC), (+)-catechin, their dimers procyanidins B2 (PB2) and B1, and polymeric flavanols [1]. In addition, cocoa contains other polyphenols at minor amounts (luteolin, apigenin, naringenin, quercetin, isoquercitrin, *etc.*), and methylxanthines, mainly theobromine, and caffeine in small quantities [1].

Accumulating epidemiological evidences suggest that cocoa could play a role in the prevention of chronic diseases that constitute a world health burden and are responsible of death and incapacity to millions of people, such as cardiovascular diseases (CVD), cancer, diabetes, obesity, and neurodegenerative diseases [2–6,7••]. Different molecular mechanisms have been proposed to explain the underlying preventive effects of cocoa flavanols, although the regulatory machinery involved remains largely unknown. Interestingly, it should be noticed that because of the relatively low bioavailability of catechins and their extensive metabolism small tissular and circulating concentrations have been reported [8,9]; however, flavanol metabolites could also play a role on the potential health beneficial effects [10••].

This review describes and discusses the potential health benefits of cocoa flavanols in the prevention of relevant chronic diseases highlighting the underlying molecular mechanisms.

Effects of cocoa flavanols in CVD

The protective cardiovascular effects of cocoa flavanols have been extensively investigated over the last decades in many epidemiological and nutritional intervention trials. Altogether, these studies indicate that appropriate intakes of cocoa reduce the incidence of cardiovascular disease and of several of its risk factors [6]. The most recent epidemiological studies show that cocoa consumption reduced the relative risks of coronary heart diseases, stroke and cardiovascular mortality [11••]. Accordingly, data obtained from interventional studies confirm a major participation of cocoa flavanols in mechanisms positively affecting significant markers of cardiovascular disease such as oxidation of low-density lipoprotein (LDL), lipid profile, nitric oxide (NO), endothelial dysfunction and blood pressure [12,13]. The mechanisms involved in these effects include vasodilatory, anti-inflammatory, antithrombotic or antiatherogenic activities [14]. Although these biological properties were mainly attributed to its antioxidant activity, nowadays due to its low bioavailability other pharmacological mechanisms should also be considered.

Cocoa flavanols are thought to principally exert their cardiovascular benefits *via* protection of the bioactivity of the endothelium-derived nitric oxide (NO), an essential regulator of the endothelial function. NO from endothelium leads to vascular relaxation and prevents leucocyte adhesion and migration, smooth muscle cell proliferation, and platelet adhesion and aggregation. Studies carried out on rat aorta rings and mesenteric arteries demonstrate that EC, one of the main polyphenol present in cocoa, may induce endothelium-dependent relaxation [15]. At the molecular level, it has been shown that EC increases endothelial derived NO synthase activity (eNOS), which should facilitate the conversion of L-arginine into NO, by phosphorylation at Serine^{1177} with consequent enzyme activation and NO production [16]. Additionally, cocoa flavanols can also exert inhibitory effects on pathways that may negatively affect NO. In this line, incubation of human umbilical vein endothelial cells with a cocoa extract inhibits angiotensin converting enzyme activity and thus enhances NO production but had no effect on NO levels *in vivo* in humans [17]. Likewise, EC inhibits the expression of arginase-2 in cultured endothelial cells, which could increase substrate availability (L-arginine) for NO synthesis *via* eNOS [18]. Also cocoa decreased erythrocyte arginase in humans [18].

Antioxidant effects of cocoa could also play a role in the protection against thrombosis and atherosclerosis. Oxidized LDLs play a crucial role in the progression of atherosclerosis and, in this regard, it has been shown that cocoa flavanols decrease the oxidation of LDL in *in vitro* studies [13] and acutely in humans [19]. Cocoa also chronically decreases plasma oxidized LDL levels in humans [20]. Together with this, oxidative stress may also promote atherogenesis through the induction of inflammatory factors such as interleukins and chemokines. Actually, the effects of cocoa polyphenols on cardiovascular-related inflammation have been recently discussed [13,21]. Accordingly, several *in vitro* studies have demonstrated the protective effect of cocoa flavanols by modulating inflammatory mediators such as adhesion molecules, cytokines, chemokines, growth factors, and enzymes (metalloproteases, cyclooxygenases and lipoxygenases) [21]. Finally, the antithrombotic effect of cocoa flavanols may be related, at least in part, to its antiinflammatory and antiatherogenic properties. Since the low level of oxidative compounds could be associated to a reduced inflammatory environment.

Effects of cocoa flavanols in cancer

Epidemiologic and interventional human studies have proved an inverse correlation between cocoa intake and cancer incidence [2,22,23], although some epidemiological studies have failed to demonstrate any relation between cocoa, chocolate or flavanol intake and the prevalence of different types of cancer [24,25]. Importantly, a number of human studies have established a negative effect of cocoa intake on the incidence of colorectal cancer [26].

Studies in cancer cultured cells and animal models have evidenced that cocoa and its flavanols may interfere at the initiation, promotion and progression stages of this disease. Indeed, cocoa may exert an anti-carcinogenic effect as prevents the DNA damage caused by free radicals or carcinogenic agents through direct radical scavenging and metal-chelating effects, modulates enzymes related to oxidative stress and alters the procarcinogenic metabolism to facilitate its inactivation and/or its elimination [4]. Additionally, cocoa regulates molecular signals connected to the cell cycle, apoptotic and survival/proliferative routes, as well as inflammation, angiogenesis and metastasis processes [4]. In this regard, a cocoa polyphenolic extract exerted an antimutagenic effect through the inhibition of the carcinogen metabolic activation by cytochrome P450-1A [27]. Procyanidin-enriched cocoa extracts caused G2/M cell cycle arrest and growth inhibition of cancer cells [28]. A cocoa-rich diet also induced antiproliferative effects by regulating the cellular redox status [glutathione, glutathione peroxidase (GPx), glutathione reductase, glutathione-S-transferase, *etc.*], and key proteins involved in apoptosis (caspase-3, Bax, Bcl-xL) and in cell survival/proliferation pathways [cyclin D1, protein kinase B (PKB/AKT), extracellular signal-regulated kinase (ERK)] [29,30]. Likewise cocoa downregulated the vascular endothelial growth factor through the activation of key regulators [nuclear factor-κB and activator protein-1] and the inhibition of their upstream modulators phosphoinositide-3-kinase (PI3K), MEK1 and MKK4 [31]. Cocoa polyphenol extracts also attenuated the inhibition of gap-junction intercellular communication by preventing the phosphorylation and internalization of connexin 43, and ERK activation [32].

Interestingly, cocoa flavanols can also become pro-oxidants at high concentrations and in the presence of redox-active metals [33], which could be useful as it might contribute to augment the anticancer effect. In this regard, cocoa flavanols provoked oxidative DNA damage in cancer cells at high doses (200 μM for 18 h) [33], and might induce a synergistic effect in combination with drugs used in therapy to increase the oxidative stress and cell death [34].

Effects of cocoa flavanols in diabetes

Evidence from both observational and experimental studies have suggested that consumption of cocoa and cocoa products may ameliorate important hallmarks of diabetes type 2 (DT2), the most common form of diabetes. Epidemiological studies have suggested that moderate consumption of cacao-derived products may reduce the risk of diabetes [35,36]. In addition, the few clinical intervention studies aimed to evaluate the effects of cocoa products in humans have shown promising effects, including improved insulin sensitivity and lipid profile in medicated DT2 patients [7••]. Nevertheless, these findings also highlighted that the positive effect of cocoa flavanols on DT2 seems to be more related to their proved beneficial effects on vascular function than on glycaemic control.

Experimental data from both animal and *in vitro* studies have suggested that cocoa and its main phenolic compounds can act as potential antidiabetic agents by