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Cocoa polyphenols in oxidative stress: Potential health implications

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Highlights

- Cocoa and its flavanols have a strong antioxidant activity.
- Modulation of redox status by cocoa flavanols could prevent chronic diseases.
- Preventive effects of cocoa against chronic diseases involve different mechanisms.
- Preventive effects of cocoa are connected to an antioxidant-related response.
- Mechanistic studies and clinical trials with cocoa and its flavanols are needed.

Abstract

Oxidative stress has been related to the pathogenesis of chronic diseases. Therefore, prevention of these pathologies by avoiding the damaging effects of free radicals and oxidants has become an important potential chemopreventive and therapeutic approach. In this line, epidemiologic studies have demonstrated that dietary antioxidants seem to play a main role in the prevention of chronic diseases caused by oxidative stress, such as cancer, cardiovascular disease and diabetes. Indeed, cocoa and its flavanols can interfere in the initiation and progression of the mentioned diseases through different mechanisms. This review summarises recent progress on the health benefits of cocoa and its flavanols associated to the antioxidant effects, and discusses their potential molecular mechanism of action in the prevention and/or treatment of relevant chronic diseases.

Introduction

Oxidative stress is recognised as a main responsible for the pathogenesis of chronic diseases such as cancer, cardiovascular diseases (CVD) and diabetes (Ramos, 2008, Valko et al, 2007). These pathologies constitute a global health problem and cause death and disability to millions of people (World Health Organization, 2014). Accumulating evidence suggest that a high consumption of fruits and vegetables, which are rich in phenolic compounds, is inversely correlated with the risk and/or incidence of cancer, CVD and diabetes (Arranz et al, 2013, Ramos, 2008, Ríos et al, 2015, Shahidi, Ambigaipalan, 2015).

Cocoa is a rich source of phenolic compounds and has the highest flavanol (a polyphenol class) content of all foods on a per-weight basis (Vinson, Proch, & Zubik, 1999). Cocoa mainly contains high quantities of flavanols such as (−)-epicatechin (EC), (+)-catechin and their dimers procyanidins B2 (PB2) and B1 (Fig.1), although other polyphenols such as quercetin, isoquercitrin (quercetin 3-O-glucoside), hyperoside (quercetin 3-O-galactoside), quercetin 3-O-arabinose, apigenin, luteolin and naringenin, have also been identified at minor amounts (Table1) (Belscak et al, 2009, Gu et al, 2006, Kim et al, 2014, Miller et al, 2009, Sánchez-Rabaneda et al, 2003). However, it should be considered that phenolic compound content can enormously vary between cocoa beans and cocoa-derived products depending on the processing conditions and the origin of the beans (Andrés-Lacueva et al, 2008, Gu et al, 2006, Kim et al, 2014, Miller et al, 2009, Vinson et al, 1999). Indeed, the alkalinisation treatment that takes place during cocoa processing, results in 60% loss of the mean total flavonoid content (Andrés-Lacueva et al., 2008). (−)-Epicatechin shows a larger loss (67%, as a mean percentage difference) than (+)-catechin (38%), probably because of its epimerisation into (−)-catechin. Similarly, a reduction is also observed for di-, tri-, and tetrameric procyanidins (69% for dimer B2, 67% for trimer C, and 31% for tetramer D); for flavonols, quercetin seems to present the highest loss (86%, being under the limit of

quantification), whereas quercetin-3-arabinoside, and isoquercitrin showed a similar reduction (62 and 61%, respectively) (Andrés-Lacueva et al., 2008). Moreover, it is essential to distinguish between the natural product cocoa and the processed product chocolate, which is a combination of cocoa, sugar, fat and other components (Gu et al, 2006, Miller et al, 2009).

Cocoa and cocoa-derived products are highly consumed in many countries in Europe and United States (Vinson et al., 1999) and because of its high content in polyphenols have recently attracted a great interest. Cocoa flavanols seem to act as highly effective chemopreventive agents against chronic diseases including cancer, heart disease, diabetes, neurodegenerative disease, and ageing (reviewed in Kerimi, Williamson, 2015, Martín et al, 2013, Martín et al, 2016, Ramos, 2008). Numerous mechanisms have been proposed to account for the preventive effects of cocoa and its flavanols in cultured cells and animal models.

These mechanisms include the stimulation of tumour suppressor genes, induction of nitric oxide (NO) signalling, and activation of the insulin pathway, among many others (revised in Kerimi, Williamson, 2015, Martín et al, 2013, Martín et al, 2016, Ramos, 2007, Ramos, 2008). The antioxidant activity of cocoa polyphenols has also been suggested as potential mechanisms for cancer, CVD and diabetes prevention (Andujar et al, 2012, Martín et al, 2016, Ramos, 2008, Shahidi, Ambigaipalan, 2015). Interestingly, the direct antioxidant effects of cocoa and its flavonoids seem to be partly based on their structural characteristics, including the hydroxylation of the basic flavan-ring system, especially 3',4'-dihydroxylation of the B-ring (catechol structure), the oligomer chain length, and the stereochemical features of the molecule (Andujar et al, 2012, Shahidi, Ambigaipalan, 2015). The chemical structure of flavanols is responsible for their hydrogen donating (radical-scavenging) properties and their metal-chelating antioxidant properties (Lambert, Elias, 2010, Nakagawa et al, 2004, Shahidi, Ambigaipalan, 2015). It is worth mentioning that due to the relatively low bioavailability of catechins and extensive metabolism it is supposed that hydrogen donation reaction seems not to play a major role *in vivo*, but despite the levels of transition metals being tightly regulated *in vivo*, metal catalysis flavanol oxidation may occur (Lambert & Elias, 2010). More importantly, cocoa and its flavanols can avert free radical-induced damage by modulating enzymes related to oxidative stress [catalase (CAT), nitric oxidase synthase (NOS), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), etc.], and by modifying the metabolism of damaging agents through the regulation of phase I drug-metabolising enzymes (cytochrome P450) and/or phase II conjugating-enzymes (glucuronidation, sulfation, acetylation, methylation and conjugation), as well as

through the regulation of redox-sensitive transcription factors [nuclear factor erythroid 2 related factor 2 (Nrf2), nuclear factor-kappaB (NF-κB), etc.].

In this regard, it should be highlighted that the biological relevance of the antioxidant effects of flavonoids (flavanols) against oxidative stress-related diseases remains to be established. Indeed, health beneficial effects of flavanoids because of the direct antioxidant action (radical-scavenging and metal-chelating properties) is likely to be limited in humans (Fraga, 2007, Hollman et al, 2011) due to their low bioavailability and extensive metabolism, which lead to low tissue and circulating concentrations in comparison to other exogenous and endogenous antioxidants (Fraga, 2007, Hollman et al, 2011, Shahidi, Ambigaipalan, 2015). Consequently, it should also be considered that flavanol metabolites could play a role on the final health beneficial effect (Lotito, Frei, 2006, Natsume et al, 2004, Shahidi, Ambigaipalan, 2015) and that the modulatory effect of flavonoids on enzymes related to the oxidative stress, as well as phases-I and -II and transcription factors, as mentioned above and among other activities, play a relevant role to prevent the oxidative damage.

In view of this, in the present review, the potential role for the antioxidant effects and close-related molecular mechanisms of cocoa flavanols in the prevention of relevant chronic diseases will be comprehensively revised, giving special emphasis to the underlying molecular mechanisms involved.

Section snippets

Oxidative stress

Aerobic organisms cannot avoid free radical and reactive oxygen and nitrogen species (RONS) production. Free radicals and oxidants are generated during the normal cellular metabolism, and also during the metabolism of toxins, of drugs by cytochrome P450, monooxygenases, or during cell exposure to certain environmental factors [ultraviolet (UV) radiation, etc.] (Finkel & Holbrook, 2000). It is well established that RONS can exert beneficial or detrimental effects depending on their…

Effects of cocoa flavanols in cancer

Carcinogenesis is a multistep complex process that has conventionally been defined by three different stages: initiation, promotion and progression (Ramos, 2008). During the initiation phase cells are exposed to the carcinogen and there is an interaction between the carcinogenic agent and the cell, especially with DNA. At the promotion phase, which is relatively lengthy when compared to the rapid previous stage, abnormal cells persist and replicate, and focus of preneoplastic cells may appear.…

Effects of cocoa flavanols in CVD

Cardiovascular disease, involving peripheral vascular disease, atherosclerosis, heart failure, ischaemic strokes and myocardial infarction, remains the leading cause of death in developed countries (World Health Organization, 2014). The aetiology of CVD is very complex but it has been described that oxidative stress plays an essential role in the development of atherosclerosis and contribute to the progress of cardiovascular events (Dhalla, Temsah, & Netticadan, 2000). In fact, most…

Effects of cocoa flavanols in diabetes

Diabetes mellitus is a complex metabolic disorder characterised by persistent elevated blood glucose (hyperglycaemia). Type 2 diabetes (T2D) is the most common form of diabetes and results from a combination of genetic and acquired factors that provoke a progressive insulin secretory defect in pancreatic beta cells and cellular failure to respond properly to insulin, a condition known as insulin resistance (American Diabetes Association, 2014). T2D is one of the most common chronic diseases and …

Conclusions

Oxidative stress plays a pivotal role in the pathogenesis of chronic disease. Cocoa and its flavanols have been shown to have a strong antioxidant activity in cultured cells, animal models and in humans. The modulatory effect exerted by cocoa and its flavanols on the redox status and diverse cellular processes (apoptosis, inflammation, etc.) has demonstrated that they would be able to prevent and/or slow down the initiation-progression of different chronic diseases related to oxidative stress,…

Conflict of interest

The authors have declared no conflict of interest.…

Acknowledgements

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2021, Heliyon

> *Citation Excerpt :*
>
> …A good example of a plant-based material with exceptional potential for antioxidant capacity intervention is Theobroma cacao L. due to the large group of phenolic compounds reported in cocoa. Although most studies agree that they are flavanols (mainly epicatechin and catechin), as well as flavonols (such as quercetin and some of its derivates), the other compounds in the polyphenols group (such as anthocyanins, flavanones, flavones and phenolic acids) are reported in trace concentrations or not reported in most papers [4, 5, 6, 7]. Figure 1 shows the chemical structure of the main phenolic compounds present in cocoa and its derivatives reported in previous studies.…

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