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Invited Review

Potential for preventive effects of cocoa and cocoa polyphenols in cancer

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ABSTRACT

Prevention of cancer through the diet is receiving increasing interest, and cocoa because of its polyphenolic compounds has become an important potential chemopreventive and therapeutic natural agent. Cocoa and its main polyphenols have been reported to interfere at the initiation, promotion and progression of cancer. Cocoa flavonoids have been demonstrated to influence several important biological functions *in vitro* and *in vivo* by their free radical scavenging ability or through the regulation of signal transduction pathways to stimulate apoptosis and to inhibit inflammation, cellular proliferation, apoptosis, angiogenesis and metastasis. Nevertheless, these molecular mechanisms of action are not completely characterized and many features remain to be elucidated. The aim of this review is to provide insights into the molecular basis of the potential chemopreventive activity of cocoa and its polyphenolic components by summarizing cell culture and animal models studies, as well as interventional and epidemiological studies on humans.

Contents

Abbreviations: AhR, aryl hydrocarbon receptor; AKT/PKB, protein kinase B; AOM, azoxymethane; AP, Acticoa power; AP-1, activator protein-1; ARE, antioxidant response element; CDK, cyclins-dpendent kinase; CLPr, cacao liquor proanthocyanidins; COX-2, cyclooxygenase-2; CYP, cytochrome P450; DEN, diethylnitrosamine; EC, (−)-epicatechin; DMBDD, 2,2'-dihydroxy-di-n-propylnitrosamine; DOC, deoxycholic; ERK, extracellular regulated kinase; DMBA, dimethylbenz[a]anthracene; FAK, focal adhesion kinase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GST, glutathione-S-tranferases; IκB, inhibitor of κB; HUVEC, human endothelial cell; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associating protein-1; LPS, lipopolysaccharide; MAPKs, mitogen-activated protein kinase; MEK, mitogen activated protein kinase kinase; MNU, N-methylnitrosourea; NF-κB, nuclear factor kappa B; Nrf2, nuclear-factor-E2-related factor 2; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; PhIP, 1-methyl-6-phenylimidazo [4,5-b]-pyridine; PI3K, PI-3-kinase, phosphatidylinositol-3-kinase; PKC, protein kinase C; PMA, phorbol 12-myristate 13-acetate; PB2, procyanidin B2; ROS, reactive oxygen species; SOD, superoxide dismutase; *t*-BOOH, *tert*-butylhydroperoxide; TPA, 12-*O*-tetradecanoylphorbol 13-acetate; TNFα, tumour necrosis factor α; Topo, topoisomerase; VEGF, vascular endothelial growth factor.

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1. Introduction

Carcinogenesis is generally a slow process and often takes decades from tumor initiation to diagnosis, offering a considerable time frame for chemopreventive approaches. Chemoprevention is defined as the use of specific natural (dietary) or synthetic agents to prevent, delay, or slow the carcinogenic process (Kelloff et al., 2006). Accumulating epidemiological and experimental studies suggest that a high consumption of fruits and vegetables and the intake of certain non-nutrients that are present in foods reduce the risk of different cancers (Ramos, 2008; Surh, 2003). Therefore, the identification of dietary components as potential cancer chemopreventive agents in the form of functional foods or nutraceuticals has become an essential subject for study in current research. This is the case for polyphenols, natural dietary compounds present in fruits and vegetables, which have attracted a great deal of interest because of their potential ability to act as highly effective chemopreventive agents (Ramos, 2008). In addition, the low toxicity and the very few adverse side effects linked to polyphenols consumption give them potential advantages.

Cocoa, the dried and fermented seeds derived from *Theobroma cacao*, has been consumed since 1100 B.C. by ancient civilizations such as the Mayans and Aztecs (Hurst et al., 2002). In the 16th century cocoa was introduced into Europe by Hernan Cortes and, three centuries later, Conrad van Houten developed cocoa powder as we know it today (Dillinger et al., 2000; Rössner, 1997). Cocoa powder is a rich source of fiber (26–40%), proteins (15–20%), carbohydrates (about 15%) and lipids (10–24%) and it contains minerals and vitamins (Ramiro-Puig and Castell, 2009). Out of more than 200 compounds found in the cocoa bean that are thought to be beneficial for the human body, research is mainly focused on polyphenols, particularly the flavanols, that are so abundant in this ancient plant (Visioli et al., 2009). Cocoa has the highest flavanol content of all foods on a weight basis and is a significant contributor to the total dietary intake of flavonoids (Lee et al., 2003; Rusconi and Conti, 2010; Vinson et al., 1999). Principally, cocoa contains high amounts of flavonoids (−)-epicatechin (EC), (+)-catechin and their dimers procyanidins B2 (PB2) and B1, although other polyphenols such as quercetin, isoquercitrin (quercetin 3-O-glucoside), quercetin 3-O-arabinose, hyperoside (quercetin 3-O-galactoside), naringenin, luteolin and apigenin have also been found in minor quantities (Sánchez-Rabaneda et al., 2003).

Cocoa is a rich source of antioxidants; in a study that measured the total concentration of redox compounds in 1113 different foods, of the 50 foods with the highest antioxidant capacity, 5 were cocoa based (Halvorsen et al., 2006). Besides, cocoa and derivatives are widely consumed worldwide due to the highly attractive organoleptic characteristics. Indeed, cocoa products constitute a larger proportion of the diet of many individuals than green tea, wine, or soy beans (Arts et al., 2001; Tabernero et al., 2006). The mean intake of catechins and procyanidins estimated for USA is higher than the estimated intake of other flavonoids (Gu et al., 2004). Chocolate consumption contributed 2–5 mg of daily catechin intake out of an estimated total of 50 mg per day in a report from the Netherlands (Arts et al., 2001). For the Spanish diet, it was estimated that cocoa products account for 10% of the total antioxidant capacity of dietary intake (Tabernero et al., 2006).

Health effects derived from cocoa flavonoids depend on their bioavailability (absorption, distribution, metabolism, and elimination), a factor which is also influenced by their chemical structure (Manach et al., 2005). In this regard, different studies have shown the absorption of catechin, EC and dimeric procyanidins after the intake of different cocoa by-products by animals and humans (Lamuela-Raventós et al., 2005; Urpi-Sarda et al., 2009). In particular, monomeric flavonoids are absorbed in the small intestine and they and their metabolites (e.g., methylated, sulfated, and glucuronidated compounds), which could also be bioactive, are rapidly detected in plasma at concentrations in the range of nM to μM (Baba et al., 2000; Holt et al., 2002; Roura et al., 2005; Uhlenhut and Högger, 2012) and urine (Tsang et al., 2005). Accordingly, absorbed flavonoids are widely distributed and can be detected in lymphoid organs, including the thymus, spleen and mesenteric lymphoid nodes, as well as in the liver and testes at different concentrations (Urpi-Sarda et al., 2010). In contrast, procyanidins (dimers and trimers) and large proanthocyanidins appear to be 10- to 100-fold less absorbed (Manach et al., 2005; Serra et al., 2010); therefore, their beneficial effects could be restricted to the gastrointestinal tract where they may have an important local function (Ramiro-Puig and Castell, 2009). In addition, oligomers and polymers of flavanols that are not absorbed through the gut barrier could be metabolized by the intestinal microbiota into various phenolic acids of low molecular weight, which are more bioavailable, and might be well absorbed through the colon (Urpi-Sarda et al., 2009, 2010). Interestingly, recent findings have demonstrated that some of these microbial metabolites derived from cocoa consumption also possess biological properties (Monagas et al., 2010).

The present review will focus on the molecular basis of the potential chemopreventive activity of cocoa and their polyphenolic components. Firstly, this paper summarizes recent *in vitro* studies which have evaluated the potential anti-carcinogenic properties of cocoa and their components and the molecular mechanism involved. Although *in vitro* studies will provide a hint to potential cancer preventive effects *in vivo,* chemopreventive efficacy of natural products can only be demonstrated in animal models or human intervention studies. Therefore, in the second part, investigations on the effect of cocoa in various animal models of carcinogenesis are also presented. Finally, this review briefly describes the current evidence on the link between cocoa and cancer occurrence, based on interventional and epidemiological studies on humans.

2. Studies in cell culture

Cell culture studies constitute a useful tool to elucidate the molecular mechanisms of action of cocoa extracts and its