Journal of Nutrition & Food Sciences
ISSN: 2155-9600

Ranneh et al., J Nutr Food Sci 2013, 3:2
DOI: 10.4172/2155-9600.1000193

Review Article Open Access

The Protective Effect of Cocoa (*Theobroma cacao L.*) in Colon Cancer

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Abstract

Colon cancer is considered one of the primary causes of death-related cancer in Western universe. Although it is recommended in most of advanced cases of this disease, cytotoxic chemotherapeutic agents are relatively become ineffectual. Increasing the dietary intake of fruits and vegetables in order to reduce this disease is thought to be a viable and alternative path. Polyphenols are commonly found in cocoa beans and cocoa products. One potential strategy to reduce inflammation and oxidative stress is consumption of polyphenol-rich foods like cocoa or their by products, which have anti-inflammatory effects. Based on those properties, there is a promising scenario on the therapeutic contribution of cocoa on colon cancer. Very currently, few studies have examined the anti-carcinogenic role of cocoa. Therefore, the present review critically evaluates cocoa's effect in colon cancer as conducted, both *in-vivo* and *in-vitro*.

Keywords: Colon cancer; Cocoa; Polyphenols; Apoptosis; Prevention

Introduction

Cancerous colon is considered as a universal problem, with about occurrence of 1 million conditions and more than 500,000 of mortality per year [1]. This increased number in the next few decades is due to the developing of lifestyle and population over the world. About 150,000 diagnostic cases of colonic tumor are annually found in the United States, and the recent colorectal cancer cases that is well-estimated in 2010 will be 72.090 and 70.480 for males and females, respectively; at the same time, the mortality will get 26.580 and 24.790 [2]. The individuals who are over 50 are forming most of the cases. Even though the responsibility of colorectal cancer in creating about 52,000 deaths per year has been well-expected, it is strongly curable if diagnosed early, which reflects the importance of cancer screening in individual. In addition to USA, New Zealand, Canada, Australia and parts of Europe have a highest rate in colon cancer incidence [1,3-5] although several significant programs against colon cancer is found there. People with colonic tumor are still looking for another therapy, despite of the diversity of treatment in this disease, such as chemical drugs and radiation. Practically, a lot of international studies have suggested that the quest of using naturally complementary therapy is made by well-educated, high socioeconomic status and young persons, and most likely, to be females. To explain more, dietary ploy phenolic supplementation has been used as a complementary therapeutic agent. The conclusion of several preclinical studies is that dietary polyphenols can exert a desirable result, when offered in large amount [6].

Cocoa had been considered from long time, as a food-rich polyphenols. Flavonoids and phenolic acids are mainly forming the type of polyphenols. In cocoa and chocolate, the monomeric modules of the main flavonoids are flavan-3-ols, epicatechin and catechin, and polymers of these are proanthocynidins, which are called procyanidins [7]. As mentioned by Dreosti [8], the rate of total polyphenols in raw cocoa is reached to be 60% in monomeric (epicatechin and catechin) and oligomeric (procynidins) forms. Based on the method used in producing cocoa powder, the rate of flavonoids can formalize 10% in dried weight basis [9]. The chemical structure of polyphenols can determine the bioavailability in humans, with changeable rate inter-individual [10].

Cocoa and its compounds have drawn recently a lot of attention because of its contributory role as a chemopreventive agent. In several studies, the highly anti-oxidative effect of cocoa has been demonstrated, comparing with other products, a special characteristic related to its high content of procynidins [11-13], which in turn prevent the oxidation of cholesterol-LDL [14]. In experimental trails, cocoa phenolics have presented several beneficial effects against platelet aggregation [15], high blood pressure [16], atherosclerosis [17], hyperglycemia and hyperchoelstrolemia [18,19], inflammation [20], hepatocarcinogenesis [21], DNA damage and clastogenic effect [22]. The purpose of this review is to shed the light on promising results of cocoa's role in colon cancer, based on what have been conducted in this respect.

In vivo Studies: Suppressing the Formation of Aberrant Crypt Foci

Rodríguez-Ramiro et al. [23] have examined effect of cocoa rich diet on early levels of bowl tumorgenesis for the first time *in vivo.* 120 g/kg of cocoa powder to AIN-93G was given to rats during 8 weeks. Cocoa rich diet was modified to supplement 1 g of polyphenols per kg of diet. Through using Azoxymethane for inducing colon cancer, aberrant crypt foci (ACF) were used to detect the early stage of bowl carcinogenesis. The results have shown a reduction, not only in formation of aberrant crypt foci, but also crypt multiplicity in rats-induced colon cancer fed with diet rich in cocoa. Considered as markers of oxidative stress, carbonyl and malondialdehyde groups (protein and lipid oxidation marker, respectively) were reduced significantly in distal bowl of AOM-injected rat treated with cocoa-rich diet, comparing with control group. In addition, glutathione levels and the activity of glutathione peroxidase, glutathione reductase and glutathione S-transferase were preserved in colonic tissue of rat-fed diet rich in cocoa, comparing with the control group. The antiproliferative effect of cocoa-rich diet was demonstrated by reducing the expression of extracellular regulated kinases, protein kinase B and cycline D1; at the same time, pro-apoptosis effects were evidenced by reducing levels of Bcl-xL and increasing levels of Bax, as well as caspase 3 activity.

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Received February 06, 2013; **Accepted** February 27, 2013; **Published** March 07, 2013

Citation: Ranneh Y, Ali F, Esa NM (2013) The Protective Effect of Cocoa (*Theobroma cacao L.*) in Colon Cancer. J Nutr Food Sci 3: 193. doi:10.4172/2155-9600.1000193

The previous study was the first study to examine the effect of cocoa powder in early colon carcinogenesis. Because ACF is not the only reliable cancerous biomarker, several early precancerous lesions have not been detected (namely MDF; Mucin Depleted Foci, BCAC; Beta-Catenin-Accumulated Crypts, Flat-ACF), which could be better biomarkers than ACF [24]. In the same manner, carbonyl group do not form the only marker of protein oxidation, where there are others group, namely protein hydroperoxide (P-OOH), advanced protein products oxidation (AOPP), 4-mitrotyrosine. Even though MDA was used as a marker for lipid peroxidation, Trevisan et al. [25] mentioned that other sources could produce MDA. Therefore, measuring MDA can be a generic marker of oxidative stress, instead of private indicator of lipid peroxidation [26]. In the other hand, perhaps the most forceful stimulator of apoptosis is TNF, which is absent in the previous research, satisfied with detecting two members of Bcl-2 and one type of effectors caspase.

In vitro Studies

Various studies have been conducted on caco-2 cell line, which is considered as human epithelial colonic adenocarcinoma cells [27]. Indeed, one study only has experienced the direct effect of cocoa on the bioactivity of caco-2 cell line.

Stéphanie and his colleagues have investigated the effect of cocoa procyanidin and flavanols on the growth of cancer cells in cacao-2 cell line. The cocoa powder extract have shown no arrest on the growth of cells, meanwhile crud procyanidin and procynidin-enriched extract have an inhibitory effect, at concentration of 50 µg/mL, about 25% and 75%,respectively. The obstructed effect of the extract on the G2/M phase of the cell cycle has been noticed, leading to non-apoptotic cell death. The same extract also has decreased significantly, the activities of ornithine decarboxylase and S-adenosylmethionine decarboxylase, which are two clef enzymes for polyamine biosynthesis. Therefore, the intracellular pool of polyamine has been reduced. This could indicate to be an important target, in terms of the anti-proliferative effect of cocoa extract, rich in procyanidin.

Furthermore, Rodríguez-Ramiro et al. [28] have examined the potential inhibition of cocoa extract on the pro-inflammatory mediators on TNF-α-sensitized Caco-2 cells. IL-8, cyclo-oxygenase-2 and inducible nitric-oxide synthase were effectively down-regulated, by inhibiting NF-kB translocation and JNK phosphorylation.

In an attempt to show the indirectly anti-inflammatory and anticarcinogenic effect of cocoa's oligomers, by protecting the intestinal epithlum barrier from toxic substances, a study was conducted by Erlejman et al. [29], to experience the cytoprotective effect of isolated-procynidine cocoa on Caco2-cell line, a standard design of cancerous intestinal cells. Considered as a kind of bile acids and pathogenic factor, Deoxycholic can support the tumorogenesis of intestine. In this study, it has been proven that the protective effect of hexameric procynidine on Caco2-cell from DOC-induced membrane damage and oxidative production has been cleared. In this sense, there was no detection for other compounds-related to carcinogenic effect, which arise us to ask, is protecting cell membrane from DOC enough to inhibit any inflammatory or carcinogenic attempt in the human body cells. On the other hand, studying the direct effect of procynidine on colon cancer cell line growth, such as cocoa 2 cells and HT-29, is considerably more effective.

Conclusion

In order to determine potential health benefits of cocoa polyphenols, large scale, long term, randomized, placebo controlled studies with a cross ideal design, as well as prospective studies, are warranted**.** It is, therefore, suggested that before drawing conclusions, confirmation by further epidemiological and experimental studies on cocoa polyphenols is needed. Furthermore, the inhibitory effect of phenolic compounds-derived cocoa in colon cancer development may be through cancer regulating genes, such as oncogenes, tumor suppressor genes, resulting in altered cellular processes, namely (apoptosis, cell cycle, inflammation, angiogenesis, invasion and metastasis [30]. Studies in human Caco2 cells [31], have been reported that the changes in the expression of signal transducer and activator of transcription 1 (STAT1), mitogen-activated protein kinase kinase 1 (MAPKK1), and ferritin heavy polypeptide 1(FTH1) genes, which are involved in the cellular response to oxidative stress, are in agreement with the antioxidant properties of cocoa flavonoids. In addition, the changes in the expression of topoisomerase 1 suggest novel mechanisms of action of flavonoids at the molecular level. More specifically, study on the effects of cocoa polyphenols on the expression of the hereditary colon cancer genes, such as familial adenomatous polyposis (FAP) and adenomatous polyposis coli (APC), is also needed in the future.

Thus, extensive studies at the molecular level are still required to reveal the efficiency of the anti-carcinogenic activity of polyphenols–rich cocoa products, as well as provide us novel information about the mechanisms of action of cocoa polyphenols in colorectal cancer. However, it should be considered that the products used in controlled studies, often contain much higher polyphenol contents than most of the commercial products [32]; as much as large amount of polyphenols may be lost due cocoa processing [33]. Thus, it needs to be established whether the consumption of products with lower polyphenol content are associated with any health benefits in humans, especially on colon [34,35]. Finally the food industry is encouraged to label the polyphenolic content on their cocoa derived products.

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