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Review

Cocoa-induced (*Theobroma cacao*) effects on cardiovascular system: HDL modulation pathwaysHeitor O. Santos ^{a,*}, Rodrigo C.O. Macedo ^b^a School of Medicine, Federal University of Uberlandia (UFU), Uberlandia, Minas Gerais, Brazil^b University of Santa Cruz do Sul (UNISC), Santa Cruz do Sul, Brazil

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1. Introduction

High-density lipoprotein (HDL) came to center of cardiovascular attention, whose quality and quantity of this molecule are substantial to heart health [1–3]. Several evidences demonstrate increased serum levels of HDL caused by cocoa (*Theobroma cacao*) consumption [4–8]. Also, better modulation of plasma lipid markers mainly by reducing oxidative damage is shown in recent data [9].

Cocoa is a polyphenol-rich fruit, which provides benefits to vascular functions through several pathways. On the one hand, the antihypertensive effect is already well-understood [10–15] but on the other hand, the lipid profile improvement is controversial. The antioxidant components obtained from cocoa is apparently the main substances responsible for the lipid profile modulation [12]. However, the mechanism of action and the physiological impacts of the cocoa intake and its derivatives on HDL modulation require a greater establishment.

Although nutrition is an encompassed topic in recent guidelines showing clinical conducts into reduction of HDL levels [16,17], investigations concerning the food effects on HDL metabolism improvement are necessary. Hence, the aim of the present review was to discuss the impacts of cocoa intake and its derivatives on blood pressure (BP), cardiovascular comorbidities and the relationship with serum HDL levels and the modulation of this lipoprotein in humans.

2. Nutritional facts of cocoa

A serving of 100 g of cocoa powder contains considerable amounts of macronutrients, dietary fibers, magnesium, potassium and caffeine, but the consumption of this quantity is not feasible. Eighty percent of the cocoa fibers are insoluble, while the remainder are soluble [18]. Cocoa has a higher proportion of saturated fat, representing 62% of the total fat of the fruit, whereas monounsaturated and polyunsaturated fats correspond 33% and 5%, respectively [5,19,20]. Cocoa has low density, since one tablespoon of cocoa powder is equivalent to 5 g, and therefore 100 g of cocoa powder intake is unreasonable. Nutritional facts of considerable and tolerable cocoa powder amount are showed in Table 1, whose physiological benefits are known.

The Recommended Dietary Allowances (RDA) of magnesium for men and women over 30 years are equivalents to 420 and 320 mg, respectively [21]. The intake of 40 g of cocoa powder per day provides 200 mg of magnesium. In contrast, one tablespoon of cocoa powder provides only 25 mg of magnesium. Therefore, the amount of magnesium in cocoa does not appear to be the responsible for improving on hypertension and others cardiovascular diseases. Thus macronutrients and minerals of cocoa are not the main components for its benefits. Rather, polyphenols are the most likely substances of cocoa which improve cardiovascular health [4,22–24].

3. Effects of cocoa intake on blood pressure and lipid profile

Several meta-analysis showed that cocoa intake and its derivatives may decrease systolic and diastolic BP [4,11,22–24,26]. The main substances of cocoa for improving BP are the polyphenols, particularly those of the flavonoids class [14].

Polyphenol amounts of cocoa selected by meta-analysis and its impacts on BP decrease are shown in Table 2. These studies included cocoa derivatives as dark chocolate, cocoa powder and milk with cocoa. Polyphenol capsules extracted from cocoa was also selected [4,11,22–24,26].

The majority of meta-analysis included normotensive individuals [4,11,22–24,26]. The recent meta-analysis of Ried et al. (2017) showed a mean reduction of ~1.8 mmHg on systolic and

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Table 1

– Nutritional facts of cocoa and its derivatives.

Nutrients	Cocoa powder (40 g)	Dark chocolate, 70–85% of cocoa (40 g)	Milk chocolate (40 g)	White chocolate (40 g)
Energy (kcal)	177.3	246	215.2	219.2
Total fats (g)	5.5	17.7	12	12.8
Saturated fats (g)	3.2	9.8	7.6	7.6
Monounsaturated fats (g)	1.8	5.2	2.8	3.6
Polyunsaturated fats (g)	0.2	0.5	0.6	0.5
Carbohydrates (g)	24	18.5	23.6	23.6
Sugar (g)	0	9.7	20.8	23.6
Total fibers (g)	8	4.4	1.36	0.7
Protein (g)	8	3.2	3.20	2.4
Caffeine (mg)	92	32	17.2	0
Magnesium (mg)	199.6	92	25.2	4.8
Potassium (mg)	609.6	288.8	148.8	114.2

Adapted from the USDA Food Composition Database [25].

Table 2

– Summary results of meta-analysis studies evaluating the effects of cocoa derivatives intake on blood pressure.

Authors (year)	Quantity of studies	Quantity of analyzed individuals	Amount of polyphenols or its derivatives (mg/d)	Duration (weeks)	Mean difference of SBP (mmHg)	Mean difference of DBP (mmHg)
Ried et al. (2017) [22]	40	1804	30 to 1218 of flavonols; mean of 670	2 to 18	–1.76	–1.76
Hooper et al. (2012) [4]	42	1297	~50 to 100 of epicatechin	0 to 18	–1.60	–1.50 ^a
Ried et al. (2012) [23]	20	856	30 to 1080 of flavonols; mean of 545.5	2 to 18	–2.77	–2.20
Ried et al. (2010) [24]	15	578	30 to 1000 of flavonols	2 to 18	–3.16	–2.02
Desch et al., 2010 [11]	10	297	6.8 to 902 of flavonols	2 to 18	–4.52	–2.5
Taubert et al., 2007 [26]	5	97	213 to 500 of polyphenols	2	–4.7	–2.8

^a not statistically significant; DBP, diastolic blood pressure; SBP, systolic blood pressure.

diastolic BP in cocoa products consumption. When the subgroup of hypertensive individuals was analyzed, the cocoa intake and its derivatives exhibited greater potential, reducing mean systolic BP in 4 mmHg [22].

Regarding meta-analysis which the impact of cocoa intake and derivatives on the lipid profile were evaluated, Hooper et al. (2012) showed cocoa epicatechins intake increased HDL levels by 1.2 mg/dL and decreased LDL levels by 2.7 mg/dL, whereas there was no improvement in serum cholesterol and triglycerides [4]. Another meta-analysis showed a reduction of LDL and serum total cholesterol levels in 5.9 and 6.2 mg/dL, respectively, but HDL and triglycerides levels did not change [27].

4. Relationship between cocoa intake and HDL

HDL raising effects of cocoa intake is still controversial. Two meta-analysis showed consumption of cocoa powder and its derivatives significantly increased HDL in about 2 mg/dL [4,6], while two others showed no difference [27,28]. Among the meta-analysis that demonstrated increase of HDL levels, one selected 24 randomized controlled trials, totaling 1106 participants, in whom HDL increased by 1.9 mg/dL after two weeks of cocoa powder intake and its derivatives [6]. The other meta-analysis also involved randomized studies, which screened 42 trials and resulted in 1297 individuals undergoing cocoa intake up to 18 weeks. HDL levels increased only in groups that cocoa and derivatives intake for more than three weeks, corresponding to a mean raise of 1.8 mg/dL [4].

Khan et al. (2012) noticed a serum HDL increase of 2.8 mg/dL after 40 g per day of cocoa powder added to 500 mL of skimmed milk during four weeks in high-cardiovascular risk subjects. Similarly, 42 elderly overweight (19 men and 23 women) were randomized into two groups: 1) intervention: received two sachets of 20 g of soluble cocoa powder with 250 mL of skimmed milk twice daily, 2) control: intake only of skimmed milk. The group that consumed cocoa powder increases HDL in ~3 mg/dL ($p = 0.008$ compared milk plus cocoa group to milk group), while the group that did not intake cocoa showed no increase [5].

Recent study found that mean HDL levels increased by 2 mg/dL in 92 patients with human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS) after 15 days consuming 64 g of dark chocolate containing 36 g of cocoa [7]. Likewise, several intervention studies showed intake of cocoa powder and dark chocolate during 2–4 weeks may increase serum HDL levels between 2 and 7 mg/dL [5,7,8].

The highest increase of HDL levels through cocoa intake and its derivatives was 5 and 7 mg/dL. In a 3 weeks protocol, 45 healthy individuals (12 men and 33 women) were divided in 3 groups [1]: 75 g per day of dark chocolate [2]; enriched dark chocolate with cocoa polyphenols (about twice as many catechins as traditional dark chocolate) [3]; white chocolate. HDL levels increased 5 mg/dL dark chocolate group and 7 mg/dL in enriched dark chocolate with cocoa polyphenols group. On the other hand, HDL levels did not increase in the group that consumed white chocolate [8].

Cocoa powder intake is also capable of increasing postprandial HDL levels, and this effect was probably caused by the antioxidant action of polyphenols. In a randomized double blind, crossover trial, involving type 2 diabetics, there was an increase of postprandial HDL levels about 1.5 mg/dL compared to placebo drink. The individuals consumed 20 g of cocoa powder diluted in warm water with a high-calorie, high-fat breakfast (766 kcal and 50 g of total fats, of these 25 g of saturated). The cacao beverage contained 960 mg of polyphenols and 480 mg of flavanols, whereas the placebo contained little amounts of these substances [29].

5. Pathways of cocoa-induced HDL improvement

Apolipoprotein A-1 (apoA-1) is the major apolipoprotein of the HDL composition [30,31]. The effects of cocoa intake on serum apoA-1 levels are paradoxical. In vitro analysis of cocoa polyphenols demonstrate increased levels of apoA-1 in intestinal and hepatic tissue [32,33]. Souza et al. suggested that phenolic compounds of cocoa may increase HDL levels by increasing expression, synthesis, and secretion of apoA-1. However, in their new study, cocoa intake did not increase serum apoA-1 levels [7]. Likewise, Khan et al., who

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