Acta Scientific NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 7 Issue 3 March 2023

Review Article

Cocoa and Hepatic Health

Nidhi Kaku*

Clinical Nutritionist, Registered Dietitian, Certified Diabetes Educator, Mumbai, India

***Corresponding Author:** Nidhi Kaku, Clinical Nutritionist, Registered Dietitian, Certified Diabetes Educator, Mumbai, India.

DOI: 10.31080/ASNH.2023.07.1205

Received: February 06, 2023

Published: February 20, 2023

Abstract

Cocoa, in the form of chocolate is one of the most known and universally relished product. Cocoa is a rich source of phenolic compounds, especially flavanols. The consumption of cocoa flavonoids has multiple health benefits by contributing to preventing or decreasing the risk of chronic diseases like certain forms of cancer, cardiovascular diseases, immune conditions, neurological conditions, diabetes, obesity and ageing etc. This review is designed based on the recent researches, highlighting the potential health benefits of cocoa flavanols related to the different liver conditions along with the molecular mechanisms involved. This paper reflects the antioxidant, anti-carcinogenic, lipolytic and genetic-modulating properties of cocoa at the hepatic level. Cocoa, thus, has been linked to improving the hepatic health.

Keywords: Cocoa; Cocoa Flavanols; Hepatic Health; Dark Chocolate

Abbreviations

AKT: Protein Kinase B; ALT: Alanine Transaminase; Bax: Bcl Associated X Protein; Bcl-xl: B- Cell Lymphoma- Extra Large; C57BL/6J mouse: Multipurpose Model that can be used for Research into Physiology, Immunology, Safety and Efficacy, Oncology and Genetics, as Well as Mouse Model Creation; CAT: Catalase; cAMP: Cyclic Adenosine Monophosphate; CCl4: Carbon Tetrachloride; Cho: Total-Cholesterol; COX: Cyclooxygenase; DEN: Diethylnitrosamine; DNA: Deoxyribonucleic Acid; EC: Epicatechin; ERK: Extracellular Signal-Regulated Kinase; FOX03a: Forkhead Box 03a; GPx: Glutathione Peroxidase; GR: Glutathione Reductase; GSH: Gamma-L-Glutamyl-L-Cysteinyl-Glycine Or Gutathione; GST: Glutathione S- Transferase; HDL-Cho: High Density Lipoprotein Cholesterol; HF: High Fat; iNOS: Inducible Nitric Oxide Synthase; LDL-Cho: Low Density Lipoprotein Cholesterol; MEK1: MAP Kinase/ERK Kinase; MDA: Malondialdehyde; MKK4: MAP Kinase Kinase 4; mtDNA: Mitochondrial Deoxyribonucleic Acid; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; NAFLD: Non Alcoholic Fatty Liver Disease; NF-κb: Nuclear Factor-Kappab; NOS: Nitric Oxidase Synthase; NOX: Nitrogen Oxides; Nrf1: Nuclear Respiratory Factor 1; Nrf2: Nuclear Factor Erythroid 2 Related Factor 2; PB1: Procyanidins B1; PB2: Procyanidins B2; PGC1α: Peroxisome Proliferator-Activator Receptor-Gamma Coactivator 1 Alpha; PI3K: Phosphoinositide-3-Kinase; PKB: Protein Kinase B; p-(Ser)-IRS-1: p- (Somatosensory Evoked Response)-Insulin Receptor Substrate-1; Pparg: Peroxisome Proliferator-Activator Receptor-Gamma; PPAR: Peroxisome Proliferator Activated Receptors; SIRT3: Mictochondrial Sirtuin 3; SOD: Superoxide Dismutase; TAG: Triacylglycerol; Uqcrc1: Ubiquinol- Cytochrome Reductase Core Protein 1

Introduction

Cocoa powder, derived Theobroma cacao, is commonly consumed in chocolate [21].

Cocoa is a globally consumed among people and is a rich source of flavanols. These Flavanols (phenolic compounds) have been associated with multiple health benefits like reducing the risk of cancer, diabetes, obesity, neurodegenerative diseases, cardiovascular diseases, aging and metabolic disorder [1-9].

But the total polyphenol content varies depending on the origin and the processing of cacao beans for cocoa production. It is found that the alkalinization treatment performed during the cocoa processing, leads to 60% loss of the total flavonoid content [15].

Majorly, monomeric flavanols such as epicatechin (EC), catechin, their dimers procyanidins B2 (PB2) and B1, and polymeric flavanols form the polyphenolic content in the cocoa. Other polyphenols which are present in the minor amounts are luteolin, apigenin, naringenin, quercetin, isoquercetin (quercetin 3-O-glucoside), hyperoside (quercetin 3-O-galactoside), quercetin 3-O-arabinose, etc. Also, methylxanthines, mainly theobromine, and caffeine are also found in small amounts [3,16].

Multiple pathways have been identified in the preventive role of cocoa in different diseases. But this review describes and discusses the potential health benefits of cocoa flavanols in the hepatic health.

Antioxidant

Free radical damage can be prevented by cocoa and its flavanols by regulating catalase (CAT), nitric oxidase synthase (NOS), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), etc. Also, it is known to be involved in the regulation of phase I drug metabolizing enzymes (cytochrome P450) and/or phase II conjugating-enzymes (glucuronidation, sulfation, acetylation, methylation and conjugation), along with redoxsensitive transcription factors [nuclear factor erythroid 2 related factor 2 (Nrf2), nuclear factorkappaB (NF-κB), etc.], thus, changing the metabolism and the impact of damaging substances [16]. The low bioavailability and extensive metabolism of cocoa and its flavanols makes the antioxidant properties (free radical-scavenging and metal-chelating) limited in humans [16,25,26].

Anti-carcinogenic

A study was conducted by Granado-Serrano., *et al*. in the year 2009, where, rats were fed with a cocoa-supplemented diet (16% Natural Forastero cocoa powder, with 755 mg total flavanols/100g cocoa powder) for 6 weeks. The rats were simultaneously injected with (DEN) (liver toxic), to cause cancer of the liver. The results of their study showed DEN related postnecrotic proliferation was attenuated and there was also an improvement in the hepatic GSH levels, GPx, GST and CAT activities [28].

Procyanidin B2 (PB2), which is found in cocoa powder, was administered in animals (100 mg/kg) for 7 days, by Yang., *et al*. (2015), and they found that the liver damage caused by carbon tetrachloride (CCl4), was prevented by PB2. PB2 was found to reduce malondialdehyde (MDA), cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS) levels and blocked NF-κB translocation. Their findings also supported that PB2 improved the liver activities of SOD, CAT and GPx, in the animals [30].

Another study showed a similar results where a Madagascarian cocoa cake (34.5 mg/kg) was used. This cake constituted of 50.4 mg total flavanols/g of dry matter of which 17.38 mg/100g dry matter were (-)-epicatechin (EC). This cake along with EC (2.51 mg/kg) was administered twice weekly for 2 weeks and was found to be hepato-protective against carbon tetrachloride (CCl4), which was administered at 1 mL/kg body weight, twice a week. But the cocoa extract was found to enhance the CAT activity (which was found to be decreased by CCl-4 administration) far better in comparison to EC [27].

When 15 mg/kg body weight of EC was administered in the mice for 3 days, it showed a protective action against g-irradiation-induced damage [29]. EC also prevented the rise of lipid peroxidation and NF-κB translocation [16].

Thus multiple researches have shown that cocoa may exert an anti-carcinogenic by preventing the free radical DNA damage or that caused by carcinogenic agents. This preventive role of cocoa is performed via direct radical scavenging, metal-chelating effects, modulation of the enzymes and changes in the pro-carcinogenic metabolism to promote its inactivation and/or its elimination [34]. Also, it modulates molecular signals linked to cell cycle, apoptotic and survival/proliferative routes, along with inflammation, angiogenesis and metastasis processes [34]. A study showed that, antimutagenic impact of cocoa is regulated by cytochrome P4501A [35]. Another study showed the G2/M cell cycle arrest and growth inhibition of cancer cells by the use of Procyanidin-enriched cocoa extracts [36].

Research studies conducted by Rodriguez-Ramiro I., *et al*. 2011 and Kim JE., *et al*. 2010, found that cocoa was linked to anti-proliferative properties via 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 signalregulated kinase (ERK)] [37,38]. Cocoa was also found to downregulated the vascular endothelial growth factor by activating nuclear factor-κB and activator protein-1, along with the inhibition of phosphoinositide-3-kinase (PI3K), MEK1 and MKK4 [39]. Higher amounts of Cocoa flavanols may enhance its anticancer properties, in the presence of redox- active metals, by inducing oxidative DNA damage in cancer cells [40]. Also, cocoa may have synergistic effects along with chemotherapy to induce cell death [41].

Thus, these research findings show the preventive role of cocoa flavanols in hepatic cancer.

Lipid metabolism

Cocoa regulates lipid metabolism. The expression of proteins associated with fatty acid and cholesterol synthesis (fatty acid synthase, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, etc.), were found to be downregulated by cocoa. Also, the expression of proteins linked with lipolysis [peroxisome proliferator activated receptors (PPAR) α, β/γ/δ], and fatty acid transporter proteins (fatty acid transporter, apoprotein E) were upregulated with cocoa intake [10-13]. Consumption of cocoa or dark chocolate enhances nitric oxide availability [8], which is associated to lipolysis, glucose and fatty acid oxidations, and blocks the fatty acid synthesis [14].

Two studies have shown that when mice and rats were fed with high fat diet along with cocoa supplementation, their plasma concentrations of adiponectin increased significantly, and hepatic triglyceride content decreased. [31,32]. Natsume., *et al*. (2009), conducted research, wherein, the animals were fed a high cholesterol diet, supplementing one group with polyphenol extract (from cocoa powder), and the other group with a mixture of catechin (0.024%) and epicatechin (0.058%). The results of their study concluded that the plasma cholesterol concentrations were significantly lower and feal cholesterol and total bile acid excretion was significantly higher in the animal group which consumed the polyphenol supplement as compared to the group who consumed the mixture of catechin and epicatechin as well as the control group [33].

A study showed that the diet which included cocoa, were found to protect the liver by improving the antioxidant capacity of liver cells in Zucker Diabetic Obese rats [17]. Cocoa was also found to be associated with improving the hepatic insulin resistance by terminating the raised p-(Ser)-IRS-1 levels and preventing the inactivation of the glycogen synthase pathway [18]. Cocoa was also linked with improving circulating and hepatic lipid profiles (decreased triglycerides, non-esterified fatty acids, total-cholesterol (Cho), and LDL-Cho, and increased HDL-Cho values) [19].

A research study conducted by Loffredo., *et al*. (2016), showed that 40gram of dark chocolate intake, per day, resulted in significant drop of in plasma 8-isoprostane, alanine aminotransferase (ALT), and soluble NADPH oxidase (NOX)2- derivative peptide in human subjects with NAFLD [23]. Another study by Janevski., *et al*. (2011), revealed that dietary supplementation of 125 mg/g cocoa powder for 108 days, reduced hepatic steatosis and inflammation among Sprague-Dawley rats fed with high fat/methionine deficient diet [22]. The underlying mechanisms for these effects were unclear. A research done in 2014 by Gu Y., Yu S. and Lambert JD, among high fat (HF)-fed C57BL/6J mice, showed that plasma ALT levels, relative liver mass, and hepatic triacylglycerol (TAG) levels decreased with the intake of 80 mg/g cocoa powder [21]. The mechanism linked to these effects included drop in systematic inflammation markers and insulin-resistance, but hepatic molecular changes were not explored.

Sun., *et al*., conducted a study in the year 2021. The results of their study showed that mice fed with cocoa-supplemented high fat diet had 28%, 56% and 75% of lower hepatic triglyceride, hepatic lipid peroxides and mtDNA damage levels, respectively, compared to high fat-fed control mice. They also found that there was a 30% and 44% higher hepatic SOD and GPX enzyme activity, respectively, among mice who were fed on cocoa supplemented diet [20].

Genetic modulation

The research conducted on mice by Sun., *et al*. showed that Hepatic mtDNA copy number was 49% more among mice who were fed with cocoa in comparison to the control group. Their study also quoted that they observed a higher hepatic expression of Ndufs8 (39% higher) and Uqcrc1 (58% higher), which encodes for the components of respiratory complex I and complex III, among the cocoa fed mice in comparison to HF-fed control mice. Other genetical research findings revealed that the SIRT3 protein expression was 51% higher in cocoa-treated mice [20]. FOXO3a is transcription factor that regulates antioxidant-enzyme expressions, including SOD2. And FOXO3a transcriptional activity is related to PGC1α through the SIRT3 activity [24], as SIRT3 can indirectly influence cAMP-response element binding protein, which results in increase in the PGC1α expression [20]. Also, expression of Ppargc1, Fox03a, and 233 Nrf1 were 62.4%, 57.9%, and 52.7% higher, respectively, compared to HF-fed control mice [20].

Conclusion

Thus, multiple studies support the potential role of cocoa and its phenolic compounds in modulating the hepatic health positively. And therefore cocoa supplementation may be considered for hepatic conditions.

Bibliography

1. Martín MA and Ramos S. "Health beneficial effects of cocoa phenolic compounds: a mini review". *Current Opinion in Food Science* (2017).

2. Martín MA and Ramos S. "Impact of cocoa flavanols on human health". *Food and Chemical Toxicology* 151 (2021): 112121.

3. Lamuela-Raventós RM., *et al*. "Health effects of cocoa flavonoids". *Food Science and Technology International* 11 (2005): 159-176.

4. Maskarinec G. "Cancer protective properties of cocoa (2009). A review of the epidemiologic evidence". *Nutrition and Cancer* 61 (2009): 573-579.

5. Farhat G., *et al*. "Dark chocolate: an obesity paradox or a culprit for weight gain?" *Phytotherapy Research* 28 (2014): 791-797.

6. Ramos S. "Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways". *Molecular Nutrition and Food Research* 52 (2008): 507-526.

7. Scholey A and Owen L. "Effects of chocolate on cognitive function and mood: A systematic review". *Nutrition Reviews* 71 (2013): 665- 681.

8. Corti R., *et al*. "Cocoa and cardiovascular health". *Circulation* 119 (2009): 1433-1442.

9. Martín MA., *et al*. "Antidiabetic actions of cocoa flavanols". *Molecular Nutrition and Food Research* 60 (2016): 1756-1769.

10. Cordero-Herrera I., *et al*. "Cocoa and cocoa flavanol epicatechin improve hepatic lipid metabolism in *in vivo* and *in vitro* models. Role of PKCζ". *Journal of Functional Foods* (2015): 761-773.

11. Ali F., *et al*. "Transcriptomics expression analysis to unveil the molecular mechanisms underlying the cocoa polyphenol treatment in diet-induced obesity rats". *Genomics* 105 (2015): 23-30.

12. Ali F., *et al*. "Molecular mechanisms underlying the potential antiobesity-related diseases effect of cocoa polyphenols". *Molecular Nutrition and Food Research* 58 (2014): 33-48.

13. In this recent review are provided evidences about the molecular mechanisms of cocoa polyphenols on obesity-associated diseases such as CVD and diabetes that could potentially contribute to explain the beneficial effect of this food (2014).

14. Matsui N., *et al*. "Ingested cocoa can prevent high-fat dietinduced obesity by regulating the expression of genes for fatty acid metabolism". *Nutrition and Cancer* 21 (2005): 594-601.

15. Jobgen WJ., *et al*. "Regulatory role for the arginine-nitric oxide pathway in metabolism of energy substrates". *The Journal of Nutritional Biochemistry* 17 (2006): 571- 588.

16. Andrés-Lacueva C., *et al*. *Journal of Agricultural and Food Chemistry* 56 (2018): 893 3111-3117.

17. Martín MA and Ramos S. "Cocoa polyphenols in oxidative stress: potential health implications". *Journal of Functional Foods* (2016).

18. Cordero-Herrera I., *et al*. "Cocoa intake ameliorates hepatic oxidative stress in young Zucker diabetic fatty rats". *Food Research International* 69 (2015): 194201.

19. Cordero-Herrera I., *et al*. "Cocoa rich diet ameliorates hepatic insulin resistance by modulating insulin signaling and glucose homeostasis in Zucker diabetic fatty rats". *The Journal of Nutritional Biochemistry* 26 (2015): 704-712.

20. Cordero-Herrera I., et al. "Cocoa and cocoa flavanol epicatechin improve hepatic lipid metabolism in *in vivo* and *in vitro* models. Role of PKCζ". *Journal of Functional Foods* (2015): 761-773.

21. Sun M., *et al*. "Dietary cocoa ameliorates nonalcoholic fatty liver disease and increases markers of antioxidant response and mitochondrial biogenesis in high fat-fed mice". *The Journal of Nutritional Biochemistry* 92 (2021): 108618.

22. Gu Y., *et al*. "Dietary cocoa ameliorates obesity-related inflammation in high fat fed mice". *European Journal of Nutrition* 53 (2014): 149-158

23. Janevski M., *et al*. "The effect of cocoa supplementation on hepatic steatosis, reactive oxygen species and LFABP in a rat model of NASH". *Comparative Hepatology* 10 (2011): 10.

24. Loffredo L., *et al*. "Effects of dark chocolate on NOX-2-generated oxidative stress in patients with nonalcoholic steatohepatitis". *Alimentary Pharmacology and Therapeutics* 44 (2016): 279-286.

25. Kong X., *et al*. "Sirtuin 3, a new target of PGC496 1alpha, plays an important role in the suppression of ROS and mitochondrial biogenesis". *497 PloS One* 5 (2010): e11707.

26. Fraga CG. "Plant polyphenols: how to translate their in vitro antioxidant actions to in vivo conditions". *IUBMB Life* 59 (2007): 308-315.

27. Hollman PCH., *et al*. "The biological relevance of direct antioxidant effects of polyphenols for cardiovascular health in humans is not established". *Journal of Nutrition* 141 (2011): 989S1009S.

28. Giacometti J., *et al*. "Cocoa polyphenols exhibit antioxidant, antiinflammatory, anticancerogenic, and antinecrotic activity in carbon tetrachlorideintoxicated mice". *Journal of Functional Foods* 23 (2016): 177-187.

29. Granado-Serrano A., *et al*. "Time course regulation of survival pathways by epicatechin on HepG2 cells". *Journal of Nutritional Biochemistry* 20 (2009): 115-124.

30. Sinha M., *et al*. "Epicatechin ameliorates ionising radiation-induced oxidative stress in mouse liver". *Free Radical Research* 46 (2012): 842-849.

31. Yang BY., *et al*. "Protective effect of procyanidin B2 against CCl4-induced acute liver injury in mice". *Molecules* 20 (2015): 1225012265.

32. Catrysse L and Van Loo G. "Inflammation and the Metabolic Syndrome: The Tissue-Specific Functions of NF-κB. Trends". *Cell Biology* 27 (2017): 417-429.

33. Rabadan-Chávez G., *et al*. "Cocoa powder, cocoa extract and epicatechin attenuate hypercaloric diet-induced obesity through enhanced β-oxidation and energy expenditure in white adipose tissue". *Journal of Functional Foods* 20 (2015): 54-67.

34. Natsume M., *et al*. "Cacao procyanidins reduce plasma cholesterol and increase fecal steroid excretion in rats fed a high-cholesterol diet". *BioFactors* 33 (2009): 211-223.

35. Ramos S. "Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways". *Molecular Nutrition and Food Research* 52 (2008): 507-526.

36. Oleaga C., *et al*. "CYP1A1 is overexpressed upon incubation of breast cancer cells with a polyphenolic cocoa extract". *European Journal of Nutrition* 51 (2012): 465-476.

37. Carnésecchi S., *et al*. "Flavanols and procyanidins of cocoa and chocolate inhibit growth and polyamine biosynthesis of human colonic cancer cells". *Cancer Letter* 175 (2002): 147-155.

38. Granado-Serrano AB., *et al*. "A diet rich in cocoa attenuates N-nitrosodiethylamine-induced liver injury in rats". *Food and Chemical Toxicology* 47 (2009): 2499-2506.

39. Rodriguez-Ramiro I., *et al*. "Cocoa-rich diet prevents azoxymethane-induced colonic preneoplastic lesions in rats by restraining oxidative stress and cell proliferation and inducing apoptosis". *Molecular Nutrition and Food Research* 55 (2011): 18951899.

40. Kim JE., *et al*. "Cocoa polyphenols suppress TNF-a-induced vascular endothelial growth factor expression by inhibiting phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase kinase-1 (MEK1) activities in mouse epidermal cells". *British Journal of Nutrition* 104 (2010): 957-964.

41. Sakano K., *et al*. "Procyanidin B2 has anti- and pro-oxidant effects on metal-mediated DNA damage". *Free Radicals in Biology and Medicine* 39 (2005): 1041-1049.

42. Papiez MA., *et al*. "(-)-Epicatechin enhances etoposide-induced antileukaemic effect in rats with acute myeloid leukaemia". *Anticancer Research* 32 (2012): 2905-2914.