Acta Sci. Pol. Technol. Aliment. 22(4) 2023, 441–454
www.food.actapol.net pISSN 1644-0730 eISSN 1898-9594 http://dx.doi.org/10.17306/J.AFS.2023.1187

ORIGINAL PAPER

Received: 02.11.2023
Accepted: 27.11.2023

HOW DOES COCOA WASTE AFFECT HEALTH? A SYSTEMATIC REVIEW

Rita Irma[1,2]✉, Ridwan Amiruddin[2], Nurhaedar Jafar[2], Wahiduddin[2], Gemini Alam[3], Toto Sudargo[4], Sudirman Nasir[2], Apik Indarty Moedjiono[2]

[1]Department of Nutrition, Health Polytechnic of Kendari
Jl. Pattimura no.45, Kendari, 93114, **Indonesia**
[2]Faculty of Public Health, Hasanuddin University, Tamalanrea Campus
Jl. Perintis Kemerdekaan km.10 90245, Makassar, **Indonesia**
[3]Faculty of Pharmacy, Hasanuddin University, Drug Discovery and Development Centre, Hasanuddin University, Tamalanrea Campus
Jl. Perintis Kemerdekaan km.10, 90245, Makassar, **Indonesia**
[4]Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University
Jl. Farmako, Sekip Utara, Sleman 55281, Yogyakarta, **Indonesia**

ABSTRACT

Cocoa pod husk (CPH) and cocoa bean shell (CBS) are cocoa by-products that remain after cocoa bean extraction and often become environmental pollutants (cocoa waste). Numerous studies have demonstrated that both of them are sources of bioactive compounds. This review outlines the potential effects of cocoa waste on health and discusses current knowledge regarding the health potential of cocoa waste. Most of the research on this topic has been conducted in vitro and has shown some potential health benefits of cocoa waste products, both for CPH and CBS. Cocoa waste can influence body weight and food intake, increase serum protein concentrations, lower blood pressure, exhibit hypolipidemic effects, elevate HDL, act as an antidiabetic, possess antibacterial properties, and serve as an antioxidant that combats inflammation and reduces MDA levels. Cocoa waste holds significant potential for health, although its effectiveness is still largely studied in vitro. Further research is needed to demonstrate in vivo the potential of bioactive compounds from cocoa shell waste products to address various health issues, such as cardiovascular disease and diabetes.

Keywords: cocoa waste, cocoa pod husk, cocoa bean shell, potential health benefits

INTRODUCTION

Currently, non-communicable diseases (NCDs) are a global health issue and pose a serious health threat worldwide (Cheng et al., 2013; Riley et al., 2016). This is because NCDs such as cardiovascular disease, cancer, chronic respiratory disease (chronic obstructive pulmonary disease and asthma), and diabetes are the leading causes of death worldwide (Hanson and Gluckman, 2011; WHO, 2021a). More than 50% of global deaths each year are attributed to NCDs. In fact, the WHO has estimated that there will be a 17% increase in NCDs in the next decade, and this will occur globally, including in low- and middle-income countries (Hanson and Gluckman, 2011; Riley et al., 2016; WHO, 2021a). In Indonesia, NCDs are the leading cause of death, exhibiting an increasingly concerning trend, primarily due to a shift in disease patterns from

✉rima.gizikendari99@gmail.com

the elderly population to the productive age group (PTM kini ancam usia muda_Kemkes, 2020). This is supported by basic health research from 2018, which indicates a rising trend in NCDs compared to 2013, particularly in cardiovascular disease and diabetes (Balitbangkes, 2013, 2018).

NCDs can pose a threat to sustainable development, and the WHO has set a goal of reducing premature deaths due to NCDs by one third by 2030 (WHO, 2021b). NCDs have significant social and economic implications, as they impact productivity, result in decreased functional status, affect quality of life, and deplete household resources due to high and prolonged medical costs. Additionally, the loss of income due to prolonged illness leads to impoverishment, causing many individuals to fall into poverty each year, which hampers development (Peli et al., 2013; Riley et al., 2016; WHO, 2021b).

Various prevention techniques and new therapy strategies for NCDs are being actively sought due to their detrimental effects (Pangestuti and Kim, 2017). Currently, alternative treatments for NCD patients to complement conventional therapy are widely utilized by a significant portion of the global population, particularly in developing countries (Hermann and Von Richter, 2012; Cragg and Newman, 2013; Ekor, 2014). This is especially prevalent in large populations in several Asian and African countries (Secretariat, 2012; Ondieki et al., 2017), because alternative treatments are believed to be quite effective, safe, have fewer side effects, are easily accessible, and are relatively more affordable (Hermann and Von Richter, 2012; Ondieki et al., 2017). Typically, these treatments consist of herbal products, traditional remedies, and supplements derived from plants (Peltzer et al., 2016; Li and Weng, 2017), which have long served as primary therapeutic agents in the treatment of various diseases.

One plant with biofunctional potential is cocoa. In the processing of a single cocoa fruit, various residues are generated, including the fruit skin, which is the primary by-product of the cocoa industry (67–76%), the bean skin (2.1–2.3%), and cocoa mucilage/paste (8.7–9.9%), which are discarded and become waste, potentially polluting the environment (Daud et al., 2013; Campos-Vega et al., 2018). Processing cocoa beans into chocolate products also results in a significant amount of cocoa waste. On average, 1 ton of dried cocoa beans produces approximately 10 tons of cocoa waste (Hennessey-Ramos et al., 2021).

Cocoa by-products, which are commonly treated as low-value waste, represent a renewable, abundant, and cost-effective resource (Lu et al., 2018; Picchioni et al., 2020). Many studies have shown that CPH contains various bioactive compounds such as polyphenols, theobromine, pectin, minerals, and dietary fiber, which have the potential to produce nutraceuticals or functional foods (Nguyen and Nguyen, 2017; Campos-Vega et al., 2018). Similarly, CBS has biofunctional potential for human health, including antibacterial, antiviral, anticarcinogenic, antidiabetic, or neuroprotective activity, benefits for the cardiovascular system, and anti-inflammatory capacity (Rossin et al., 2019; Rojo-Poveda et al., 2020).

This systematic review's objective is to assess the potential and effectiveness of cocoa waste to be beneficial for health and provide health products in the future.

METHOD

The study search was conducted using the Scopus database through the Publish or Perish application, while searches in the ScienceDirect, Google Scholar, PubMed, and ProQuest databases were carried out through their respective websites. The search process in this study utilized Boolean operators with keywords such as: cocoa by-product OR cocoa pod husk OR cocoa bean shell OR cocoa waste AND health benefit. There were no restrictions based on study design.

The criteria for studies in this review were that they should be on cocoa by-products (waste), not cocoa fruit, and they should have been published from 2005 to 2023. These studies aimed to investigate the potential of cocoa by-products for health, including laboratory experiments (in vitro), pre-clinical studies on animals, or clinical studies on humans. Review studies, studies related to the potential use of cocoa by-products as ruminant feed, and studies related to animal health were not included in this review. Out of the 37,785 studies identified in the initial search phase, 17 studies met the criteria for inclusion in this review.

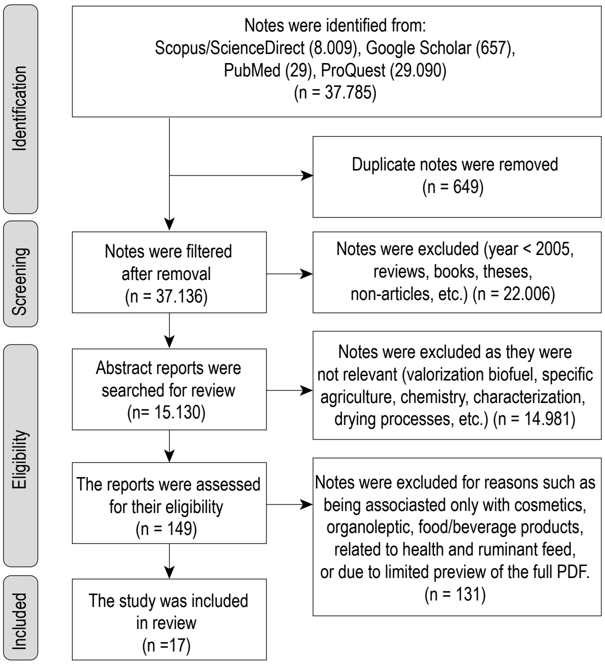

Fig. 1. Flow diagram for study based on PRISMA 2015 Guidelines

RESULTS

Several relevant studies related to the potential health benefits of cocoa waste, both from the CPH and CBS, were identified. Out of the 17 studies reviewed, almost all of them demonstrated more than one potential health benefit of cocoa waste.

The potential effects of cocoa waste on food intake and body weight

Research conducted on rats showed a relatively lower weight gain in rats fed with cocoa waste-containing diets (Ramos et al., 2008; Sánchez et al., 2010). In another study, there was weight loss, a decrease in body mass index, and a reduction in waist circumference in patients receiving cocoa husk cookie, although the results were not significantly different from the placebo group (León-Flores et al., 2020). Conversely, another study indicated a significant increase in total final body weight and weight change in rabbits fed with 12.5% FCPHM; although the results also showed an influence of rabbit type on the final body weight, it was

Table 1. List of potential health benefits of cocoa waste products from the reviewed studies

No	Potential health benefit	Cocoa waste products in the reviewed studies
1	Maintaining weight stability; reducing abdominal fat-waist circumference	CPH fiber (Ramos et al., 2008), soluble cocoa fiber product (SCFP) (Sánchez et al., 2010), cookies and CPH extract (CCPHE) (Hidalgo et al., 2019), fermented cocoa pod husk meal (FCPHM) (Olugosi et al., 2021), cocoa husk cookies (CHC) (León-Flores et al., 2020).
2	Elevating serum protein	Diet containing CPH (Adeyeye et al., 2017), FCPHM (Olugosi et al., 2021), CPH extract (CPHE) (Cura et al., 2021).
3	Lowering blood pressure, endothelium vasodilation, and vasorelaxation	Soluble cocoa fiber product (SCFP) (Sánchez et al., 2010), CCPHE (Hidalgo et al., 2019), CBS extract (CBSE) (Rodríguez-Rodríguez et al., 2022).
4	Hypolipidemic effect	SCFP (Ramos et al., 2008), diet containing CPH (Adeyeye et al., 2017), cookies and cocoa skin extract (Hidalgo et al., 2019), CHC (León-Flores et al., 2020).
5	Increase in HDL (High-Density Lipoprotein)	CCPHE (Hidalgo et al., 2019), CHC (León-Flores et al., 2020), diet containing CPH (Adeyeye et al., 2017).
6	Antidiabetic / lowering blood sugar	CBSE (Rebollo-Hernanz et al., 2019), CBS biscuits (Rojo-Poveda, Barbosa-Pereira, Orden, et al., 2020), CPHE (Indrianingsih et al., 2021), CPHE (Cura et al., 2021), SCFP (Sánchez et al., 2010).
7	Antibacterial	CPHE (Indrianingsih et al., 2021), CPHE (Santos et al., 2014), CPHE (Diniardi, Argo and Wibisono, 2020).
8	Antioxidant (addressing oxidative stress / reducing malondialdehyde (MDA) levels and anti-inflammatory)	CPHE (Felice et al., 2020), SCFP (Ramos et al., 2008), SCFP (Sánchez et al., 2010), CBSE (Rebollo-Hernanz et al., 2019), CBSE (Rossin et al., 2019), ice cream enriched with CBS (Rossin et al., 2021).

not significant. However, the group given FCPHM 25% actually had the lowest total body weight (Olugosi et al., 2021). The research results in the group of rats given SCFP showed a significantly lower food intake compared to the control group, even in the group receiving a normocholesterolemic diet (Ramos et al., 2008; Sánchez et al., 2010). On the other hand, another study indicated a significant increase in total food intake and daily average intake in both the control and FCPHM 12.5% experimental groups, but not in the FCPHM 25% group.

Cocoa waste and serum protein

Across the studies, in groups treated with a cocoa fruit husk diet, total serum protein was higher compared to control groups (Adeyeye et al., 2017; Olugosi et al., 2021). Although one study reported a slight decrease after treatment with higher CPH concentrations (30%), it was still higher than in the group given a CPCH-free diet (control) (Adeyeye et al., 2017).

Cocoa waste and blood pressure

A study on spontaneously hypertensive rats showed a significant decrease in systolic and diastolic blood pressure from the early stages of feeding until week 14. Conversely, in the control group, systolic and diastolic blood pressure remained high until the end of the study. Additionally, when compared to the control group, the SCFP-treated group exhibited lower angiotensin converting enzyme (ACE) activity (Sánchez et al., 2010). Studies on obese rat models receiving a high-fat diet along with cocoa husk cookies and cocoa husk extract at different concentrations all demonstrated a significant reduction in blood pressure compared to the group receiving only a high-fat and fructose diet (Hidalgo et al., 2019).

Cocoa husk waste and hypolipidemic effects

Studies on cocoa husk waste and its association with serum lipid profiles included in this study consistently demonstrated a reduction in total cholesterol and LDL levels (Ramos et al., 2008; Adeyeye et al., 2017; Hidalgo et al., 2019) and serta TG (Ramos et al., 2008; Adeyeye et al., 2017; Hidalgo et al., 2019; León-Flores et al., 2020) in the groups receiving cocoa husk products.

Cocoa husk waste and HDL (high density lipoprotein)

Some studies found a correlation between the administration of cocoa waste products and HDL levels. Although 2 out of 3 studies that addressed this topic showed non-significant effects, both of them demonstrated a slight increase in HDL levels in the groups treated with cocoa husk waste products compared to the control (Hidalgo et al., 2019; León-Flores et al., 2020). Meanwhile, the other study showed a significant increase in HDL levels in the groups given a diet of 20 and 30 percent PCPH (Adeyeye et al., 2017).

Cocoa husk waste as an antidiabetic agent

A study in rats showed that the glucose levels in both the SCFP treatment group and the control group did not differ significantly, although there was a slight decrease in the SCFP group during the follow-up phase (Sánchez et al., 2010). In a study of overweight humans without diabetes, at the end of the study, the treatment group receiving cocoa husk cookies showed a reduction in blood sugar levels (León-Flores et al., 2020). An in vitro study demonstrated that both purple and yellow variants of cocoa fruit husk have glucosidase inhibition activity (Indrianingsih et al., 2021).

Cocoa husk waste as an antibacterial agent

Cocoa husk waste is effective in inhibiting gram-positive bacteria compared to gram-negative bacteria (Indrianingsih et al., 2021). However, another study shows that cocoa fruit husk extract is not effective against gram-positive bacteria and exhibits bactericidal activity against gram-negative bacteria, even being quite effective against E. coli (a gram-negative bacterium; Santos et al., 2014; Diniardi, Argo and Wibisono, 2020).

Cocoa husk waste as an antioxidant (inflammation, oxidative stress, and MDA)

One study indicates that cocoa husk extract significantly protects cells from oxidative stress (Felice et al., 2020). Administration of cocoa bean shell extract reduces excessive production of IL-8 and MCP-1, along with an increase in the Nrf2 gene (Rossin et al., 2021). Cocoa husk modulates the phosphorylation status of proteins, thereby suppressing the production of reactive oxygen species (free radicals) and mitochondrial superoxide (Rebollo-Hernanz et al., 2019)

DISCUSSION

It is worth noting here that cocoa waste has the potential to help maintain stable changes in body weight, whether for weight loss or weight gain. Similarly, it also affects food intake. Cocoa waste is a reasonably potent source of dietary fiber, which makes up approximately 59.0% of its volume (Yapo et al., 2013). Dietary fiber can have an impact on body weight and food intake. In one of the studies described above, the lower food intake in the group subjected to cocoa waste treatment was likely due to the satiating effect of the dietary fiber contained in cocoa waste products (Ramos et al., 2008). A prolonged feeling of fullness can be attributed to the indigestible and unabsorbable nature of the fiber, which can reduce food intake. Conversely, reduced food intake leads to delayed glucose absorption, resulting in a decreased insulin response. The reduced insulin response triggers lipolysis and the oxidation of stored lipids in adipose tissue. This, in turn, can lead to weight gain (Fernandez et al., 1994). Dietary fiber also influences intake through its role in triggering intestinal hormone production, subsequently leading to leptin production and impacting lipid metabolism and energy expenditure, thereby affecting body weight (Delzenne et al., 2005; Gaysinskaya et al., 2007; Ramos et al., 2008). Moreover, increased intake and body weight, particularly in fermented CPH products, may be related to the fermentation process, which includes factors like enhanced protein content, improved flavor, and reduced roughage (Adejinmi et al., 2007).

The increase in total serum protein in fermented cocoa waste is likely an effect of the fermentation of cocoa waste. A study which also examined protein digestibility indicated that the addition of 37.5% FCPHM led to the highest value of crude protein digestibility. Conversely, the lowest crude protein digestibility was found in raw CPHM with the highest concentration of 37.5% (Ozung et al., 2017). Studies on the protein characteristics of cocoa waste remain quite limited. One possible reason for this limitation may be the scarcity of research examining its utilization in food or focusing solely on animal feed (Campos-Vega et al., 2018). Out of the 144 identified proteins, nearly half play a role in energy metabolism, including processes such as glycolysis, the tricarboxylic acid cycle, and the Calvin cycle. Some of these proteins produce products like flavonoids, phytoalexins, and lignin (Azwan et al., 2010).

The relationship between CPHE and blood pressure is associated with the phytochemical compounds it contains. A study indicated that CPHE is rich in flavonoid content (115.50 mg CE/g of sample weight) (Nguyen et al., 2021). Phenolic compounds like catechin/epicatechin and quercetin, found in CPH (Felice et al., 2020), have a strong influence on endothelial function. These compounds, particularly procyanidins, induce vasodilation, inhibit the synthesis of the vasoconstrictor ET-1, and inhibit ACE activity, leading to a reduction in blood pressure (Hügel et al., 2016).

The high content of soluble dietary fiber and polyphenols in cocoa waste products exerts a hypolipidemic effect. The soluble fiber present in cocoa bean husk waste products binds to dietary fats and bile acids, forming emulsions that limit the action of pancreatic lipase. This, in turn, reduces the absorption of dietary fats and triglyceride hydrolysis, subsequently lowering cholesterol absorption due to a decrease in the release of free fatty acids in the small intestine (Chai et al., 2003; Ramos et al., 2008). Similarly, polyphenols, one of whose main phenolic compounds is catechin/epicatechin (EPI), can, among their various functions, intervene in the process of lipid β-oxidation and induce mitochondrial biogenesis. Through this mechanism, they can lower blood lipid concentrations, especially VLDL, LDL, and TG (Ramirez-Sanchez et al., 2011; Felice et al., 2020; León-Flores et al., 2020). Additionally, cocoa bean husk waste may contain other compounds that can inhibit, either directly or indirectly, the enzyme hydroxymethylglutaryl-coenzyme A reductase, which is involved in cholesterol synthesis (Adeyeye et al., 2017).

Cocoa bean husk waste is associated with an increase in serum HDL levels, linked to theobromine as one of the active compounds present in cocoa and its derivatives. In a study involving human subjects who had been given cocoa fruit containing 150 mg of theobromine, there was an increase in HDL cholesterol levels, although it was not statistically significant. This suggests that higher theobromine doses may be needed to demonstrate an effect on serum HDL cholesterol (Neufingerl et al., 2013). The increase in plasma HDL concentration due to polyphenols is dose-related. Although

Table 2. Methods and findings of the reviewed study

No	Author	City / country of origin of cocoa waste product	Study method	Research findings
1	2	3	4	5
1	Felice et al., 2020	Costa Rica and Madagascar	a. Type: Laboratory experiments (in vitro, in vivo). b. Subjects: Male Wistar rats; HUVECs as in vitro media. c. Data analysis : One-way ANOVA test, Tukey, Bonferroni.	The polyphenols in CPH extract protect cells from oxidative damage at concentrations ranging from 5 to 50 g GAE/ml.
2	Rebollo-Hernanz et al., 2019	Castrocontrigo, León, Spain.	a. Type: Laboratory experiment (in vitro). b. Subjects: Coffee husks, cocoa husks. c. Data analysis: ANOVA test, Tukey post hoc analysis, Pearson correlation, and regression.	Extract of coffee or cocoa by-products: a. Modulates the phosphorylation of the insulin receptor signaling pathway and stimulates GLUT-4 translocation (52.4-72.9%). b. Enhances glucose absorption. c. Effectively reduces inflammatory markers in macrophages and adiposity, as well as ROS production
3	Indrianingsih et al., 2021	Yogyakarta, Indonesia	a. Type: Laboratory experiment (in vitro). b. Leaves of Annona muricata L and cocoa fruit husks (yellow and purple variants). c. Triple-blind testing, one-way ANOVA, and Duncan's test.	a. Presence of phenolic molecules in all extracts. b. The highest free radical scavenging capacity was observed in the yellow and purple variants of CPHE, with IC50 values of 41.3 and 44.5, respectively. c. The hexane-soluble fraction extract from the purple variant of CPH exhibited the highest glucosidase inhibition activity with an IC50 of 10.8 g/ml, followed by the methanol extract from the purple variant at 27.7 g/ml. The methanol extract from the yellow variant and its dichloromethane fraction also demonstrated good activity, with IC50 values of 41.6 g/ml and 29.6 g/ml, respectively. d. CPHE and its fractions (purple and yellow variants) are active sources of glucosidase inhibitors. e. The purple CPH fraction exhibited the most bactericidal activity against Staphylococcus aureus with an MBC value of 1.25 mg/ml.
4	Rojo-Poveda, Barbosa-Pereira, Khattabi, et al., 2020	São Tomé / supplied by Pastiglie Leone S.r.l. (Turin, Italy)	a. Type: Design: Laboratory experiment (in vitro). b. Subjects: CBS powder, CBS biscuits; using α-amylase from human saliva, pepsin from pig gastric mucosa, bile salts, and pancreatin from pig pancreas as in vitro media. c. Data analysis: Chromatographic analysis. Analysis: one-way ANOVA, followed by Duncan's post hoc test.	a. There was a significant difference ($p < 0.05$) among the three types of treatments (polyphenol extract with organic solution, in vitro digestion, no digestion) with the same samples (biscuit, cocoa fruit husk powder). b. The highest glucosidase inhibition value was observed in 20% concentration of CBS biscuit after in vitro digestion.

Table 2 cont.

1	2	3	4	5
5	Cura et al., 2021	Calinan, Davao City, Philippines	a. Type: Laboratory experiment (in vitro). b. Subject: CPHE, metformin, diclofenak. c. Data analysis: Egg albumin denaturation test to determine protein denaturation inhibition; Analysis: one-way ANOVA followed by Tukey's post hoc HSD test.	a. Glucose Dialysis Retardation Index (GDRI) decreases with decreasing CPHE concentration. Furthermore, 10% TCE (Test Compound Extract) exhibits a significantly higher GDRI compared to other concentrations ($P < 0.05$), and its potential is comparable to metformin. TCE 7% also shows a significantly higher GDRI compared to TCE 5%, 3%, and 1% ($P < 0.05$), and its potential is comparable to metformin 5% after 60 minutes and 180 minutes of incubation. b. Glucose uptake increased with the increasing concentration of the samples using different glucose solutions. It was also demonstrated that 10% CPHE exhibited a significantly higher percentage of glucose uptake compared to the other samples in all glucose solutions ($P < 0.05$) and showed activity comparable to 5% metformin. c. The samples inhibit protein denaturation in a dose-dependent manner. The results also demonstrate that 10% CPHE has a significantly higher inhibitory effect compared to the other samples ($P < 0.05$) and exhibits activity comparable to 5% diclofenac
6	Ramos et al., 2008	Natra cacao, Valencia-Spanyol	a. Type: True experimental (in vivo). b. Subjects: 30 male Sprague-Dawley rats aged 10 weeks. c. Data analysis: One-way ANOVA, followed by Bonferroni (if data is homogenous) / Tamhane's T2 test (if data is not homogenous). Homogeneity was tested using Levene's test.	a. Total cholesterol increased 4 times, LDL increased 9 times in the hipercholesterolemic control (HC) group compared to the normocholesterolemic control (NC) group, and HDL significantly decreased in the HC group. b. A reduction of 58% in total cholesterol and 68% in LDL was observed in the SCFP + HC group compared to the HC group. c. TG (triglycerides) decreased by 40% in the SCFP + HC group compared to the NC & HC group. This indicates a reduction in the atherogenic effects of a high-fat diet when consumed with SCFP. b. There was a reduction in MDA in the treatment group when compared to the control group d. Food intake was significantly higher in the HC group compared to the NC group. In contrast, the SCFP + HC group had significantly lower food intake compared to the NC group. e. The body weight in the HC group showed the highest increase, while the SCFP group exhibited the lowest weight gain. Despite receiving a high-cholesterol diet with an approximately 30% lower food intake than the HC group, the SCFP group only experienced half the weight gain of the HC group.

Table 2 cont.

1	2	3	4	5
7	Sánchez et al., 2010	Natraceutical Group, Valencia, Spain	a. Type: True experimental (in vivo). b. Subjects: Ten male rats, aged three weeks, with spontaneous hypertension were divided into two groups: control (tap water) and treatment (cocoa husk fiber solution) at a dosage of 0.75 g of fiber per day. c. Data analysis: One-way ANOVA, Bonferroni.	a. The group of rats given tap water showed a gradual increase in blood pressure from weaning at 3 weeks of age until week 17, which remained high until the end of the study. In contrast, the group given SCFP exhibited an initial increase in SBP (systolic blood pressure) and a significant decrease in DBP (diastolic blood pressure) from the beginning to week 14. b. There was a difference in the plasma MDA concentration between the group given tap water and the group given cocoa husk fiber solution. The group that consumed the cocoa husk fiber solution had a lower MDA level. c. The glucose levels in the control and SCFP groups were 104.2 ± 2.4 and 112.6 ± 1.3, respectively. At the end of the treatment, they were 108 ± 6.3 and 101.4 ± 2.3, respectively. d. The ACE plasma activity values were slightly lower in the SCFP group compared to the control group. This difference became even more pronounced towards the end.
8	Olugosi et al., 2021	Nigeria	a. Subjects: 180 rabbits divided into 2 breeds, true experimental (in vivo) type (90 New Zealand White breed, 90 Chinchilla breed). b. Subjects: 180 rabbits divided into 2 breeds (90 New Zealand White breed, 90 Chinchilla breed). c. Data analysis: Two-way ANOVA.	a. The concentration of MDA was significantly influenced by both treatments of FCPHM at 12.5% and 25%. b. The increase in body weight in the treatment group was influenced by the administration of FCPHM 12.5% + rabbit breed compared to the group given 25% FCPHM, which actually had the lowest total body weight. c. The total intake and daily average intake increased in the control group and the 12.5% FCPHM group compared to the 25% FCPHM group. d. The serum protein levels significantly increased in both the 12.5% and 25% FCPHM groups.
9	Hidalgo et al., 2019	Tabasco, Mexico	a. Type: True experiment (in vivo). b. Subjects: 25 experimental animals (Male Wistar Rats). c. Data Analysis: One-way ANOVA, Tukey test.	a. Decrease in blood pressure was observed in the treatment groups High Fat Diet (HFD) + pellet + CPHE 1%, 10%, 100%. Conversely, the HFD + fructose group experienced a significant increase in blood pressure. b. No groups that were given pellets with CPHE until the end of the 5th week experienced a significant increase in body weight compared to the control group (HFD + fructose). c. Reduction in abdominal fat was observed in all pellet groups with the addition of the extract, but the differences in reduction among the three groups were not significant in CPHE 1%, 10%, and 100%. Conversely, the HFD group experienced a significant increase in body weight.

Table 2 cont.

1	2	3	4	5
10	Rodríguez-Rodríguez et al., 2022	Castocontrigo Leon, Spanyol	a. Type: True experiment (in vivo). b. Subject: Male and female Sprague Dawley rats, aged 4–5 months (adult) and 15 months (old). c. Data Analysis: Shapiro-Wilk for testing data normality; differences in concentration-response curves were analyzed using two-way ANOVA.	a. CBS extract provides vasodilation action through the endothelium with lower efficacy but higher potential compared to the vasodilator acetylcholine. b. CBS extract induces vasorelaxation in female rat arteries. However, in male rats, the maximum arterial relaxation was significantly lower with KBK extract compared to acetylcholine.
11	Ozung et al., 2017	Cocoa Research Institute of Nigeria (CRIN)	a. Type: Completely randomized design. b. Subject: 60 Mixed Breed Male and Female Rabbits (Chinchilla, New Zealand, California) aged 5–6 Weeks. c. Data Analysis: One-way ANOVA	a. The group subjected to the highest CPHM treatment (37.5%) also experienced the highest weight gain, both in the raw and fermented CPHM groups. b. The least weight gain, was observed in the hot water-treated CPHM group, followed by the raw CPHM group, and then the fermented CPHM group, with weight gain values of 390 grams, 557.50 grams, and 570.83 grams, respectively. c. Raw CPHM with a concentration of 37.5% had the lowest crude protein digestibility value (75.07%). d. Fermented and hot-water-treated CPHM had crude protein digestibility values of 78.11% and 77.74%, respectively. e. The crude fiber digestibility values for raw CPHM at concentrations of 0, 12, 12.5, and 37.5 were 77.92%, 78.44%, 75.05%, and 74.50%, respectively. f. The crude fiber digestibility values for CPHM fermentation at concentrations of 0, 12, 12.5, and 37.5 were 76.79%, 71.03%, 61.14%, and 76.68%, respectively. g. The crude fiber digestibility values for CPHM in hot water at concentrations of 0, 12, 12.5, and 37.5 were 77.42%, 85.973%, 80.80%, and 82.19%, respectively.
12	León-Flores et al., 2020	–	a. Experiment. b. Subject: 24 non-DM patients with overweight (BMI 25–29.9), aged 20–60 years, serum TG 150–350 mg/dl, who gave informed consent. c. Data Analysis: ANOVA, Tukey.	a. GD in the placebo group decreased by 4.3 mg/dl (5%, not significant). b. In the experimental group, it decreased by 10 mg/dl (10.9%, P=0.01). c. Body weight in the placebo cake group decreased by 5.5 kg, while in the CPH Cookies group, it decreased by 3.2 kg. d. BMI decreased by 2 kg/m² in the placebo group and 1.3 kg/m² in the CPH Cookies group. e. Waist circumference decreased by 4.1 cm in the placebo group and 3.9 cm in the CPH Cookies group.

Table 2 cont.

1	2	3	4	5
13	Adeyeye et al., 2017	Oda, Akure, Nigeria	a. Type: Pure experiment (in vivo). b. Subject: 120 Mixed Breed Rabbits of New Zealand and Chinchilla, Aged 5 Weeks. c. Data Analysis: ANOVA and Regression.	a. Total serum protein in rabbits given the PCPH diet was significantly higher compared to the control group. b. Cholesterol and LDL decreased significantly in the PCPH group. c. HDL significantly increased in the groups given a PCPH diet of 20% and 30% compared to the control group and the PCPH 10% group.
14	Rossin et al., 2021	Sao Tome / Supplied Pastiglie Leone Srl (Turin, Italy)	a. Type: Molecular experiment (in vitro). b. Subject: Cocoa Bean Shell (CBS), Digestive Fluids (Saliva, Stomach, Intestines, Duodenum), Glucose-Enriched Cell Culture, Fetal Bovine Serum, Trypsin as an In Vitro Medium. c. Data Analysis: One-way ANOVA, Bonferroni, Duncan tests.	Administration of CBS peel extract and CBS ice cream reduced the production of IL-8 and MCP-1, along with an increase in the expression of the Nrf2 gene.
15	Rossin et al., 2019	Honduras / supplied by Guido Castagna S.r.l. (Turin, Italy)	a. Jenis: Molecular experiment (in vitro). b. Subject: CBS; Human Colorectal. Adenocarcinoma Cells (CaCo2). c. Data Analysis: t-Test, One-Way ANOVA, Bonferroni.	The fractionation groups CBS HF3 and HF4 were able to completely inhibit the production of IL-8 at concentrations of 10 and 25 µg/mL.
16	Diniardi et al., 2020	Malang regency, Indonesia	a. Type: Experiment (in vitro). b. Subject: E. coli as a bacterial model. c. Data Analysis: Antibacterial Activity Test Using the Disk Diffusion Method.	CPH extract exhibits antibacterial activity against E. coli, even at the lowest concentration (5 mg/dl). As the extract concentration increases, the inhibitory zone against the bacteria also increases.
17	Santos et al., 2014	Ilhéus, Bahia	a. Jenis: Experiment (in vitro). b. Cocoa fruit peel extract against six types of gram-negative and gram-positive bacteria. c. Antibacterial and antifungal bioassay.	a. The strongest inhibition activity was observed against Pseudomonas aeruginosa at a concentration of 5 mg/ml. b. The CPH extract was ineffective against one of the gram-positive bacteria at doses of 1–10 mg/ml, but it exhibited varying degrees of bactericidal activity against gram-negative bacteria.

not statistically significant, there is a tendency toward a positive correlation between urinary catechin excretion and plasma HDL cholesterol (Baba et al., 2007).

Cocoa waste is rich in polyphenols and acts as a glucosidase inhibitor, which can slow down the breakdown of polysaccharides and disaccharides into glucose, thereby reducing the amount of glucose absorbed by the intestines (Chen et al., 2005; Kwon et al., 2006). These antioxidant-capable polyphenols can prevent cell damage caused by free radicals and also inhibit glucosidase and amylase (Perron and Brumaghim, 2009). In an in vitro study, it was shown that cocoa waste extract can balance disruptions in the insulin transduction pathway, which has an impact on insulin resistance (Rebollo-Hernanz et al., 2019). Polyphenols have an effect on insulin secretion and the signaling of glucagon-like peptide-1 (GLP-1), where insufficient and improper functioning of both can lead to diabetes (Domínguez Avila et al., 2017).

Flavonoid compounds found in cocoa bean husk exhibit potent activity against both gram-positive and gram-negative bacteria (Xie et al., 2015). Flavonoids act as antibacterials by denaturing proteins that can lead to the cessation of bacterial cell metabolism. This inhibits growth, ultimately resulting in bacterial cell death. At high concentrations, phenolic compounds can disrupt and penetrate the cell wall, precipitating bacterial cell proteins, while at low concentrations, they deactivate crucial enzyme systems within the bacterial cell (Diniardi et. al., 2020).

Cocoa waste serves as an antioxidant that protects against and addresses inflammation and oxidative stress and reduces MDA levels. Inflammation, oxidative stress, and MDA are interconnected processes. Oxidative stress is initially triggered by inflammation as an immune response of macrophages and mitochondrial dysfunction due to excessive substrate oxidation (Salmon, 2016). Plasma MDA serves as a biomarker for free radical production, oxidative stress, and lipid peroxidation. MDA levels decrease with reduced lipid peroxidation (Ramos et al., 2008; Sánchez et al., 2010). Polyphenols abundant in cocoa bean husk waste exhibit potent antioxidant abilities and have the potential to mitigate inflammation and reduce oxidative stress, which is associated with the development of chronic non-communicable diseases (Correia et al., 2012; Rebollo-Hernanz et al., 2019). Some phenolic compounds, such as caffeic acid and epicatechin, protect against the inflammatory action of oxysterols in colonic cells (Rossin et al., 2019).

CONCLUSION

Cocoa waste holds significant potential for health benefits, although, so far, the evidence of its effectiveness is predominantly based on in vitro studies. Further research is needed to establish the in vivo potential of bioactive compounds and the appropriate dosage in the use of cocoa bean husk waste products to prevent and manage various diseases, particularly metabolic syndrome, which continues to significantly increase in prevalence each year in various countries.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest.

REFERENCES

Adejinmi, O. O., Hamzat, R. A., Fapohunda, J. B. (2007). Performance and nutrient digestibility of rabbits fed fermented and unfermented cocoa pod husk. Niger. J. Anim. Prod., 1, 63–68. https://doi.org/10.51791/njap.v34i1.2422

Adeyeye, S. A., Agbede, J. O., Aletor, V. A., Oloruntola, O. D. (2017). Processed cocoa (*Theobroma Cacao*) pod husks in rabbits diet: effect on haematological and serum biochemical indices. Asian J. Adv. Agric. Res., 2(4), 1–9. https://doi.org/10.9734/AJAAR/2017/36141

Azwan A., Karim, R., Toshiaki, M. (2010). Proteome analysis of Theobroma cacao pod husk. J. Appl. Glycosci., 57, 245–264. https://doi.org/10.14841/jspp.2010.0.0193.0

Baba, S., Naomi, O., Yoji, K., Midori, N., Akiko, Y., …, Kazuo K. (2007). Continuous intake of polyphenolic compounds containing cocoa powder reduces LDL oxidative susceptibility and has beneficial effects on plasma HDL-cholesterol concentrations in humans. Am. J. Clin. Nutr., 85(3), 709–717. https://doi.org/10.1093/ajcn/85.3.709

Balitbangkes (2013). Riset Kesehatan Dasar 2013. Kemenkes RI. Jakarta: Balitbangkes Kemenkes RI.

Balitbangkes (2018). Riset Kesehatan Dasar 2018. Kemenkes RI. Jakarta: Balitbangkes Kemenkes RI.

Campos-Vega, R., Nieto-Figueroa, K. H. Oomah, B. D. (2018). Cocoa (*Theobroma cacao* L.) pod husk:

Renewable source of bioactive compounds. Trends Food Sci. Technol., 81, 172–184. https://doi.org/10.1016/j.tifs.2018.09.022

Chai, Y. M., Lim, B.-K., Lee, J.-Y., Kim, M.-N., Park, M.-R., Rhee, S.-J. (2003). Effects of manufactured soluble dietary fiber from *Quercus mongolica* on hepatic HMG-CoA reductase and lipoprotein lipase activities in epididymal adipose tissue of rats fed high cholesterol diets. J. Med. Food, 6(4), 329–336. https://doi.org/10.1089/109662003772519886

Cheng, L., Tan, L., Zhang, L. , Wei, S., Liu, L., …, Nie, S., (2013). Chronic disease mortality in rural and urban residents in Hubei Province, China, 2008-2010. BMC Public Health, 13(713), 1–9. https://doi.org/10.1186/1471-2458-13-713

Correia, R. T., Borges, K. C., Medeiros, M, F, Genovese, M. I. (2012). Bioactive compounds and phenolic-linked functionality of powdered tropical fruit residues. Food Sci. Technol. Int., 18, 1–9. https://journals.sagepub.com/doi/10.1177/1082013211433077

Cragg, G. M., Newman, D. J. (2013) Natural products: A continuing source of novel drug leads. Biochim. Biophys. Acta, 1830(6), 3670–3695. https://doi.org/10.1016/j.bbagen.2013.02.008

Cura, J. K. Basilio, A., Llagas, M. C. D. L. (2021). Antidiabetic, anti-inflammatory and cytotoxic potential of *Theobroma cacao* Linn. husk aqueous extracts. Clin. Phytosci., 7(94), 1–7. https://doi.org/10.1186/s40816-021-00320-1

Daud, Z. Sari, A., Kassim, A. S. M., Aripin, A. M., Awang, H., …, Patah, B. (2013). Chemical composition and morphological of cocoa pod husks and cassava peels for pulp and paper production. Aust. J. Basic Appl. Sci., 7(9), 406–411.

Delzenne, N. M., Cani, P. D., Daubioul, C., Neyrinck, A. M. (2005). Impact of inulin and oligofructose on gastrointestinal peptides. Brit. J. Nutr., 93(S1), S157–S161. https://doi.org/10.1079/BJN20041342

Diniardi, E. M., Argo, B. D., Wibisono, Y. (2020). Antibacterial activity of cocoa pod husk phenolic extract against Escherichia coli for food processing. IOP Conference Series: Earth and Environmental Science, Volume 475, International Conference on Green Agro-industry and Bioeconomy 26–27 August 2019, Malang East Java Indonesia. DOI: 10.1088/1755-1315/475/1/012006

Domínguez Avila, J. A., Rodrigo García, J., González Aguilar, G. A., De la Rosa, L. A.. (2017). The Antidiabetic Mechanisms of Polyphenols Related to Increased Glucagon-Like Peptide-1 (GLP1) and Insulin Signaling'. Molecules 22(903), 1–16. https://doi.org/10.3390/molecules22060903

Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front. Pharmacol., 4, 1–10. https://doi.org/10.3389/fphar.2013.00177

Felice, F., Fabiano, A., De Leo, M., Piras, A. M, Beconcini, D., …, Di Stefano, R. (2020). Antioxidant Effect of Cocoa By-Product and Cherry Polyphenol Extracts: A Comparative Study. Antioxidants (Basel), 9(2), 132, PMID: 32028655. https://doi.org/10.3390/antiox9020132

Fernandez, M. L., Sun, D. M., Tosca, M. A., McNamara, D. J. (1994). Citrus pectin and cholesterol interact to regulate hepatic cholesterol homeostasis and lipoprotein metabolism: A dose-response study in guinea pigs. Am. J. Clin. Nutr., 59(4), 869–878. https://doi.org/10.1093/ajcn/59.4.869

Gaysinskaya, V. A., Karatayev, O., Chang, G.-Q., Leibowitz, S. F. (2007). Increased caloric intake after a high-fat preload: Relation to circulating triglycerides and orexigenic peptides. Physiol. Behav., 91(1), 142–153. https://doi.org/10.1016/j.physbeh.2007.02.002

Hanson, M., Gluckman, P. (2011). Developmental origins of noncommunicable disease: Population and public health implications. Am. J. Clin. Nutr., 94(suppl), 1754S–8S. https://doi.org/10.3945/ajcn.110.001206

Hennessey-Ramos, L., Murillo-Arango, W., Vasco-Correa, J., Paz Astudillo, I. C. (2021). Enzymatic extraction and characterization of pectin from cocoa pod husk (*Theobroma cacao* L.) using celluclast 1,5 l. Molecules, 26, 1473. https://doi.org/10.3390/molecules26051473

Hermann, R., Von Richter, O. (2012). Clinical evidence of herbal drugs as perpetrators of pharmacokinetic drug interactions. Planta Med., 78(13), 1458–1477. DOI: 10.1055/s-0032-1315117

Hidalgo, I., Ortiz, A., Sanchez-Pardo, M., Garduño-Siciliano, L., Hernández-Ortega, M., …, Ceballos, G. M. (2019). Obesity and cardiovascular risk improvement using cacao by-products in a diet-induced obesity murine model. J. Med. Food, 22(6), 1–11. https://doi.org/10.1089/jmf.2018.0210

Chen, H. M., Yan, X. J., Lin, W. (2005). Progress in α-glycosidase inhibitors. Marine Sci., 29, 73–76.

Hügel, H. M., Jackson, N., May, Brian, Zhang, A. L., Xue, C. C. (2016). Polyphenol protection and treatment of hypertension. Phytomed., 23, 220–231. https://doi.org/10.1016/j.phymed.2015.12.012

Indrianingsih, A. W., Wulanjati, M. P., Windarsih, A., Bhattacharjya, D. K., Suzuki, T., Katayama, T. (2021). In vitro studies of antioxidant, antidiabetic, and antibacterial activities of *Theobroma cacao*, *Anonna muricata* and *Clitoria ternatea*. Biocatal. Agric. Biotechnol., 33, 101995. https://doi.org/10.1016/j.bcab.2021.101995

Khan, N., Monagas, M., Andres-Lacueva, C., Casas, R., Urpí-Sardà, M., …, Estruch, R. (2012). Regular consumption of cocoa powder with milk increases HDL cholesterol and reduces oxidized LDL levels in subjects at high-risk of cardiovascular disease. Nutr. Metab. Cardiovasc. Dis., 22, 1046–1053. https://doi.org/10.1016/j.numecd.2011.02.001

Kwon, Y.-I., Apostolidis, E., Shetty, K. (2006). Evaluation of pepper (*Capsicum Annuum*) for management of diabetes and hypertension. J. Food Biochem., 31(3), 370–385, https://doi.org/10.1111/j.1745-4514.2007.00120.x

León-Flores, P., Nájera, N., Pérez, E., Pardo, B., Jimenez, F., …, Meane, E. (2020). Effects of cacao by-products and a modest weight loss intervention on the concentration of serum triglycerides in overweight subjects: proof of concept. J. Med. Food, 23(7), 745–749. https://doi.org/10.1089/jmf.2019.0201

Li, F. S., Weng, J. K. (2017). Demystifying traditional herbal medicine with modern approaches. Nature Plants, 3, 1701, 1–7. https://doi.org/10.1038/nplants.2017.109

Lu, F., Rodriguez-Garcia, J., Van Damme, I., Westwood, N. J., Shaw, L., …, Charalampopoulos, D. (2018). Valorisation strategies for cocoa pod husk and its fractions. Curr. Opin. Green Sust. Chem., 14, pp. 80–88. https://doi.org/10.1016/j.cogsc.2018.07.007

Megari, K. (2013). Quality of Life in chronic disease patients. Health Psych. Res., 1(e27), 141–148. https://doi.org/10.4081/ijfs.2016.5832

Neufingerl, N., Zebregs, Y. E. M. P., Schuring, E. A. H., Trautwein, E. A. (2013). Effect of cocoa and theobromine consumption on serum HDL-cholesterol concentrations: A randomized controlled trial. Am. J. Clin. Nutr., 97(6), 1201–1209. https://doi.org/10.3945/ajcn.112.047373

Nguyen, V. T. , Le, M. D., Nguyen, T. T. T. , Khong, T. T., Nguyen, V. H.,…, Trang, T. S. (2021). Microwave-assisted extraction for optimizing saponin yield and antioxidant capacity from cacao pod husk (*Theobroma cacao* L.). J. Food Process. Preserv., 45(2). https://doi.org/10.1111/jfpp.15134

Nguyen, V. T., Nguyen, N. H. (2017). Proximate composition, extraction, and purification of theobromine from cacao pod husk (*Theobroma Cacao* L.). Technologies, 5(2), 14. https://doi.org/10.3390/technologies5020014

Olugosi, O. A., Ogunribido, T., Agbede, J. O., Ayeni, A. O. (2021). Effect of biologically upgraded cocoa pod husk meal on growth, serum and antioxidant properties of two rabbit breeds. Bull. Natl. Res. Cent., 45, 11. https://doi.org/10.1186/s42269-020-00454-1

Ondieki, G., Nyagblordzro, M., Kikete, S., Liang, R., Wang, L., He, X. (2017). Cytochrome P450 and P-Glycoprotein-Mediated Interactions Involving African Herbs Indicated for Common Noncommunicable Diseases. Evid Based Complement Alternat Med., 2582463. DOI: 10.1155/2017/2582463

Ozung, P. O., Kennedy Oko, O. O., Agiang, E. A., Eburu, P. O., Evans, E. I. (2017). Growth Performance and Apparent Nutrient Digestibility Coefficients of Weaned Rabbits Fed Diets Containing Different Forms of Cocoa Pod Husk Meal. Agric. Food Sci. Res., 4(1), 8–19. https://doi.org/10.20448/journal.512.2017.41.8.19

Pangestuti, R., Kim, S. K. (2017). Bioactive peptide of marine origin for the prevention and treatment of non-communicable diseases. Mar. Drugs, 15(67), 1–23. https://doi.org/10.3390/md15030067

Peltzer, K., Pengpid, S., Puckpinyo, A., Yi, S., Anh le, V. (2016). The utilization of traditional, complementary and alternative medicine for non-communicable diseases and mental disorders in health care patients in Cambodia, Thailand and Vietnam. BMC Complement Altern Med., 8, 16, 92. https://doi.org/10.1186/s12906-016-1078-0

Perron, N. R., Brumaghim, J. L. (2009). A review of the antioxidant mechanisms of polyphenol compounds related to iron binding. Cell Biochem. Biophys., 53, 75–100. https://doi.org/10.1007/s12013-009-9043-x

Picchioni, F., Warren, G. P., Lambert, S., Balcombe, K., Robinson, J. S., …, Chatzifragkou, A. (2020). Valorisation of natural resources and the need for economic and sustainability assessment: the case of cocoa pod husk in Indonesia. Sustainability, 2020, 12, 8962. https://doi.org/10.3390/su12218962

PTM kini ancam usia muda_Kemkes (2020) Kemenkes RI. Available at: https://www.kemkes.go.id/article/view/20070400003/penyakit-tidak-menular-kini-ancam-usia-muda.html (accessed: 5 November 2021).

Ramirez-Sanchez, I., Moreno, A. , Ceballos, G., Villarreal, F. (2011). Epicatechin (EPI) Induces Mitochondrial Biogenesis (MB) in Human Coronary Artery Endothelial Cells (HCAEC) Cultured Under High Glucose Conditions. The FASEB Journal, 25 (Suppl), 686.6–686.6. https://doi.org/10.1096/fasebj.25.1_supplement.686.6

Ramos, S., Moulay, L., Granado-Serrano, A. B., Vilanova O., Muguerza, B., Goya, L., Bravo, L. (2008). Hypolipidemic Effect in Cholesterol-Fed Rats of a Soluble Fiber-Rich Product Obtained from Cocoa Husks. J.

Agric. Food Chem., 56(16), 6985–6993. https://doi.org/10.1021/jf8009816

Rebollo-Hernanz, M., Zhang, Q., Aguilera, Y., Martín-Cabrejas, M. A., Gonzalez de Mejia, E. (2019). relationship of the phytochemicals from coffee and cocoa by-products with their potential to modulate biomarkers of metabolic syndrome in vitro. Antioxidants (Basel), Aug 5;8(8), 279. https://doi.org/10.3390/antiox8080279

Riley, L., Guthold, R., Cowan, M., Savin, S., Bhatti, L., Armstrong, T., Bonita, R. (2016). The World Health Organization STEPwise approach to noncommunicable disease risk-factor surveillance: methods, challenges, and opportunities. Am. J. Public Health., Jan. 106(1), 74–8. https://doi.org/10.2105/AJPH.2015.302962

Rodríguez-Rodríguez, P., Ragusky, K., Phuthong, S., Ruvira, S., Ramiro-Cortijo, D., …, Martín-Cabrejas, M. A. (2022). Vasoactive Properties of a Cocoa Shell Extract: Mechanism of Action and Effect on Endothelial Dysfunction in Aged Rats. Antioxidants, 2022, 429. https://doi.org/10.3390/antiox11020429

Rojo-Poveda, O., Barbosa-Pereira, L., El Khattabi, C., Youl, E. N. H, …, Stévigny, C. (2020). Polyphenolic and Methylxanthine Bioaccessibility of Cocoa Bean Shell Functional Biscuits: Metabolomics Approach and Intestinal Permeability through Caco-2 Cell Models. Antioxidants, 9(11), 1164. https://doi.org/10.3390/antiox9111164

Rojo-Poveda, O., Barbosa-Pereira, L., Orden, D. (2020). Physical properties and consumer evaluation of cocoa bean shell-functionalized biscuits adapted for diabetic consumers by the replacement of sucrose with tagatose. Foods, 9(6). https://doi.org/10.3390/foods9060814

Rojo-Poveda, O., Barbosa-Pereira, L., Zeppa, G., Stévigny, C. (2020). Cocoa bean shell—a by-product with nutritional properties and biofunctional potential. Nutrients, 12, 1123. https://doi.org/10.3390/nu12041123

Rossin, D., Barbosa-Pereira, L., Iaia, N., Sottero, B., Danzero, A. C., …, Biasi, F. (2021). Protective effect of cocoa bean shell against intestinal damage: an example of by product valorization. Antioxidants, 10, 280. https://doi.org/10.3390/antiox10020280

Rossin, D., Barbosa-Pereira, L., Iaia, N., Testa, G., Sottero, B., …, Biasi, F. (2019). A dietary mixture of oxysterols induces in vitro intestinal inflammation through TLR2/4 activation: the protective effect of cocoa bean shells. Antioxidants, 8, 151. https://doi.org/10.3390/antiox8060151

Salmon, A. B. (2016). Beyond diabetes: Does obesity-induced oxidative stress drive the aging process? Antioxidants, 5(24), 1–14. https://doi.org/10.3390/antiox5030024

Sánchez, D., Quiñones, M., Moulay, L., Muguerza, B., Miguel, M., Aleixandre, A. (2010). Changes in arterial blood pressure of a soluble cocoa fiber product in spontaneously hypertensive rats. J. Agric. Food Chem., 58(3), 1493–1501. https://doi.org/10.1021/jf902080b

Santos, R. X, Oliveira, D. A, Sodré, G. A., Gosmann, G., Brendel, M., Pungartnik, C. (2014). Antimicrobial activity of fermented Theobroma cacao pod husk extract. Genet Mol Res., Sep 26,13(3), 7725–7735. https://doi.org/10.4238/2014.September.26.10

Secretariat, A. (2012). e-Health Bulletin Towards Harmonisation of Traditional Medicine Practices ASEAN + 3 FETN : A Step Forward in', e-Health Bulletin, pp. 1–8. Available at: https://asean.org/book/asean-e-health-bulletin-towards-harmonisation-of-traditional-medicine-practices/

WHO (2021a). Noncommunicable disease. Available at: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases (Accessed: 5 November 2021).

WHO (2021b). Noncommunicable Diseases. Available at: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases (accessed: 5 November 2021).

Xie, Y., Yang, W., Tang, F., Chen, X., Ren, L. (2015). Antibacterial activities of flavonoids: structure-activity relationship and mechanism. Curr. Med. Chem., 22(1), 132–149. https://doi.org/10.2174/0929867321666140916113443

Yapo, B. M., Besson, V., Koubala, B. B., Koffi, K. L. (2013). Adding value to cacao pod husks as a potential antioxidant-dietary fiber source. Am. J. Food Nutr., 1(3), 38–46. https://doi.org/10.12691/ajfn-1-3-4