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Cocoa Pod Husk: A High-Pectin Source with Applications in the Food and Biomedical Fields

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Abstract

Cocoa liquor, butter, and powder represent derived products from a small portion of the fruits, compared with the cocoa pod husk (CPH) which accounts for ~ 70 % of fresh weight. CPH, improperly disposed in plantations, can cause diseases threatening worldwide chocolate production. However, this biomass can be a potential source of bioactive compounds aligned with the circular economy. An overview on the different methods for extracting pectin, resulting in variable extraction yields with a critical discussion on the obtained physicochemical characteristics, is presented. Additionally, the potential applications of the extracted pectin for food and biomedical application are discussed, including thickener, stabilizer, excipient, drug-release modifier, macrophage activator, etc. Despite these potential outputs, new extraction methods need to be considered for improving efficiency and sustainability. Finally, potential approaches are introduced that can help to minimize the environmental impact, making the extraction cost- and time-efficient, and, therefore, more ssustainable for a further successful translation to industry.

Keywords: Biowaste valorization, Cocoa pod husk, Food processing, Galacturonic acid, Pectin extraction

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1 Introduction

Cocoa beans, being the main ingredient in the manufacture of chocolate, cocoa powder, and cocoa butter represent the most economically important part of the fruit [1]. Furthermore, in 2019 the world-wide production of cocoa was approx. 4.7 million tons [2] and, given that 60–70 % of the fruit is cocoa pod husk (CPH) [3], 7800 million tons of CPH remained as waste biomass in farms. The cocoa production can be subdivided in three stages: 1) crop management before harvest; 2) postharvest, where the beans are fermented, dried, packed, and stored, which accounts for the highest percentage of waste biomass (70–80 %); and 3) manufacturing, where the beans are roasted, threshed, milled, and the production of cocoa-based products is carried out. Fig. 1 summarizes these three stages for cocoa production reporting the percentages of biomass and waste obtained.

Although cocoa production is increasingly being approved for its sustainability (4.03 of the Circular Economy Level (CEL) indicator ranking), most production systems follow the linear economy model [4], providing cost-effective materials because recycling and reusing processes are neglected and no emphasis is focused on the waste biomass [5]. Furthermore, cocoa pods disposed improperly generate risky effects in the plantation, e.g., during pods degradation, the production of spores can cause the spread of diseases, such us of *M. perniciosa*, a serious pathogenic agent affecting cocoa with dangerous consequences for the chocolate industry [6, 7] and *Phytophthora* spp., that can affect up to 30 % of worldwide production [8]. However, this residual waste biomass represents a potential source of recovery

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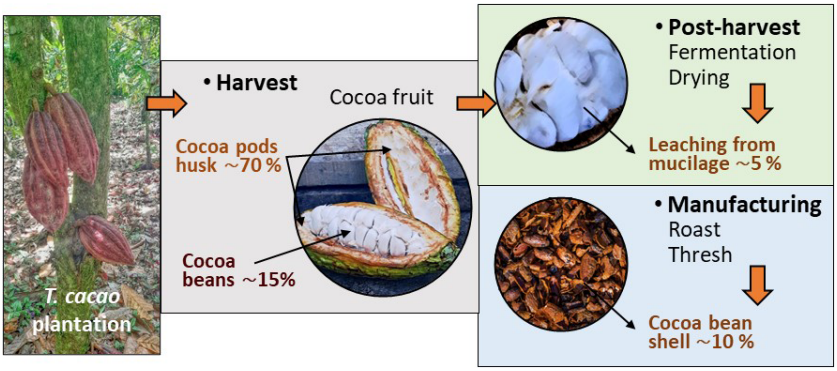

Figure 1. Percentage of biomass in the cocoa production stages, where the produced biowaste consisted by cocoa pods husk, mucilage, and bean shell is ~ 85 % of the fresh fruit, much higher than the main component of cocoa (beans ~ 15 %) used for the industrial development of products.

of bioactive compounds to develop profitable basic products in different industries [9] and its current management is not fully exploited when considering its chemical composition.

CPH is mainly composed of primary metabolites, such as carbohydrates, proteins, lipids [10–12], and secondary metabolites, such as alkaloids [11], flavonoids, and pectin [13]. Particularly pectin, due to its characteristics such as gelling, thickening, and structural behavior, makes it a promising component for applications in different industries ranging from food to biomedicine [14]. According to Campos-Vega et al. [15], pectin obtained from cocoa pod husk has a high potential to be investigated via optimization of the extraction process focused on achieving high yield and quality. Furthermore, applied research shows the great potential of pectin extracted from CPH in the pharmaceutical and biomedical industry, focused on the creation of matrices and excipients. This is due to the suitable assimilation results of the pectin tested in animal in vivo studies, where no biochemical changes, organ damage, presence of bacteria or intoxication are reported [1, 16–18].

This review will investigate pectin extracted from CPHs by providing a critical analysis of the advantages and limitations of the current extraction methodologies, new perspectives in its characterization, and usage in different fields ranging from food to biomedical applications. Also, the chemical composition of CPH and methods for characterizing the extracted pectin are briefly described.

2 Cocoa Pod Husk

2.1 Chemical Composition

CPH can be subdivided in epicarp, mesocarp, sclerotic part, and endocarp, and contains different components such as fiber, phenols, carbohydrates, lignin, protein, and minerals [19]. The moisture content of CPH ranges from 85 to 90.5 % [10, 20–22].

Specifically, the main compounds of CPH are carbohydrates with 32.3 % [7] and total dietary fiber with 36.6–56.1 % [23]. Regarding carbohydrates, the monosaccharides reported in CPH are glucose, uronic acid, xylose, arabinose, galactose, rhammose, mannose, fucose, and cellulose [10] while the dietary fibers, that are mainly insoluble, include cellulose 19.7–26.1 %, hemicellulose 8.7–12.8 %, lignin 14–28 %, and pectin 6.0–12.6 % [15]. Particularly, pectin contained in CPH is low methoxylated and highly acetylated [22], but its yield and quality depends on the extraction method.

In addition to the carbohydrates, polyphenols' content is around 4.6 % [10] and Delgado et al. [22] reported the three main polyphenolic compounds, i.e., catechin, epicatechin, and isoquercetin, that contribute to the pectin antioxidant capacity. Boungo-Teboukeu et al. [24] showed in their investigation that the total phenolic content and antioxidant activity varied from 4.83 to 115.16 mg GAE g^{-1} and 45.64 to 88.63 %, respectively.

Finally, for the ash content a value around 8 % was found in CPH [21]. Particularly, potassium (K) was the predominant mineral with a value of 276.8 $\pm$ 5.2 g kg^{-1} (dry matter), followed by calcium (Ca) (25.4 $\pm$ 1.1 g kg^{-1}), magnesium (Mg) (11.09 $\pm$ 0.01 g kg^{-1}). In intermediate concentrations other elements such as sodium (Na) (1.05 $\pm$ 0.06 g kg^{-1}), iron (Fe) (0.58 $\pm$ 0.01 g kg^{-1}), manganese (Mn) (3.57 $\pm$ 0.03 g kg^{-1}) and zinc (Zn) (3.98 $\pm$ 0.06 g kg^{-1}) were found, in lesser proportions copper (Cu) (0.61 $\pm$ 0.02 g kg^{-1}), and selenium (Se) (1.0 $\pm$ 0.6 mg kg^{-1}) [10].

In addition, this study reported that variations in mineral content can be affected by different geographical origins of the raw material and measurement techniques. Studies on the health benefits of bioactive compounds extracted from CPH are not available. Notwithstanding, Campos-Vega et al. [15] reported that pectin from other plants has several positive effects on human health, such as reduction of cholesterol and serum glucose levels and immune response stimulation. Additionally, it acts as a natural prophylactic substance against poisoning with toxic cations. It also removes lead and mercury from the intestinal tract.

2.2 Cocoa Pod Husk Pectin Extraction

Pectin contained in CPH can be recovered in different ways. In most literature, common methods are hot water, organic acids solutions or with enzymes. However, microwave and ultrasound extraction have also been reported (Tab. 1). As indicated in Tab. 1, the yields are different for each method: water (2.0–23.3 %), acid (1.3–11.73 %), enzymatic (10.23 %), ultrasound (8.3 %), and microwave-assisted (1.93–42.0 %).

This variability may be due to changes in the extraction conditions such as pH, temperature, time, raw/solvent ratio, acid, or enzyme concentration, which have been of interest to different authors. The variation of the mentioned extraction conditions allows the improvement of more relevant characteristics of pectin such as uronic acid content, degree of O-methyl esterification (DE) and acetylation (DA) (Fig. 2).

Table 1. Comparison of the yield of pectin obtained from cocoa pod husk by different methodologies.

Extraction type	Extraction parameters	Yield pectin [%]	Ref.
Water	Solvent: water pH 7 Time: 60–180 min Ratio (w/v): 1:25	2.0–4.7	[25]
	Solvent: water Temperature: 50–100 °C Time: 90 min Ratio (w/v): 1:25	7.5–12.6	[10]
	Solvent: water Temperature: 50 °C Ratio (w/v): 1:25	10.5–23.3	[1]
	Solvent: water Temperature: 100 °C; Time: 90 min Ratio (w/v): 1:20	14.7	[26]
	Solvent: deionized water Temperature: 95 °C Time: 15 min Ratio (w/v): 1:13	10.6	[23]
	Solvent: water Temperature: 95–50 °C Time: 90–180 min pH 2.5–4.0 Ratio (w/v): 1:10–1:25	3.4–4.8	[27]
Acid	Solvent: sodium hexametaphosphate pH 3.5 Temperature: 75 °C Time: 60 min Ratio (w/v): 1:30	1.3	[28]
	Solvent: vitric acid pH 2.5 Temperature: 95 °C Time: 95 min Ratio (w/v): 1:25	10.2	[19]
	Solvent: hydrochloric acid pH 2.5 Time: 1 h Temperature: 95 °C Ratio (w/v): 1:25	9.0	[25]
	Solvent: EDTA at 0.5 % pH 3–5 Temperature: 60, 75, 90 °C Ratio (w/v): 1:30	~4.0: pH 3, 60 °C ~3.8: pH 3, 75 °C ~4.6: pH 3, 90 °C ~2.8: pH 4, 75 °C ~4.0: pH 4, 90 °C ~2.7: pH 5, 75 °C ~3.3: pH 5, 90 °C	[29]

Table 1. Continued.

Extraction type	Extraction parameters	Yield pectin [%]	Ref.
Acid	Solvent: nitric acid Temperature: 100–50 °C Time: 30–90 min pH 1–3 Ratio (w/v): 1:25	6.8–9.5	[10]
	Solvent: citric acid Temperature: 50–100 °C Time: 30–90 min pH 2–3 Ratio (w/v): 1:25	3.7–10.6	[30]
	Solvent: citric acid and hydrochloric acid Temperature: 95–50 °C Time: 90–180 min pH 2.5–4.0 Ratio (w/v): 1:10–1:25	3.6–7.0: citric acid 5.0–6.0: hydrochloric acid	[27]
	Solvent: hot aqueous citric acid (4 % w/v) Temperature: 50 °C Ratio (w/v): 1:25	10.5	[1]
	Solvent: nitric acid (2 M) Temperature: 30, 50, 70, 90, 100 °C Time: 30, 60, 90, 120, 150 min pH 2.5	11.7: 150 min, 100 °C	[31]
	Solvent: nitric acid Temperature: 100 °C Time: 30 min pH 3.5 Ratio (w/v): 1:25	10.7	[7]
	Solvent: citric acid Ratio (w/v): 1:25 pH 3.0 Temperature: 85 °C Time: 90 min	6.2	[32]
	Solvent: ascorbic acid (0.25 % w/v) Temperature: 95 °C Time: 45 min pH 2.5 Ratio (w/v): 1:10	4.2	[33]
	Solvent: citric acid (4 % w/v) pH 3.0 Temperature: 95 °C Time: 95 min Ratio (w/v): 1:25	8.3	[21]

Table 1. Continued.

Extraction type	Extraction parameters	Yield pectin [%]	Ref.
Microwave–assisted	Solvent: citric acid and hydrochloric acid Microwave power: 180, 300, 450, 600 W Time: 10–30 min	42.0	[38]
	Solvent: water Microwave power: 750 W Time: 15 min Ratio: 1:2.5	9.3	[25]
	Solvent: water pH 2.5 and 12 Temperature: 70, 85, 100 °C Time: 5, 15, 25 min Ratio (w/v): 0.030, 0.045, 0.060	17.2–34.2	[26]
	Solvent: oxalic acid pH 1.16–2.84 Time: 6.6–23.4 min Ratio (w/v): 1:15–1:30	1.9–9.6	[34]
Assisted ultrasound	pH 2.5 Temperature: 60 °C Time: 40 min Amplitude: 90 % with 10 s pulses Ratio (w/v): 1:25	8.3	[19]
Enzymatic	Feedstock concentration 6.0 % 40 µL g^{-1} of enzyme, Time: 18.54 h	10.2	[19]
	Feedstock concentration 0–82.9 µL L^{-1} of enzyme, Temperature 50 °C pH 5	8.0–13.5	[37]

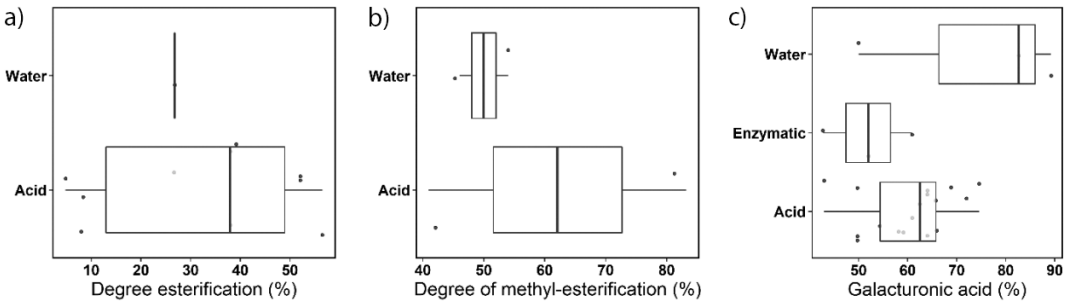

Figure 2. Effect of cocoa pod husk pectin extraction method on the esterification (A) and methyl esterification (B) degrees, and galacturonic acid content (C).

In this regard, pectin extraction with hot water and neutral pH showed to double the yield (23.3 %) compared with a 4 % w/v citric acid extraction method [1]. These results may be associated with a better interaction of water with the hydroxyl bonds of pectin. On the other hand, it has been reported that water-extracted pectin is particularly rich in uronic acid content compared with acid-extracted pectin, such as hydrochloric acid [27]. It is also possible to obtain high contents of methoxyl esters by increasing the pH (24 % and 55 % for pH 2.5 and 7, respectively). These water-soluble pectic fractions are highly acetylated and their structures consist mainly of low-esterified homogalacturonans (HG) and type I homogalacturonans (RG-I) with galactan or arabinogalactan side chains [10].

For the CPH pectin treated under acidic conditions with citric acid a pH of 2.5 has been considered as ideal in function of yield, i.e., the result is about doubled (9.0 %) with respect to that obtained at neutral pH, namely, 5.0 %, corresponding to the maximum amount of extractable pectin [25]. Temperature is also a contributing factor to improve extraction performance under acidic conditions [10]. The heated acid helps to solubilize pectin, producing demethylation and fragmentation of the polygalacturonic chain and other pectic components retained in the cell wall (protopectin), thus increasing the pectin yield [25, 27].

So far, it has been reported that the highest pectin yield is obtained using citric acid at pH 2.5 at 95 °C for a time of

1.0–3.0 h [25, 27]. Furthermore, Vriesmann et al. [30] found that pH variation ranging from 1 to 3 had no significant effects on pectin yield and uranic acid content. These authors recommend that a possible condition to maximize the yield of pectin from cocoa pod husks could be the use of aqueous citric acid at pH 3.0, 95 °C, for 95 min to achieve approximately 0.9 g kg^{-1} yield.

Chan et al. [27] reported that in acid extraction processes an increase of temperature can lead to a lower galacturonic acid content by generating an accelerated acid hydrolysis of pectin sugar side chains [27]. For example, it has been observed that an increase in extraction temperature from 50 to 95 °C using citric acid at pH 2.5 produced pectin with a higher degree of methylation (DM) in the range of 38–58 %, associated with 31.2–45.4 % of galacturonic acid. On the other hand, the degree of acetylation (DA) of pectin depends largely on the nature of the extractant and a combination of factors such as extraction temperature and type of extractant [27].

Notably higher degrees of esterification and degree of methyl esterification can be observed in pectin extracted by acid hydrolysis (Fig. 2). The importance of this relation influences the mechanical properties of pectin gels. Indeed, they depend on galacturonic acid and DM content, showing better stability with higher DM and galacturonic acid content [39]. On the other hand, associated with the degrees of esterification, different emulsifying, texturizing, and gelling properties have been observed [40]. In general, high-DM pectin has a degree of esterification higher than 50 % (thickening and gelling properties), whereas low-DM pectin has a lower degree of esterification.

Research on enzymatic extraction using CPH is still not well investigated if compared with other plant biowaste such as citrus [35] or apple [36]. Few works are presented recently in literature, particularly Hennessey-Ramos et al. [19] found that the enzymatic extraction generated higher pectin yields (10.2 %) compared to the chemical process (8.02 %) that used solutions of citric acid as solvent. However, pectin extracted by an enzymatic method showed also lower galacturonic acid content (Fig. 2). Similar results were found by Mendoza et al. [37], where the reported extraction yield was 13.5 %, that was related linearly with the enzyme volume load. Moreover, another advantage of the enzymatic method is the temperature reduction, which would implicitly reduce the environmental impact of the extraction process [19].

Moreover, sonication and microwave have also been coupled with traditional and enzymatic methods, leading to a reduction on energy cost of the process by operating at lower temperatures [19]. Indeed, an extraction yield of 8.2 % with a galacturonic acid content of 42.77 % by assisted sonification has been reported [19]. Microwave heating has shown little influence on the yield (9.3 %), with an increase of only 0.3 % compared to chemical treatment (9.0 %) under the same conditions [25].

Pangestu et al. [34] presented an optimized oxalic acid microwave-assisted method (pH 1.16, 25.0:1 v/w, 15 min) obtaining an extraction yield of 9.6 %, that could reduce the times reported for traditional methods. Interestingly, an increase in extraction yield (47 %) was also found using citric acid and microwave heating for 30 min at 300 W [38].

2.3 Physicochemical Characteristics of Pectin Extracted from Cocoa Pod Husk

The composition of pectin is influenced by the botanical source, method of extraction, and environmental factors [39]. Pectin from different sources has not the same gelling ability due to variations in molecular size and degree of methoxylation [39]. In particular, the effect of the extraction method can be seen in Fig. 3, in agreement with the data reported for CPH pectin. For moisture, the reported results were very variable

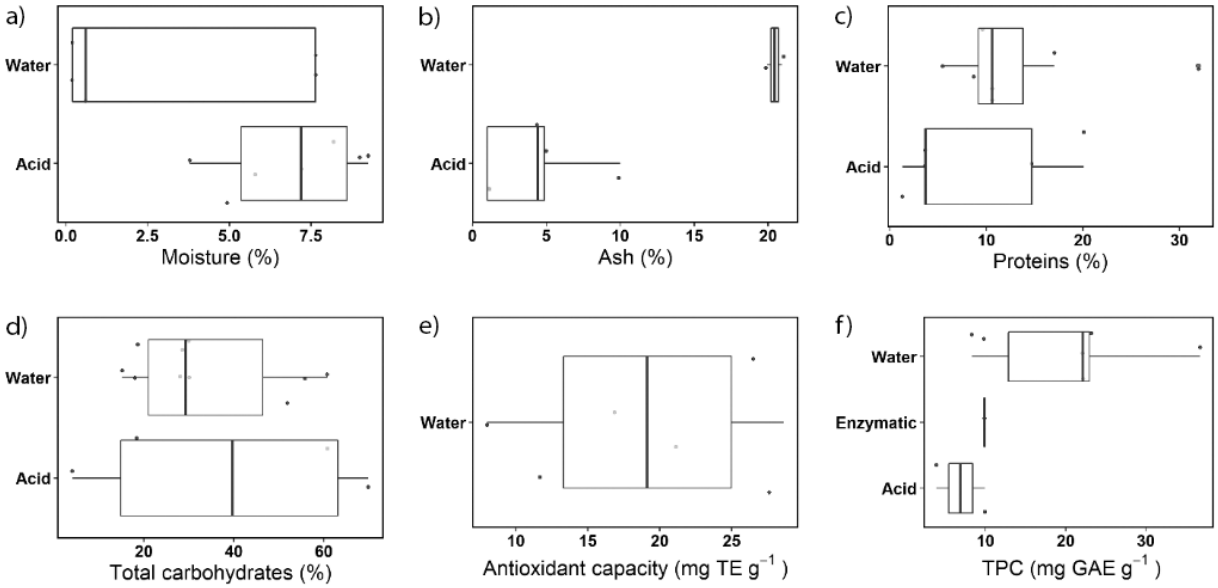

Figure 3. Effect of extraction method on physicochemical properties of pectin: moisture (A), ash (B), proteins (C), total carbohydrates (D), antioxidant capacity (E), and total polyphenolic content (F).

where chemical extraction exhibited lower values (3.5–9.0 %). The optimization of this parameter is fundamental in order to preserve the shelf life of pectin, to prevent oxidation and hydrolysis by microbial activity [38].

Additionally, when pectin is extracted by hot water, the lower values of moisture improved its mechanical properties [1]. Furthermore, acid extraction and hot water provided different values of pectin ash content. In particular, Oloye et al. [31] reported the formation of a gel by using pectin extracted with hot water, characterized by an ash content between 4.14–5.07 %. Indeed, a lower content of ash (around 10 %) is considered suitable for the gel formation.

The total polyphenol contents (TPCs) are favored by extraction with water at neutral pH than by extractions with acid (pH 1.5–3.0) or enzymes (pH 4.5–5.0) (Fig. 3). This may be due to a greater affinity of phenolic compounds with water than with acids such as citric acid. At high pH values, the deprotonation of the hydroxyl groups present in polyphenols can occur [26]. The importance of TPCs lies in their antioxidant, antiviral, antibacterial, and radical scavenging potential. For example, it has been found that TPCs from CPH pectin can significantly promote the resistance of *L. vannamei* against *V. alginolyticus* infection and hypothermic stress [23].

Finally, very similar values of protein content are reported for the hot water and acid extraction (5–31 % and 1.3–20.7 %, respectively). Furthermore, no substantial differences are observed for polysaccharide content under acid and hot water extraction conditions. In particular, rhamnose (52.62 %), fructose (24.73 %), and glucose (15.21 %) have been reported as the main components [23]. Other authors have found rhamnose and galactose as the most abundant neutral sugars, followed by xylose and arabinose [21]. These concentrations vary according to the pectin source, e.g., pectin extracted from grapefruit peel was characterized by high concentration of monosaccharides galacturonic acid, rhamnose, and galactose [35].

The amount and composition of neutral sugars have a great influence on their rheological properties and structure, because these provide hydroxyl groups that stabilize the gel and contribute to the formation of hydrogen bonds to immobilize free water [40]. Furthermore, protein from other sources is characterized by a lower content ranging from 1.1 to 7.2 % in sugar beet pulp [41] and banana and papaya mixed peels [42] using acid citric solutions

3 Application of Cocoa-Based Pectin in Food and Biomedical Applications

3.1 Application of Cocoa Pods Pectin in Food Field

Cocoa pods represent a suitable source for extracting pectin for food applications, due to the abundance of these food biomass in producing countries in the cocoa belt, between 20 degrees latitude south and north around the equator. Particularly, in literature different works are focused on the physical properties, mainly the rheological features of this type of pectin, to demonstrate its technological feasibility as food stabilizer including gelification and thickening agent.

When studying gel formation, it was found that CPH pectin characterized by a low methoxylation degree did not form gels at pH higher than 4.5 in presence of Ca^{2+} ions [7]. While, it has been reported that pectin forms gels under high sucrose concentration of 0.6–0.65 % (sugar g kg^{-1} (w/w)) leading to reduced water activity solutions and low pH (2.5–3) [7, 19, 30, 43]. Moreover, other gelling conditions have been reported, e.g., Barazate et al. [29] described the gelification of the extracted pectin at 0.5 % concentration with the addition of sugar (30 %), $CaCl_2$ (30 mg pectin g^{-1}), and citric acid (0.5 %). This gelled pectin was characterized by a degree of esterification over 48 % while at lower values viscous solutions were generated. As an example of application, the gelled pectin at 0.4 % concentration has been used to prepare a strawberry jam using 65.5 % fresh fruit, 34.0 % sugar, and 0.1 % citric acid, resulting in a product with moderate acceptance in sensory analysis [29].

Another important physical property of pectin is the flow behavior. Different works have evaluated this characteristic by fitting the flow curves obtained from diluted pectin in distilled water at different concentrations (up to 2 wt %) at 25 °C with different models based on, e.g., the Ostwald-de Waele relationship (power-law fluid) [10, 19, 30] or Williamson equation [33], that is used with low shear rates where the power law model fails. When the power law works, the results exhibited flow index values of 0.38–0.57 [44] for the pectin extracted with hot water, 0.62 [30] and 0.83 [19] under citric acid and enzymatic conditions, respectively.

When the Williamson equation was applied, lower values were reported ranging from 0.062 to 0.095 [33] for pectin extracted with ascorbic acid. All these results indicated that pectin showed a non-Newtonian flow and a pseudoplastic behavior [7, 19, 30, 33, 42, 45] where the viscosity decreased with the increase of the shear stress [43] and pectin concentration [19, 41]. Furthermore, Pryangini et al. [33] reported values of the consistency factor k of 1.48 and 1.44 at 0.5 % and 2 % concentration [33]. The consistency factor was proportional to the viscosity of the samples.

Storage and loss modulus have been also evaluated in CPH pectin/water solutions for studying the sol-gel transition. De Oliveira Petkowicz's research group [7, 30, 33, 43] reported that a pectin solution (0.5 g kg^{-1}) presented a better gel behavior, where $G' > G''$, under sucrose concentration of 60 % and pH values from 2.5 and 2.7, by applying low frequencies up to 10 Hz at 25 °C [7, 30, 43]. However, the same authors found different results with a viscous character ($G' < G''$) with similar processing but increasing the pH to 3.0 [7]. Additionally, they reported $G' < G''$ for frequencies higher than 0.1 Hz described the samples as more elastic or weak gel-like behaviour systems [7, 30]. Thus, a change in the sol-gel behavior of the pectin solutions was observed for pH values lower than 3.

Moreover, literature reported the potential of the CPH pectin as emulsifier and stabilizer when added to an oil/water nanometric emulsion. Particularly, the droplets of the pectin-based emulsion exhibited an area volume of 113.6 nm, which increased to 162.0 nm after 28 days of storage at 4 °C [32]. Furthermore, when complexing the system with whey protein hydrolysate, the droplet sizes presented lower values around 86.9 nm and the emulsion did not show significant changes during the storage time. The authors attributed this behavior to

the steric repulsion originated by the soluble complex adsorption layers around the oil droplets.

Another use of CPH pectin is to produce edible films to be used as packaging material. Literature reports works on the mixing of cocoa pectin with glycerol as plasticizer and the presence of calcium carbonate as crosslinker [46] or other polysaccharides such as cassava starch [45]. Generally, high concentration of $CaCO_3$ caused a hard and brittle behavior of the edible films. To reduce this condition, the addition of glycerol or sorbitol in different concentrations up to 8 % was proposed, because these plasticizers increased the percentage of elongation. Indeed, 1 % glycerol concentration provided elongation higher than 2 % and 3 % glycerol concentration. However, when adding glycerol at a concentration of > 1 %, the mixture reached a saturation point which caused the interaction between glycerol molecules with the starch chains causing a steric obstruction. This reduced the elongation value [46]. Moreover, water vapor permeability increased with higher rate of plasticizers to the edible films [43, 46].

Recently, Lee et al. [23] reported an application of the CPH pectin as bioactive compound for improving food production, particularly applied for shrimps. Pectin was injected in white shrimps (*L. vannamei*) at concentrations up to 6 µg for up to seven days to produce an immune response against *V. alginolyticus*, a common Gram-negative bacteria in aquaculture, that has an 80 % mortality rate for shrimps [47]. The highest administration (6 µg) of cocoa pectin increased the phagocytic and clearance efficiency and the survival ratio against *V. alginolyticus*. Moreover, phenoloxidase activity in the granular and semigranular cells, which are the main immune hemocytes that fight invasion by foreign substances [48], was elevated at 1-day post injection. The results demonstrated the biocompatibility and immunostimulation of cocoa pectin for *L. vannamei* being a safe and feasible bioactive compound to be used for further feeding trials.

3.2 Application of Cocoa Pods Pectin in Biomedical Field

The properties of CPH pectin for biomedical applications are not well exploited compared to other pectin sources. Indeed, literature reports a few research works on the synthesis and characterization of cocoa pectin extracted by using water or acidic solutions. In this section, recent works are described that showed great potential for using CPH pectin in this field.

Firstly, CPH was found to be suitable as pharmaceutical excipient, because its physicochemical parameters, such as compressibility index (14.58 %), Hausner ratio (1.17), and angle of repose (∼ 38°), showed a cohesive behavior with good flow properties [1]. These indicators can provide an indirect idea about the bulk properties of a powder for the further excipient manufacturing [49]. Related to this, the rheological properties of the polysaccharides mentioned above within food applications [10, 30, 43, 50]) are also suitable for pharmaceutical excipients purpose [51]. As example, carbon double bonds were incorporated into citric pectin to increase its synergistic viscosity, resulting in a better adhesive material for pharmaceutical systems [52].

Moreover, in addition to these physicochemical requisites, Adi-Dako et al. [50] demonstrated the safety in long-term administration. Indeed, in-vivo studies showed no toxicity when pectin was dosed up to 71.4 mg kg^{-1} to male and female rats. After a 90-day period there was no evidence of adverse effects on, e.g., target organs, biochemical markers, food and water intake, and hematological indices, showing normal histopathological findings [17, 50]. However, in female rats a reduction of the alkaline phosphatase values on day 30 at medium and high doses was observed. These similar results were found by other authors which administered citrus pectin to rats [44]. Even though at reduced levels of the alkaline phosphatase, its function of producing systemic inflammatory mediators was maintained [53]. Regarding the hematological parameters, an incidental decrease in the mean cell volume after day 30 was detected, when to male rats pectin at a dose of 7.14 mg kg^{-1} daily was administered [50]. However, at the end of the study, no toxicological relevance was reported.

Another application of CPH pectin is for improving antimicrobial treatments, that have been assessed by agar diffusion and determining the minimum inhibitory concentration [50]. CPH pectin presented some potential antimicrobial activities, although lower compared with standard antibiotic agents such as ciprofloxacin and a combination of amoxycillin with clavulanic acid [1]. Particularly, the extracted pectin showed moderate dose-dependent antibacterial activity in concentrations of 1.25–10 mg mL^{-1} against *S. aureus, P. aeruginosa, B. subtilis, E. coli, S. typhi*, and *Shigella* spp. The minimum inhibitory concentrations of cocoa pectin were reported against Gram-negative than Gram-positive bacteria, while antifungal results against *A. niger* were found four times higher than nystatin, a common antifungal agent used as control [1].

Furthermore, the ability of CPH pectin, after acidic and water extraction treatments, was tested to tune the drug release. Amponsah et al. [16] described pectin-based multiparticulate matrices prepared by mixing CPH pectin, $CaCl_2$, hydroxypropyl methylcellulose and carbamazepine (∼ 100 mg), that is a widely used and poorly water-soluble antiepileptic drug [54]. These products were tested in simulated intestinal conditions (pH 6.8, 37 ± 0.5 °C, and 50 rpm) for 8 h, showing an initial burst followed by a slow release of drug indicative of a biphasic release pattern useful for the maintenance of sustained drug concentration. The authors reported that ∼ 80 % of carbamazepine was released within 8 h for all prepared formulations. Then, they evaluated the administration of 200 mg kg^{-1} of carbamazepine to male Sprague-Dawley rats, over a period of 36 h, through the aforementioned formulations. Pure carbamazepine powder and commercial tablets of the anticonvulsant were used as controls. It was found that pectin-based multiparticulate matrix of carbamazepine exhibited a high peak plasma concentration, prolonged total drug exposure, and led to a long half-life. Additionally, based on the carbamazepine serum concentration, the authors suggested a more controlled absorption rate exhibited by the citric acid-extracted pectin compared with the hot water-soluble extracted pectin. Thus, CPH pectin in interaction with the other components played a role in enhancing the pharmacokinetic parameters and may aid in reduction of dosing frequency.

Furthermore, preliminary studies are reported in literature for evaluating the release of hydrocortisone from a pectin-based matrix on simulated gastrointestinal conditions [55]. Tablets were manufactured by compression and wet granulation techniques with CPH pectin extracted under citric acid solution and water. The tablets also included hydroxypropyl methylcellulose (15 %) as coating agent and functional polymers (12.5 %) for sustained release in simulated gastrointestinal digestion in addition to hydrocortisone (~ 10 mg). Regarding the physicochemical properties, no drug-pectin interactions were found after analyzing the tablets by infrared spectroscopy (FTIR). Principal component analysis (PCA) revealed that pectin extracted with hot water presented a similar chemical behavior to pure hydrocortisone compared with pectin extracted with citric acid. However, a higher number of samples needed to confirm the information provided by PCA. In terms of dissolution profile, the optimized tablets exhibited a lag phase of ~ 6 h followed by accelerated drug release in the simulated conditions. Furthermore, citric acid-extracted pectin showed greater suppression of drug release in aqueous medium than pectin extracted with hot water.

After these findings, the authors evaluated the pharmacokinetic profiles of CPH pectin-based hydrocortisone capsules in vivo in another research work [56]. Capsules containing hydrocortisone (10 mg), prepared by CPH pectin crosslinked with $CaCl_2$ or zinc acetate, were administered orally to Sprague-Dawley rats. The results showed that pectin-based capsules exhibited a higher exposure, greater bioavailability and versatility compared with the commercial tablets containing cortisol. To notice, the capsules crosslinked with $CaCl_2$ presented a delay on the release profile compared with the other capsules crosslinked with zinc acetate.

Finally, CPH pectin can be chemically modified (deacetylated and de-esterified) to promote distinct and increased biological activities in relation to the initial fraction. Indeed, this modified form of the pectin has been tested to investigate the development of cellular and humoral immunity [18]. The authors isolated peritoneal macrophage cells from mice and cultivated them in the presence of modified pectin on concentrations up to 400 g mL^{-1} (Fig. 4) and they observed an increase of ~ 80 % of macrophages with the activated-stage morphology for cells incubated at 100 and 200 g mL^{-1} with a triggered secretion of pro- and anti-inflammatory mediators by these cells. However, the studied pectin did not stimulate yeast phagocytosis by macrophages.

This result is in contrast with the work published by Busato et al. [57] where the pectin extracted from *B. oleracea* showed a phagocytic activity of peritoneal macrophage cells increased by 63 %. The phagocytic behavior was also observed by Kuo et al. [58] who proposed a different approach. It consisted of CPH pectin (5 g kg^{-1} diet) and/or *L. plantarum* (up to 1010 cfu kg^{-1}) which were introduced to the diets of *L. vannamei* for a 56-day feeding trial. These shrimps presented higher survival rate and shown increased immunostimulant and phagocytic activity and clearance efficiency in response to *V. alginolyticus* [59].

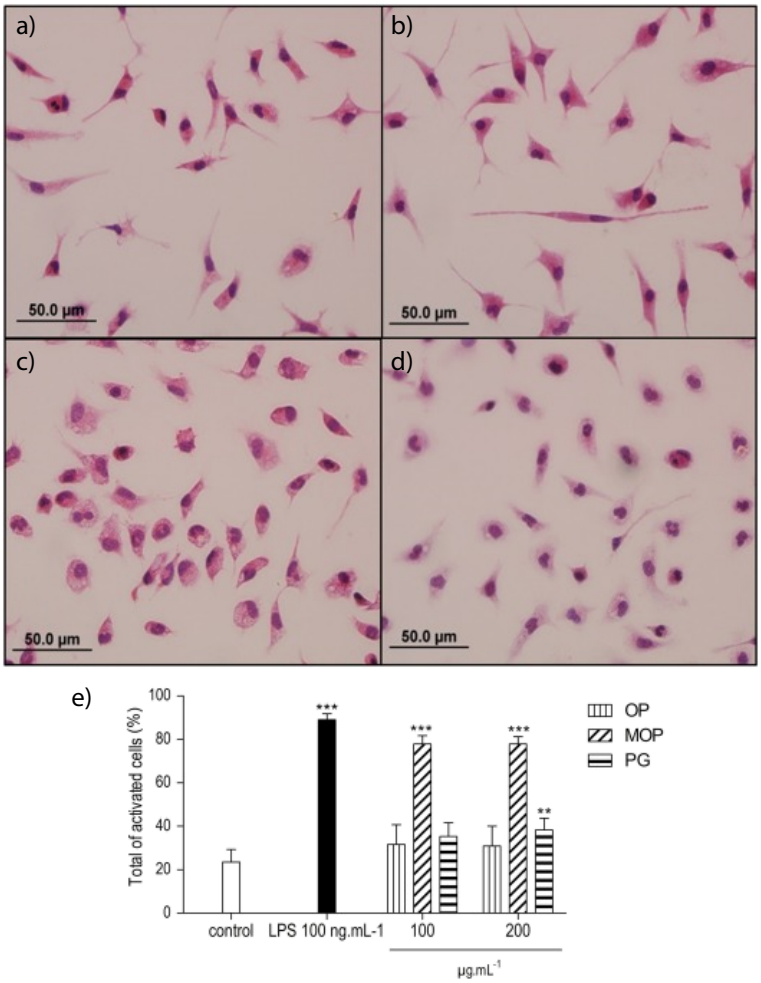

Figure 4. Representative micrographs of mice peritoneal macrophages incubated with acetylated pectin (OP), modified pectin (MOP), and commercial homogalacturonan (PG) at concentrations of 200 µg mL^{-1}. After 48 h of treatment with the polymers at 37 °C under 5 % CO_2, the cells were processed for light microscopy by staining with hematoxylin-eosin. Control (A), OP (B), MOP (C), and PG (D). Percentage of activated macrophages in relation to total counted macrophages (E) [18].

4 Current Challenges of Pectin Extraction from Cocoa and its Translation in Industry

Following the circular economy principles, green procedures are fundamental to be considered for extracting pectin from cocoa biowaste, including pod husk, because this can be extremely beneficial to minimize the environmental impact, making the processing extraction more cost- and time-efficient, and therefore sustainable. Particularly, scientists and researchers from both academia and industry state the "green extrac-

tion" term and establish the six principles that intend to act on the main inputs and outputs regarding a global extraction process (Fig. 5).

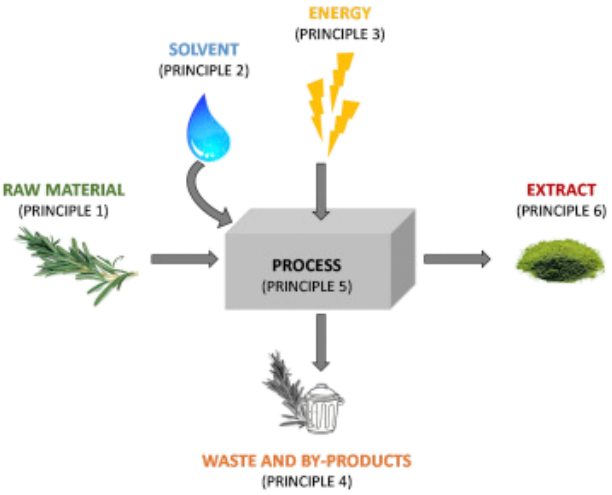

Figure 5. Essential inputs and outputs of the extraction process related to the six principles of green extraction [57].

In this regard, energy management is the key to saving energy and reducing part of the cost of the process. Within the current literature there were no reports about energy consumption of the extraction of pectin from CPH. Therefore, there is a need to optimize the use of energy on the different unit operations involved in the extraction process. Particularly, the cocoa-producing countries are present on the equatorial zone; therefore, solar drying should be investigated specifically to reduce the water content of the raw biowaste mass and to dry the hydrogel formed after the ethanol precipitation of the pectin.

Additionally, energy consumption during the extraction can be reduced by lowering the temperatures as much as possible without affecting the quality and extraction yield and assisting the procedures with ultrasound and microwaves. In many extraction processes the application of these technologies results in a reduction of the duration, and therefore energy consumption compared to the conventional process, and, mainly, an increased extraction yield [61]. These procedures help to face the global need to save energy. In this sense, patents on biocatalytic extractions, where microorganism and/or an enzyme with cellulase activity are used for treating mainly orange juice or biowaste mass to release pectin [61], are an interesting alternative that can reduce the use of energy, because their working conditions are in the range of 20–37 °C. Other advantages of using biocatalytic methodologies are the removal of methyl esters without the breakdown of pectin, block-wise de-esterification, and avoiding chemical waste generation [62].

Moreover, the overuse of ethanol (~ 96 %) is crucial for precipitating the pectin, washing, and removing its impurities. Thus, considerable volumes of solvent are mentioned in the applied methodologies (enzymatic or acidic), and after its technological purpose these large quantities of used ethanol needs to be disposed. In many cases, solvents can be regained after the reaction through distillation or a filtration [63]. Therefore, investigating ways to recover, regain, reuse, or reduce ethanol are crucial to reduce economic costs and the environmental impact of the cocoa pectin extraction process.

Furthermore, a process scale-up for extracting pectin is another aspect that needs to be investigated and the literature presented optimized methodologies, but several steps should be arranged before translating them into a validated industrial process. Particularly in the cocoa belt country, the supply of the biowaste mass could be reduced due to the CPH deterioration because of the humid climatic conditions. Furthermore, the provision of materials and reagents for pectin extraction, such as microorganisms, enzymes, or buffers, is fully imported causing significant delays of the process.

Additionally, the construction of a pilot plant to confirm all the data acquired at laboratory scale can be investigated. Thus, an effective translation in addition to gain a detailed knowledge of chemical engineering should consider the analysis of crucial factors on the producing areas such as landscape, environmental conditions, way of organizing, executing, and sociocultural characteristics [64]. Particularly, for successful industrial application, Talekar et al. reported that firstly it is necessary to enhance pectin methylesterase (PME) productivity by genetic modification and optimization of culture conditions [62]. Particularly, the use of a bioreactor, applied successfully to the bioconversion of agricultural waste into poly-c-glutamic acid in scale-up fermentation [65], can be proposed also for pectin extraction conducted by creating a more stable and suitable processing environment.

Finally, extracted CPH pectin has been reported to contain a wide range of macro- and microminerals, as well as polyphenol molecules, offering opportunities of this polymer to perform as a plant-based antimicrobial agent and nutraceutical [1]. Particularly, it is interesting to deeply investigate pectin composition and its potential use in food and biomedical scenarios, targeting spoilage organisms, foodborne pathogens, medical-related microorganisms, or spores. However, this scope could be extended also to cosmeceuticals.

Furthermore, the application of extracted pectin from CPH on industrial fields should be more investigated. As example, pectin can be used as building block (acting as polyelectrolyte) in manufacturing nanotechnology, like the layer-by-layer assembly, applied in developing new drug delivery systems. CPH combined with its own antioxidants and/or other components, i.e., polysaccharides, plasticizers etc. can open new scenarios for developing materials with improved properties. Finally, after extraction, several debris will result from the overall reaction. Exploring the potential uses of these residues is interesting because the system can be expanded beyond the extraction of pectin to other applications, such as the synthesis of carbon-based materials to be employed in different fields of engineering, including the biomedical area [66].

Conflicts of Interest

The authors declare no conflict of interest.

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Abbreviations

CPH	cocoa pod husk
DM	degree of methylation

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Biomass derived from cocoa pod husk (CPH) can be a potential source of bioactive compounds aligned with the circular economy. This review focuses on pectin extracted from CPHs, providing a critical analysis of the advantages and limitations of the current extraction methodologies, new perspectives for its characterization, and applications in different fields ranging from food to biomedical fields.

Cocoa Pod Husk: A High-Pectin Source with Applications in the Food and Biomedical Fields

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