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REVIEW ARTICLE

Recent advances in bio-based extraction processes for the recovery of bound phenolics from agro-industrial by-products and their biological activity

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ABSTRACT

Usually found bound to other complex molecules (e.g., lignin, hemicellulose), phenolic compounds (PC) are widely present in agro-industrial by-products, and their extraction is challenging. In recent times, research is starting to highlight the bioactive roles played by bound phenolics (BPC) in human health. This review aims at providing a critical update on recent advances in green techniques for the recovery of BPC, focusing on enzymatic-assisted (EAE) and fermentation-assisted extraction (FAE) as well as in the combination of technologies, showing variable yield and features. The present review also summarizes the most recent biological activities attributed to BPC extracts until now. The higher antioxidant activity of BPC—compared to FPC—coupled with their affordable by-product source make them medicinally potent and economically viable, promoting their integral upcycling and generating new revenue streams, business, and employment opportunities. In addition, EAE and FAE can have a biotransformative effect on the PC itself or its moiety, leading to improved extraction outcomes. Moreover, recent research on BPC extracts has reported promising anti-cancer and anti-diabetic activity. Yet further research is needed to elucidate their biological mechanisms and exploit the true potential of their applications in terms of new food products or ingredient development for human consumption.

KEYWORDS

Phenolic compounds; agro-industrial by-products; bound phenolics; bio-based extraction; antioxidant activity

Introduction

Phenolic compounds (PC) are organic compounds naturally produced by plants as secondary metabolites. PC possess at least one aromatic ring with one or more hydroxyl groups in the structure (de la Rosa et al. 2018; Haminiuk et al. 2012) and are secreted by plants in high amounts, especially in periods of stress (Vuolo, Lima, and Maróstica Junior, 2018). Currently, more than 8,000 PC have been described, and they can be broadly classified according to their molecular structure in (1) flavonoids—which are the most abundant PC in the plant kingdom—and (2) non-flavonoids (Del Rio et al. 2013). PC are important molecules to human health because—besides showing a remarkable antioxidant activity (Vuolo, Lima, and Maróstica Junior, 2018)—they are biologically active substances that have shown potential in many different fields (e.g., anti-inflammatory, anticancer, antimicrobial, antidiabetic, antihypertensive…), and these biological activities have been extensively reviewed (Fraga et al. 2019; Manach et al. 2004; Medina-Remon et al. 2013; Tomás-Barberán and Andrés-Lacueva, 2012; Zhang et al. 2022).

Recently, there has been an increased interest in the recovery of PC and other biomolecules (e.g., carotenoids) in plant by-products as a way of upcycling this material otherwise wasted (Baiano, 2014) or used by biofuel production (Koryś et al. 2019; Taghizadeh-Alisaraei et al. 2017). In fact, plant by-products contain high amounts of PC and other biomolecules (Baiano, 2014; Dzah et al. 2020), which makes more than interesting the possibility of upcycling this waste stream for the benefit of human health. According to the Food and Agriculture Organization (FAO), the most important food loss in the agro-food industry before distribution and retail worldwide occur in post-harvest (28.35%), pre-harvest (8.65%), and processing (5.5%). In addition, considering that roots, tubers, oil-bearing crops, fruits, and vegetables account for a whopping percentage of 47% of all food losses (Socas-Rodríguez et al. 2021); the upcycling of this waste stream is not only interesting but needed.

In the food processing industry, the agro-industrial by-products are of great importance. In the fruits industry, for example, by-products such as bagasse, peels, stems, shells, and seeds represent more than 50% of fresh fruit and have

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at times a nutritional or functional content higher than the final product. In fruit processing, these by-products are always going to be produced, so solutions must be sought to reduce serious pollution issues (Green House Gas emissions) and high handling costs (handling of solid waste in landfills). A sustainable alternative is the use of these by-products in the generation of new bio-based value-added products such as PC. Currently, industries are interested in innovations to obtain "zero waste", these actions help to transition toward a circular economy and can directly impact the Global Sustainability Goals (SDGs).

Nevertheless, agro-industrial by-products have a very complex composition, being built mostly by polysaccharides such as lignin, cellulose, or hemicellulose, making the extraction of PC quite a challenge. Within these complex matrices, PC can be found in different forms depending on the type of bound they present. Rocchetti et al. (2022) recently published a very interesting work summarizing the structural diversity of PC and identifying the different sorts of bounds that these compounds can present and, more importantly, the nature of the compound to which they can be bound. Generally, they present two big groups of PC, namely free phenolic compounds (FPC) and bound phenolic compounds (BPC). On the one hand, FPC is those generally soluble in aqueous or organic solvents and are either free of any interaction or can be bound to a low-molecular-mass moiety, such as sugars or oligosaccharides, fatty acids, or low molecular weight oligopeptides (Schefer, Oest, and Rohn, 2021; Tian et al. 2020). On the other hand, BPC is not soluble possibly due to the interaction with higher molecular weight compounds, such as proteins, cellulose, or lignin (Rocchetti et al. 2022). The BPC is usually bound with plant cell wall compounds with covalent bounds (e.g., ether, ester, or C–C), which difficult their extraction. Pectin and hemicellulose are the most important polysaccharides interacting with BPC (Figure 1), and these interactions have been found to be dependent on the degree of methylation and metal ion present in the matrix (Siemińska-Kuczer, Szymańska-Chargot, and Zdunek, 2022).

The nature of the compounds makes FPC relatively easy to extract through conventional liquid-solid extractions, and it is generally the first step toward the extraction of the BPC (Wang et al. 2020). In contrast, the extraction of BPC is more tedious, and it usually requires chemical digestion of the insoluble material to recover a higher percentage of these compounds. The extraction of BPC in specific agro-industrial by-products has been explored using different techniques and has been reviewed recently (Dzah et al. 2020; Hu, Yang, and Chang, 2021). However, the vast majority of articles published mainly focus on physical and/or chemical techniques, including but not limited to the use of deep eutectic solvents, supercritical fluid extraction, or ultrasound-assisted extraction (Panzella et al. 2020). In addition, the use of different technologies in the same extraction process is often overlooked.

The biological properties of polyphenols have mostly been investigated as FPC, ignoring the BPC. Information on the biological activity of BPC is particularly important as these forms of phenolics often go unnoticed (Sun et al. 2020), possibly because the extraction methods (mechanical, chemical, and biological) are insufficient to completely extract them (Wang et al. 2018). This underestimates the functional potential of the total phenolic (FPC and BPC) present in the agro-industrial by-products.

The present review aims at elucidating the latest advances in the bio-based extraction processes of BPC and FPC from agro-industrial by-products, including enzyme-assisted and fermentation-assisted extractions, concluding with a remark

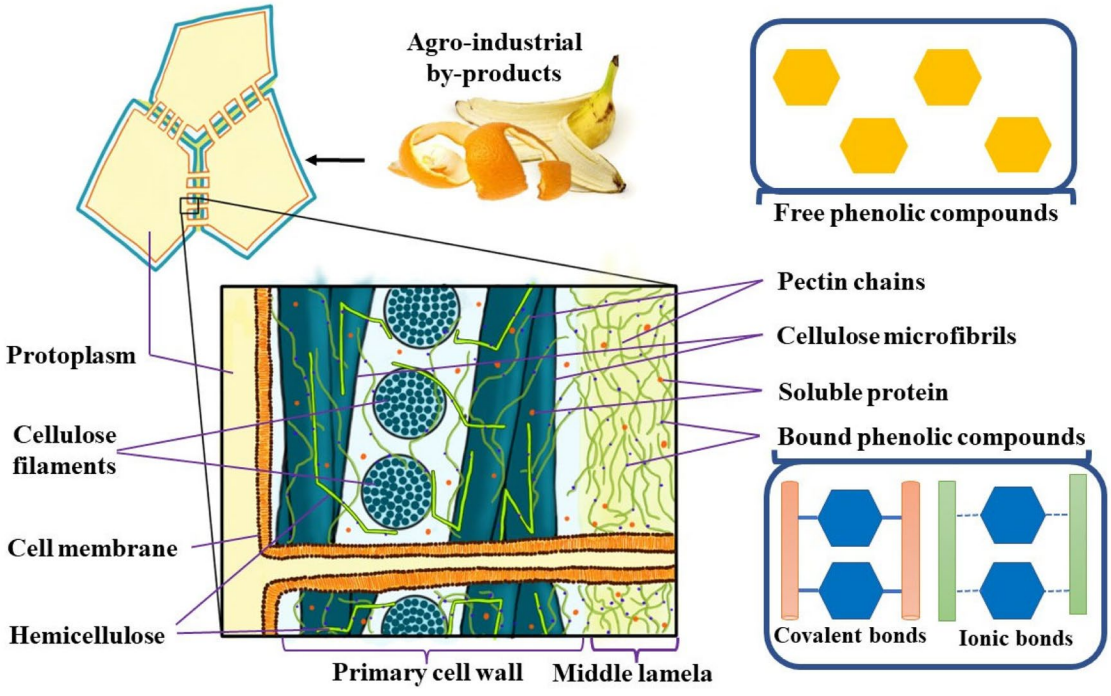

Figure 1. Graphic representation of a plant cell wall and its main components, including the BPC.

on the combination of technologies for the extraction of BPC. In addition, the most important biological activities reported in FPC and BPC are also critically described.

Bound phenolic compounds in plant by-products

Plant by-products rich in polyphenols have been the focus of numerous valorization studies (Sagar et al. 2018). These by-products have grown in interest since they are a significant source of PC, carotenoids, and vitamins, all with known health benefits. Peels, seeds, skins, florets, and pomace are typical plant by-products with interesting phytochemicals that could be used by the food industry. Antioxidant PC have been isolated from date seeds (Al-Tamimi, Alfarhan and Rajagopal, 2021), citrus peel waste (Liu et al. 2021), apple peel (Ranjha et al. 2020), or mango peel (Kaur, Panesar, and Anal, 2022), to name some. Specific phenolics such as the xanthone mangiferin has been industrially extracted from the leaves and bark of mango trees (Lerma-Torres, Navarro-Ocaña, Calderón-Santoyo, et al. 2019) and anthocyanin monomers have been isolated from grape skins (Zhao et al. 2020).

Besides the high presence of PC and other bioactive compounds, plant by-products could also be a significant source of fat, soluble proteins, and carbohydrates. This is important as PCs can be bound to these components in different manners. The most interesting macromolecules are carbohydrates, as they are the most present. The residues coming from agro-industrial production usually still have unbroken carbohydrate chains, mainly composed of dietary fiber (i.e., hemicellulose, cellulose, and lignin), to which PCs are usually bound (BPCs). The complexity of these carbohydrates renders all the different fiber–PCs interactions that have been reported (Palafox-Carlos et al. 2011). Therefore, the full understanding of the fiber–PCs interactions is a requirement to understanding the type of technological process that would be more efficient for their extraction.

Fruit peels and seeds

Citrus

The fruit juice industry generates huge amounts of waste materials every year, consisting of peels, membranes, and seeds. In the case of citrus fruit, almost half of the wet waste consists of peel (Sharma et al. 2017). As with other waste products, the environmental impact of citrus peel could be minimized by exploiting its nutritional and bioactive constituents for a range of applications, notably in protective therapeutics. In a study on the phenolic content of citrus peels, Gómez-Mejía et al. (2019), found that flavanone hesperidin to be the most abundant polyphenol in all the analyzed samples (280–673 mg/g). The flavonoid narangin was also identified in all the extracts in high amounts, while flavonol rutin was determined in the concentration range of 3.3–4.7 mg/g. Lower quantities (<1.4 mg/g) of trans-Ferulic and p-coumaric antioxidants were found in all peel extracts.

The peel of *Citrus sinensis* L. Osbeck, also known as sweet orange, contains a wide range of PC, yet much of it is discarded unused by the processing industries. In a study by Wang et al. (2022), the concentrations of free and bound phenolics in orange peel were found to differ according to the ripening stage of the fruit and the location within the peel. Generally, the highest levels of PC were detected in the peel of immature and semi-mature fruit and the lowest at the mature stage. The glycosylated phenolic fraction was significantly greater than the other three phenolic forms studied: free, esterified, and insoluble-bound. Yet, esterified and insoluble-bound ferulic and p-coumaric acids were abundant, as was glycosylated and insoluble-bound hesperetin. These data provide further evidence that orange peel waste constitutes a feasible source of functional ingredients, whose exploitation would contribute to a circular economy.

Mango

Mango processing generates approximately 14,000,000 tons of by-products per year in the world (Torres-León et al. 2021). The main mango by-products are the seed and peel. Mango peel has an interesting proportion of insoluble and soluble dietary fiber which contains significant amounts of polyphenols, especially phenolic acids such as gallic acid, protocatechuic acid, syringic acid, and ferulic acid; and flavonoids like rutin, quercetin, and kaempferol. The concentration of polyphenols greatly depends on the variety and also de ripeness of the fruit but varies approximately from 8 to 30 mg of gallic acid equivalents (GAE). Gómez-Caravaca et al. (2016) studied the BPC in mango by-products by HPLC-DAD-ESI-qTOF-MS. According to the results, 13 BPC were identified in mango by-products. In a recent review, it was found that mangiferin and gallic acid derivates were the most abundant polyphenols (Marçal and Pintado, 2021).

Tomato

Industrial tomato by-products are mainly composed of peels and seeds, and PC is mostly bound to the structural components of cell walls. Therefore, an extraction method should be used prior to the quantification of these compounds. According to Perea-Domínguez et al. (2018), each gram of tomato by-product contains 104 mg of GAE, of which only 12% are soluble free phenolics, 50% are BPC, 30% acid-hydrolyzable phenolics, and 7% alkaline-hydrolyzable phenolics. Total flavonoids, especially naringenin, are mainly found in the bound fraction, whereas phenolic acids, especially caffeic acid, and p-coumaric, are more abundant in the acid-hydrolyzable fraction (Perea-Domínguez et al. 2018).

Cereals and millets

PC, especially phenolic acids, are found in the bran fraction of cereal grains and occur in free, soluble conjugated, and insoluble-bound forms (Bueno-Herrera and Pérez-Magariño 2020). In an investigation of brown rice, Zeng et al. (2019) reported that the bound phenolic content was dominated by p-hydroxycinnamic acid derivatives,

namely ferulic acid, p-coumaric acid, and diferulic acid. A storage effect on various free and BPC of rice grains has been described (Zhou et al. 2014) and a 15%–20% reduction in phenolic, flavonoid, and proanthocyanin content was observed after storage at 37 °C for 6 months. The proportion of BPC was less affected, suggesting that the pool of FPC is more sensitive to the aging process. In contrast, in a similar study carried out on brown, black and red rice stored for 6 months (Ziegler et al. 2018), an increase in the free phenolic content was observed in brown rice, regardless of the storage temperature (16, 24, 32, 40 °C). Possibly, the BPC, which are esterified/etherified with cell wall components and other macromolecules, was released by hydrolysis. No change was found in the bound phenolic content of red and black rice.

Another group studied the effect of different solvents and temperatures on the extraction of the phenolic fraction of Thai rice by-products (husk and bran). Heated water (from 50 to 80 °C) was the best solvent to extract free and BPC compared to acetone and ethanol. The amount of BPC was greater than the free ones in all the samples studied (Wanyo et al. 2016).

Brewer's spent grains

Brewer's spent grain is an agro-industrial by-product produced by breweries, composed of the barley malt residue after wort manufacture (obtained during lautering of the wort) (Jackowski et al. 2020). This by-product consists primarily of barley grain husks and fractions of pericarp and seed coat layer fragments. It is estimated that worldwide the annual output is around 200 tons of wet spent grain (Socaci et al. 2018). This by-product is currently disposed of or used as a low-value supplement for animal feed, although it contains significant amounts of phenolic compounds (Zuorro, Iannone, and Lavecchia 2019). In these by-products, most phenolic acids are found in their bound form (McCarthy et al. 2013). The content of bound phenolic compounds oscillates between 133 µg/g and 523 µg/g, and that of free phenols between 4.6 µg/g and 23 µg/g (Idehen, Tang, and Sang 2017). Ferulic and p-coumaric acids are the main bound phenolics in brewer's spent grains, while catechin was the most abundant polyphenol in the free phenolic fractions (Birsan et al. 2021).

The high content of bound phenols indicates the need to use hydrolysis for its complete extraction. According to Abdel-Aal et al. (2012), free phenolics in black, blue, and yellow barley can be extracted based on aqueous methanol, whereas bound phenolics were extracted following alkaline hydrolysis. Since brewer's spent grains predominantly contain bound phenolics, chemical or enzymatic hydrolysis protocols are routinely used to release the phytochemicals bound to the cellular-wall components (Birsan et al. 2019). Guido and Moreira (2017) reported that enzyme-assisted extraction is an effective way to release bound compounds and increase overall yield on these by-products; the saponification with NaOH is also a suitable method to extract the bound phenolic compounds from brewer's spent grains (Birsan et al. 2021).

Pomace

Grapes

A residue of grape processing in wine and juice production, grape pomace represents approximately 20% of the total weight of the fruit, and its disposal, therefore, poses a challenge for the wine and grape juice industry (Galanakis, 2017). Jiang et al. (2022) analyzed the bound phenolic fraction of grape pomace after an alkaline extraction and found the main compounds to be conjugated forms of salicylic acid, chlorogenic acid, syringic acid, epigallocatechin, p-coumaric acid, and ferulic acid. The recovery of BPC associated with insoluble dietary fibers was enhanced by alkaline hydrolysis, an analytical technique that breaks their strong linkages with macromolecules (Sanz-Pintos et al. 2017).

Meini et al. (2019) studied a method to optimize the aqueous enzymatic extraction of PC from Syrah grape pomace and then tested the method in other grape varieties. At optimal conditions of temperature and pH, the enzymatic treatment incremented the polyphenolic extraction by 66% and reduced the incubation time and enzyme doses. The type of enzyme, tannase or cellulase, lead to the extraction of different phenolic profiles. For instance, tannase liberated more gallic acid and syringic acid, while cellulase was particularly effective for p-coumaric and malvidin-3-O-glucoside (Meini et al. 2019).

Olives

The semi-solid wastes generated by the olive oil industry, known as olive pomace, have been extensively studied for potential valorization, due to their content of high-value compounds (e.g., dietary fiber, unsaturated fatty acids, and polyphenols). Ribeiro et al. (2021) developed two types of powder from olive pomace with potential use in food formulation as multi-functional ingredients: a liquid-enriched (LOPP) and a pulp-enriched powder (POPP). LOPP, which had a significant content of mannitol (141 g/kg), potassium (54 g/kg), and hydroxytyrosol derivatives (5 mg/g), and high antioxidant and antimicrobial activities, could be explored not only for its health benefits but also as a food preservative. On the other hand, POPP was rich in dietary fiber (620 g/kg) associated with a significant amount of BPC with antioxidant properties (7.41 mg GAE/g fiber DW) and also in unsaturated fatty acids (76% of total fatty acids, similar to olive oil). These combined qualities might give rise to synergic effects benefitting gut health.

Apple

Apple pomace is the solid residue obtained after crushing and pressing apples for juice production. Millions of tons of apple pomace are produced annually, and most of this by-product currently goes to waste, with harmful impacts on the environment (Ghinea and Leahu, 2022). Exploring a strategy to valorize apple pomace, Li et al.(2020) compared different methods to extract FPC and BPC involving base and acid hydrolysis. The content of FPC in aqueous-methanol extracts was 5.56 mg gallic acid equivalents (GAE)/g dry weight (DW) pomace, and the major identified compounds

were chlorogenic acid, quercetin-3-O-galactoside, quercetin-3-O-rhamnoside, and phloridzin. Regarding BPC, sequential base and acid hydrolysis followed by extraction with diethyl ether/ethyl acetate yielded 6.82–8.12 mg GAE/g DW. After base hydrolysis, the major BPC identified in the aqueous-methanol extract were phloridzin, 4-hydroxybenzoic acid, and quercetin-3-O-galactoside, and after subsequent acid hydrolysis, significant amounts of 4-hydroxybenzoic acid and isoferulic acid were also released. When the aqueous-methanol extract underwent acid hydrolysis first, mainly 4-hydroxybenzoic acid, protocatechuic acid, and isoferulic acid were identified, and subsequent base hydrolysis released significant amounts of protocatechuic acid, catechin, and 4-hydroxybenzoic acid. Base hydrolysis was found to be more efficient for releasing BPC than acid hydrolysis, the respective yields being 10.62 mg GAE/g DW and 5.55 mg GAE/g DW.

Other products

Peanut skins

Peanut skins, a waste product of the peanut processing industry, currently have little commercial value despite being significant sources of bioactive PC. Ma et al. (2014) used fractionation to determine the BPC in peanut skins (Ma et al. 2014). After the extraction of the FPC using diethyl ether, the aqueous phase was base-hydrolyzed and acid-hydrolyzed to convert the ester derivatives to their carboxylic acid or flavonoid analogs before analysis by LC-MS. A wide range of PC were released from esters and glycosides, including phenolic acids (hydroxybenzoic acids, ethyl protocatechuate, hydroxycinnamic acids, phenylacetic acid, and phenyllactic acid), stilbenes (trans-piceatannol and trans-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene), flavan-3-ols (e.g., (−)-epicatechin, (+)-catechin, (−)-epiafzelechin, and their polymers (proanthocyanidins)), other flavonoids (e.g., isoflavones, flavanols, and flavones), and biflavonoids.

Sunflower florets

Sunflowers (*Helianthus annuus* L) are grown worldwide to use seeds either as food or to obtain oil. The petioles and the flowers can be used as traditional remedies or to prepare delicacies but most of them are discarded as byproducts of agriculture. To upcycle this waste, Liang et al. (2013) aimed to quantify nutrients and PC in the florets of sunflowers. They identified sixteen PC, nine free and eight bounds, by RP-HPLC-DAD/ESI-TOF-MS and stated that the majority of PC were hydroxycinnamic acid derivatives, mainly 1,5-di-O-caffeoylquinic acid. Only 10% of the total phenolics were bound (193 to 319 mg/100g).

Coffee extracts

Besides being one of the most consumed beverages in the world, coffee is one of the main dietary sources of polyphenols, and the spent coffee that remains after the brewing process is a potential source of bioactive components such as phenolic acids that keep linked to melanoidin macromolecules or other Maillard reaction products. This by-product could be used by the food industry as a potential ingredient to increase the beneficial health properties of other food products. Polyphenols from spent coffee, mainly caffeoylquinic acids, are easily extracted by water/ethanol extraction, a process that has been recently optimized (Solomakou et al. 2022). The alkaline method is the preferable one to determine total (free and bound) PC and the saline method is suitable to quantify ionically BPC.

Caffeoylquinic acids—especially chlorogenic acid—are the most abundant phenolic compound in the coffee brew and spent coffee extract. The work done by Monente et al. (2015) shows that the total amount of caffeoylquinic acid in the lyophilized spent coffee extract was 258 µmol/g, of which 54% were bound. The main phenolic acid, in descending order, were ferulic acid, caffeic acid, p-coumaric acid, sinapic acid, and 4-hydroxybenzoic acid.

Biochemical and microbiological approaches for the extraction of phenolics from agro-industrial by-products

The extraction of BPC has been attempted with several techniques, from solvent extraction (Safdar et al. 2017) to enzymatic extraction (Hemker et al. 2020), or the recently applied technique Ohmic heating (Kutlu et al. 2021). It is difficult to understand how much and how many BPC are extracted when using different extraction techniques, as usually the total phenolic concentration (TPC) is employed as a parameter to understand the extraction efficiency, and this parameter is not necessarily linked to any release of BPC (it can be an increase in free phenolics recovery). Nevertheless, when several extraction techniques are compared, the TPC can be a good strategy to understand changes in the release of PC (free, bound, glycosylated…). Only in some cases, the BPC fraction has been quantified after the extraction using a novel technique (i.e., fermentation (Torres-León, Ramírez-Guzmán, et al. 2019)). Hence understanding the recovery of BPC from vegetable by-products using different extraction methods is highly challenging since the BPC fraction is often not measured. These challenges can be spotted in recent reviews on the recovery and purification of PC from plant by-products (Alexandre et al. 2018; Jha and Sit, 2022; Panzella et al. 2020). For instance, Dzah et al. (2020) have recently summarized some ideas about by-product preparation and extraction to optimize the BPC fraction recovery, with limitations in the reporting of BPC extraction. In addition, the general focus of these reviews has been extensively on the understanding of microwave-assisted (MAE), ultrasound-assisted (UAE), or other conventional techniques such as solvent extraction (Coelho et al. 2020; Panzella et al. 2020). In recent years, more evidence has been added to the field, including the use of novel green technologies such as fermentation, which at the same time makes the process more sustainable. Thus, the present section aims at elucidating the recent use of bioprocesses (enzymatic extraction and fermentation) as well as the combination

of different technologies on the extraction of polyphenols—mainly quantified as TPC—from plant by-products and their biotransformation.

Enzyme-assisted extraction

Enzymes are nowadays used in a wide range of applications, including the extraction of bioactive compounds from vegetable matrices, as they can significantly improve the process yield (Singh, Kundu, Das, and Banerjee, 2022). Recently, different enzymes have been tested in different products, either in a single dose or in combination with other enzymes. Enzymes having cellulase activity, also generally referred to as cellulase, have been greatly used in the enzymatic degradation of agro-industrial by-products, as generally agro-industrial by-products contain great amounts of cellulose and hemicellulose. The application of 1,4-(1,3:1,4)-β-D-Glucan 4-glucanohydrolase from *Aspergillus niger* has shown a 7-fold increase of total phenolics when compared to the same extraction using water as a solvent without changing the pH in red seaweed by-product after agar extraction (Trigueros et al. 2021). The use of enzymes with cellulase activity has also led to an approximate increase of 50 mg GAE/g of olive pomace compared to conventional solvent extraction with water. Nonetheless, using a mixture of ethanol and water 1:1 (v/v) recovered greater amounts of polyphenols when compared to the cellulase extraction on olive pomace (Macedo et al. 2021). Cellulases also significantly increased the levels of soluble conjugate phenolics when compared to non-enzymatic extraction in guava leaves, yet the effect was not seen in the extraction of syringic acid and ferric acid as individual phenolic acids (Wang et al. 2017). This enzymatic family also showed great potential in the extraction of narirutin and hesperidin when compared to pectinase, tannase, or β-glucosidase in citrus juice by-products—consisting of peels, pulp residues, and seeds—achieving a recovery of more than 20 mg and 100 mg/100 g of the by-product's dry matter (respectively) when compared to any other enzyme used (Ruviaro, Barbosa, and Macedo, 2019). Ferulic acid has also been recovered in great amounts when using Celluclast® (1,4-β-D-endoglucanase from Trichoderma ressei) on wheat and rye bran (Juhnevica-Radenkova et al. 2021).

Other enzymes have been tested in single doses as well for the extraction of PC from agro-industrial by-products. For instance, several researchers have used xylanases and pectinases; others have used alcalases, ferulic acid esterases, and pectinases (Table 1). The choice of specific enzymes can be mainly justified depending on the economic value of the final product and the composition of the starting raw matrix. However, the complexity of the starting matrix often makes arduous the choice of a specific enzyme. In addition, its cost can also become a barrier. Instead, the use of an enzymatic cocktail—such as Viscozyme®—is recommended, as the mixture of different enzymes can act in diverse molecule bonds, occasionally allowing for better accessibility of other specific bonds, which could translate into an increased recovery of BPC from the plant by-product (Liu, Zhang, et al. 2017; Ruviaro, Barbosa, and Macedo, 2019; Wang et al. 2017). EAE is nowadays being more exploited as it allows to obtain greater recovery yields of many bioactive compounds in a relatively short processing time—including bound polyphenols—making the process interestingly cost-efficient (despite the high cost of enzymatic solutions). In addition, EAEs use aqueous solutions, therefore being a greener alternative than conventional solvent extractions. Nonetheless, the use of enzymes intrinsically carries some drawbacks; it is a high pH and temperature-dependent process, and it requires the addition of water for the enzymes to work at their optimum depending, which strongly depends on the water content of the initial raw material. In addition, agitation is most of the time recommended to facilitate the contact of the enzyme with the substrate, and in some cases, the enzyme deactivation is desirable after the process is completed to avoid further degradation and thus to maintain a similar final quality of the resulting product at the end of the process. Finally, as the enzymatic treatment breaks down complex polysaccharides, sterility should be ideally implemented over the whole process to avoid microorganism spoilage. In most cases, this is controlled by dehydration or drying of the product before the enzymatic treatment (Coniglio et al. 2022; Görgüç, Özer, and Yılmaz, 2020), which wastes more energy and water resources, as water has to be added after drying for optimal enzymatic activity.

Fermentation-assisted extraction

Fermentation-assisted extraction (FAE) is a biotechnological process by which bioactive compounds can be extracted by the growth and/or biological activity of microorganisms. Furthermore, secondary metabolites can be produced by microorganisms under specific conditions, providing an added value to using this biotechnological process. In general terms, fermentation can be performed in a liquid medium (i.e., submerged fermentation) or solid particles in the absence or limited amounts of free water (i.e., solid-state fermentation; (Ghandahari Yazdi et al. 2019)). Solid-state Fermentation (SSF) is one of the most sustainable techniques recently proposed to be used in the FAE of bioactive compounds from different agro-industrial by-products, as it conveniently uses the raw material without the addition of water. SSF has been applied to different agro-industrial by-products, including but not limited to fruits such as grapefruit (Teles et al. 2019), nejayote (Acosta-estrada et al. 2019), and fig (*Ficus carica* L.) by-products (Buenrostro-Figueroa et al. 2017)or cereal by-products (Chen et al. 2019). This biotechnological process is performed by using microorganisms able to naturally produce enzymes of wide diversity, such as lignases, cellulases or hemicellulases that break fiber hard structure (Lemes et al. 2022). Enzymatic hydrolysis derived from fermentation can have multiple effects; it can (a) release bioactive compounds that may be bound to the fiber (including PC) and (b) break down complex molecules such as pectin or cellulose to produce low-molecular-weight compounds that have numerous health-promoting effects (i.e., oligosaccharides) (Bhatia,

Table 1. Enzymes recently used in the extraction of bound phenolics from different agro-industrial by-products, their activity, and their source.

Enzyme name	Main enzymatic activity	Source of enzyme	By-product	Extraction compound(s)	Working conditions	Enzyme inactivation	Main results	Reference
Ferulic acid esterase (FAES)	Carboxylic ester hydrolase	*Clostridium thermocellum*	Sweet corn cob (SCC)	FA	Deffatted SCC, FAES (0.00 to 0.04 U/g), 45 to 65 °C, 3h, pH 4.5 to 6.5	90 °C for 5 min	0.03 U/g yielded the highest FA concentration (1.45 g/kg)	(Lau, Harbourne, and Oruña-Concha, 2020)
Xylanase (XY)	Endo-1,4-β-xylanase	*Trichoderma viride*	Sweet corn cob (SCC)	FA	Deffatted SCC, XY (0.00 to 18,093.50 U/g) , 45 to 65 °C, 3h, pH 4.5 to 6.5	90 °C for 5 min	4,526.00 U/g yielded the highest FA concentration (1.45 g/kg)	(Lau, Harbourne, and Oruña-Concha, 2020)
Cellulase	1,4-β-D-endoglucanase	*Trichoderma ressei*	Wheat and rye bran	FA	5 and 10 U/g, 44 °C, 4/8/12/24h, pH not specified	None applied	Higher recovery of FA (4.31 g/kg) after 24h and 10 U/g	(Juhnevica-Radenkova et al., 2021)
	1,4-(1,3:1,4)-β-D-Glucan 4-glucanohydrolase	*Aspergillus niger*	Red seaweed by-product (DMR)	Total phenolic compounds, free amino acids	Enzyme:DMR at 0.25, 0.5, 1, 2, 4, 6, 8%, enzyme activity not disclosed, 50 °C, 0 to >24h (specific times not disclosed), pH 5	100 °C for 5 min	Highest extraction yield at 8% cellulase (73%) and highest phenolic recovery at 6% cellulase (6.5 mg GAE/g DMR)	(Trigueros et al., 2021)
			Longan peel extracts	Free and conjugated phenolic compounds	Defatted longan peel 1:5 (w/v) with buffer at pH 6.5, 105 and 210 U, 50 °C, 180 min	None applied	Highest extraction of corilagin, ferulic acid, quercetin and o-coumaric acid when using 210 U. Highest extraction of esterified and free phenolics compared to other enzymes.	(Rakariyatham et al., 2020)
			Jujube peel	Total phenolic extraction, and pigment extraction and analysis of the main structure compounds	Sample to buffer 1:10 (w/v), 10,000 U, and mixture CE:PE:PR (5,000U:2,500U:2,500U), 55 °C, 70 min	90 °C for 5 min	Highest extraction of total phenolics with enzymatic mixture (8 mg GAE/g). Cellulase alone 6.8 mg GAE/g. Total flavonoids follow a similar pattern. Both values higher than alkali hydrolysis.	(Shen et al., 2021)
	1,4-β-D-endoglucanase	*Trichoderma reesei*	Raspberry pomace (RP)	Total phenolic compounds, ellagic acid and ellagitannin	0.03:1 RP:water (w/v), combination with Pectinex® Ultra SPL 700 and 2,500 U/g respectively, 45 °C, 2h, pH 4.5	None applied	Highest extraction reported for alkaline protease. CE and PE use showed little increase in total phenolics when compared to non-enzyme	(Saad et al., 2019)
	1,4-β-D-endoglucanase	*Trichoderma reesei*	Tomato pomace	Lycopene and individual phenolics, optimization study	EAE coupled with solvent extraction, 4:27.2:0.8 of TP:water:enzyme, 50 °C, 1h, pH not disclosed	None applied	No difference between cellulase-assisted and ethyl-acetate extraction for total phenolics. Potential synergic application of CE and ethyl acetate on the recovery of rutin and naringenin.	(Catalkaya and Kahveci, 2019)

(*Continued*)

Table 1. Continued.

Enzyme name	Main enzymatic activity	Source of enzyme	By-product	Extraction compound(s)	Working conditions	Enzyme inactivation	Main results	Reference
			Roasted guarana seeds (RGS)	Catechins and methylxanthines	RGC:water 1:3 (w/w), combination with PE (50:50), 40 and 50 °C, 4h, pH 5.7	Hydrolisis reduced to minimum by ice-bathing the samples for 15 min	CE extraction at both temperatures recovered 350 mg GAE/100 g extract at 4h. Control values were higher at the same time. No higher extraction of individual phenolics when using CE.	(Santana and Macedo, 2019)
		Aspergillus niger	Grape pomace (GP)	Total phenolic compounds	0–200 U /g of GP, 25–45 °C, 2–6h, pH 4–5.5	Hydrolisis reduced to minimum by ice-bathing the samples for 15 min	Optimal extraction of total phenolics (0.76 g GAE/100 g GP) obtained at 2h, 45 °C and pH 5.	(Meini et al., 2019)
		Trichoderma reesei	Pistachio green hull (PGH)	Total phenolic compounds and specific phenolics	PGH:water at 1:20–1:150 (g/ml), particle size (0.4–1 mm), 0–5 U/ml, 37 °C, 1–5h, pH 5	None applied	Higher phenolic extraction (11.5 g GAE/100 g PGH) at 2.5 U/ml, 1:100 mg/ml, 3h, 0.4–0595 mm. Higher extraction of phloroglucinol (35.7 mg/g dry extract) using CE when compared to other enzymes.	(Ghandahari Yazdi et al., 2019)
β-glucosidase			Longan peel extracts	Free and conjugated phenolic compounds	Defatted longan peel 1:5 (w/v) with buffer at pH 6.5, 15 and 30 U, 50 °C, 180 min	None applied	Higher extraction of total phenolics (405.3 µmol GAE/g DM) and extraction yield (24.8 g/100 g DM) at 30 U.	(Rakariyatham et al., 2020)
Pectinase			Jujube peel	Total phenolic extraction, and pigment extraction and analysis of the main structure compounds	Sample to buffer 1:10 (w/v), 10,000 U, and mixture CE:PE:PR (5,000U:2,500U:2,500U), 55 °C, 70 min	90 °C for 5 min	Highest extraction of total phenolics with enzymatic mixture (8 mg GAE/g). PE alone 7 mg GAE/g. Total flavonoids 9 mg GAE/g. All values higher than alkali hydrolysis.	(Shen et al., 2021)
	Pectinases, hemicellulases and β-glucanases (Pectinex® Ultra SPL)	*Aspergillus aculeatus*	Tomato pomace	Lycopene and individual phenolics, optimization study	EAE coupled with solvent extraction, 4:27.2:0.8 of TP:water:enzyme, CE:PE 1:1, 50 °C, 1h, pH not disclosed	None applied	Higher extraction of TPC when using PE with ethyl-acetate (24.7 mg GAE/g) similar to using acetone:ethyl-acetate (26.4 mg GAE/g). Combination of PE:CE yielded similar results on TPC. High recovery of naringerin (6.43 mg/g) and lycopene (9.16 mg/g) when using CE:PE and ethyl actate.	(Catalkaya and Kahveci, 2019)

			Guarana seeds (RGC)	Catechins and methylxanthines	RGC:water 1:3 (w/w), combination with CE (50:50), 40 and 50 °C, 4h, pH 5.7	Hydrolisis reduced to minimum by ice-bathing the samples for 15 min	PE extraction at both temperatures achieved phenolic extractions of about 500 mg GAE/100 g extract at 4h. Control values were higher at the same time (550 mg GAE/ 100 g). Combination of enzymes yielded lower values of TPC. Higher extraction of catechin and epicatechin when using PE.	(Santana and Macedo, 2019)
	Pectinases and hemicellulases (Pectinex® Ultra Color) Polygalacturonse and pectin lyase		Grape pomace	Anthocyanins	Enzyme:substrate 0.25–1.25%, different grape varieties tested, 40 and 40–50 °C, 30min, pH 4, light-protected conditions	None applied	Higher recovery of anthocyanins in all grape varieties at 1.25% and 50 °C when compared to any other condition.	(Montibeller et al., 2019)
	Pectinex® BE Color	*Aspergillus niger* *Aspergillus aculeatus*	Pistachio green hull	Total phenolic compounds and specific phenolics	PGH:water at 1:20–1:150 (g/ml), particle size (0.4–1 mm), 0–5 U/ml, 37 °C, 1–5h, pH 5	None applied	Higher phenolic extraction (11.5 g GAE/100 g PGH) at 2.5 U/ml, 1:100 mg/ml, 3h, 0.4–0595 mm. Higher extraction of phloroglucinol (35.7 mg/g dry extract) using CE when compared to other enzymes.	(Ghandahari Yazdi et al., 2019)
Tannase		*Aspergillus oryzae*	Grape pomace	Total phenolic compounds	0–200 U /g of GP, combination CE:TA, 25–45 °C, 2–6h, pH 4–5.5	Hydrolisis reduced to minimum by ice-bathing the samples for 15 min	Optimal extraction of TPC with tannase (0.74 g GAE/100 g GP) obtained at 2h, 45 °C and pH 5. Combination treatment with cellulase obtained 0.81 g GAE/100 g GP.	(Meini et al., 2019)
		Aspergillus oryzae	Pistachio green hull	Total phenolic compounds and specific phenolics	PGH:water at 1:20–1:150 (g/ml), combination of cellulase:pectinase:tannase, particle size (0.4–1 mm), 0–4 U/ml, 37 °C, 1–5h, pH 5	None applied	Highest phenolic extraction (12 g GAE/100 g PGH, 51% more than the control) at 4 U/ml, other parameters not specified. Higher extraction of gallic acid (68.61 mg/g dry extract) using TA when compared to other enzymes.	(Ghandahari Yazdi et al., 2019)
Alfa-amylase			Longan peel extracts	Free and conjugated phenolic compounds	Defatted longan peel 1:5 (w/v) with buffer at pH 6.5, 100 and 200 U, 50 °C, 180 min	None applied	Highest extraction of total phenolics (415.2 µmol GAE/g DM) and extraction yield (22.9 g/100 g DM) at 100 U.	(Rakariyatham et al., 2020)

(*Continued*)

Table 1. Continued.

Enzyme name	Main enzymatic activity	Source of enzyme	By-product	Extraction compound(s)	Working conditions	Enzyme inactivation	Main results	Reference
Proteases			Longan peel extracts	Free and conjugated phenolic compounds	Defatted longan peel 1:5 (w/v) with buffer at pH 6.5, 0.24 and 0.48 U, 50 °C, 180 min	None applied	Highest extraction of total phenolics (414.7 µmol GAE/g DM) at 0.48 U yet higher extraction yield (23.0 g/100 g DM) at 0.24 U.	(Rakariyatham et al., 2020)
			Jujube peel	Total phenolic extraction, and pigment extraction and analysis of the main structure compounds	Sample to buffer 1:10 (w/v), 10,000 U, and mixture CE:PE:PR (5,000U:2,500U:2,500U), 55 °C, 70 min	90 °C for 5 min	Highest extraction of TPC with enzymatic mixture (8 mg GAE/g). PR alone 7 mg GAE/g. Total flavonoids 8.5 mg GAE/g. All values higher than alkali hydrolysis.	(Shen et al., 2021)
	Alcalase		Sesame bran (SB)	Total phenolics and proteins	SB:water 1:10 (w/v), 0.12–2.40 Anson Unit/100g, 25–55 °C, 10–120min, pH 6–11	None applied	Highest extraction of TPC (6.24mg GAE/g) and protein (74.7%) at 1.272 AU/100g, 55 °C, 65min, pH 8.5	(Görgüç, Bircan, and Yılmaz, 2019)
	Alcalase Neutral protease Pepsin Papain	*Bacillus licheniformis* *Bacillus amyloliquefaciens* Porcine gastric mucosa *Papaya carica*	Raspberry pomace	Total phenolic compounds, ellagic acid and ellagitannin	0.03:1 RP:water (w/v), alcalase 2.4 U/ml, neutral protease 0.8 U/ml, pepsin 2,500 U/mg, papain 10 U/mg, 45 °C, 1h, pH optimal value per each enzyme (not disclosed)	None applied	Highest extraction reported for alkaline protease, followed by systems with other enzymes, neutral protease and papain.	(Saad et al., 2019)
Enzyme cocktails								
Own mixtures	Cellulase:xylanase:beta-glucosidase 1:1:1		Leaves and seeds from framboise production (FL and FS)	Bound phenolic compounds	Enzymatic treatment followed by ultrasound assisted extraction, FL or FS:enzymatic mixture 1:0.3 (w/w), 50 °C, 12h, pH 5	105 °C for 5 min	Higher extraction of bound phenolics in FL and FS after using enzymatic extraction (17 and 4.8 mg GAE/g DM, respectively) when compared to alkaline, methanolic or water extractions, but not to acid hydrolysis (32.5 and 10 mg GAE/g DM).	(Wang et al., 2019)
	Glucoamylase:protease:cellulase (1:3:3)		Defatted rice bran	Free and soluble conjugate phenolic compounds	DRB:water 1:5 (w/v), glucoamylase 100,000 U/g, PR 50,000 U/g and CE 35,000 U/g, 57.5 °C, 190min, pH 6	90 °C for 5 min	Highest extraction of free phenolics (30.01 mg GAE/100 g DM) and soluble conjugates (100.49 mg GAE/100 g DW) by complex enzymatic hydrolysis, 100% and 30% more recovery when compared to gelatinization or liquefaction methods.	(Liu, Zhang, et al., 2017)
	Cellulase and pectinase (1:2, 1:1 and 2:1)		Rhizome knot from lotus plant (RK)	Total phenolic compounds	RK:water at 1:20 (w/v), CE 50,000 U/g, PE 30,000 U/g, solution at 0.15 mg/ml, 62 °C, 90min, pH 4	None applied	Higher extraction of TPC at ratio 2:1 CE:PE (4%) when compared to other combitation ratios.	(Zhu et al., 2018)

Cellulase, pectinase, tannase and beta-glucosidase		Citrus juice by-products (CJBP)	Total phenolic compounds, specific phenolics	CJBP:water at 1:12.5 (w/v), 40 °C, 6, 12 and 24h, pH 5. Combinations used: CE:PE (5 U/g DM each), TA:CE:PE (5 U/g DM each), BG:CE:PE (5 U/g DM each).	Hydrolisis reduced to minimum by ice-bathing the samples for 15 min	Higher recovery of TPC with TA:CE:PE combination for 24h (>1,000 mg GAE/100g DM). Highest recovery of hesperidin and narirutin with CE:PE combination for 6h (120.6 mg/100 g DM) and 24h (19.4 mg/100 g) respectively, higher recovery of naringenin with BG:CE:PE combination for 24h (24.2 mg/100 g DM)	(Ruviaro, Barbosa, and Macedo, 2019)
Cellulase:xylanase:beta-glucosidase (1:1:1)		Guava leaves (GL)	Bound phenolics, soluble conjugate phenolics and free phenolics. Specific phenolics assessed.	GL:water 1:4, 1.5g of enzyme mixture, enzyme activity not disclosed, 50 °C, 12h,, pH 5	80 °C for 20 min	Highest extraction of free (27 mg GAE/ g DM), and soluble conjugate (20 mg GAE/ g DM) when using the complex enzymatic mixture, but highest release of insoluble bound phenolics (17 mg GAE/ g DM) when using xylanase alone or non-treated.	(Wang et al., 2017)
β-glucosidase, 1,4- β -D-cellobiohydrolase, xylan-1,4- β -xylosidase, xylan-1,4- β -xylosidase, endo-1,4- β -xylosidase and 1,4- β -D-endoglucanase	*A. fuscosuccinea*	Sugar cane bagasse (SCB)	Phenolic compounds and proteins	SCB (2%), enzymatic activity from 15.9 to 288.9 IU/g DM (enzyme dependant), 50 °C, 8h, pH 4.8	100 °C for 5 min	Highest solubilization of TPC (79.5 mg GAE/L) with enzymatic assisted extraction when compared to conventional, Viscozyme or buffer-assisted.	(Coniglio et al., 2022)
Cellulase and pectinase		Guarana seeds	Catechins and methylxanthines	RGC:water 1:3 (w/w), PE:CE (50:50), 40 and 50 °C, 4h, pH 5.7	Hydrolisis reduced to minimum by ice-bathing the samples for 15 min	Combination of enzymes yielded lower values of TPC (400 mg GAE/100 g) compared to isolated enzymes and the control (500–570 mg GAE/100 g) at the same temperature.	(Santana and Macedo, 2019)
Cellulase, pectinase and protease (5000u:2500U:2500U)		Jujube peel	Total phenolic compounds, and pigment extraction and analysis of the main structure compounds	Sample to buffer 1:10 (w/v), CE:PE:PR (5,000U:2,500U:2,500U), 55 °C, 70 min	90 °C for 5 min	Highest extraction of TPC (8 mg GAE/ g DM) and TFC (10 mg RE/ g DM) with enzymatic mixture when compared to isolated enzymes or alkali extraction.	(Shen et al., 2021)
Xylanase and Cellulase		Red rice bran	Phenolic compounds, modeling and optimization	Red rice bran 1g, water ratio not disclosed, XY and CE concentration 5, 7.5 and 10 mg/g, 50 °C, 60, 75 and 90 min, pH not disclosed	50 °C for 90 min	Higher recovery of TPC (2,959.58 mg FAE/100 g) at 75 °C, XY 7.5 mg/g, CE 11.58 mg/g, when compared to any other combination.	(Prabhu and Jayadeep, 2017)

(*Continued*)

Table 1. Continued.

Enzyme name	Main enzymatic activity	Source of enzyme	By-product	Extraction compound(s)	Working conditions	Enzyme inactivation	Main results	Reference
	Cellulase, amylase, protease and beta-glucosidase		Longan peel extracts	Free and conjugated phenolic compounds	Defatted longan peel 1:5 (w/v) with buffer at pH 6.5, 0.24 and 0.48 U, 50 °C, 180 min. Combinations CE:BG, AM:BG, CE:AM:PR, CE:AM:BG, CE:AM:PR:BG with different enzymatic activities	None applied	Highest extraction of TPC (444.1 µmol GAE/g DM) with the combination of CE:AM:PR:BG at CE 210, AM 200, PR 0.48 BG 30 U, which were lower when compared to CE 210 U alone (446.0 µmol GAE/g DM). Higher extraction yield (27.3 g/100 g DM) with the combination of CE:AM:PR:BG at CE 105, AM 100, PR 0.24 BG 15 U.	(Rakariyatham et al., 2020)
	Different concentrations of β-1,3-glucanase, pectinase and cellulase	β-1,3-glucanase and cellulase from *Trichoderma reesei* and pectinase from *Aspergillus niger*	Blackcurrant press cake (BPC)	Total phenolic compounds, anthocyanins	Pasteurized BPC with different enzymatic combinations, tested at different experimental conditions	Applied differently depending on the enzymatic combination used.	Highest reported anthocyanin extraction (424 mg cya-3-glu Eq/100 g) with CE at solvent:liquid ratio 1:10, 60 °C, 4h. Highest extraction of TPC (1,349 mg GAE/100 g) observed for the control at solvent:liquid ratio 1:10, 60 °C, 4h when compared to any other enzymatic treatment.	(Granato et al., 2022)

Viscozyme L	Combination of carbohydrases including arabinose cellulase, beta-glucanase, hemicellulase and xylanase	*Aspergillus aculeatus*	Sugar cane bagasse	Total phenolic compounds and proteins	SCB (2%), 6IU/g DM, 50 °C, 8h, pH 4.8	100 °C for 5 min	No difference on the extraction of TPC using Viscozyme (59.8 mg GAE/L) compared to buffer-assisted (52.9 mg GAE/L) or conventional (56.70 mg GAE/L). Highest extraction of proteins when using Viscozyme (1,177.2 mg/L).	(Coniglio et al., 2022)
			Sesame bran	Total phenolics and proteins	Sesame bran:water 1:10 (w/v), 0.12–2.40 Anson Unit/100g, 25–55 °C, 10–120min, pH 6–11	None applied	Highest extraction of TPC (2.99 mg GAE/g) and protein (41.8%) at 63.6 AU/100g, 55 °C, 65min, pH 4.3, lower values compared to AL (used alone in the same experiment).	(Görgüç, Bircan, and Yılmaz, 2019)
			Chokeberry pomace	Total phenolic compounds and other soluble material	Different processes used before EAE, optimization of enzyme treatment using enzyme:susbtrate ratio (1–10% v/w), 25–55 °C, 1–8h, pH 3.5–5.5. Optimal conditions used for TPC and comparison to other conditions	100 °C for 10 min	No difference in the recovery of TPC when compared to other enzymatic treatments or the control.	(Kitrytė et al., 2017)
			Wheat and rye bran	Ferulic acid	1 ml of buffer with enzyme to 100 µg of sample, 6 fungal β-glucanase U/ml, 44 °C, 4/8/12/24h, pH not specified	None applied	Highest recovery of FA in wheat bran (8.60 g/kg) and in rye bran (11.30 g/kg) after 24h. Both extractions higher compared to Celluclast	(Juhnevica-Radenkova et al., 2021)
			Sweet orange peel (SOP)	Total phenolic compounds	Solvent:solid ratio 20/30/40 ml/g, enzyme concentration 0.7/0.8/0.9%, 4/5/6h, 60 °C, pH 4.8. Model performed and tested	90 °C for 5 min	Highest recovery of TPC (3,381 mg GAE/100 g) at 30 ml/g, 0.8%, 5h. EAE achieved higher values than ultrasound in TPC (1,408 mg GAE/100 g).	(Nishad, Saha, and Kaur, 2019)
			Tomato pomace	Lycopene and individual phenolics, optimization study	EAE coupled with solvent extraction, 4:27.2:0.8 of TP:water:enzyme, Viscozyme used together with other enzymes, all at 50 °C, 1h, pH not disclosed	None applied	Highest extraction of TPC when using CE:Viscozyme with ethyl-acetate (28.9 mg GAE/g) higher than using acetone:ethyl-acetate (26.4 mg GAE/g). Viszocyme and ethyl acetate yielded lower results on TPC (21.9 mg GAE/g).	(Catalkaya and Kahveci, 2019)

(*Continued*)

Table 1. Continued.

CeluStar XL	Mainly xylanase but also cellulase, beta glucanase activity	Chokeberry pomace	Total phenolic compounds and other soluble material	Different processes used before EAE, optimization of enzyme treatment using enzyme:susbtrate ratio (1–10% v/w), 25–55 °C, 1–8h, pH 3.5–5.5. Optimal conditions used for TPC and comparison to other conditions	100 °C for 10 min	Highest recovery of TPC (20.25 mg GAE/g DM) when using Celustar compared to control (16.53 mg GAE/g DM) or the use of Viscozyme (16.31 mg GAE/g DM)	(Kitrytė et al., 2017)
Depol 740L, Promod 439L and Pectinase 62L	Feruloyl esterase, pectinase and other activity depending on the mixture	Depol 740L from *Humicola* sp., Promod 439L from *Bacillus licheniformis* and Pectinase 62L from *Aspergillus* sp.	Sweet cherry pomace (SCP)	Bound phenolic compounds	SCP:water 0.38g/ml, enzyme concentration 40/65/90 µl/g for Depol, 90/115/140 µl/g for Promod, 0.5/25.25/50 µl/g for Pecinase, 60/70/80 °C, 5/22.5/40min, pH 6/8/10	None applied	Highest extraction of TPC with Promod (100 mg GAE/g) at enzyme concentration 140 µl/g, 15 min, pH 10, with Depol (25 mg GAE/g) at enzyme concentration >70 µl/g, 25 min, pH 10, and with PE (80 mg GAE/g) at 20–40 µl/g, 15–30 min and pH 10	(Domínguez-Rodríguez, Marina, and Plaza, 2021)

CE: cellulase, PE: pectinase, PR: protease, AL: alcalase, TA: tannase, XY: xylanase, BG: β-glucosidase, AM: amylase, TPC: total phenolic compounds, EAE: enzymatic assisted extraction, TFC: total flavonoid content, RE: rutin equivalents, GAE: gallic acid equivalents, FA: ferulic acid, FAE: ferulic acid equivalents

Sharma, Bachheti, and Chandel, 2019). In addition, the metabolism of each microorganism can be crucial for the production of secondary metabolites that can have beneficial effects—for instance, the production of short-chain fatty acids or vitamins by probiotic bacteria (LeBlanc et al. 2017). However, the degree of the effect depends on several factors including the use of a suitable solid substrate, the microorganism's performance, and the growing conditions. Filamentous fungi are particularly appropriate for SSF, as they are well-fitted for the decomposition of biomass from plant waste and are able to grow in a low water environment (Torres-León, Ramírez-Guzmán, et al. 2019). Even more interesting, the fungi usually employed for this purpose can express the enzymes out of their fungal cell wall, increasing the efficiency of the enzyme. Yeast and some species of bacteria (e.g., *Bacillus subtilis*, *Bacillus thuringiensis*, and Lactobacillus sp. and other strains of lactic acid bacteria (LAB)) are considered the second-best choice for upcycling by-products from the agricultural industry. Recently, LAB has been used as biocatalysts to transform secondary substances in nature into more powerful antioxidant compounds, such as for the degradation of hydrolyzable tannins to gallic acid and the transformation of gallic acid into pyrogallol (Khubber et al. 2022). Within microbial enzymes, β-glucosidases, phenolic acid reductases and decarboxylases (PAD), and tannases have been associated with the main phenolic metabolism (Acin-Albiac et al. 2021). Microbial degradation during fermentation may improve the bioavailability and/or functionality of the newly derived products, producing simpler PC that may be more efficiently absorbed in the duodenum, especially their aglycones or conjugated glycoside forms (Lee and Paik, 2017). SSF has several environmental advantages as well, since it uses low amounts of water and the use of plant-based agro-industrial residues to produce valuable products such as enzymes, biofuels, nanoparticles, and other bioactive compounds (Leite et al. 2021), (Costa et al. 2021; Guajardo-Flores et al. 2021). Furthermore, this process is easy to implement as it requires lower capital and reduced operating coast (Cerda et al. 2019). However, SSF also faces a range of challenges, some of which are associated with its operation (such as the long operation hours in comparison with other techniques), while others are associated with its downstream processing along with its scale-up (Kumar et al. 2021). Furthermore, the separation of product from the fermented solids represents a challenging process (Kumar et al. 2021).

Factors related to the substrate used, such as chemical nature, mechanical properties, particle size (including inter- and intra-particle spaces), or water retention capacity—among others—affect the overall fermentation and product development (Cerda et al. 2019; Kumar et al. 2021). Furthermore, water addition is required in some cases as it can improve the fermentation process, which is not uncommon during LAB fermentation (Yan et al. 2019). In the scientific literature, there are some recent studies where agro-industrial by-products are used as substrate support for FAE and the release of bioactive compounds has been extensively observed (Table 2).

Table 2. Fermentation-assisted extraction of bound phenolics, fermentation conditions and microorganisms used.

Food by-product	Microorganisms	Inoculum size/ Incubation time	Phenolic analyses	Results	Reference
Nejayote	*Pleurotus ostreatus* Perla and *Hericium erinaceus*	25 °C/3 days; 3% *w/w* inoculum	F-C + HPLC	31.40% increased release of ferulic acid when fermented with *P. ostreatus* Perla compared to non-fermented	(Acosta-Estrada et al., 2019)
Fig (*Ficus carica* L.)	*Rhizopus oryzae*, *Trichoderma* sp., *Aspergillus niger* HT4, *Aspergillus niger* GH1	30 °C/72 h; 1×10^6 spores/g	F-C + HPLC - MS	A 4.67-fold increase in total phenolic concentration compared to non-fermented sample (4.77 mg of GAE/g of dry matter)	(Buenrostro-Figueroa et al., 2017)
Rice bran	*Rhizopus oryzae* (AS3.866)	30 °C/5 d; 1×10^4 spores/g bran	F-C + HPLC	The free, bound and total phenolic content increased by 99.4, 40, 71.6% in fermented defatted rice bran, respectively, when compared with the unprocessed one sample	(Chen et al., 2019)
Apple peel	*A. niger* ZDM2 and *A. tubingensis* ZDM1, *A. aculeatus* ZGM6, *A. japonicus* ZGM4	30 °C / 7 d; 10^7 spores/mL	F-C + HPLC-PDA, and LC-MS/MS	A 4-fold increase in phenolic and flavonoid content as well as antioxidant activity in the fermented samples.	(Gulsunoglu et al., 2020)
Coffee pulp	*Lactobacillus plantarum* TISTR 543	30 °C/ 168 h; 10^9 CFU/mL stock	F-C + LC-QQQ	Fermented samples at time 24, 72 and 168h significantly raised the total phenolic content when compared to initial concentration.	(Myo, Nantarat, and Khat-udomkiri, 2021)
Rice bran (Khao Bahn Nah and Thai jasmine)	*Lactobacillus plantarum* FNCC 0027 *and Lactococcus lactis* FNCC 0080	37 °C/72 h h; 10% w/v	F-C + HPLC	Highest phenolic concentration after fermentation with *L. plantarum* (2.88 mg/ml)	(Sawangwan, Porncharoennop, and Nimraksa, 2021)
Grape pomace	*Aspergillus niger* 3T5B8	37 °C/ 96h; 10^7 spores	F-C	An increase of almost 2-fold in TPC in fermented samples when compared to the control.	(Teles et al., 2019)
Mango seed	*Aspergillus niger* GH1	SSF; 30 °C / 7 d; 10^7 spores/mL	F-C + RP-HPLC-ESI-MS	2.5-fold increase in TPC up to 3,288 mg GAE/100 g fermented product after 20h of fermentation.	(Torres-León, Ramírez-Guzmán, et al., 2019)
Blueberry pomace	*Lactobacillus rhamnosus* GG *and Lactobacillus plantarum*-1	LSF; 37 °C/28 h; 7.5 Log CFU/ mL	F-C	A 4-fold increase of TPC up to 4,269.21 µg AGE/mL in the fermented samples when compared to the control	(Yan et al., 2019)
Hass avocado seed	*Aspergillus niger* GH1	30 °C/ 120 h; 2×10^7 spores/g	F-C + HPLC	Highest release of total phenolic compounds (14.56 mg GAE/g) observed at 60% moisture content particle size ≤2.5mm and 120h of fermentation time.	(Yepes-betancur et al., 2021)
Grape, apple and pitahaya residue	*Rhizomucor miehei* NRRL 5282	SSF; 37 °C/18 d; 5×10^6 spores/g	F-C + HPLC	All fermentations achieved significantly greater TPC when compared to the control	(Zambrano et al., 2018)
Rambutan peel	*Aspergillus niger* GH1, PSH and HT4	SSF; 30 °C/5 d; 2×10^7 spores/g	F-C + HPLC-ESI-MS	Fermentation at 24 h presented a recovery yield of 37.1%, higher than non-fermented samples.	(Cerda-Cejudo et al., 2022)

TPC: total phenolic count; LSF: Liquid State Fermentation; SSF: Solid State Fermentation

Biotransformation of phenolic compounds

EAE and FAE are biochemical processes that can help improve the recovery or extraction of bound polyphenols from food matrices, yet these processes can also influence the phenolic profile. Articles that describe differences in phenolic concentration often report differences in the phenolic profile as well—when analyzed (Gulsunoglu et al. 2020; Ruviaro, Barbosa, and Macedo, 2019; Torres-León et al. 2019). These differences derive from the action of one or more enzymes, either used individually or secreted by microorganisms during fermentation. Considering the different compounds to which phenolics can be bound, biotransformation can happen at different levels. Overall, it can entail the whole molecule of which the polyphenol constitutes an important part—or, in other words, to the moiety to which the polyphenol is attached—and/or to the specific phenolic compound as an individual molecule. In general terms, we could talk about "moiety biotransformation (MB)" and "phenolic biotransformation (PB)" respectively.

EAE is usually employed to improve the recovery of polyphenols and therefore it is better to consider the quantity over the quality. In addition, enzymes are also used to solubilize material and can be used as a pretreatment before fermentation (Singh, Kundu, Das, and Banerjee, 2022). The fact that enzymes are used to improve the presence of polyphenols in the outcoming extract makes imperative the use of more general enzymes that can break down larger molecules such as cellulose or pectin. In fact, as presented in Table 1 the most used enzymes are proteases, cellulases, hemicellulases, or pectinases among others, which—although they are

target-specific enzymes—their substrate is not the PC but the moiety to which it is bound. The MB is the easiest to study since to evaluate any effect, the researcher could employ the same technique and target the same phenolic compound(s). The study of Ruviaro, Barbosa, and Macedo (2019) represents a clear example. They found that depending on the enzyme or enzymatic cocktail used, the concentration of each PC—focusing on specific flavanones—in the extract solution from citrus by-products differed greatly. As they assertively discuss, one of the enzymatic treatments improved the recovery of all targeted PC, which derived from the promotion of these specific polyphenols into their respective aglycones. Therefore, the enzymatic treatment separated the carbohydrate moiety from the flavanone backbone, freeing the latter during the extraction process and therefore increasing its concentration in the final product. Another example is provided by the production of aglycone flavanones (hesperidin, hesperetin, naringenin) from citrus pectin by-product by the use of β-glucosidase (Barbosa, Ruviaro, and Macedo, 2021).

PB, in contrast, is a term that could be employed to designate the transformation that a specific phenolic compound could undergo regardless of its bond to other larger or smaller molecules. PC can undergo different reactions that can biotransform the molecule, including but not limited to decarboxylation, reduction, or hydrolyzation (e.g., esterase-catalyzed reactions). These reactions have been well depicted by Gulsunoglu-Konuskan and Kilic-Akyilmaz (2022) and can eventually produce new compounds of high biotechnological interest. However, these biotransformations are much more specific, and although most of them can be catalyzed by enzymes, using very specific enzymes is not cost-efficient. FAE emerges then as an interesting tool to tackle this problem. As detailed before, many different microorganisms have been studied for their ability to ferment agro-industrial waste streams and produce high phenolic-rich extracts (Section 3.2.). Additionally, the employment of microorganisms makes it possible to have greater amounts of target-specific enzymes, which enable a PB.

Among all the microorganisms used to ferment agro-industrial by-products, *L. plantarum* takes the cake. Its high resilience comes from the ability of this species to produce many different enzymes that can act at the phenolic molecule level for its biotransformation. For instance, *L. plantarum* has been proven to have an important effect on the biotransformation of hydroxybenzoic acid-derived compounds, such as tannins, due to its tannase or gallate/protocatechuate esterase production activity, to other potent antioxidants, such as gallic acid or ultimately propylgallate (Muñoz et al. 2017). Production of tannases makes this species very important for the processing and fermentation of lignocellulosic material, as it is a difficult material for the bacteria to thrive due to the limited concentration of simple sugars, low water content, and high complexity of the matrix (Ajala et al. 2020). In addition, *L. plantarum* has been reported to have the ability to metabolize hydroxycinnamic acid-derived compounds due to the expression of esterases and decarboxylases which originates the formation of 4-vniyl derivatives, considered flavoring agents, and due to the expression of phenolic acid reductases, leading to the formation of hydrocaffeic acid and hydroferulic acid from its starting counterparts caffeic and ferulic acid (Muñoz et al. 2017). Recently, Santamaría et al. (2018) described ethylphenol formation, a potent antifungal compound Ge et al. (2021) by *Lactobacillus plantarum* through a specific VprA reductase. There are also other bacterial species that have recently been used to understand their implication in specific PB. *Bacillus licheniformis* TAB7 is commonly used as a deodorizing agent for compost in Japan, whose ability to ferment waste products derives from the wide array of enzymes it can produce (Mpofu et al. 2019). It was shown that *B. licheniformis* TAB7 could efficiently produce 4-vinylguaiacol and 4-ethylcatechol from ferulate and caffeate respectively, two ester groups from two hydroxycinnamic acids (ferulic and caffeic acid) that are widely present in the agro-industrial waste. The genomic analysis revealed the production of phenolic acid decarboxylases, vanillate decarboxylases, and other enzymes used to degrade protocatechuate (Mpofu et al. 2019).

Among the fungi that have been employed for the fermentation of agro-industrial by-products, biotechnologically speaking Aspergillus is the most important genus, as it has been widely studied and used for this purpose (Table 2). In addition, recent genetic manipulation has allowed researchers to improve enzyme production and eliminate mycotoxins production for product safety (Li et al. 2020). *A. luchuensis* has been proven to be effective in the production of vanillin from other former PC (Taira et al. 2018). They show that vanillin can be produced by *A. luchuensis* from vanillin glucoside by glucosidase activity or from ferulic acid by the expression of feruloyl CoA synthase and hydratases/lyases. This is especially important for lignocellulosic material, where ferulic acid is greatly present. In fact, Tang and Hassan (2020) have shown that inoculation with A. niger could be a good strategy for the production of vanillic acid and vanillin from pineapple peel. Therefore, the biotransformation of ferulic acid to vanillin and vanillic acid is not only dependent on one but on many different strains. Although different species can show different enzymatic activity, several species of Aspergillus have recently shown potential for the production of taxifolin (*A. japonicus* and *A. aculeatus*) and eriodictyol (*A. niger* and *A. tubingensis*) from apple waste (Gulsunoglu et al. 2020), compounds with industrial applications and attributed health benefits. Aspergillus ssp. was also able to significantly improve the concentration of ellagic acid in the chestnut shell (Gulsunoglu-Konuskan, Karbancioglu-Guler, and Kilic-Akyilmaz, 2021) and reduce significantly the concentration of hesperidin and the subsequent formation of its hydroxyflavanones and aglycones, improving the antioxidant activity of the resulting product (Pérez-Nájera et al. 2018). Other microorganisms may be used for the PB of agro-industrial by-products. For instance, the use of *P. citrinum* for the production of genistein and daidzein from former isoflavones through soy waste fermentation by the expression of β-glucosidase (Doan et al. 2019).

Both MB and PB are processes that can happen in the fermented material simultaneously, especially when using fermentation techniques. Nevertheless, the use of microorganisms has its limitation. Not all microorganisms grow well in the former materials, as some have a very high concentration of lignin and other complex polysaccharides, which difficult access to sugar sources (Ajala et al. 2020). Fungi and some species of Bacillus ssp. (Jiang, Xu, and Tao, 2019) are the preferred choice as they can ferment this type of material. Nevertheless, differing from other bacterial species (such as LAB), the use of fungi—especially Aspergillus ssp.—and some Bacillus ssp. can be detrimental as they are generally spore-producers, and some can be toxin-producers, which has a direct effect on the cost of the process. To overcome these issues, genetically modified microorganisms can be used to eliminate toxin production, and pretreatments can be applied to the lignocellulosic material to facilitate bacterial growth (Rahmati et al. 2020). However, whereas MB with the use of enzymes is quicker and more effective, there is also an inherently high cost from enzyme purification. There is a need to keep exploring different fermentation and enzymatic strategies for the recovery of specific polyphenols and thus deeply understand the MB and PB of the targeted compounds.

Recent advances in the use of EAE and FAE for the recovery of BPC

In the past recent years, different technologies have been combined in order to improve the recovery of polyphenols and other bioactive compounds. Jha and Sit (2022) have recently summarized possible technology combinations to extract bioactive compounds from plant matrices, although the focus has not exclusively been on plant by-products. There are different treatments that can be combined, and most of the time, the combination relies on the compatibility between technologies. The use of a liquid matrix is important, as it is the most efficient way of extraction. In that line, the conventional solvent extraction—using a wide array of solvents—has been combined with microwave and ultrasound in the past, leading to the introduction of MAE and UAE, techniques that are able to recover greater amounts of bioactive compounds. In recent years, MAE and UAE have been combined with other methodologies, including but not limited to the use of pressurized solvents for the extraction of PC from pomegranate peel (Sumere et al. 2018), the use of ohmic heating (Kutlu et al. 2021) and the use of deep eutectic solvents (DES) in the recovery of FPC and BPC from mulberry leaves, apricot pomace, and wheat waste biomass (Cherif et al. 2020; Vorobyova et al. 2021; Zhou et al. 2018). In addition, MAE and UAE extraction techniques have been jointly used for the solubilization of material and extraction of BPC, achieving an overall yield of 11% greater than using these techniques individually (Xu et al. 2018).

Recent advances have revealed the potential benefits of combining EAE with other technologies. For instance, Zhang et al. (2019) found that the order of combining techniques influenced the recovery of hypericin. Interestingly, the combination of MAE followed by EAE resulted in a 15% higher yield compared to their simultaneous combination. This order-dependent effect should be further investigated for different sample matrices and compounds. In addition to combining techniques, modulating enzymatic activity through pressure application has shown promise. Cascaes Teles et al. (2021) recently demonstrated differences in the recovery of TPC from grape pomace extract when using 50 MPa compared to higher pressures. Vacuum-assisted EAE-UAE has also shown promising results in TPC recovery (Görgüç, Özer, and Yılmaz, 2020).

In contrast, the simultaneous combination of FAE with other technologies presents challenges, as microorganisms are generally more sensitive compared to EAE. Suri et al. (2022) reported a negative effect on the recovery of naringenin when UAE and FAE were applied simultaneously compared to FAE alone (SSF). Nonetheless, a two-step approach involving UAE and FAE has successfully been applied to pineapple peels, resulting in significantly higher recovery of PC compared to UAE or FAE alone (Polanía et al. 2022).

Furthermore, recent studies have explored the simultaneous utilization of fermentation with other technologies. For instance, the application of a low-frequency alternating magnetic field was found to enhance mycelium and metabolite production of *Antrodia camphorata* in submerged fermentation (Liu et al. 2023). However, the concurrent use of FAE with other technologies remains a challenging and relatively unexplored field. Future research should focus on investigating the potential benefits of combining FAE with other technologies for the recovery of bioactive compounds from vegetable by-products.

Biological activity and functional properties of BPC

BPC has a wide pharmacological potential, suggesting possibilities for developing value-added products that benefit health. The development of additives or extracts with greater functional potential can be favored by solubilizing the BPC. However, information on the functional properties of bound and free phenols in agro-industrial by-products is still limited. Despite this, the biological properties reported for bound phenols are promising. This section aims to critically report the recent findings on the functional properties of BPC from agro-industrial by-products.

Antioxidant activity

Antioxidants have the potential to inhibit oxidation processes and prevent diseases related to oxidative stress. PC is widely recognized as having a high antioxidant activity (Torres-León et al. 2017). This characteristic benefits human health by scavenging free radicals, inhibiting lipid peroxidation, decreasing oxidative stress, and protecting DNA from damage (Zhang et al. 2022). In recent years, the interest in compounds with antioxidant activity has increased by the reports that show the beneficial effects of antioxidants on human health (Ali et al. 2020). As shown in Table 3, free

and bound phenols present in agro-industrial by-products have high antioxidant activity according to DPPH, ABTS, and FRAP tests. In some by-products, BPC has higher antioxidant activity than free phenols (Irakli et al. 2018; Prakash, Baskaran, and Kudachikar, 2019). For instance, in apple peel the antioxidant activities of the BPC extract were found to be 17 and 20-fold higher than those of FPC extract (Gulsunoglu et al. 2019) and in tea seed oil the BPC extract accounted for up to 49.7% of the total antioxidant capacities of PC (Wang et al. 2021). The higher contribution of BPC to antioxidant activity has also been reported in cereal brans (Özkaya et al. 2017), tea seeds (Kang, 2017), and Araticum (an exotic Brazilian fruit) by-products (Arruda et al. 2018).

The results show that the solubilization of BPC increases the functional potential of the extract with FPC. Although in other by-products such as seeds and peels of grapes (G. Y. Tang et al. 2018) and mango (López-Cobo et al. 2017; Torres-León, Ramírez-Guzmán, et al. 2019), FPC showed higher antioxidant activity, BPC have shown very important antioxidant properties such as cell permeability (Pacheco-Ordaz et al. 2018). BPC from mango peels has better permeability and antioxidant potential than FPC present in the same by-product (Pacheco-Ordaz et al. 2018). The differences in the antioxidant activity values of free and bound phenols in agro-industrial by-products could be justified by the different mechanisms of the methods and by the presence of different compounds. For example, in pomegranate residues, FPC showed a higher activity due to a significant amount of punicalagin derivatives (molecules with high antioxidant activity). The free and bound fractions could be joined in a by-product recovery process, and a final product with a high combined antioxidant power could be obtained (Gulsunoglu et al. 2019).

Anti-cancer activity

According to the World Health Organization (WHO), cancer is a generic term for a large group of diseases that can affect any part of the body when the cells grow uncontrollably, go beyond their usual tissue boundaries, and/or spread to other organs. Researchers have been looking for alternative and newest therapeutic strategies to chemotherapy. Lately, edible and natural products such as phenols have gained more attention due to their low toxicity and anti-cancer activity (Zhou et al. 2022). The free and bound PC of finger millet (Eleusine coracana) exhibited diverse effects when tested against cancer cell lines. BPC with high antioxidant activity (such as those present in tomato peels and seeds) (Perea-Domínguez et al. 2018) have recently shown high anticancer activity against the cancer cell line MCF-7 (Perea-Domínguez et al. 2022). The results showed BPC has higher anticancer activity than FPC (Perea-Domínguez et al. 2022). Li et al. (2022) found this trend in tomato seed-bound phenols against HCT-116 cells (human colon cancer cell line).

The quantity of research articles addressing the anticancer activity of BPC from agro-industrial by-products against various cell lines is scarce. Moreover, recently published data in other agro-industrial products (i.e., finger millet seeds) show that BPC extracts could contribute to the cancer cell growth in some cell lines whereas the FPC could induce cell death in breast and colorectal cancer cells (Kuruburu et al. 2022). This could indicate that the most important anti-carcinogenic effect relies on the properties of the phenolic compound itself regardless of its bound with the original matrix. Therefore, new research should continue to study the anticancer potential of BPC present in other agro-industrial by-products and investigate the cytotoxic activity of these compounds.

Anti-diabetic activity

Diabetes is a chronic disease distinguished by a lack of secretion or action of endogenous insulin resulting in the elevation of blood glucose (Ishwarya et al. 2022). Diabetes is the greatest public health problem and is considered the silent epidemic of the twenty-first century (Baharvand-Ahmadi et al. 2016). Though many different medicines are available to manage diabetes, side effects (like stomach ulcers, bleeding, and cardiovascular strokes) are generated due to their application (Wang et al. 2018). PC has shown strong inhibitory activity against α-glucosidase; which is a key enzyme to regulating glucose absorption in the small intestine. Within PC, BPC from mung bean skin has shown a strong inhibitory activity on α-amylase and α-glucosidase (Zheng et al. 2020). Results reported to date have revealed that FPC extracts exhibit stronger inhibitory activities than BPC (Table 3). However, there are few reports on the antidiabetic activity of BPC. Therefore, new residues must be investigated to make a complete discussion. The inhibition activity of α-amylase and α-glucosidase of BPC shows an interesting antidiabetic potential.

Neurodegenerative diseases

Neurodegenerative diseases encompass a range of disorders that affect the brain. Common neurodegenerative diseases include Parkinson's disease, Huntington's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. The PC has a potential effect on biological activities that would maintain brain health (Hadrich, Chamkha, and Sayadi, 2022). Higher dietary intake of PC may be associated with a reduced risk of developing Alzheimer's disease (Holland et al. 2020). Oboh et al. (2017) investigated the activity of free polyphenols and BPC (from Clerodendrum volubile leaves) on enzymes relevant to neurodegenerative diseases. The results revealed that free phenols had higher enzymatic inhibitory effects than PCBs. However, free phenols and PCBs exhibited antioxidant activity and may contribute to increasing the antioxidant status of the body; since brain cells are susceptible to oxidative stress-induced cell injury.

Recent advances in the biological activity of BPC show promising effects in anti-cancer and anti-diabetic applications. However, these applications are limited as the recent findings are not enough to draw conclusions. Furthermore, there is an outstanding number of residues where BPC can

Table 3. Main functional properties reported in plant by-products bound phenolic extracts.

Functional properties	By-product	Target/Assay	Activity		References
			Free	Bound	
Antioxidant	Mango leaves[a]	DPPH	IC_{50}= 45 µg/mL	IC_{50}= 32 µg/mL	(Zhang et al. 2022)
	Mango leaves[a]	ABTS	IC_{50}= 122 µg/mL	IC_{50}= 74 µg/mL	
	Mango Peel[a]	FRAP	620 FeSO4µM /mg	3 FeSO4 µM /mg	(López-Cobo et al. 2017)
	Mango Peel[a]	ABTS	475 µmol TE/g	1 µmol TE/g	
	Mango Seed[a]	FRAP	2062 FeSO4µM /mg	19 FeSO4 µM /mg	
	Mango Seed[a]	ABTS	484 µmol TE/g	29 µmol TE/g	
	Araticum peel[a]	DPPH	11 µmol TE/g	41 µmol TE/g	(Arruda et al. 2018)
	Araticum peel[a]	ABTS	19 µmol TE/g	63 Mmol TE/g	
	Araticum peel[a]	ORAC	40 µmol TE/g	117 Mmol TE/g	
	Araticum seed[a]	DPPH	33 µmol TE/g	14 µmol TE/g	
	Araticum seed[a]	ABTS	48 µmol TE/g	22 µmol TE/g	
	Araticum seed[a]	ORAC	169 µmol TE/g	59 µmol TE/g	
	Guava leaves[a]	Reducing power	7 mmol TE/g	11 mmol TE/g	(Wang et al. 2018)
	Rice bran[a]	ORAC	50 µmol TE/g	75 µmol TE/g	(Chen et al. 2019)
	Apple pomace[a]	ORAC	222 µmol TE/g	207 µmol TE/g	(Li et al. 2020)
	Grape peels[a]	FRAP	11–115 µmol Fe(II)/g	0.07–0.61 µmol Fe(II)/g	(Tang et al. 2018)
	Grape peels[a]	ABTS	3–39 µmol TE/g	0.03–0.4 µmol TE/g	
	Grape seeds[a]	FRAP	44–144 µmol Fe(II)/g	0.38–2 µmol Fe(II)/g	
	Grape seeds[a]	ABTS	24–64 µmol TE/g	0.16–0.32 µmol TE/g	
	Mango seed[a]	DPPH	IC_{50} = 0.16 mg/mL	IC_{50} = 0.46 mg/mL	(Torres-León, Ramírez-Guzmán, et al. 2019)
	Apple peel[a]	DPPH	1 mg TE/g	16 mg TE/g	(Gulsunoglu et al. 2019)
	Apple pomace[a]	DPPH	2 mg TE/g	4 mg TE/g	
	Pomegranate peel[a]	DPPH	140 mg TE/g	34 mg TE/g	
	Pomegranate seed[a]	DPPH	30 mg TE/g	10 mg TE/g	
	Chestnut shell[a]	DPPH	30 mg TE/g	59 mg TE/g	
	Black carrot pomace[a]	DPPH	6 mg TE/g	10 mg TE/g	
	Sorghum bran[a]	FRAP	8 µmol Fe^{2+} E/g	1 µmol Fe^{2+} E/g	(Miafo et al. 2020)
		ABTS	23 µmol TE/g	3 µmol TE/g	
		DPPH	45 µmol TE/g	7 µmol TE/g	
	Sorghum spent grain[a]	FRAP	1 µmol Fe^{2+} E/g	4 µmol Fe^{2+} E/g	
		ABTS	2 µmol TE/g	9 µmol TE/g	
		DPPH	2 µmol TE/g	13 µmol TE/g	
	Tomato byproduct[a]	DPPH	25 µmol TE/g	83 µmol TE/g	(Perea-Domínguez et al. 2018)
	Tomato by-product[a]	ORAC	141 µmol TE/g	852 µmol TE/g	
	Tea seed[a]	DPPH	8 mM TE/100g	61 mM TE/100g	(Kang, 2017)
	Tea seed[a]	FRAP	62 mM TE/100g	1249mM TE/100g	
	Tea seed[a]	ABTS	302 mM TE/100g	3640 mM TE/100g	
	Rice bran[b]	FRAP	152 mg TE/100g	211 mg TE/100g	(Liu, Wen, et al. 2017)
	Rice bran[b]	ORAC	38 mg TE/100g	97 mg TE/100g	
	Passion fruit peel[a]	DPPH	0.6 g TE/100 g	0.7 g TE/100 g	(Nguyen et al. 2019)
	Mango peel[a]	DPPH	5 g TE/100 g	1 g TE/100 g	
	Logan peel[a]	DPPH	4 g TE/100 g	3 g TE/100 g	
	Rambutan peel[a]	DPPH	46 g TE/100 g	30 g TE/100 g	
	Dragon fruit peel (white)[a]	DPPH	0.1 g TE/100 g	0.3 g TE/100 g	
	Dragon fruit peel (Red)[a]	DPPH	0.1 g TE/100 g	0.3 g TE/100 g	
	Passion fruit seed[a]	DPPH	0.6 g TE/100 g	2 g TE/100 g	
	Mango seed[a]	DPPH	32 g TE/100 g	4 g TE/100 g	
	Logan seed[a]	DPPH	5 g TE/100 g	6 g TE/100 g	
	Rambutan seed[a]	DPPH	0.1 g TE/100 g	0.5 g TE/100 g	
	Dragon fruit peel (white)[a]	DPPH	0.3 g TE/100 g	0.9 g TE/100 g	
	Dragon fruit peel (Red)[a]	DPPH	0.7 g TE/100 g	1.3 g TE/100 g	
	Rice Bran[a]	ABTS	612 mg TE/100 g	818 mg TE/100 g	(Irakli et al. 2018)
	Rice Bran[a]	FRAP	607 mg TE/100 g	592 mg TE/100 g	
	Rice husk[a]	ABTS	236 mg TE/100 g	710 mg TE/100 g	
	Rice husk[a]	FRAP	338 mg TE/100 g	687 mg TE/100 g	
Anti-cancer	Mango peel[a]	Caco-2	IC_{50}= 135 µg/mL	IC_{50}= 242 µg/mL	(Pacheco-Ordaz et al. 2018)
	Mango peel[a]	HT-29	IC_{50}= 190 µg/mL	IC_{50}= 227 µg/mL	
	Tomato by-products[a]	MCF-7	IC_{50}= 8.4 µg/mL	IC_{50}= 7.6 µg/mL	(Perea-Domínguez et al. 2022)
Anti-diabetic	Millet bran[a]	α-amylase	IC_{50} = 39 µg/mL	IC_{50} = 54 µg/mL	(Pradeep and Sreerama, 2017)
	Millet bran[a]	α-glucosidase	IC_{50} = 12 µg/mL	IC_{50} = 35 µg/mL	
	Millet hulls[a]	α-amylase	IC_{50} = 32 µg/mL	IC_{50} = 41 µg/mL	
	Millet hulls[a]	α-glucosidase	IC_{50} = 10 µg/mL	IC_{50} = 335 µg/mL	
	Guava leaves[a]	α-glucosidase	IC_{50} = 29 µg/mL	IC_{50} = 71 µg/mL	(Wang et al. 2018)

[a]Alkaline hydrolysis extraction
[b]Enzymatic hydrolysis extraction
[c]Model: *In vitro*

be extracted from, leading to differences in the extracted solution in terms of composition (e.g., type of phenolics, complexity) and quantity. Yet the antioxidant activity of BPC extracts from agro-industrial by-products has shown vast differences when compared against the FPC fraction of the same product. At this point, more research should be conducted on the possible biological effects that bound phenolic fractions could have on different fields, including but not limited to those explored herein, to be considered as upcycled and natural ingredients for the nutraceutical, pharmaceutical, and food industries.

Conclusions and further research

By-products from agro-industrial processes are a great source of PC, both FPC and BPC, and the recovery of the latter is gaining more importance. Among different processing techniques that can be applied to these products for the recovery of BPC, sustainable techniques have been optimized, including but not limited to enzyme technology and the use of microorganisms. On one hand, the use of fiber degrading enzymes has been proven to increase substantially the concentration of polyphenols in the soluble material, releasing them from complex polysaccharides by modification of their moiety. On the other hand, the use of microorganisms allows not only for the solubilization of material—and therefore BPC—but also for the biotransformation of the phenolic compound itself (PB), leading to the formation of new PC that in occasion has been proved to have higher antioxidant capacity or different biological activity, as well as anti-cancer and anti-diabetic applications. In either case, the use of EAE or FAE is intrinsically accompanied by the usage of aqueous solutions, therefore being a greener alternative than conventional solvent extractions, aligning with the Sustainable Development Goals laid down by the United Nations.

Although many different aspects have been investigated on the BPC of agro-industrial by-products, there is still much room for improvement. Since agro-industrial by-products mainly consist of BPC rather than FPC, further research should consider their quantification, targeted and untargeted, to understand the effect of the extraction process applied in every matrix. In addition, more research should be conducted to fill in the knowledge gaps regarding the biotransformation that PC goes through when employing bio-based extraction techniques (MB and PB), eagerly seeking to bring light into the critical connection between their biotransformation and their biological activity.

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