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An overview of the extraction and characterization of bioactive phenolic compounds from agri-food waste within the framework of circular bioeconomy

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The recycling and revalorization of wastes from the agri-food industry (AFI) have emerged in the scientific scenario as a multidisciplinary working field in the framework of the circular bioeconomy. Residues and side materials from AFI result in a great source of raw products with increasing social and economic impact. In this regard, phenolic compounds are possibly the most relevant group of phytochemicals from AFI wastes because of their multiple healthy properties, including antioxidant, anti-inflammatory, hypolipidemic, and antibacterial activities. Among other sources, olive oil, winemaking, and fruit and vegetable juice wastes have been considered to assess their revalorization. The paper reviews the recovery and characterization of AFI waste extracts to generate by-products rich in polyphenols for chemical, nutraceutical, and food science applications. Polyphenols are recovered from AFI waste by solvent extraction with conventional and advanced techniques. The resulting extracts are complex, and the major phenolic compounds should be identified and quantified. The profiling of analytes such as proanthocyanins, curcuminoids, resveratrol derivatives, caffeic acids, and oleuropein is often performed by liquid chromatography with UV/Vis or fluorescence detection. Additionally, liquid chromatography coupled to mass spectrometry is the technique of choice for the unambiguous identification of target compounds and structural elucidation of new and unknown molecules. Complementarily, the antioxidant activity of the extracts can be determined using spectrophotometric assays.

1. Introduction

Currently, the linear economy model is the predominant scenario worldwide. It relies on “producing, using and throwing away” and the vast majority of wastes are disposed of in landfills or incinerators whereas just a low proportion is recycled (ca. 12%). An alternative framework relies on the so-called circular economy, a system in which the consumption of materials and waste generation are minimized while also recycling and reusing the residues to produce new materials. In this way, the concept of turning waste into a resource is especially interesting in terms of sustainability [1].

Agri-food industries (AFI) generate high amounts of processing waste. For instance, peels, seeds, leaves, and stems stand out among the most common wastes generated in fruit and vegetable processing [2,3]. Some well-established applications of these wastes include their use as soil fertilizers or animal feed; currently, they are also used as biomass for producing energy or fuels. However, these AFI by-products are noticeably rich in a wide range of high added-value bioactive components, such as polyphenolic compounds [4–6]. Polyphenols are a vast group of secondary plant metabolites that comprise thousands of compounds. They can be classified into four principal families according to their chemical structures (see Table S1 in Supplementary Material) namely: phenolic acids, flavonoids, stilbenes, and lignans. Briefly, phenolic

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acids are the simplest molecules, with two main subclasses (hydroxybenzoic and hydroxycinnamic acids). Flavonoids result in the most abundant group; the flavonoid skeleton consists of two aromatic rings linked by an oxygen heterocycle and different subfamilies are defined depending on the oxidation degree and substitutions of the heterocycle. Stilbenes rely on a double bond connecting two aromatic rings. Lignans are a minor class based on two phenylpropane units. In addition, a miscellany of related phenolic molecules is included sometimes under an extended conception of polyphenols [7,8].

Phenolic compounds are scavengers of free radicals, which are harmful products of aerobic metabolism leading to oxidative stress in the organism. Multiple in-vitro, in-vivo, and epidemiological studies have shown that polyphenols are of great interest in the prophylaxis and treatment of cardiovascular and neurological diseases, cancer, and aging-related disorders, mainly due to their remarkable antioxidant activity [9,10]. The claimed anti-inflammatory activity also appears to be related to antioxidant power. Complementarily, the metal chelation ability is another protective effect of polyphenols which is especially noticeable against the toxicity caused by heavy metals. Compounds such as proanthocyanins, curcumin, resveratrol, caffeic acid, or oleuropein, have been extensively investigated, and their structures have been the basis to design new drugs with enhanced activity for the treatment of cancers and microbial infections [11]. Recently, dozens of studies have been published regarding the possible use of polyphenols to treat SARS-CoV-2 based on previous evidence on the phenolic activity against different viruses [12,12]. The use of phenolic compounds for pharmaceutical applications is not new. Oriental traditional medicine is a good example, with herbs, plants and spices rich in polyphenols acting as active principles. The food industry has also incorporated polyphenols as natural additives in food products, cosmetics, and packaging [13,14].

Thus, bioactive phenolic acids and flavonoids are on the top of the well-known value pyramid of biomass (Fig. S1, Supplementary Material), which makes AFI waste very attractive from a circular bioeconomy approach, with great prospects in the pharmaceutical, cosmetics, and food industries. In this context, recovering natural polyphenols from AFI waste is an excellent option, in line with the United Nations Sustainable Development Goals. The overall strategy is even more remarkable when green technologies are applied, with the design of processes aiming to eliminate, or at least reduce significantly, the use and generation of hazardous substances and prevent environmental and health impacts. In this scenario, the extraction, characterization, and purification of phenolic acids and polyphenols stir up an increasing scientific and commercial interest.

In the following sections, we present a general discussion on the most relevant extractive techniques for the recovery of polyphenols from agri-food waste, with brief references to the purification of the resulting extracts, always keeping in mind their feasibility for scaling up at the pilot plant and industrial scale. The chromatographic extract characterization is also discussed, both to determine the most noticeable compounds and estimate some remarkable features, such as the global antioxidant capacity. Spectrophotometric assays to measure the total phenolic content (TPC) or the antioxidant activity (AC) are briefly presented. This overview covers the most recent applications on this topic, mainly corresponding to articles published in the last five years.

2. Sources of polyphenols from agri-food residues

Within the global ranking of waste generation, AFI waste generated during food production processes represents approximately 25% of total industrial residues. As an example, in the case of production of both fruit and vegetable juices, most of the raw material, mainly skins, seeds, leaves, and stalks, remains as waste. Likewise, a large volume of waste is obtained during the production of olive oil or wine. Tree leaves, nut hulls, and coffee production waste, among others, are also examples of AFI waste. These residues are very often a rich source of bioactive compounds, such as vitamins, carotenoids, alkaloids, and polyphenols [15]. For these reasons, a great opportunity arises to recover the phytochemicals contained in these residues within the framework of the circular economy.

Data obtained from a bibliographic search in the Scifinder database with the keywords “agri-food wastes” and “polyphenols” in the period 2018–2022 is presented in Fig. 1, which shows the matrices worked most on during the last five years.

The wine industry's main byproduct is the grape pomace, a mixture of seeds, stems, grape skin, and remaining pulp. Approximately 9 million tons of this waste are generated annually around the world, representing about 20% w/w of the total grapes used for wine production [16–18]. This matrix is rich in hydroxycinnamic acids (e.g., caftaric and coutaric acids) and flavonoids (astilbin, catechin, etc.) [19]. Another industry that generates a high quantity of byproducts is the olive oil industry. The principal residue is the olive pomace which consists of the remaining pulpy material after olive oil extraction. This matrix is particularly rich in hydroxytyrosol, oleuropein, and luteolin glycosides, which are compounds with a high antioxidant capacity [20]. Other remarkable fruit byproducts come from the production of apple, citrus, and pineapple juices. In the vegetable byproducts group, onions are noted, which production is more than 450,000 tons only in Europe [21]. The major byproduct resulting from the industrial peeling of onions is represented by the skin, the outer fleshy leaves, and the top and bottom bulbs. The main phenolic compounds present are flavonoids such as quercetin and kaempferol glycosides (Table 1). Other types of waste that can be underlined are tree leaves, such as olive tree leaves, and nut byproducts, especially from walnuts [22,23].

3. Recovery and purification of polyphenols from agri-food residues

The recovery of bioactive molecules encompasses two different stages. The first stage relies on the extraction of the compounds of interest from the waste material, avoiding, as much as possible, the extraction of undesirable components. The second step deals with purification, in which extracts should be treated to remove all those reagents and components not compatible with their subsequent use and to concentrate the compounds of interest.

3.1. Extraction solvents

Before the extraction step, the material of interest needs to be pretreated to obtain homogenous and reduced-size particle samples that is essential to increase the contact area between the raw material and the extractant and, thus, to maximize their interaction [33,34]. After cleaning (if needed), the waste material is often dried or lyophilized to obtain a dehydrated sample that is subsequently cut, milled, and sieved [35].

The extraction of polyphenols from the solid pretreated AFI waste relies on solid-liquid extraction using hydro-organic solvents such as methanol, ethanol, acetone, and ethyl acetate. However, for toxicological and environmental reasons, green extractants are preferred (especially for addressing food and nutraceutical applications) so that the organic solvent is eventually almost restricted to ethanol [36]. Additionally, some extraction methods also include a small percentage of an organic or mineral acid, such as formic, acetic, or hydrochloric acid, in the extraction solvent to improve the

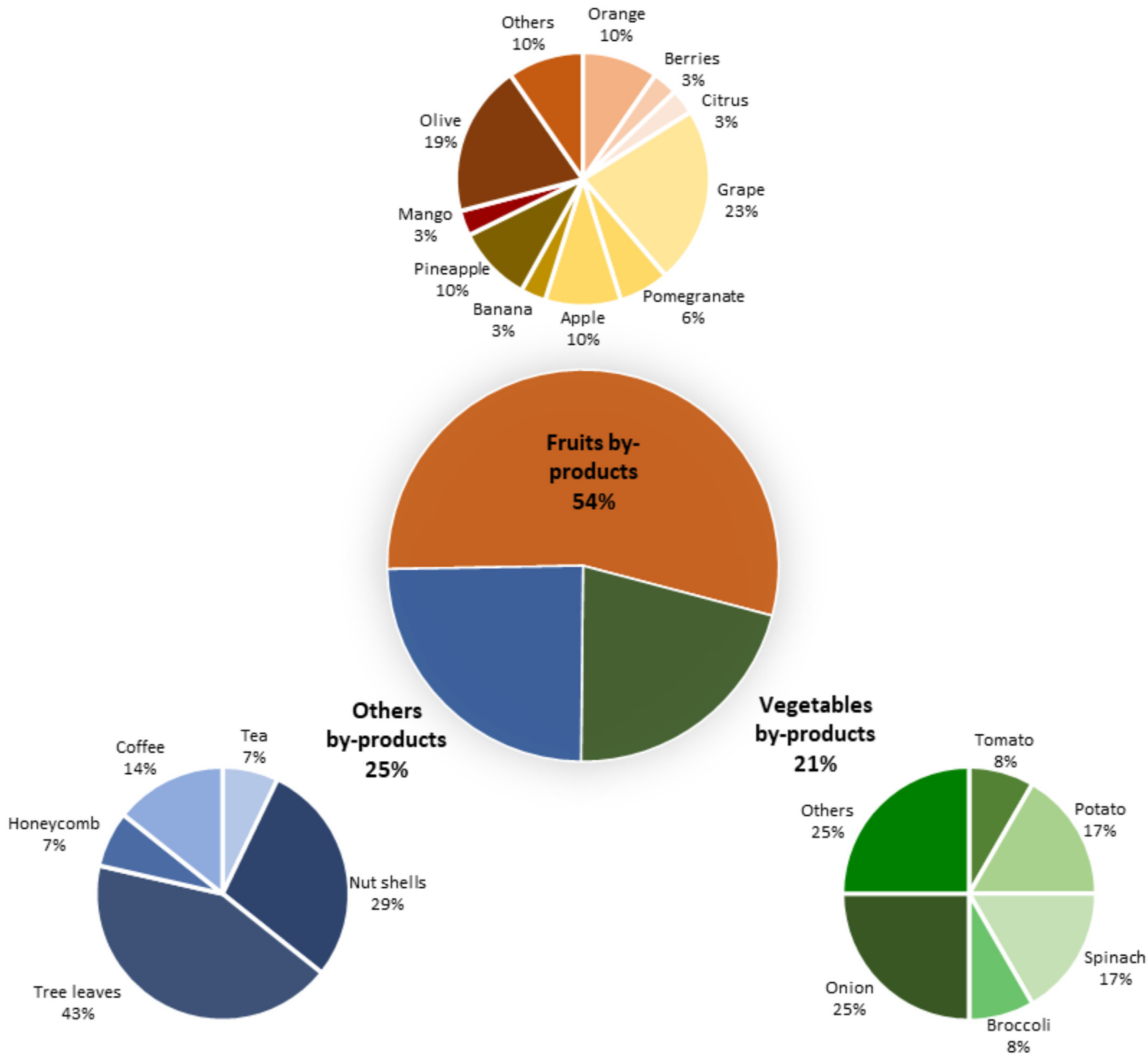


Fig. 1. Main agri-food waste matrices studied for the recovery of phenolic compounds.

Table 1
Phenolic rich residues from the agri-food industry.

Type of industry	By-product	Main phenolic compound	Residue fraction (%)	Waste volume in the world (tons per year)	Ref.
Olive oil	Leaves, pomace residues and peels	Oleuropein, Luteolin-7-O-glucoside, Luteolin, 3-Hydroxytyrosol and Apigenin-7-O-rutinoside	75%	≈2 million	[24,25]
Wine	Pomace, seeds and peels	Catechin, Epicatechin, Malvidin-3,5-diglucoside, Proanthocyanins and Gallic acid	25%	≈6 million	[26,27]
Orange	Pulp, seeds and peels	Naringenin, Naringin, Hesperidin and Rutin	30–40%	≈17–22 million	[28]
Apple and pear	Pulp, seeds and peels	Phloridzin, Epicatechin Chlorogenic acid, Procyanidin B1 and B2	5–20%	≈5–21 million	[29–31]
Onion	Skin and external layers	Quercetin-3,4′-O-diglucoside, Quercetin-4′-O-glucoside, Isorhamnetin-4′-O-glucoside, Delphinidin-3-O-glucosyl-glucoside	17%	≈15 million	[32]

solubility of the analytes and the stability of extracts. Apart from the solvent composition, other process variables such as pH, solvent volume, time, or temperature may be relevant to improve the recovery yield. The wide range of physicochemical characteristics (e.g., molecular mass, solubility, polarity, stability, and acid-base properties) of compounds belonging to the diverse families of polyphenols entails relevant differences in the extraction procedures.

As can be seen in Fig. 2, apart from conventional solvents based on water or hydroalcoholic mixtures, deep eutectic solvents (DES) or, preferably, natural DES (NADES) are gaining popularity in the polyphenol extraction scenario. (NA)DES, considered green solvents [37], are eutectic mixtures of hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA). The resulting mixtures have an enhanced extraction power of both polar and non-polar compounds. NADES are compatible not only with conventional extraction but also with other advanced technologies (see below). Common HBAs are betaine, tetrabutylammonium, proline, and, especially, choline. Regarding HBD, a wide range of compounds are used, including organic acids (such as lactic acid), ethylene glycol, glycerol, sugars (such as glucose), or urea.

Various illustrative examples based on NADES are commented as follows. For instance, Husanu et al. screened the combination of choline chloride with a variety of HBD such as acids, sugars, and polyalcohols for the extraction of polyphenols from chestnut waste, obtaining the highest extraction yield with the combination of choline and oxalic acid (1:1) [38]. In our laboratory the choline-based NADES have been used to recover polyphenols from several AFI wastes. In the example of Fig. 3, the performance of a choline-glycerol (1:2 m/m) solvent and a water/ethanol mixture is compared for the extraction of phenolic compounds and flavonoids from olive leaves. As can be seen, the NADES combination has shown a superior recovery for the target analytes, being up to 4-fold higher for astilbin (Fig. 3). Also, in the case of the revalorization of grape pomace, the use of NADES (betaine-citric acid) was suitable as a green alternative to organic solvents [39]. A comprehensive review concerning the use of NADES for the extraction of phenolic compounds from food by-products is given elsewhere [40].

Apart from NADES, other green options, such as supramolecular solvents (SUPRAS) or ionic liquids, although not yet extensively used, have also appeared as an alternative to the more conventional extractants. For example, SUPRASs, which are generated from aqueous or hydro-organic colloidal dispersions of amphiphilic compounds [37,41], were evaluated for the valorization of spent coffee grounds [42] and the purification of ellagic acid from waste pomegranate peel [43]. Regarding ionic liquids, mono-ethanolammonium acetate, for instance, was successfully used for the recovery of polyphenols from mate leaves, obtaining extraction yields significantly higher than the ones achieved with hydro-alcoholic mixtures [44]. Anyway, the controversy on the greenness

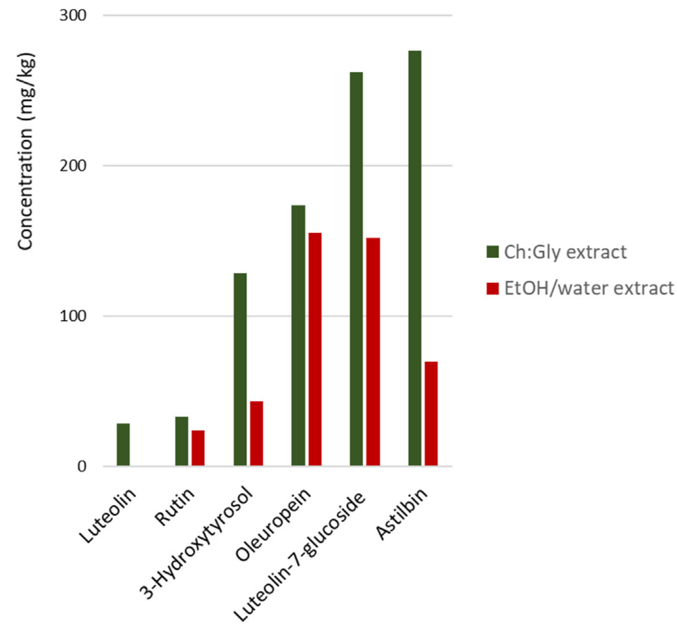
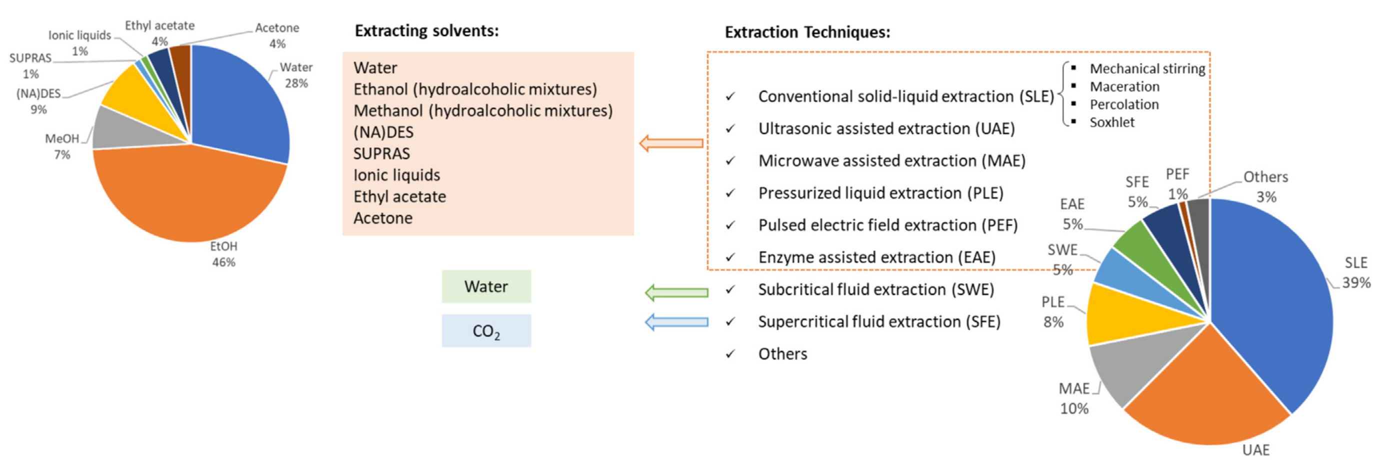


Fig. 3. Comparison of the extraction of various phenolic compounds and flavonoids with choline-glycerol (1:2 m/m) and water/ethanol as the extracting solvents.

of ionic liquids, SUPRAS and even NADES is a recurrent issue, still a matter of debate [45,46].

3.2. Extraction methodologies

Conventional solvent extraction (solid-liquid extraction, SLE) is the most common technique to recover polyphenols from AFI wastes, accounting for 40% of the last five years' applications (Fig. 2). SLE comprises sample maceration, extraction by shaking (spinning or magnetic stirring), and, to a lesser extent, percolation or Soxhlet extraction. As commented before, classical organic solvents are being replaced by more environmentally friendly options to develop greener and more sustainable extraction methods [36]. In addition, advanced technologies have also been implemented to reduce solvent waste, extraction time, and energy requirements while increasing extraction efficiency by promoting cell lysis and, thus, the release of bound polyphenols [47,50]. In the last five years, efforts have been made to develop techniques such as ultrasonic-



Fig, 2. Extracting solvents and techniques applied to the extraction of polyphenols from agri-food residues.

assisted extraction (UAE), microwave-assisted extraction (MAE), pressurized liquid extraction (PLE), pulsed electric field extraction (PEF), enzyme-assisted extraction (EAE), subcritical fluid extraction (SWE), and supercritical fluid extraction (SFE) for the recovery of polyphenols from a wide range of matrices. A more detailed discussion of the principles, advantages, and drawbacks of these advanced techniques as well as a thorough description of contemporary applications is given in reviews focused on extractive methods [35,47–49]. Here, a brief overview of the state of the art is provided to familiarize readers with these techniques.

UAE has been successfully used to recover polyphenols from several fruit and vegetable by-products using mainly hydroethanolic mixtures as solvent. For instance, UAE extraction provided better efficiencies than SLE to extract active ingredients from lemon residues using water or 50% ethanol [50,51]. The combination of UAE with (NA)DES, has also been demonstrated to be a successful option for the extraction of ellagic acid and other phenolic compounds from chestnut shells [52] and olive oil, onion tomato, or pear industries [53] reducing the use of organic solvents.

Another emerging technique in the extraction of polyphenols from AFI wastes relies on microwave-assisted extraction (MAE), which consists of the application of electromagnetic radiation of wavelength in the range of microwaves (frequency ca. 2.45 GHz). The intense thermal energy generated leads to the rupture of cell membranes, releasing the cell content to the medium and, thus, improving extraction efficiencies [54]. As in the case of UAE, water or water/ethanol mixtures are the solvents of choice as extractants. For instance, Mena-García et al. evaluated different solvents, such as water, ethanol, methanol, water/ethanol (50/50), and water/methanol (50/50), for the extraction of bioactive compounds from artichoke by-products, obtaining the most favorable results using water/ethanol (50/50) [55]. Differently, Hoskin et al. developed a continuous flow MAE method using water as the solvent for the recovery of phytoactive polyphenols from grape and blueberry pomaces [56]. An interesting application of MAE, avoiding the addition of extractant, relies on the dehydration of broccoli by-products while water-soluble bioactive components were simultaneously recovered [57].

PLE, SFE, and SWE apply external pressures and temperatures to increase the interaction of the solvent with the solid matrices, thus improving the solubility of the target compounds [58–60]. PLE relies on a closed flow system that uses (hydro)organic solvents at high temperatures and pressure, allowing the reduction of extraction time and solvent consumption. Although technology is greatly attractive, the equipment at a lab scale, pilot plant, or industrial facilities is expensive. Even so, several studies have been conducted during the last years to evaluate its efficiency [61–64]. Regarding SFE, besides its green character, it is easily scalable for industrial applications. Supercritical CO_2 ($scCO_2$) is the most important fluid in food and pharmaceutical industries, and it has been successfully implemented for the extraction of bioactive compounds from *Capsicum annuum* pepper (Jalapeno) industrial wastes [65] or mandarin leaves [66]. Water below its critical point is the solvent of choice when dealing with SWE. SWE pistachio hull and onion skin extracts obtained by UAE or SLE using organic solvents as the extractants were compared to evaluate the performance of this technique [67,68]. In these cases, the total phenolic content (TPC), total flavonoid content (TFC), and antioxidant capacity of SWE extracts resulted to be similar or higher than UAE or SLE extracts, demonstrating that SWE is an excellent green alternative.

The use of enzymes (mainly cellulase, pectinase, or tannase) to recover polyphenols (enzyme-assisted extraction, EAE) from AFI wastes has risen during the last years. Enzymes decompose cell membranes improving the extraction of the compounds with a minimum impact on the environment. EAE is applied in combination not only with conventional extraction (SLE) but also with UAE and MAE [69,70]. In these studies, Gorguc et al. evaluate the effectiveness of combining EAE with UAE [69] or MAE [70] for the extraction of protein and antioxidant compounds from sesame bran. The highest TPC and protein yield were acquired with the ultrasound- or the microwave-assisted enzymatic extraction technique. In both cases, the enzyme alcalase was more effective than viscozyme L, and the optimal enzyme concentration was 1.2 AU/100 g or 1.9 AU/100 g for UAE or MAE, respectively [69,70].

Finally, other techniques, such as those based on electrostimulation, have emerged in the scientific scenario to improve the performance of solvent-based extraction. Pulsed electric field (PEF), which accelerates diffusion processes and increases extraction efficiency due to electroporation, has been successfully applied in the extraction of bioactive compounds from AFI residue [71,72]. Differently, in high voltage electrical discharges (HVED) extraction a high voltage between two submersed electrodes forms a plasma channel that releases the energy into the extraction medium [73]. With this technique, 60 mg GAE g^{-1} were extracted from spent coffee grounds using an ethanol/water mixture as the solvent; this values is 20% higher than the yield obtained with SLE [74].

3.3. Extract purification

The extraction procedure is not only devoted to the analyte recovery by also to the sample clean-up to minimize interferences from undesired compounds. When the purity is not suitable, the resulting extracts can be further purified by solid-phase extraction and column chromatography to recover fractions or isolate compounds with remarkable antioxidant properties [75,76]. Once the extracts are obtained, the purity can be assessed by liquid chromatographic or spectroscopic methods (see below in section 4).

By-products resulting from liquid extraction processes are usually not valuable enough from the point of view of nutraceuticals and pharmaceuticals so further purification steps are often applied, employing adsorbents, membranes, or integrated procedures combining various approaches [75,77,78]. The resulting fractions are enriched in specific phytochemicals, with similar characteristics and bioactivities to be used to manufacture dietary supplements, nutraceuticals, or pharmaceuticals [11].

Solid-phase extraction (SPE) offers excellent possibilities at the lab scale to purify and enrich the liquid extracts because of its versatility. A broad range of stationary phases is commercially available to be chosen depending on the characteristics of the agri-food matrices and the phenolic families of interest –including the physicochemical features of the analytes such as acidity constants, polarity, and size (molecular mass)–. Among them, reversed-phase (RP) adsorbents are the most widely used although other interaction modes, such as ion exchange, normal phase (NP), and hydrophilic interaction liquid chromatography (HILIC), have also been introduced. Purification and fractionation of extracts can also be implemented by column chromatography with online fraction collection [75,76]. This approach is an extension of SPE to scale up the purification processes under the same interaction mechanisms.

At the pilot plant scale and industrial level, membrane-based processes may be an excellent option for processing large volumes of extracts from agri-food wastes [79,80]. Membrane separation is a pressure-driven process typically used to separate compounds based on molecular size and chemical structure. Its advantages include no solvent requirement, high efficiency, and low energy consumption for some of the techniques. Membrane processes comprise microfiltration, ultrafiltration, nanofiltration, and reverse osmosis (RO), with pore sizes of 10 to 0.1 μm, 100 to 10 nm, 10 to 1 nm, and 1 to 0.1 nm, respectively [79,80].

4. Determination of phenolic compounds in agri-food wastes

There are two main approaches to deal with the quantification of polyphenols and the determination of in-vitro activities, namely: (i) Spectrophotometric assays, which provide overall information and express the total phenolic content (TPC) or the antioxidant capacity (AC); besides, there are some assays focused on specific polyphenolic subfamilies. Although much less common, TPC and/or AC information can also be achieved electrochemically, from anodic signals generated by cyclic, square-wave, and differential pulse voltammetry [81]. (ii) Chromatographic methods, which allow determining the compositional profiles of phenolic acids and polyphenols, and the quantification of each compound of interest. In the following paragraphs, we introduce some recent trends in these global or individual approaches.

4.1. Spectrophotometric indexes

Spectrophotometric assays are widely used, and various recent reviews provide a broad outlook on their application [82–84]. The assays are based on redox or radical reactions which produce a change in the spectra, with the phenolic compounds acting as reducing or scavenging agents; among the most popular assays, we can mention Folin-Ciocalteau (FC), ferric reducing antioxidant power (FRAP), cupric reducing antioxidant capacity (CUPRAC) assay, 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay, and oxygen radical absorbance capacity (ORAC) [9]. Depending on the reaction mechanisms, the assays are classified into HAT (hydrogen atom transfer) and SET (single electron transfer) categories: FC, FRAP, CUPRAC, and DPPH are SET methods, whereas ORAC is a HAT method, and ABTS assay involves both SET and HAT mechanisms [85]. Table S2 (Supplementary section) summarizes the most relevant characteristics of the assays.

In the spectrophotometric assays, the results are expressed in terms of the concentration of the phenolic compound used to build the calibration curve, quite often gallic acid or Trolox. Although the chemical bases of the tests are equivalent, the results of the FC test are considered a measure of TPC, while the results of FRAP, CUPRAC, DPPH, ABTS, or ORAC assays are considered a measure of the AC. There is no simple relationship between AC values obtained by different assays since the contribution of each individual phenolic compound to the spectral change differ between assays [81]. For this reason, it is recommended to report AC results from various methods. However, this is not the main drawback; the major criticism is related to the reliability of AC values from chemical assays to inform about antioxidant activity at a cellular level. Despite this, these assays remain widely used due to their simplicity.

Finally, it is worthy to mention that there are assays for the analysis of (sub)families of polyphenols, such as methods based on the reaction with Al(III) for the determination of flavonoids [86], the pH differential method for monomeric anthocyanins [87], or the dimethylaminocinnamaldehyde (DMAC) assay for flavanols [88].

4.2. Chromatographic methods for polyphenolic profiling

The characterization of agri-food residues by polyphenolic profiling, i.e. determining the composition of phenolic acids and polyphenols occurring in the samples, is mainly addressed by chromatographic and related separation techniques in which the selectivity is accomplished from the separation process of the analytes. Among these techniques, those based on capillary electrophoresis (CE) [89,90] and gas chromatography (GC) [91] have been sometimes reported for the determination of phenolic compounds. However, they suffer from some disadvantages, such as the characteristic low detection capabilities of CE or the requirement of derivatization steps in GC to decrease the analyte polarity. Under these circumstances, high-performance liquid chromatography (HPLC) or ultrahigh-performance liquid chromatography (UHPLC) with spectroscopic ultraviolet–visible (UV–vis) or fluorescence (FL) detection or hyphenated with mass spectrometry (MS) [92] is nowadays the technique of choice for the determination of phenolic constituents in agri-food-related matrices.

4.2.1. Chromatographic conditions

The high versatility of (U)HPLC techniques mainly comes from the variety of separation modes, with a great range of columns commercially available. Among them, reversed-phase (RP) chromatography is the most popular option to determine phenolic acids and polyphenols in agri-food wastes. In this mode, stationary phases mainly consist of saturated aliphatic groups chemically linked to silica or polymeric particles, with the octadecyl (C18) group being the most widely employed. Besides, other groups, such as butyl, octyl, phenyl, cyano, or fluorinated columns, have also been considered when changes in selectivity are intended.

Hydro-organic mixtures with methanol or acetonitrile as the organic component with small amounts of an organic acid (e.g., 10–100 mmol L^{-1} of formic or acetic acid) are the typical mobile phases. Specific gradient elution programs are optimized to cope with the high complexity of phenolic and polyphenolic composition in agri-food samples. As a matter of example, Fig. 4 shows the chromatogram of a NADES extract of olive leaves by reversed-phase HPLC with UV detection at 280 nm. A complex mixture consisting of several compounds with high antioxidant capacity was obtained, highlighting 3-hydroxytyrosol, rutin, *p*-coumaric acid, luteolin-glucosides, apigenin-rutinoside, and luteolin. Recently, an interesting application was reported for the valorization of Ribes nigrum pomace, an agri-food by-product, to design a new green cosmetic active in compliance with circular economy principles [93]. HPLC with diode-array detection (DAD) and evaporative light scattering detection (ELSD) in reversed-phase mode was proposed for Ribes nigrum extract characterization using a C18 column and a ternary mobile phase based on 0.1% formic acid aqueous solution, acetonitrile, and 2-propanol. This method allowed the simultaneous determination of polar molecules and polyphenols with an acetonitrile-based separation; in addition, terpenes, terpenoids, and fatty acids were determined in the extracts using a 2-propanol-based separation.

C18 reversed-phase columns with high-strength silica (HSS) particle technology (such as the HSS T3 sorbents), specially designed to be compatible with 100% aqueous mobile phases and to develop separations of more polar compounds, have also been proposed in the determination of phenolic acids and polyphenols in agri-food wastes [94]. Other LC separation modes, such as normal-phase (NP) and HILIC, provide complementary separations to RP chromatography. These possibilities are successful for the most polar analytes, which are weakly retained in RP columns, and for oligomeric species. In any case, although NC and HILIC have been used to determine polyphenolic compounds in food, the number of applications to characterize agri-food wastes is still scarce.

4.2.2. LC coupled to mass spectrometry

Among the arsenal of analytical techniques available, liquid chromatography coupled with mass spectrometry (LC-MS) is widely used to assess agri-food waste characterization, either with low resolution (LC-LRMS) or high resolution (LC-LRMS) instruments. Table 2 summarizes some selected applications recently described in the literature for the identification and determination

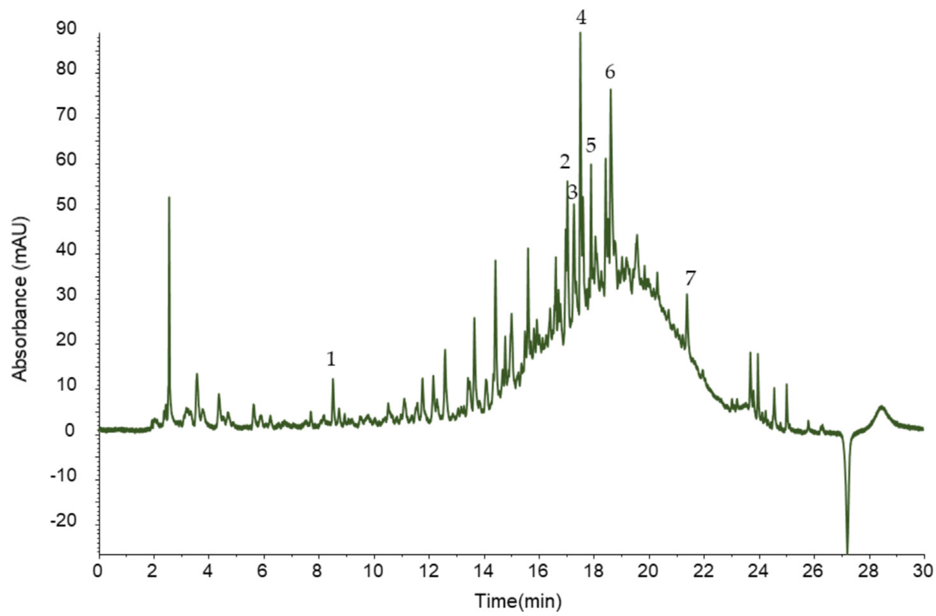


Fig. 4. Chromatogram at 280 nm of olive waste extracted with a choline/glycerol NADES. Compound identification: 1: 3-hydroxytyrosol; 2: rutin; 3: p-coumaric acid; 4: luteolin-glucoside; 5: apigenin-rutinoside; 6: isomer of luteolin-glucoside; 7: luteolin.

of phenolic acids and polyphenolic compounds in agri-food wastes.

The characterization of food matrices by LC-MS is mainly carried out by targeted and non-targeted approaches. Targeted approaches focus on quantifying pre-established compounds (or families), thus requiring the availability of commercial standards for quantitative and confirmatory purposes. LC-LRMS is the technique of choice in those cases, mainly in tandem mass spectrometry (LC-MS/MS) and using triple-quadrupole (QqQ) mass analyzers working in multiple reaction monitoring (MRM) mode, because of the enhanced selectivity and sensitivity achieved [95,96]. For example, Di Lena et al. carried out the characterization of rapeseed meal, a by-product of oilseed extraction connected to the agri-food and bio-fuel sectors currently employed as animal feed and for other low-value purposes. In the application, a much better valorization was achieved, considering the product as a source of bio-based molecules for high-value applications. A full characterization focusing on nutritional and bioactive components was performed using different techniques. Thirteen phenolic acids (see Table 2) were determined by C18 reversed-phase LC-MS/MS in a QqQ instrument using electrospray in negative ionization mode and dynamic multiple reaction monitoring (dMRM) acquisition mode. The polyphenolic extracts obtained showed significant antioxidant activity and a predominance of sinapic acid, accounting for more than 80% of the total phenolic acid content. Ion-trap mass analyzers working in full scan acquisition mode have also been proposed for the targeted polyphenolic characterization of agri-food wastes. For example, a comparative evaluation of the nutrients, phytochemicals, and antioxidant activity of two hempseed oil by-products after cold pressing was reported by Occhiuto et al. [97]. A C18 reversed-phase LC-MS method using an ion-trap mass analyzer working in full scan (m/z90-1,000) was proposed to identify and quantitate polyphenols in the analyzed products. ESI in positive and negative modes was used.

Non-targeted LC-MS approaches are typically utilized for the identification of both known and unknown compounds in the set of samples, thus focusing on obtaining as much chemical information as possible from those samples. These methodologies require both generic sample treatments and MS acquisition modes, mainly full-scan acquisition, without assuming anything about the nature or characteristics of the possible descriptor or marker compounds of the sample classes (i.e., to avoid losing essential information from unknown components that could contribute to maximize the discrimination of the families of compounds of interest). In this case, as can be seen in Table 2, HRMS techniques are preferred due to their enhanced sensitivity in full-scan modes and selectivity because of both the higher resolution (5,000–40,000 FWHM –full-width at half-maximum– with time-of-flight (TOF) instruments or 50,000–200,000 FWHM with Orbitrap analyzers) and the accurate mass measurements. These instruments also allow fast polarity changes to be performed, which widens the range of compounds that can be analyzed in a single run. For example, a non-targeted LC-HRMS method using a TOF instrument with ESI in negative ionization mode and working in full scan acquisition mode was proposed to identify bioactive molecules recovered from Avocado peels by UAE, aiming to exploit their potential for food and nutraceutical applications [98]. Phenolic acids (hydroxybenzoic and hydroxycinnamic acids), followed by flavonoids (flavanols, flavanonols, flavones, flavanones, and chalcone), phenylethanoids, and lignans were the most representative classes of the phenolic compounds found in the avocado peel extract.

The characterization of bioactive substances in agrochemical food products will often require simultaneously HRMS and tandem mass spectrometry (MS/MS), either in low- or high-resolution, to obtain chemical structural information. The elemental composition (accurate mass measurements) with the corresponding isotopic patterns by HRMS and the MS/MS information must be combined to identify and characterize bioactive substances in the analyzed samples. Besides, the possibility of performing retrospective analysis is a great advantage of working with full-scan acquisition combined with data-dependent scan modes, where two scan events are registered simultaneously (for example, full-scan as the first scan event in combination with MS/MS ion scan of specific detected signals in as a second scan event). This will allow the identification of new non-expected bioactive substances without the requirement of analyzing the samples again. Finally, the use of accurate mass and spectral databases will be fundamental in

Table 2
Selected LC-MS methodologies for the determination and characterization of phenolic and polyphenolic compounds in agri-food wastes.

Strategy	Agri-food waste	Polyphenolic compounds	Sample extraction	LC conditions	MS conditions	Reference
Targeted LC-LRMS	Residual brewing yeast	Caffeic, chlorogenic, *p*-coumaric, 3,4-dihydroxibenzoic, *trans*-ferulic and gallic acids, kaempferol, myricetin, naringin, quercetin, and rutin	Matrix-solid-phase dispersion (MSPD) using TiO_2 nanoparticles	C18 column (150 × 0.3 mm I.D., 4 μm) Mobile phase: (A) 0.2% formic acid aqueous solution, (B) methanol Gradient elution, flow-rate 0.5 mL min^{-1} Injection volume: 20 μL	LC-MS/MS ESI (−) Triple quadrupole mass analyzer Full-scan and MRM acquisition modes	[95]
	Rapeseed Meal by-product	Gallic, protocatechuic, vanillic, chlorogenic, neochlorogenic, caffeic, syringic, 4-hydroxybenzoic, cryptochlorogenic, *p*-coumaric, ferulic, sinapic, and cinnamic acids	Liquid-solid extraction with methanol:water:acetic acid 80:19.5:0.5 (v/v/v)	Ascentis C18 column (100 × 1 mm I.D., 3 μm) Mobile phase: (A) 0.05% acetic acid in water, (B) 0.05% acetic acid in acetonitrile Gradient elution, flow-rate 0.1 mL min^{-1} Injection volume: 1 μL	LC-MS/MS ESI (−) Triple quadrupole mass analyzer dMRM acquisition mode	[96]
	Hempseed oils byproducts after Cold pressing	*Identified compounds:* Gallic, protocatechuic, 4-hydroxybenxoic, vanillic, chlorogenic, p-cumaric acids, and 13 flavonoids (among them catechin, epicatechin, naringin, naringenin …)	Liquid-solid extraction with methanol:water 80:20 (v/v)	Luna Omega PS C18 column (150 × 2.1 mm I.D., 5 μm) Mobile phase: (A) 0.1% formic acid in water, (B) methanol Gradient elution Injection volume: 5 μL	LC-MS ESI (−)/ESI (+) Ion-trap mass analyzer Full-scan acquisition mode (*m/z* 90-1,000)	[97]
Non-targeted LC-HRMS	Avocado peels	*Identified compounds:* Phenolic acids, flavonoids, phenylethanoids, and lignans	Ultrasound assisted extraction (UAE) Ethanol 38.46%, 44.06 min, 50 °C	Zorbax XDB-C18 column (100 × 2.1 mm I.D., 1.8 μm) Mobile phase: (A) 0.1% aqueous formic acid, (B) 0.1% formic acid in acetonitrile Gradient elution, flow-rate 0.4 mL min^{-1}	LC-HRMS ESI (−) TOF mass analyzer Full-scan acquisition mode	[98]
	Honeycomb (*Nidus Vespae*)	*Identified compounds:* Phenolic acids and flavonoids	Liquid-solid extraction with ethanol (75% v/v), 1h at 60 °C	UPLC HSS T3 column (100 × 2.1 mm I.D., 1.8 μm) Mobile phase: (A) 0.1% formic acid in water (MS positive mode)/5 mM ammonium acetate in water (MS negative mode), (B) acetonitrile Gradient elution, flow rate 0.5 mL min^{-1} Injection volume: 1 μL	LC-HRMS/MS ESI (+)/ESI (−) Q-Orbitrap Full scan MS (70,000 FWHM) MS/MS at stepped normalized collision energy (NCE) of 20/40/60% (17,500 FWHM)	[93]
	Walnut Husk and Pellicle	*Identified compounds:* Hydrolysable tannins, flavonoids, and phenolic acids	Ultrasound assisted extraction (UAE) Methanol, 45 min, 50 °C	Hypersil GOLD column (100 × 2.1 mm I.D., 1.8 μm) Mobile phase: (A) 1% formic acid in water, (B) acetonitrile Gradient elution, flow rate 0.5 mL min^{-1} Injection volume: 10 μL	LC-HRMS/MS ESI (+)/ESI (−) Q-Orbitrap Full scan MS (70,000 FWHM) MS/MS at stepped normalized collision energy (NCE) of 20/40/60% (17,500 FWHM)	[99]

sample screening, identification, and confirmation of known and unknown bioactive substances. As an example, Zhao et al. [93] described an LC-HRMS/MS method for the identification and quantitation of bioactive components from the honeycomb, an agri-food waste within the bee product industry. For that purpose, a Q-Exactive Orbitrap was used in both positive and negative ionization modes. Full scan HRMS at a resolution of 70,000 FWHM and MS/MS fragmentation at a resolution of 17,500 FWHM (working with stepped normalized collision energies of 20/40/60%) were combined for the identification of bioactive substances. Chemical standards with in-house MS/MS databases and accurate mass comparisons between experimental ions, calculated ions, and fragment ions with those of references were employed. The authors also consulted Chem Spider, HMDB Human Metabolome Database, and Mass Bank of North America databases during the identification process. A total of 76 bioactive compounds from hydroethanolic extracts of honeycomb were identified, with polyphenols being one of the most abundant groups, and among them, phenolic acids and flavonoids. A similar approach using a C18 reversed-phase LC-HRMS/MS method with a Q-Exactive Orbitrap was proposed to study the phenolic compounds in walnut husk and pellicle, agri-food wastes in soaring demand in the walnut-product industry because of their features [99]. A total of 110 bioactive components, including hydrolyzable tannins, flavonoids, phenolic acids, and quinones, were tentatively identified, 33 of which differed between walnut husk and pellicle.

5. Conclusions

The waste produced by the agri-food industry is an extraordinary source of bioactive phytochemicals with great application potential in different areas. Some of the most studied waste is generated in the wine and olive oil industry, and in the production of fruit and vegetable juices. Still, other residues from food processing consisting of shells, skins, seeds, leaves, etc., cannot be neglected.

Although the possibilities of recovery concern a great variety of families of compounds, this manuscript focuses on phenolic compounds, to which a plethora of beneficial properties are attributed, many of them related to their enormous antioxidant power.

To reduce the environmental impact of the extraction of phenolic compounds from waste, options based on green technologies and green solvents are sought. Clean solvents, such as water or supercritical CO_2, can be used, but a given percentage of organic solvents (e.g., ethanol and acetone that are considered relatively green) may be worthwhile to improve the extractive performance of some compounds. A new extractive trend relies on deep eutectic solvents, especially those obtained with natural compounds, the so-called NADES. NADES, and especially those based on choline chloride as acceptor compound, generally show higher performance than traditional solvents. However, there is some controversy about the green character of NADES. In summary, the possibilities of NADES are real, but some technological, ecological, economic, and chemical issues remain unresolved.

The characterization of the extracts is carried out using the usual analytical techniques. Given the physicochemical features of polyphenols, liquid chromatography is the most appropriate technique. Detection is usually performed by UV/vis, fluorescence, or mass spectrometry, being this last option the option of choice for the identification and structural elucidation of compounds. Quite often, information on the overall phenolic content is required to estimate the antioxidant capacity from the point of view of reducing power or radical scavenging. The utility of simple spectrophotometric chemical assays as an index of phenolic richness is clear, but there is a lot of debate about the correlation between the antioxidant or antiradical capacity at the chemical level with the effect on biological systems or humans.

Due to the complexity of waste matrices many compounds are simultaneously extracted, many of them still pending identification. At this point, high-resolution mass spectrometry and new tandem modalities, combined with information from databases and molecular identification software, play a fundamental role. As a result, the number of phenolic compounds identified in different matrices is increasing extraordinarily.

Beyond the remarkable advances in extraction and characterization, the problems related to extract purification still require the attention of the scientific community. Although this topic is outside the scope of this publication, it should be emphasized that it is currently one of the most challenging issues concerning the revalorization of agri-food waste. The purity of the final products determines their possible applications. In this sense, high-purity products (e.g. >98%) would be required if the extracts were destined for the pharmaceutical or food industry. In contrast, less purified mixtures could be used in cosmetics or in food packaging, where polyphenols could act as a protective barrier to prevent food oxidation or degradation from exposure to sunlight.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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