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The recovery from agro-industrial wastes provides different profiles of anti-inflammatory polyphenols for tailored applications

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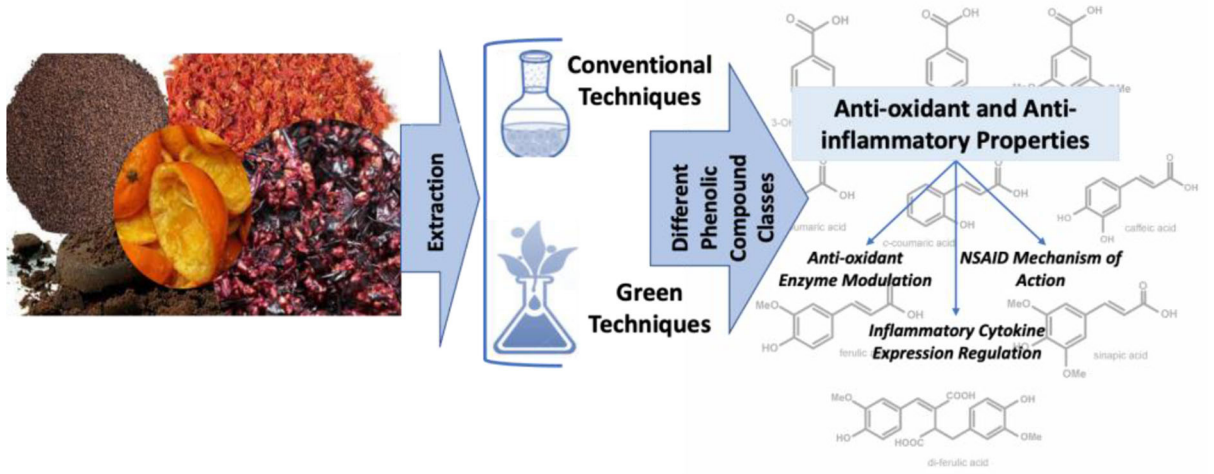
Food and agro-industrial processing produce a great amount of side-stream and waste materials that are excellent sources of functional bioactive molecules such as phenolic compounds that recover them can be beneficial not only for food sustainability but also to human for many industrial applications such as flavor compounds and therapeutic applications such as antimicrobial and anti-inflammatory. The treatments and extraction techniques have major effects on the recovery of bioactive compounds. Along with the conventional extraction methods, numerous innovative techniques have been evolved and have been optimized to facilitate bioactive extraction more efficiently and sustainably. In this work, we have summarized the state-of-the-art technological approaches concerning novel extraction methods applied for five most produced crops in Italy; Grape Pomace (GP), Tomato Pomace (TP), Olive Pomace (OP), Citrus Pomace (CP), and Spent Coffee Grounds (SCG), presenting the extraction yield and the main class of phenolic classes, with the focus on their biological activity as an anti-inflammatory *in vitro* and *in vivo* studies *via* describing their molecular mechanism of action.

KEYWORDS

agro-industrial by-products, phenolic compounds, extraction methods, antioxidants, inflammatory regulation

Introduction

For many years, agro-industrial by-products have been considered as underestimated substrates, at least because of their removal from the food production line and the complex problems posed by their discarding in the environment. Recently, the claims for sustainability in this sector led to valorization of the agro-industrial by-products as a new source of "functional ingredients" including enzyme production, dietary fibers, and phytochemicals that can be applied in different sectors, such as food/feed and



GRAPHICAL ABSTRACT |

nutraceuticals. The recovery of these chemicals by imposing the proper extracting methods can deliver value-added compounds, such as antioxidants.

Italy is one of the main producers of wine, tomato paste, olive oil, and citrus in Europe, and each year huge amount of grape pomace (GP), tomato pomace (TP), olive pomace (OP), and citrus pomace (CP) are produced (www.statista.com). Coffee is the most popular drink in Italy and a massive quantity of spent coffee grounds (SCG) made by coffee makers are produced every day (ICO, 2019) (Figure 1).

Grape pomace traditionally has been used as fertilizer or feed biomass for biogas production (Cáceres et al., 2012). Recently, they have been applied in the nutraceuticals and food sectors as well. Grape pomace can be reused as bioactive additives to foodstuff or beverages or in bakery products (Table 1) (Hayta et al., 2014; Marinelli et al., 2018). A total of 14.5 million tons of grape by-products are produced annually in Europe alone, from which about 9 million tons are related to solid grape pomace (Maicas and Mateo, 2020).

Tomato pomace usually is generated from tomato processing industries and formerly used in producing compost, biogas, or animal feed, even though recently TP has received high attention from the cosmetics and food industries (Table 1) (Lu et al., 2019).

In Mediterranean countries, the production of olive oil is of economic importance which generates about 30 million tons of olive pomace as waste annually (Mirabella et al., 2014). Olive pomace is characterized by high antioxidant activity and a characteristic profile of fatty acids and etc. (Rodrigues et al., 2015). They have the potential to be

Abbreviations: GP, Grape pomace; TP, tomato pomace; OP, olive pomace; CP, citrus pomace; SCG, spent coffee grounds; HPLC, high-performance liquid chromatography; FL, fluorescence, MS, mass spectrometry; NMR, nuclear magnetic resonance; UHPLC, ultra-high pressure liquid chromatography; AUAE, aqueous ultrasound-assisted extraction; GAE, gallic acid equivalent; TPC, total phenolic compound; UAE, ultrasound-assisted extraction; SSR, solute/solvent ratio; MAE, microwave-assisted extraction; MP, microwave power; kW, kilowatt; DW, dry weight; FW, Fresh weight; MeOH, Methanol; EAE, enzyme assisted extraction; HHP, high hydrostatic pressure; SbFE, subcritical fluids extraction; SFE, supercritical fluid extraction; SCE, supercritical CO_2 extraction; PLE, pressurized solvent extraction; HT, hydroxytyrosol; TY, tyrosol; PEF, pulsed electric field; HVED, high voltage electrical discharges; POH, pulsed ohmic heating; OH, ohmic heating; MEF, moderate electric fields; DES, deep eutectic solvent; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; ChCl, choline chloride; ROS, reactive oxygen species; RNS, reactive nitrogen species; SOD, superoxide dismutase; GPx, glutathione peroxidase; PRXs, peroxiredoxins; CAT, catalase; HO-1, heme oxygenase-1; GR, glutathione reductase; Nrf-2, nuclear factor erythroid-related factor; Keap1, Kelch-like ECH-associated protein 1; ARE, antioxidant-responsive elements; GSH, glutathione; RCC, reactive carbonyl compounds; CNS, central nervous system; AhR, aryl hydrocarbon receptor; NF-κB, Nuclear factor kappa B; TLR, toll-like receptor; MAPK, mitogen activated protein; ERK, extracellular signal-regulated kinases; JNK, c-Jun NH2 terminal kinases; P13K/Akt, phosphatidylinositol 3-kinase; IKK/JNK, kappa kinase/C-Jun amino-terminal kinases; caps-, 1caspase 1-dependent; NLRP3, pyrin domain-containing protein 3; peroxisome proliferator-activated receptor; NSAID, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; LOX, lipoxygenase; PG, prostaglandins; TX, thromboxanes; HBAS, hydroxybenzoic acids; NO, nitric oxide; PIK, phosphatidylinositol kinase; PKC, protein kinase C; cAMP, cyclic adenosine monophosphate; PIK3/AKT, serin/theronine protein kinases.

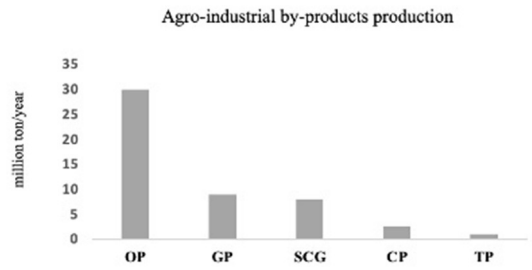


FIGURE 1
Agro-industrial by-product annual production (Year 2017).

used in skincare products and cosmetics, mainly as a natural moisturizing factor (Table 1) (Otero et al., 2021).

Sweet and red oranges, grapefruits, tangerines, mandarins, lemons, and limes are different types of citrus fruits cultivated globally. Brazil is the major sweet orange producer (~47%), United States stands for grapefruit production principally, and the European countries are the main lemons and mandarin (after China) producers alongside the orange cultivations. Global orange production for 2020/21 is estimated to be 48.57 million [Food and Agriculture Organization of the United Nations (FAO); FAOSSTAT (2020)]. Italy is one of the main citrus producers in the Mediterranean area. Annual production was more than 2.5 million tons in 2017 which mainly originated from the Southern parts of Italy, from which about 40% of total citrus production is destined for juice production, which in consequence generates large amounts of waste (Multari et al., 2020). The citrus pomace (CP) production was about 15 million tons worldwide in 2016 (FAO, 2018). Citrus bagasse is mainly reutilized for anaerobic digestion, composting, or essential oils extraction, although still contains a great source of high biological value compounds, such as pectin and phenolic compounds, that can be used in the food sectors, pharmaceutical and cosmetic industries (Table 1) (Barrales et al., 2018). Lemon by-products have been reported for pectin production and flavonoids (narirutin) extraction (Masmoudi et al., 2008), whereas orange peel has been applied for the flavonoid recovery (i.e., hesperidin) (Farhat et al., 2011). In fact, higher phenolic compounds have been detected in citrus pomace than the relative citrus juices, in particular, the presence of hesperidin, narirutin, eriocitrin, tangeretin, and luteolin has been reported in citrus by-product at least two times more than the citrus juices (Balasundram et al., 2006; Sharma et al., 2019; Multari et al., 2020). Global Tangerine/Mandarin production would be 31.6 million with declines in the European Union, Morocco, Turkey, and the United States more than offsetting a larger crop in China (FAOS, July 2020, https://downloads.usda.library.cornell.edu/usda-esmis/files/w66343603/gf06gq220/rx914c158/citrus.pdf).

In different studies, the bioactive molecules from the above wastes have been valorized vastly by conventional extraction methods (Table 2), and it has been reported that the phenolic compounds are through the main active biomolecules.

Both *in vitro* and *in vivo* studies have demonstrated that polyphenol intake is associated with numerous health effects which can be mentioned among them antioxidant activity, antimicrobial, antidiabetic, antiobesity, anti-inflammatory, and anticarcinogenic activities (Shahidi and Ambigaipalan, 2015), and therefore, they are of particular interest for the food and pharmaceutical industries due to their benefits to human wellbeing. As the secondary metabolites of plants, these compounds are widely found in vegetables (tomato, olive, etc.), fruits (grapes, cherries, apple, oranges, pear, berries, etc.), beverages (coffee and tea), cereals (wheat, corn, barley, etc.), and other foodstuffs. However, there is strong evidence that such compounds can also be present in agro-food and agro-industrial by-products (Teixeira et al., 2014; Kumar et al., 2017; Abbasi-Parizad et al., 2021). These by-products could be a new source for the recovery of polyphenols leached from both industrially processed natural products and their discarded materials.

The present review aims to provide an overview of the valorization techniques [both the conventional and green extraction methods (Tables 2, 3)] to recover the phenolic compounds from agro-industrial wastes mainly in GP, TP, OP, CP, and SCG. Further, the anti-inflammatory properties of different phenolic classes have been discussed.

Phenolic compounds: Conventional and green methods of extraction and characterization

Extraction is the first and the most important step to recover natural bioactives from by-products. Phenolic compounds recovery vigorously relies on the extraction process and so choosing an adequate procedure is fundamental to increase phenolic yields, without damaging them; since by-products endured many complex industrial processing, such as fermentation, high temperature, and pressure. In most cases, a pretreatment step could purify and homogeny the sources, which could include drying/freeze drying, filtering, or centrifugation. Different extraction items can simulate the extraction efficiency in various biomasses. In the first place, the solvent type/concentration, extraction time, and temperature are of importance. To guarantee the intact extraction of phenolics, an optimum pH should be taken into consideration, since the phenolic compounds are very sensible to pH (Amendola et al., 2010).

Various solvents have been used to extract phenolic compounds from agro-industrial by-products, which are usually based on the biomass nature and the type of desired extracting compounds. Phenolic acids and flavonoids are hydro-soluble substances; therefore, usually water, alcoholic solvents, acetone, ethyl acetate, or a mixture of them at different ratios are used for

TABLE 1 Phenolic compounds recovered from by-products, health effects and their application.

By-products	Phenolic compounds	Health benefits	Application
Grape by-products	Simple phenolics (gallic acid, syringic acid, protocatechuic acid), 4-hydroxybenzoic acid, caffeic acid, catechin, epicatechin, Hydroxytyrosol, Proantgocyanins, anthocyanins, Lignins	Antioxidant, anti-inflammatory, antimicrobial agent, anticarcinogenic, neuroprotective, cardioprotective, antidiabetics, antiobesity	Food additives, feed, Cosmetics, Food preservative and stabilizer, Food colorant
Tomato by-products	Hydroxybenzoic Acids (gallic acid, syringic acid), Hydroxycinnamic acids (cinnamic acid, ferulic acid, *p*-coumaric acid, caffeic acid), Flavanones (naringenin), Flavones (apigenin), Flavonols (kaempferol, quercetin, Myrecetin, Rutin, Chalcone, naringenin chalcone)	Antioxidant, anti-inflammatory, antidiabetic	Food preservative and stabilizer, Cosmetics, anti-inflammatory activity
Olive by-products	Hudroxytyrosol, Oleuropin and derivatives, Tyrosol, Flavones (apigenin), Hydroxycinnamic acids (ferulic acid, *p*-coumaric acid, caffeic acid, cinnamic acid), Luteolin	Antiplatelet, anti-inflammatory, Antioxidant, antimicrobial agent, Hepatoprotective, Anti-adipogenic activity	Cosmetics (skin antiaging and lightening), Food (Pasta, Bread),
Spent coffee ground	Hydroxycinnamic acids (caffeic acid, chlorogenic acids, gallic acid, coumaric acid), quinic acid, Flavonoids (Kaempferol, catechin, epicatechin, apigenin)	Antioxidant, anti-inflammatory, antimicrobial agent	Food additives (bakery, confectionary, snacks, ready-to-eat products), Cosmetics (skin antiaging and lightening)
Citrus by-products	Naringin, Narengenin, Narirutin, Hesperidin, Hesperetin, neohesperidin, Luteolin, Neoeriocitrin, Hydroxycinnamic acid, Ferulic acid, Gallic acid, caffeic acid, *p*-coumaric acid, Protocatechuic acid, Salicylic acid, Vanillic acid, Syringic acid, Chlorogenic, Sinapic acid	Anti-inflammatory, Antimicrobial agents	Food additives, Flavor

their extraction. Selecting the proper solvent and the method of extraction affects the phenolic compounds separation afterward (Ameer et al., 2017). To increase the stability of phenolic compounds in extracts, a mild acidified solvent is typically used (Fontana et al., 2013).

Different condition of conventional solvent extraction has been reviewed in Table 2; however, with growing interest for applying green methods of extraction with the intent to both lower the disadvantages of excessive time/energy consuming and the pollution due to solvents, a wide range of green techniques have been explored to extract the agro-industrial by-products (Table 2). These green extraction methods have been reviewed for their potential in terms of phenolics yield extraction and condition. However, these green techniques may have disadvantages that affect the extraction efficiencies of various subclasses of phenolic compounds (Ameer et al., 2017).

Once the phenolic compounds are extracted, they undergo the characterization methods. The most frequent methods used to separate and characterize different classes of phenolics in by-products include high-performance liquid chromatography (HPLC) which in most cases could be coupled to electrochemical detection, such as UV, fluorescence (FL), mass spectrometry (MS), and nuclear magnetic resonance (NMR) (Ignat et al., 2011; Khoddami et al., 2013). NMR is important to characterize the structure of flavonoids in complex matrices, although it presents disadvantages such as a high cost and that it may not be suitable for all applications. However, MS is the most common method used for the identification and characterization of flavonoids nowadays. Recently, ultra-high pressure liquid chromatography (UHPLC) has been also applied to MS to detect and identify the exact phenolic structures (de Villiers et al., 2016).

Different green methods and their application to recover the phenolic compound from the abovementioned agro-industrial by-products have been described in detail in the following:

Ultrasound-assisted extraction

Ultrasound is a mechanical wave that propagates in an elastic medium and its frequency is above the audible sounds (Medina-Torres et al., 2017). This technique uses ultrasonic waves to shake a submerged sample in a biological solvent and is based on

TABLE 2 Conventional extraction of phenolic compounds.

Matrix	Solvent/performance	Extraction yield	Ref.
Spent Coffee Grounds	MeOH (20–100%), solvent/solid ratios (SSR) (10–40 ml g^{-1} SCG), extraction times (30–90 min)	TPC: ranged 2.6–12.3 mg GAE g^{-1} SCG, TF: 0.51–2.50 mg QE g^{-1} SCG, CGA: 0.37–1.39 mg g^{-1} SCG, FRAP: 0.021–0.162 mM Fe (II)/g SCG. MeOH at 60% in an SSR of 40 ml g^{-1} SCG/90 min, resulted in the most suitable condition (TPC: 16 mg GAE g^{-1} SCG and FRAP: 0.10 mM Fe (II) g^{-1}.	Mussatto et al., 2011
	EtOH (60%), 1:50 (w/v- solid/solvent) shaking 30 min at 60°C	TPC:6.33–28.26 mg GAE g^{-1}, TF:2.11–8.03 mg QE g^{-1}, EC_{50}:1.47–6.74 (% v/v), CGA: 1.65–6.09 mg CQAE g^{-1}, CAF:0.0–11.5 mg g^{-1}	Panusa et al., 2013
	H_2O, 1:16 (w/v- solid/solvent); EtOH: H_2O, 10 min /80°C; MeOH: H_2O, 10 min /80°C	TPC: 2.65–17.48 mg GAE g^{-1} DW, ABTS:15.3–152.6 μmol TE g^{-1} DW, DPPH:5.02–82.4 μmol TE g^{-1} DW	Bravo et al., 2013
	H_2O, 1:10, 1:70 (w/v- solid/solvent), 15–75 min /110–190 °C	TPC: 21.09–56.59 mg GAE g^{-1}, ABTS: 7.0–32.9 mmol TE $100g^{-1}$, DPPH: 5. 6–22.4 mmol TE $100g^{-1}$. Under the optimum condition (179°C, 36 min, and 14.1 g L^{-1} SSR) TPC (88.34 mg GAE g^{-1}), antioxidant activity on ABTS•+ (88.65 mmol TE 100 g^{-1}) and DPPH (38.28 mmol TE 100 g^{-1}) were obtained.	Xu et al., 2015
	EtOH 60%, 1:10 (w/v- solid/solvent), shaking 30 min, centrifuged at 16800 g/15 min/4 °C	TPC: 19.2 % DW, 3-CQA:0.14, 4-CQA:0.23, 5-CQA:0.31, 3,4-diCQA:0.22,3,5-diCQA:0.12,4,5-diCQA:0.16% DW	Jiménez-Zamora et al., 2015
	H_2O, 1:20 (Mild hydrothermal pretreatment), 20 min /120°C	TPC yield: 32.9 mg GAE g^{-1} DW, TF: 8.3 mg QE g^{-1} DW, DPPH: 68%, FRAP:0.024 mM Fe Fe (II) g^{-1} SCG.	Conde and Mussatto, 2016
	Autohydrolysis, 5–15 ml g^{-1}, 10–50 min /160–200°C	The optimum conditions (15 ml g^{-1}/200°C/50 min) resulted in TPC: 0.36 mg GAE g^{-1} SCG), FRAP: 69.50 mg Fe (II) g^{-1} SCG, DPPH: 28.15 mg TE g^{-1} SCG, ABTS: 31.46 mg TE g^{-1} SCG, TAA: 66.21 mg α-TOC g^{-1}SCG.	Ballesteros et al., 2017
	Samples dried at 40 °C/12 h, extracted with H2O (deionized), 1:50 (w/v-solid/solvent), and 5 min /shaking, cooled 20 min / 20 °C. centrifugation (12 000g/4 °C/15 min)	Main phenolics determined by HPLC: 5-CQA: 27.2–2440 μg g^{-1}DW, CA:4.11–22.9 μg g^{-1}DW, FA:14.2 μg g^{-1}DW	Angeloni et al., 2019
Recovery chlorogenic acid from coffee	EtOH (60%), 1:25 g ml^{-1} (w/v solid/solvent), 70 °C	CGA: 31.9–37.7g CGA 100 g^{-1} total solid extracts (TSE).	Burniol-Figols et al., 2016
Exhausted Olive Pomace	H_2O (W), Acidified H_2O (AW), EtOH 50% (Et 50), EtOH 20% (Et 20), Acetone 50% (Ac)	**W**: TPC: 38.1±1.3 mg GAE, TFC: 71.4 ± 2.9 mg RE, DPPH: 22.4 ± 0.8 mg TE, ABTS: 70.7 ± 3.9 mg TE, FRAP: 39.9 ± 1.42 mg TE; **AW**: TPC: 29.7 ±0.9 mg GAE, TFC: 63.3 ± 3.4 mg RE, DPPH: 16.3 ± 1.3 mg TE, ABTS: 57.1 ± 7.5 mg TE, FRAP: 33.9 ± 1.7 mg TE; **Et50**: TPC: 39.5 ± 2.3 mg GAE, TFC: 76.3 ± 2.2 mg RE, DPPH: 27.9 ± 0.9 mg TE, ABTS: 62.9 ± 5.4 mg TE, FRAP: 41.5 ± 1.5 mg TE; **Et20**: TPC: 34.6 ± 1.9 mg GAE, TFC: 67.1 ± 5.1 mg RE, DPPH: 22.4 ± 0.9 mg TE, ABTS: 64.2 ± 4.7 mg TE, FRAP: 38.1 ± 1.1 mg TE; AC: TPC: 41.6 ± 1.7 mg GAE, TFC: 76 ± 3.1 mg RE, DPPH: 35.1 ± 2.3 mg TE, ABTS: 63.5 ± 4.1 mg TE, FRAP: 46.2 ± 1.8 mg TE.	Gómez-Cruz et al., 2020
	DMSO, acidified by phosphoric acid	661 mg kg^{-1}	Yakhlef et al., 2018
Olive Pomace	OP was Deffatted, extracted with $CHCL_3$-MeOH (9:1)/MeOH,	173.4–202.1 mg kg, DPPH (EC_{50}): 99.7–101.3.	Cioffi et al., 2010
	Water/ EtOH	TPC: 16.9 mg GAE g^{-1} DPPH: 0.81 g TE L^{-1}	Albahari et al., 2018
Lemon Pomace	Hot water optimal extraction conditions: 95 °C, 15 min, SSR: 1:100 g ml^{-1} MeOH extraction in ultrasonic bath (220 V, 50 Hz, and 250 W), Both extractions were centrifuged at 3,500 9 g / 10 min /14 °C	Hot water extracts at the optimal conditions had the same content of TPC and TF as methanol extracts obtained by ultrasound extraction. Overall, hot water could be an effective solvent for the recovery of TPC, TF from lemon pomace Hot water extracts at the optimal conditions had the same content of TPC and TF as methanol extracts obtained by ultrasound extraction.	Papoutsis et al., 2018

(Continued)

TABLE 2 (Continued)

Matrix	Solvent/performance	Extraction yield	Ref.
Citrus pomace	EtOH 70%, SSR: 1:100, at 25°C; Super-heated steam (SHS) extraction system at 100, 200, and 300 °C) for 10/20 min; Centrifuged at 1,000/15 min	TPC: 2.69–5.17 g GAE 100g^{-1}, TF: 1.27–6.67 g RE 100 g^{-1}, DPPH (IC_{50}): 0.13–0.65 mg ml^{-1}. Intracellular ROS scavenging activity (IC_{50}): 39.71–68.80 μg ml^{-1}	Wang et al., 2018
	Methanol/Ethanol/Acetone; SSR: 20:1 ml g^{-1}; temperature = 25 °C/ time:72 h.	TPC: 1.39–1.85 mg GAE 100 g^{-1}; Orange peel phenolic compounds were extracted better in methanol/acetone; DPPH (IC50) 781.9 μg ml^{-1}.	Dzah et al., 2020
Red Grape skin	EtOH (80%), 1 h / 60° C., Reextracted 2 times	TPC: 731 ± 9–3486 ± 54 mg GAE kg^{-1}; TF: 400 ± 9–2594 ± 44 mg GAE kg^{-1}; TAC: 158 ± 4–1848 ± 60 mg MglcE kg^{-1}; DPPH IC_{50} (mg GAE L^{-1}):58 ± 3-239 ± 4; Fe2+-chelating ability IC_{50} (mg GAE L^{-1}):52 ± 2–655 ± 7; FRAP (mM TE):2.7 ± 0.04-16.4 ± 0.1; CAA (%):75.5 ± 3–89.7–4.	Katalinic et al., 2010
Grape pomace	EtOH (80%), 1:10 (w/v- solid/solvent), Overnight shaking	TPC: 30.4 ± 11 mg GAE g^{-1}, TF: 22.1 ± 9 mg GAE g^{-1}, ORAC: 245.3 ± 21 mg GAE g^{-1}, % DPPH inhibition mg: 66.1 ± 0.6.	Hogan et al., 2010
	Acetone (70%) 0.1% HCl, 1:4 (w/v-solid/solvent),1 h/ Sonicated, centrifuged 10,000 ×g /15 min	TPC: 58–1,340 mg GAE kg^{-1}; DPPH: 710–936 mg AAE kg^{-1}.	Tseng, 2012
	EtOH (80%), 1:5 (w/v- solid/solvent), 48 h/ rotating mixer Aqueous extract dried, residue reextracted with H_2O	TPC: 69.3–131.7 mg GAE g^{-1} Residue, DPPH: 0.52–1.09 mmol TE g $^{-1}$ Residue, ORAC: 1.05–2.30 mmol TE g^{-1} Residue, ICA: 63–76% inhibition g^{-1} Residue.	Tournour et al., 2015
	EtOH (40%), 1:50 (w/v- solid/solvent), 22 h /25°C, Shaking, centrifuged 5,000 rpm/ 25 min	TAC: 0.75–4.25 mg cym-3-glu g^{-1} DW, TPC: 25–41 mg GAE g^{-1}DW, TF:10–22 mg CE g^{-1} DW	Ribeiro et al., 2015
	EtOH (40%), 1:20 (w/v- solid/solvent), 24 h / rotating mixer	TPC: 30.14–51.01 mg GAE g^{-1}, TF: 16.48–29.83 mg CE g^{-1}, TAC:12.46–20.92 mg cya-3-glu g^{-1}, DPPH:5.05–6.54 mg ml^{-1}, ABTS:0.71–1.34 mg ml^{-1}	Iora et al., 2015
	EtOH (50%), 1:25 (w/v- solid/solvent), 2 h /60 °C, Shaking	TPC: 196.2 ± 22.7 mg GAE g^{-1} Residue, ORAC: 2,756 ± 109 μmol TE g^{-1} Residue.	Antoniolli et al., 2015
	Samples (0.1 g ml in aceton 50%), shaking 12 h/450 rpm, centrifuged at 1,000 rpm/5 min	TPC ranged: 0.06–0.29 mg GAE mg.	Kadouh et al., 2016
	Samples [10 g 40 ml^{-1} acetone 80% (v/v)], shaking overnight, RT	TPC: 92 ± 2–154 ± 1.8 mg GAE g^{-1} extract, TF: 38.9 ± 0.7–91.7 ± 1 mg CE g^{-1} extract, TAC: 1.4 ± 10.7 mg cyn-3-glu g^{-1} extract, DPPH: 11.2–28.2 μmol TE g^{-1} extract, ABTS: 378–1,013 μmol TE g^{-1} extract	Xu et al., 2016
	MeOH (100%), 0.1% HCl, 1:15 (w/v-solid/solvent), 2 h /4 °C, Shaking, centrifuged 2,058 × g /10 min	TPC:9.8 ± 1.3-21.2 ± 2.1 mg GAE g^{-1} DW	Lingua et al., 2016
Vinery by products	Freezed dried samples (50 g 200 ml^{-1} MeOH, acidified with HCl), shaking overnight at 4 °C, sonication 3 min/ centrifuged at 5,000/20 min	TAC: 3,906 ± 245 mg L^{-1}, Quercetin:383 ± 24 mg L^{-1}, Gallic acid: 261 ± 17 mg L^{-1}; TEAC: 6.79 mM TE g^{-1} DW; IC_{50}:372 ng ml^{-1}; Anti-COX-1: at 100 μM of TAC (in which the concertation of phenolics quercetin and gallic acid were at 15 μM and 18 μM, respectively).	Trošt et al., 2016
Tomato pomace	Preparation of Lipophilic and Hydrophilic Extract Lipophilic Extracts: 4 grams lyophilized TP extracted with n-hexane until colorless extract obtained, Hydrophilic Extracts: the residue was reextracted with ethanol (100%) overnight.	Lipophilic Extracts: FRAP: 9.9 mg AAE 100 g^{-1}, DPPH (IC_{50}):146 (μg ml^{-1}); Hydrophilic Extracts: FRAP: 364 mg AAE 100 g^{-1}, DPPH (IC_{50}):164 (μg ml^{-1}), TPC: 784 mg GAE 100 g^{-1}.	Belović et al., 2016

(Continued)

TABLE 2 (Continued)

Matrix	Solvent/performance	Extraction yield	Ref.
	Samples (10 g) pretreated with Hexan, extracted with EtOH (80%), 3 times within 75 min	TPC: 1,930–5,206 μg g^{-1}, IC_{50} (hydroxyl radical. OH): 0.03–0.20 mg ml^{-1} and Superoxide anion radicals ($O^{-}2$): 0.45–4.44 mg ml^{-1}.	Cetkovic et al., 2012
Tomato pomace	Samples (4 g) pretreated with Hexan, extracted with EtOH (80%), SS ratio 5:1 (v/w)/ 60 min at RT were extracted for different fractions: soluble free phenolics (SFP), bound phenolics (BP), acid-hydrolysable phenolics (AHP), alkaline-hydrolysable phenolic (AKHP)	**SFB**: TPC (13.4 mg GAE g^{-1} DW; 10.25 CAE g^{-1} DW), DPPH (25.79 μmol TE g^{-1} DW), ORAC (141.44 μmol TE g^{-1} DW). **BP**: TPC (51.30 mg GAE g^{-1} DW; 46.36 CAE g^{-1} DW), DPPH (83.56 μmol TE g^{-1} DW), ORAC (852.40 μmol TE g^{-1} DW). **AHP**: TPC (32.23 mg GAE g^{-1} DW; 29.49 CAE g^{-1} DW), DPPH (88.17 μmol TE g^{-1} D.W.), ORAC (468.25 μmol TE g^{-1} D.W.). **AKHP**: TPC (7.33 mg GAE g^{-1} D.W.; 5.72 CAE g^{-1} D.W.), DPPH (not detected), ORAC (64.09 μmol TE g^{-1} DW). **Total**: TPC (104.26 mg GAE g^{-1} DW; 91.82 CAE g^{-1} DW), DPPH (197.52 μmol TE g^{-1} DW), ORAC (1,526.18 μmol TE g^{-1} DW).	Perea-Domínguez et al., 2018
Peel/seed by-products	MeOH (100%), 1:10 (w/v-solid/solvent), 22 h /25 °C, centrifuged at 1,400 g/3 min, Re-extracted twice	TPC: peel: 67.3 mg GAE 100 g^{-1}, 438 mg CAE 100 g^{-1}, Flavonoids: 50 mg QUE 100 g^{-1}, ABTS: 35.1 μmol TE 100 g^{-1}, DPPH: 83.6 μmol TE 100 g^{-1}, ORAC: 1,028.3 μmol TE 100 g^{-1}.	Valdez-Morales et al., 2014
	H_2O (W), EtOH (Et), Isopropanol (IP), Ethyl acetate (EA), Ethyl lactate (EL), Hexane (H), 40 min / 20°C & 60°C	**At 20°C**: **TPC** (mg GAE 100 g^{-1}): W:384.16.± 3.07, Et:101.50 ± 1.8, IP: 89 ± 1.85, EA:55.77 ± 0.73, EL:72.29 ± 0.8, H: 48.68 ± 1.05; **TF** (mg CAE 100 g^{-1}): W:42.77 ± 0.61, Et: 43.53 ± 0.65, IP: 23.95 ± 0.65, EA: 22.55 ± 0.7, EL: 42.82 ± 0.7, H: 6.68 ± 0.45; **DPPH** (EC_{50}): W: 50.42 ± 0.71, Et: 55.18 ± 0.5, IP: 87.93 ± 0.66, EA: 67.61 ± 0.51, EL: 74.44 ± 0.48, H: 12.10 ± 0.78. **At 60°C**: **TPC** (mg GAE 100 g^{-1}): W:410 ± 4.16, Et:140.83 ± 2.8, IP: 138.83 ± 2.44, EA: 69.37 ± 1.4, EL: 125.46 ± 2.26, H: 50.75 ± 1.55; **TF** (mg CAE 100 g^{-1}): W:66.88 ± 3.9, Et:61.86 ± 2.85, IP: 35.55 ± 3.41, EA: 44.91 ± 2.14, EL: 51.33 ± 2.35, H: 11.84 ± 1.36; **DPPH** (EC_{50}): W:68.82 ± 0.76, Et:42.42 ± 0.5, IP: 50.62 ± 0.5, EA: 56.97 ± 0.44, EL: 47.47 ± 0.48, H: 92.92 ± 0.58.	El-Malah et al., 2015
	EtOH (Et)/ Ethyl acetate (EA), 1:3 (w/v-solid/solvent), Centrifuge 5400g / 10 min / 4°C	TPC (mg GAE g^{-1} liquid extract): Et: 0.99 ± 0.05, EA: 1.1 ± 0.05, RSA (%): Et: 57.35 ± 3.68, EA; 64.03 ± 2.23.	Andres et al., 2017
	EtOH (75%)	TF (HPLC): 46.45 mg g^{-1} DW	Palomo et al., 2019
	MeOH (100%)	TPC: 9,452 mg GAE kg^{-1}, FRAP: 953.7 mMol AAE kg^{-1} DPPH: 2,990.4 mmol TE kg^{-1}.	Kalogeropoulos et al., 2012

TPC, Total polyphenol content; TF, Total flavonoids; MglcE, malvidin-3-glucoside equivalents; DPPH, 1,1-diphenyl-2-picrylhydrazyl radical-scavenging capacity; Fe2+-chelating ability, ferric reducing/antioxidant power (FRAP) and efficiency of investigated grape skin extract in protecting the oxidation of emulsified linoleic acid (CAA); (AAE)/g WGP, mg ascorbic acid equivalent; RT, Room temperature; ICA, iron (II) chelating ability; ORAC, Oxygen radical absorbance capacity; CGA, Chlorogenic acid; CAF, Caffein; CQA, Caffeoylquinic acid; AA, Total antioxidant activity; α-TOC, α tocopherol; CAE, Catechin equivalents; QUE, Quercetin equivalents; RSA, Radical scavenging activity; AAE, ascorbic acid equivalents.

the cavitation phenomena. The bubbles created from ultrasound amplitude grow over time until to reach a crucial point which finally can create a supreme temperature and pressure that can crush the cell walls improving the extracting procedure of bioactive compounds. The frequency and intensity, time of extraction, and temperature have direct effects on the extraction yields. The size of sample particles, type, and solvent:sample ratio can also play important role in the extraction yield.

Different wastes have been used for the ultrasound-assisted extraction of phenolic compounds (Medina-Torres et al., 2017). In red grape pomace, a variation in the extraction yield has been reported by applying UAE, due to the temperature augmentation, which may be attributed to the combination of the cavitation and thermal effects (Drosou et al., 2015). At lower temperatures, vapor pressure is low, and ultrasound produces few cavitation bubbles. However, bubbles explode with a relatively large force, which enhances cell tissue disruption during extraction. Increasing extraction temperature can result in an increase in vapor pressure and a decrease in surface tension, thus decreasing energies released during the collapse of cavitation bubbles. Bubbles may easily collapse at higher temperatures thus reducing the enhancement of the mass transfer intensity, however, at higher temperatures, ultrasonic cavitation can be differed, and

TABLE 3 Green methods to extract the phenolic compounds.

Method of extraction	Matrix	Treatment conditions	Extraction yield	Ref.
Pulsed Electric Fields (PEF)	Grape pomace	PEF conditions: 5 kV cm^{-1}, 50 pulses, 0.1 kJ kg^{-1}	Extraction yield: mg GAE g^{-1} DW, TAC: mg Mv g^{-1} GP, DW.	Fontana et al., 2013
		PEF conditions: 3 kV cm^{-1}, 3 s (Grape skin); 0.5–1.5 kV cm^{-1}, 10 μs (Grape skin)	TPC and TAC increased by 20 and 75%, respectively.	Thirumdas et al., 2020
	Tomato pomace	PEF conditions: 2 kV cm^{-1} and 700 pulses from tomato.	TPC doubled (56.16 mg GA kg^{-1}).	Andreou et al., 2020
	Olive pomace	Samples pretreated with PEF (1.0 to 6.5 kV cm^{-1}, 0.9 to 51.1 kJ kg^{-1}, and 15 μs pulse width) or HP (200 to 600 MPa and 0 to 40 min), then extracted with EtOH (50%)	TPC increased by 91.6 and 71.8% for PEF and HP methods, respectively.	Andreou et al., 2020
	Citrus by-product	1–7 kV cm^{-1}, 5–50 pulses of 3 μs (Orange peels)	TPC extraction increased by 158%; by application 5 kv cm^{-1}, Naringin and hesperidin extraction increased (From 1 to 3.1 mg 100 g^{-1} FW and from 1.3 to 4.6 mg 100 g^{-1} FW, respectively), treatments at 1, 3, 5 and 7 kV cm^{-1} increased the antioxidant activity by 51, 94, 148, and 192%, respectively.	Luengo et al., 2013
		Orange peel, EtOH 50–99.5%, Solvent/feed: 20, 140–720 W, 1-10 min, 60°C	TPC: 15.9 ± 0.2 mg GAE g^{-1} DW	Barrales et al., 2018
		3–9 kV cm^{-1} and 0–300 μs (Lemon peel residue), the optimum treatment time for the increase in permeability was determined as *30 pulses of 30 μs.*	at 7 kV cm the efficiency of polyphenol extraction increased by 300%, with maximum values of: Hesperidin: 84 mg 100 g^{-1} FW Eriocitrin 176 mg 100 g^{-1} FW	Peiró et al., 2019
		Ethanol (50%), strength = 10 $kVcm^{-1}$ for 1 h/ T: 50 °C	Increased TPC yield from 12 to 22 mg GAE g^{-1}.	Katalinic et al., 2010
		1 kV/cm and 7 kV/cm, (tPEF = 60 μs, 20 pulses, f = 1 Hz)	Polyphenol recovery yields increased (up to 159%). Naringin and hesperidin increased 2- and 3-fold, respectively.	Putnik et al., 2017
High Voltage Electrical Discharges (HVED)	Grape pomace	20 h/ 50–60°C. EtOH (30%)/ 60°C/ 30 were determined as the most efficient extraction condition.	28 mg GAE g^{-1} dry pomace.	Boussetta et al., 2011
	Olive by-products	H_2O/EtOH, 3/9 min, nitrogen/argon, 15/20/25 kV.	The highest TPC yield: sample treated with argon/9 min/20 kV/50% (3.2 times higher as compared to conventional extraction).	Žuntar et al., 2019
Pulsed Ohmic Heating (POH)	Grape pomace	Heating phase and holding treatment electric field: 80 and 16 V cm^{-1}, respectively, frequency: 25 kHz	Extraction in EtOH (30%), pretreatment at 400 V/cm followed by a diffusion step for 60 min at 50 °C resulted in the highest TPC extraction yields (36 % more than untreated samples).	Panzella et al., 2020
		40 °C during 20 min; or flash heating from 40 to 100 °C in <20 s (no holding time), Water extraction /room temperature	TAC increased from756 to 1349 μg g^{-1}, with malvidin-3-*O*-glucoside as the main.	Pereira et al., 2020
	Tomato pomace	The best extraction conditions: EtOH 70% at 70°C /15 min	Rutin was recovered of 77% higher than control samples.	Coelho et al., 2019
Ultrasound-assisted extraction (UAE)	Grape pomace	(1 g fresh/dry), Water (70 ml), Ethanol (50%), 25 kHz frequency, 300 W, 20°C/ 60 min	TPC: Water: 23,570 ppm GAE in dry extract, Water/Ethanol: 167,661 ppm GAE in dry extract. AA (IC_{50}): Water: 20.95 mg ml^{-1},	Drosou et al., 2015

(Continued)

TABLE 3 (Continued)

Method of extraction	Matrix	Treatment conditions	Extraction yield	Ref.
			Water/Ethanol: 0.91 mg ml^{-1}. Glucosylated anthocyanin: 21,099 ppm Mv3G eq in dry extract, Acetylated anthocyanin: 1,095 ppm Mv3G eq in dry extract, Coumaroylated anthocyanins: 7,952 ppm Mv3G eq in dry extract, Caffeoylated anthocyanins: 1,165 ppm Mv3G Eq in dry extract, Glycosylated flavonols: 3,504 ppm QE in dry extract, Aglycone Flavonols: 1,114 ppm QE in dry extract.	
		EtOH: 50–70%, power: 130 W, frequency: 20 kHz, 4–60 min (optimum extraction yield achieved at 34.5°C, SSR: 18.6/1 ml g^{-1}, amplitude level of 39%, pulse duration/pulse interval ratio of 8/6)	Phenolic extraction yield: 10.14 mg GAE g^{-1} dry pomace.	Goula et al., 2016
		Glycerol (90% w/v in water), LSR: 90 ml g^{-1}, Sonication at 140 W, 37 kHz, 35 W $L^{-1)}$, at 45°C/60 min.	TPC: 11.85 mg GAE g^{-1} D.W., Pigment extraction yield: mg MvE g^{-1} D.W.	Trasanidou et al., 2016
		EtOH 0–100%, amplitude: 20–60%, SSR: 8–24 g ml^{-1} at 20–60 °C	Under optimum extraction condition at 56 °C/20 min, SSR 8 ml/g, an amplitude level of 34 %, with EtOH (53 %), the extraction yield was 34.37 ± 0.87 mg GAE g^{-1} dry pomace.	Drevelegka and Goula, 2020
	Olive pomace	56 °C/ 3 min, duty cycle: 0.6 s, SSR: 3: 6%.	TPC and AA: 4.04 mg g^{-1} and 68.9%, respectively.	Bognar et al., 2013
		H_2O, 150–250 W, 47–75 min, 40 °C	TPC: 19.71 mg GAE g^{-1} DW; Optimized 250 W, 75 min.	Goldsmith et al., 2018
		EtOH concentration: 20, 50, 80%, ultrasound amplitude: 30, 50, 70%, extraction time: 5, 10, 15 min	TPC: 37.3–55.8 mg GAE g^{-1}, TFC: 81.1–119.7 mg RE g^{-1}, DPPH: 40.5–59.9 mg TE g^{-1}, ABTS: 72.1–140.5 mg TE g^{-1}, FRAP: 36.1–64.4 mg TE g^{-1}.	Martínez-Patiño et al., 2019
	Tomato pomace	extraction temperature: 30, 50 and 70°C/extraction time: 10, 30 and 50 min.	The best condition was defined as 50°C /50 min; The antioxidant activity was more correlated to the total flavonoid (R2 = 0.74).	Sengkhamparn and Phonkerd, 2019
		MeOH 80%, SSR: 1:50, 60 min/30°C, centrifuged at 18,000 rpm/10 min/1°C	TPC: ranged 35–155 mg 100 g^{-1}, Naringenin chalcone: 6.6–87.6 mg 100 g^{-1}, DPPH: 120–255 μmol TE 100 g^{-1}	Szabo et al., 2019
	SCG	MeOH 4%, ultrasound pulse: 0.903, treatment time: 60 min	TPC: 19.29–24.95 mg GAE g^{-1} and antioxidant capacity: 134.90–174.73 μmol TE g^{-1}.	Severini et al., 2017
	Citrus by-products	Ultrasonic frequency: 25 kHz/power:150 W/ Temperature: 30°C/15 min, Ethanol/Water Ratio: 50:50% (v/v)	Improved the phenolic extraction. TPC: 3 mg GAE 100 g^{-1} DW, TFC: 2.5 mg of quercetin; Polyphenols (caffeic (207%), *p*-coumaric (180%), ferulic (192%), sinapic acid (66%), *p*-hydroxybenzoic (94%).	Putnik et al., 2017
		25 kHz/50–150 W/10–40°C/15 min, 20–80;80–20% (v/v) EtOH/Water Ratio	Extraction yield: Polyphenols (naringin (38%), Hesperidin (42%), total phenolic compounds (31%).	Singanusong et al., 2015

(Continued)

TABLE 3 (Continued)

Method of extraction	Matrix	Treatment conditions	Extraction yield	Ref.
		Optimal condition defined as frequency 60 kHz, extraction time of 30 min, T: 40°C (citrus peel/water ratio 1/10 g ml^{-1})	The total yield: 4.02 % D.W.; TPC: 19.6 mg GAE g^{-1}.	Londoño-Londoño et al., 2010
		Ethanol (20%); temperature = 25, 62, 90°C, time = 15 min; ratio = 0.3:50 g ml^{-1}	Orange peel phenolic extracted as: trans ferulic acid (0.29–1.38 mg g^{-1}); rutin (3.3–4.7 mg g^{-1}); hesperidin (280–673 mg g^{-1}).	Gómez-Mejía et al., 2019
Microwave Assisted Extraction (MAE)	Grape pomace	Water/ EtOH (50%), SSR: 2/100 g ml^{-1} power: 200 W, 50°C/60 min	TPC: Water: 52,645–82,609 ppm GAE in dry extract, EtOH (50%): 200,025–231,619 ppm GAE in dry extract; AA (IC_{50}): Water: 5.95–6.64, EtOH (50%): 0.32–1.03.	Drosou et al., 2015
		SSR: 0.5 g ml^{-1} at 60°C/ 3 h, irradiation with 300 W of power: 30, 60, 120 and 150 s at 60, 80, 100 and 120°C	Highest polyphenol yield increased by 57% and AA increased by 83% at optimum condition (by 120 s pretreatment at 100°C).	Álvarez et al., 2017
		Microwave power (MP): 100–600 W/ 1–5 min, SSR:10–50 ml g^{-1}	With the optimum condition anthocyanin yield: 1.3 mg Cy g^{-1}.	Varadharajan et al., 2017
		750 W/4 min with water, using a SSR of 1,000 g L^{-1}	The highest TPC and antioxidant capacity were achieved as: 143 mg GAE 100 ml^{-1}, 239 mmol and 1,145 mmol of TE 100 ml^{-1}.	Baiano et al., 2015
		The effects of solvent type (0–100 % v/v aqueous ethanol), solvent/solid ratio (8–24 ml g^{-1}), and power (100–600 Watt)	48.76 mg GAE g^{-1} dry pomace by optimum extraction condition.	Drevelegka and Goula, 2020
		EtOH (70%), SSR: 6.6 ml g^{-1} / 60°C/ 4 min, pH: 1.5	TPC: 14.86 mg GAE g^{-1} red grape skin.	Kwiatkowski et al., 2020
		Optimal parameters from different trials were considered by higher methanol concentrations and lower temperatures (100%, v/v; at 40°C)	Extraction of flavonols and hydroxycinnamic acids than for ORAC (78.1%, v/v; at 60°C); total phenolics and tannins (62.7 and 65.3%, v/v; at 60°C).	Curko et al., 2019
	Olive pomace	MAE at 60 °C for 30 min	TPC: 10.61 mg GAE g^{-1} raw material (DW), antioxidant activity: 15.93 mg Trolox g^{-1} raw material (DW).	Chanioti and Tzia, 2017
		Power: 700 W/ 10 min, EtOH (20%)	Higher amounts of hydroxytyrosol (1.2 g kg^{-1}).	Jurmanović et al., 2019
	Tomato pomace	Power: 200 W/20 min/ 180°C, EtOH (47%) 47%, SSR: g L^{-1}, and 200 W.	Yield of 76% was obtained with TPC value: 43.9 mg GAE g^{-1} and a TFC of 3.5 mg CE g^{-1}.	Panzella et al., 2020
		temperatures (25, 55 & 90°C) and times (5 & 10 min)	TPC: 53.12 g kg^{-1}, TF: 50.36 g kg^{-1}. Kaemferol-3-*O*-rutinoside (8.5–142.5 mg kg^{-1}), *p*-coumaric acid (3–111.5 mg kg^{-1}) and chlorogenic acid derivative (10.5 to 109 mg kg^{-1}); Higher values of TPC were found in samples extracted at 55 and 90°C. The solubility of flavonoids improved by the temperature increment.	Bakić et al., 2019
	SCG	Ethanol (20%) as optimum condition to recover phenolic compounds, (40s extraction time, 240 W MWP, and 6-fold	Total yield: 7.7–31.2 mg g^{-1} DW SCG; TPC: 18.8–79.8% w/w; DPPH: 6.5%—98.2%; FRAP: 2.6 mmol Fe^{2+} L^{-1}-6.6 mmol Fe^{2+} L^{-1}. The	Ranic et al., 2014

(Continued)

TABLE 3 (Continued)

Method of extraction	Matrix	Treatment conditions	Extraction yield	Ref.
		solvent to SCG ratio resulted in the maximum yield)	yield ranged from 18.83 to 79.83% w/w.	
	Citrus pomace	Ethanol (70%) at 140°C / 8 min, SSR: 100 g/L solid to	Optimal condition (MAE and low-temperature storage (5°C, 24 h)) has identified total hesperidin of 86.8% (47.7 mg g^{-1}).	Inoue et al., 2010
		sample (1.5 g) was heated at 120, 240, 360, 480, and 600 W, for 2–5 min	the highest flavonoid content was achieved at 360 W for 5 min and 480 W for 2 min (6.28 and 6.21 mg CE/g D.W., respectively) which was 29 and 28%, respectively, higher than the untreated sample Optimum condition (at 360 W for 5 min and 480 W for 2 min), resulted to increase extraction yield by 29% with the highest flavonoid content: 6.28 mg CE g^{-1} DW	
	Citrus pomace	W: 500, °C<135, s 122, Liquid-to solid ratio 25 ml g^{-1}	Extraction yield: TPC: 12.20 mg GAE g^{-1} DW)	Dahmoune et al., 2013
		MP 152 W, T 49 s, SSR 16, and MeOH (66%) as optimum condition	TPC: 1163.33 ± 9.65 μg g^{-1}DW. Free phenolics: ferulic acid (465.49 ± 2.58 μg g^{-1}DW) *p*-coumaric (317.38 ± 5.13 μg g^{-1}DW), *p*-hydroxybenzoic (34.81 ± 3.25 μg g^{-1} DW) and gallic acid (137.94 ± 1.31 μg g^{-1}DW); Eter bound phenolics: Gallic acid (19.99 ± 1.04 μg g^{-1}DW), Ferulic acid (1,617.45 ± 14.46 μg g^{-1} DW); Glycoside bound: Gallic acid (16.97 ± 1.02 μg g^{-1} DW), *p*- hydroxybenzoic (14.39 ± 1.95 μg g^{-1} DW).	Sharma et al., 2017
		W: 400, °C<123, s -, SSR: 1g 28 ml^{-1}	Polyphenol content (15.74 mg GAE g^{-1} DW)	Londoño-Londoño et al., 2010
Enzyme Assisted Extraction (EAE)	Grape pomace	Samples treatments: A- 10 g sample was defatted and suspended in 100 ml of Viscozyme solution (2% in 0.1 M phosphate buffer, pH:4), stirred for 12 h /37°C. B- 10 g sample were defatted and suspended in 100 ml of Pronase solution (1 mg/ml in 0.1 M phosphate buffer, pH 8), stirred for 1 h. Extraction was performed by 70% (v/v) acetone (2.5%, w/v) for 20 min/30°C for both soluble (S) and insoluble (IB) phenolic compounds.	Viscozyme: Phenolics (mg GAE g^{-1} DW): S: 371.0 ± 7.8, IB: 184.6 ± 7.8. ABTS (μmol TE g^{-1} DW): S: 695.0 ± 10.5, IB: 509.6 ± 2.7. DPPH (μmol TE g^{-1} DW): S: 652.2 ± 30, IB:442.7 ± 15.1 HRSA (μmol CE g^{-1} DW): S: 414.4 ± 8.3, IB: 163.4 ± 1.2. Reducing power (μmol TE g^{-1} DW): S: 595.3 ± 35.4, IB: 471.5 ± 4.6. Inhibition of alpha-glucosidase activity (%):7.79 ± 0.6, Inhibition of lipase activity (%): 24.9 ± 0.9. Pronase: Phenolics (mg GAE g^{-1} DW): S: 301.9 ± 21, IB: 204.1 ± 0.3. ABTS (μmol TE g^{-1} DW): S: 699.9 ± 8.4.5, IB: 621.4 ± 24.9. DPPH (μmol TE g^{-1} DW): S: 728.4 ± 30.5, IB: 558.2 ± 2.3	de Camargo et al., 2016

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TABLE 3 (Continued)

Method of extraction	Matrix	Treatment conditions	Extraction yield	Ref.
			HRSA (μmol CE g^{-1} DW): S: 319.9 ± 5.4, IB: 241.5 ± 18.8. Reducing power (μmol TE g^{-1} DW): S: 250.4 ± 2, IB: 464 ± 5.5. Inhibition of alpha-glucosidase activity (%): 7.35 ± 3.1 Inhibition of lipase activity (%):9.71 ± 0.2.	
		Cellulose/tannase:50 mM in acetate buffer, SSR 10:1 ml g^{-1}, shaking at 125 rpm	Phenolics yield increased by 66% (gallic acid, *p*-coumaric acid and malvidin-3-*O*-glucoside as the main compounds); Antioxidant activity increased by 80%.	Dzah et al., 2020
		Celluclast/fungamyl (celluclast: 790 U ml^{-1}, fungamyl: 881 U ml^{-1}). Temperature: 24 °C; time: 2 h; ratio: 1:5 g ml^{-1}. Ethanol (95%) time = 24 h shaking at 150 rpm.	Higher (2.4-fold) polyphenol levels (346.1 mg GAE L^{-1} with gallic acid, catechins, quercetin, stilbenes, rutin, vanillin, vanillic acid, epigallocatechin and epigallocatechin gallate as the main), Quercetin increased by 47.5-fold.	Dzah et al., 2020
		Cellulose/tannase in acetate buffer (50 mM), pH 5 at 45°C for 2 h	TPC: 0.75 g GAE 100 g^{-1} (gallic, *p*-coumaric, and syringic acids; catechin and malvidin-3-*O*-glucoside were the most predominant compounds).	Costa et al., 2020
	Tomato pomace	Tomato pomace/dH_2O:4 grams/27.2 ml; enzyme solution (0.8 ml) and shaked for 1 h, The treated was performed as: C-A = Celluclast-Acetone, C-EA = Celluclast-Ethyl acetate, C-A:EA = Cellucalst-Acetone:Ethyl acetate, P-A = Pectinex-Acetone, P-EA = Pectinex-Ethylacetate, P-A:EA = Pectinex-Acetone:Ethyl acetate, V-A = Viscozyme-Acetone, V-EA = Viscozyme-Ethyl acetate, V-A:EA = Viscozyme-Acetone:Ethyl acetate, C:P-A = Celluclast:Pectinex-Acetone, C:P-EA = Celluclast:Pectinex-Ethyl acetate, C:P-A:EA = Celluclast:Pectinex-Acetone:Ethyl acetate, C:V-A = Celluclast:Viscozyme-Acetone, C:V-EA = Celluclast:Viscozyme:Pectinex-Ethyl acetate, C:V-A:EA = Celluclast:Viscozyme-Acetone:Ethyl acetate, P:V-A = Pectinex:Viscozyme-Acetone,P:V-EA = Pectinex:Viscozyme-Ethyl acetate, P:V-A:EA = Pectinex:Viscozyme-Acetone:Ethyl acetate.	***C-A:*** TPC:1.76 ± 0.19, DPPH:0.59 ± 0.12, ABTS:3.47 ± 0.39; ***C-EA***: TPC: 26.9 ± 7.07, DPPH: 9.39 ± 3.51 ABTS:55.9 ± 18.2; ***C-A:EA:*** TPC:14.5 ± 7.80, DPPH: 6.45 ± 3.57, ABTS: 31.9 ± 18.7; ***P-A:*** TPC: 1.34 ± 0.13, DPPH: 0.49 ± 0.06, ABTS: 3.28 ± 0.37; ***P-EA***: TPC: 24.7 ± 6.95, DPPH: 7.96 ± 2.08, ABTS: 62.8 ± 16.4; ***P-A:EA:*** TPC: 2.89 ± 0.31, DPPH: 1.52 ± 0.14, ABTS: 6.89 ± 0.85; ***V-A:*** TPC: 1.47 ± 0.38, DPPH: 0.78 ± 0.20, ABTS: 4.69 ± 1.25; ***V-EA:*** TPC: 21.9 ± 5.13, DPPH: 10.9 ± 2.56, ABTS:66.6 ± 17.3; ***V-A:EA:*** TPC: 4.44 ± 0.67, DPPH: 2.59 ± 0.26, ABTS: 13.7 ± 2.48; ***C:P-A:*** TPC: 2.77 ± 0.52, DPPH: 1.16 ± 0.30, ABTS:6.16 ± 0.58; ***C:P-EA:*** TPC: 24.3 ± 6.89, DPPH: 9.88 ± 2.33, ABTS: 58.4 ± 17.0; ***C:P-A:EA:*** TPC: 5.46 ± 1.65, DPPH: 2.72 ± 0.70, ABTS: 12.2 ± 3.86; ***C:V-A:*** TPC: 6.29 ± 1.34, DPPH: 2.57 ± 0.483, ABTS: 18.4 ± 3.49; ***C:V-EA:*** **TPC: 28.9 ± 3.13, DPPH: 12.7 ± 1.67, ABTS: 86.5 ± 8.10;** ***C:V-A:EA:*** TPC: 15.6 ± 3.88, DPPH:7.68 ± 1.68, ABTS:47.3 ± 10.8; ***P:V-A:*** TPC: 0.73 ± 0.03, DPPH: 0.38 ± 0.02, ABTS: 2.22 ± 0.15; ***P:V-EA:*** TPC: 23.4 ± 7.17, DPPH: 11.6 ± 3.02; ABTS: 71.7 ± 17.4; ***P:V-A:EA:*** TPC: 3.28 ± 0.40, DPPH: 1.88 ± 0.22, ABTS: 9.75 ± 1.32. Therefore, Celluclast:	Catalkaya and Kahveci, 2019

(Continued)

TABLE 3 (Continued)

Method of extraction	Matrix	Treatment conditions	Extraction yield	Ref.
			Viscozyme:Pectinex-Ethyl acetate resulted in higher total polyphenol content and antioxidant activity. (TPC is expressed as: mg GAE g^{-1}, DPPH and ABTS in mg TEAC g^{-1}).	
	Citrus by-products	Enzyme-assisted extraction on pomelo waste was followed by UAE and MAE; enzyme Pectinex Ultra SP-L (0, 1, 2, 3, or 4%, v/w sample), water-solid ratio of 40 ml g^{-1}, temperature: 50°C, of 60 min. The optimal UAE conditions were identified as 40 kHz, water-solid ratio of 40 ml g^{-1} / room temperature for 60 min.	TPC: 5.65–7.38 mg GAE g^{-1}; TF: 0.96–2.07 mg RE g^{-1}; Naringenin: 0.68–1.10 mg g^{-1}: Hesperidin: 0.14–0.54 mg g^{-1}. The TPC, TFC, naringin, and hesperidin contents significantly increased in the following order of the extraction techniques: UAE < EAE < UEAE < E-UAE ($p < 0.05$). The combined E-UAE technique was the most effective technique for bioactive compound extraction with the highest antioxidant and antimicrobial activities.	Van Hung et al., 2020
		Tannase (Paecilomyces variotii CBMAI 1157) & commercial β-glucosidase (10 U per gram sample) in acetate buffer (20 mM, pH: 5.0) / 40 °C & 120 rpm/ 24 h.	TPC extracted with EAE was 1.5-fold higher than conventional hydro-alcoholic extraction method, (Narirutin: 1.1 μg mg^{-1}; Naringin: 0.3 μg mg^{-1}; Naringenin: 2.5 μg mg^{-1}; Hesperidin: 6.6 μg mg^{-1}; Hesperetin: 23.3 μg mg^{-1}; diosmetin: 1.2 μg mg^{-1}; Tangeretin: 0.1 μg mg^{-1}). Tannase and β-glucosidase are effective to cleave β-glucoside linkages in flavanones' structure to release aglycones with higher biological activities.	Barbosa et al., 2021
	Olive pomace	Enzymatic mixture (Cellulase, Hemicellulase, Pectinase) 1:1:1 ratio, pH 5.75, hydrolysis time 40 min/ 55 °C/200 W and ethyl acetate (EA), petroleum ether (PE) and *n*-butyl alcohol (BA) as solvent. Phenolics were extracted in an ultrasonic bath with frequency and input power of 40 kHz y/200 W.	With Ethyl acetate, higher concentration of phenolic compounds was extracted (36.2 mg g^{-1}). DPPH (IC_{50} μg ml^{-1}): EA: 7.580 ± 0.5, PE: 41.21 ± 0.3, BA: 2.850± 0.3. ABTS (IC_{50} μg ml^{-1}): EA: 370.9 ± 1.2, PE: 4,715.6 ± 2.5, BA: 574.7 ± 1.7. FRAP (μmol L^{-1}): EA: 106.2 ± 3.3, PE: 43.5 ± 2.9, BA: 84.8 ± 063.	Wang et al., 2017
Subcritical Fluid Extraction (SbFE)	Grape pomace	SFE-CO2 + EtOH (20%) as co-solvent (100 bar, 55 °C, 20 g min^{-1} CO2, 5 g min^{-1} ethanol for 3 h	TAC: 0.3–2 mg malvidin chloride g^{-1} dry grape pomace; Phenolic Content: 2.1–4.5 mg GAE g^{-1} dry grape pomace.	Otero-Pareja et al., 2015
	Citrus pomace:	Water extraction at flow rate = 10 ml min^{-1} & temperature = 150 °C.	Increased flavanones yield from orange peel by 21%.	Dzah et al., 2020
	SCG:	Subcritical water extraction (SWE), pressure: 100 bar, temperatures up to 220 °C	higher TPC (19.9 mg GAE g^{-1} dry SCG), higher AA (EC_{50} of 20.6 μg ml^{-1}) for fraction collected up to 140°C, For fraction collected from 140 to 220 °C: TPC: 5.7 mg GAE g dry SCG, EC_{50} of 132.2 μg ml^{-1}.	Ribeiro et al., 2018
		Subcritical water extraction (SWE) T: 160–180 °C, Extraction time: 38–55 min, CG/Solvent ratio (g/g): 14.1 g L^{-1}	Phenolic yields: 86.2 mg GAE g^{-1}.	Xu et al., 2015

(Continued)

TABLE 3 (Continued)

Method of extraction	Matrix	Treatment conditions	Extraction yield	Ref.
Supercritical fluid extraction (SFE)	Grape pomace	20 MPa, 40 °C, 180 min/ with SbEF-CO2 containing ethanol 10% (w/w)	Phenolic compounds extracted: Syringic acid, vanillic acid, gallic acid, p-hydroxybenzene formic acid, protocatechuic acid, *p*-coumaric acid, and quercetin.	Farías-Campomanes et al., 2013
		Pretreat with Ultrasound (80 °C, 4 min) combined with SFE	TPC: 3,493 mg GAE 100 g^{-1} DW, antioxidant activity: 7,503 mg α-tocopherol 100 g^{-1} DW	Da Porto et al., 2015
pressurized liquid extraction (PLE)	Grape pomace	Pressurized solvent: 50% ethanol/water, 90 bar, 120 °C, flow rate: 5 g min^{-1} for 90 min	Total Anthocyanins: 10.1–49.7 mg malvin chloride g^{-1} dry grape pomace. PC: 15.5–28.9 mg GAE g^{-1} dry grape pomace.	Otero-Pareja et al., 2015
	Citrus by-products	T = 200 _C, P = 1.4 MPa, t = 60 min	The main flavones extracted were sinenstin, nobiletin, and tangeretin.	Lee et al., 2009
	Olive pomace	PLE optimized condition: T = 184.0 °C, EtOH 90.0%, SSR = 0.8 g ml^{-1}	hydroxytyrosol (HT) and tyrosol (TY) extraction increased by 5-fold and 3-fold (9.5 vs 1.79 mg HT g^{-1} and 5.3 vs 1.78 mg TY g^{-1} dry extract, respectively). TPC also doubled (340 instead of 180 mg GAE g^{-1} dry extract)	Katsinas et al., 2021
Ohmic Heating (OH)	Grape pomace	Pretreatment: 1.5 g dry grape skins were rinsed in NaCl solution (0.1 mol L^{-1}), and then aqueous extraction with 20 ml of distilled water in 3 ways: a): 40°C / 20 min using OH (labeled as OH40) and room temperature; b) 40°C / 20 min using conventional indirect heating (COV40); and c) HTST using OH – i.e., ∼100°C /1 s. Electric field: 80, 16 V cm^{-1}, frequency: 25 kHz	The OH100 pretreatment at HTST conditions gave the best extraction with an increase in TPC, and anthocyanins to the maximum values of 320 mg GAE 100 g^{-1} DW and 600 μg g^{-1} DW; increasing their initial values by 60% and 120%, respectively.	Pereira et al., 2020
	Grape vine	Extracts were obtained by Low electric field (LEF) (496.0 V cm^{-1}); and Intermediate electric field – IEF (840.0 V cm^{-1}). 1g sample in 40 ml ethanol–water extraction: 45% (v/v)/ 80 °C at different extraction times (20–90 min); conventional heating (CH): constant heating in water bath; Voltages were 1 Hz−25 MHz, and 1–10 V) with a sinusoidal wave at a 25 kHz frequency, and the electric fields ranged from 400 to 1,600 V cm^{-1}.	IEF: TPC: 3.4 ± 0.1g GAE 100 g^{-1}; FRAP: 4.6 ± 0.2 g FE 100 g^{-1}; DPPH: 4.1 ± 0.1 g TE 100 g^{-1}, IC_{50}: 0.76; ABTS: 3.1 ± 0.1g TE 100 g^{-1}, IC_{50}: 0.34; LEF: TPC: 3.1 ± 0.2 g GAE 100 g^{-1}; FRAP: 4.1 ± 0.3 g FE 100 g^{-1}; DPPH: 3.2 ± 0.1 g TE 100 g^{-1}, IC_{50}: 0.90; ABTS: 1.9 ± 0.2 g TE 100 g^{-1}, IC_{50}: 0.44; CH: TPC: 3.0 ± 0.2 g GAE 100 g^{-1}; FRAP: 3.7 ± 0.1 g FE 100 g^{-1}; DPPH: 2.7 ± 0.2 g TE 100 g^{-1}, IC^{50}: 0.95; ABTS: 1.9 ± 0.1 g TE 100 g^{-1}, IC^{50}: 0.4.	Jesus et al., 2020
	Grape by-products	Pretreatment: 2.5 g Sample in 5 ml NaCl (0.1 M); OH condition: 100°C in 13 s; requency of 25 kHz and an electric field of ≈30 V cm^{-1}, T: 23°C. Water, acidified water (lactic and citric acid 1%), and methanol/water solution (80:19:1 v/v) acidified with hydrochloric acid usually are used as a conventional method (CONV).	CONV: TPC: 2.84 ± 0.037 mg g^{-1} DW GAE; AA: 2.02 ± 0.007 g 100 g^{-1} ascorbic acid equivalent. OH: TPC: 3.28 ± 0.46 mg g^{-1} DW GAE; AA: 2.34 ± 0.066 g 100 g^{-1} ascorbic acid equivalent. Major identified anthocyanins were: malvidin-3-*O*-acetylglucoside, delphinidin-3-*O*-glucoside, petunidine-3-*O*-glucoside,	Coelho et al., 2021

(Continued)

TABLE 3 (Continued)

Method of extraction	Matrix	Treatment conditions	Extraction yield	Ref.
			cyanidin-3-*O*-glucoside, and peonidine-3-*O*-glucoside; OH provides similar recovery yields of anthocyanins respect to conventional condition with reduced treatment times, less energy consumption, and no need for organic solvents.	
	Olive pomace	2 g OP in 20 ml solvent (ultrapure water or ethanol 50% (v/v); electric field: 4 V cm^{-1}, T= 83 ± 2°C/ per 30 min; centrifugation (2,500 g, 20 min), filtered through 0.22 μm.	In water: TPC: 12.08 ± 1.52 mg GAE g^{-1} OP, DPPH: 3.23 ± 0.10 μmol TE g^{-1} OP; FRAP: 80.41 ± 1.12 μmol Fe (II) g^{-1} OP, Yield (%): 28.54 ± 0.14. EtOH 50%: TPC: 17.67 ± 3.12 mg GAE g^{-1} OP, DPPH: 3.82 ± 0.04 μmol TE g^{-1} OP; FRAP: 150.16 ± 9.29 μmol Fe (II) g^{-1} OP, Yield (%): 27.39 ± 1.54.	Quero et al., 2022
Deep Eutectic Solvent (DES) Extraction	Grape pomace	A: citric acid–based DES was prepared, and citric acid/maltose 4:1 molar, B: lactic acid-sodium acetate at molar ratio of 5:1 has also been C: Longer extraction times (50 min, at 65 °C, with a solid-to-liquid ratio of 100 g L^{-1}) have been instead reported in the case of UAE using ChCl-oxalic acid as DES in presence of 25% water to extract phenolic compounds from grape skin	A: higher total anthocyanin content (TAC), B: efficient for pigment extraction.	Bubalo et al., 2016; Panzella et al., 2020
	Olive pomace	Glycerol–glycine–water 7:1:3 molar ratio.	Optimized condition was 80% in water (w/w) DES concentration, a solid-to-liquid ratio of 3:1 g L^{-1}, at 70 °C. Leave polyphenol extraction yield increased by 18–30% by DES than ethanol (60%), methanol, or water, with higher antiradical activity and reducing power capacity.	Athanasiadis et al., 2018
		LGH (lactic acid and glucose, 5:1); CGH (citric acid and glucose, 1:1) and FCH (fructose and citric acid, 1: 1;, temperature) (40–80°C), Water percentage (0–15%) & buffer concentration (0–0.1%). Lactic acid-glucose 5:1 mol mol^{-1} combined with 30–60 min UAE at 40 °C, using an SSR of 75 g L^{-1}.	Luteolin and Hydroxytyrosol were extracted as the main phenolic compounds in olive cake.	Fernández et al., 2018
	Tomato pomace	LGH (lactic acid and glucose, 5:1); CGH (citric acid and glucose, 1:1) and FCH (fructose and citric acid, 1: 1; temperature) (40–80°C), Water percentage (0–15%) & buffer concentration (0–0.1%). Lactic acid-glucose 5:1 mol mol^{-1} combined with 30–60 min UAE at 40 °C, using an SSR of 75 g L^{-1}.	Rutin and Catechin were extracted as the main phenolic compounds in tomato pomace.	Fernández et al., 2018
	Citrus pomace	Optimal conditions were found to be DES containing 10% w/w of water, a temperature of 60 °C, a solid-to-liquid ratio of 100 g L^{-1}, and an extraction time of 100 min (Orange peel)		Ozturk et al., 2018

the phenolic compounds may be oxidized (Drosou et al., 2015).

In the study by Goula et al. (2016), the phenolic extraction yield from grape pomace increased with ultrasonic time, especially from 2 to 10 min and slowly from 10 to 60 min. Thus, the efficient extraction period for achieving a maximum yield of phenolics in grape pomace was about 10 min. The direct ultrasound-assisted extraction of phenolics had a maximum yield of 9.57 mg GAE g^{-1} of dry pomace. Nevertheless, a higher total polyphenol content (33.88 mg GAE g^{-1} DW) was reported by prolonging the time to 20 h. In the latest study, different extraction factors were monitored to find the optimized condition for extracting the higher polyphenol contents (Goula et al., 2016).

Anthocyanins extraction also enhanced together with other polyphenols under UAE by using glycerol (90% w/v, SSR: 11 g L^{-1}) from winery by-products (Trasanidou et al., 2016). In ultrasound extraction, temperature (20–60°C), solvent type (0–100% v/v aqueous ethanol), amplitude (20–60%), and solvent/solid ratio (8–24 ml g^{-1}) were the factors investigated to evaluate the phenolic compound extraction, and the optimum condition was verified as extraction temperature of 56°C, a solvent/solid ratio of 8 ml g^{-1}, and an amplitude level of 34%, with 53% aqueous ethanol at 20 min, resulting in total phenolic content of 34.37 ± 0.87 mg GAE g^{-1} dry pomace (Drevelegka and Goula, 2020).

González-Centeno et al. (2014) studied the extraction of compounds with antioxidants activity from grape pomace in UAE. The phenolic extraction yield was reported at 0.32 mg GAE g^{-1} on dry weight, where the optimum conditions were reported for 25 min of extraction time (González-Centeno et al., 2014). They also explored the effect of different temperatures in the UAE. The results demonstrated that the highest TPC was obtained after 1 h of UAE at 50 °C (up to 3.3-fold higher content of TPC, i.e., 7.7 mg GAE g^{-1} dry pomace with respect to that of conventional extraction at 20 °C) (González-Centeno et al., 2014).

The various UAE conditions were performed to extract phenolic compounds from tomato pomace, including extraction temperatures of 30, 50, and 70 °C and extraction times of 10, 30, and 50 min. The results showed that once again, the extraction temperature is the main factor to extract bioactive compounds with antioxidant activity since it showed higher relation to the total flavonoid and carotenoid extracted ($r = 0.86$, $p < 0.05$). In this case, UAE condition of 50 °C for 50 min was determined as the best condition to obtaining the highest antioxidant activity (Sengkhamparn and Phonkerd, 2019).

The UAE performed on the olive pomace resulted in TPC of 4.04 mg GAE g^{-1} and 68.9%, antioxidant activity under the extraction condition at 56°C for 3 min and the duty cycle of 0.6 s (Mojerlou and Elhamirad, 2018).

The best chlorogenic and protocatechuic acids recovery from spent coffee grounds was yielded under mild temperatures and a short time of extraction by UAE. The total polyphenol content and antioxidant capacity at this condition were 19.29 and 24.95 mg GAE g^{-1} (Severini et al., 2017). These values for Robusta, Arabica, and Liberica types of SCG ranged between 18.94 ± 0.06 and 26.23 ± 0.86 mg GAE g^{-1}, and total flavonoid ranged between 47.62 ± 0.05 and 56.20 ± 0.08 mg GAE g^{-1} with the highest content for Arabica type (Zainol et al., 2020).

By application of UAE on *Citrus* by-products, a greater extraction efficiency was observed for hesperidin (Singanusong et al., 2015). The optimal condition was reported by Londoño-Londoño et al. (2010) with the frequency of 60 kHz, extraction time of 30 min, and temperature of 40 °C on the citrus peel by using water with the ratio of 1/10 g ml^{-1}. The extraction yield ranged between 58.68 and 74.80 mg GAE g^{-1} of total phenolic content for lime, orange, and tangerine peels (Londoño-Londoño et al., 2010). Aqueous ultrasound-assisted extraction (AUAE) was applied to recover TPC and rutin from lemon by-products at conditions of 35–45 min, 45–55°C, and 150–250 W. The optimum condition was obtained at the time of 35 min, 48 °C, and 150W with a value of 3.213 ± 0.03 mg g^{-1} DW for rutin, and 17.97 ± 0.21 mg GAE g^{-1} for TPC (Papoutsis et al., 2018).

Therefore, the advantages of UAE are a lower production cost than the conventional procedures with a higher purity of final product, however, as the temperature reached is not very high, sonication is suitable for extracting thermolabile compounds, such as phenolic compounds (Ameer et al., 2017). Despite the advantages of UAE, requiring some filtration steps and the possible degradation of compounds at high frequencies could be defined as this technique limitation (Medina-Torres et al., 2017).

Microwave-assisted extraction

Microwave-assisted extraction (MAE) is relatively a new extraction technique that combines microwave irradiation and traditional solvent extraction. Electromagnetic waves generated by microwave energy can changes the cell structure and help to extract the compounds. This method provides rapid and selective techniques with high recovery than the conventional extraction methods, such as Soxhlet, maceration, and infusion. So, the advantages of this method include lower energy consumption, lower solvent/solid ratio, and quicker heating arising inside the solids; however, the disadvantages are: (a) dissolution of the extract components that may cause in somehow the degradation of thermosensitive phenolic compounds, (b) small quantity of vegetal tissues can be extracted in each extraction cycle, (c) the high costs owing to its high-pressure resistance and air-tightness (Zhang et al., 2011).

The phenolic extraction by MAE from grape pomace has been performed in various studies. Baiano et al. (2015) applied microwave power of 750 W for 4 min with a solid-to-liquid (water) ratio of 1,000 g L^{-1} in the grape pomace. The highest

total polyphenol content was 143 mg GAE 100 ml^{-1}, and the highest antioxidant activity was reported as 239–1,145 mmol of Trolox Eq 100 ml^{-1} (Baiano et al., 2015). MAE conditions were applied to recover anthocyanins from grape juice wastes. The microwave power (MP) (100–600 W), exposure time (1–5 min), and solvent/solid ratio (10–50 ml g^{-1}) were considered to set the assay. The optimum condition for the anthocyanin recovery was predicted by response surface methodology at MP of 435 W, exposure time of 2.3 min, and solid-to-solvent (water) ratio of 52 g L^{-1}, by which the anthocyanin yield of 1.3 mg g^{-1} was achieved (Varadharajan et al., 2017). Wang et al. (2012) applied MAE to extract resveratrol from GP. To do so, a solid-to-solvent (ethanol) ratio of 50 g L^{-1}, an extraction time of 30 min, a temperature of 55°C, and MP of 1.0 kW was recognized as the best conditions to extract resveratrol from grape pomace (Wang, 2012). In a recent study, the optimal parameters for the extraction of flavonols and hydroxycinnamic acids (78.1%, v/v), total phenolics, and tannins (62.7 and 65.3%, v/v) were shown by the higher methanol concentrations and lower temperatures (100%, v/v; at 40 °C). The number of MAE cycles was also found as a key factor for completing the extraction of phenolics from grape skin pomace (Curko et al., 2019). The phenolic extraction from dried grape pomace by MAE achieves a savings of 83% after 3 cycles of extracting for three cultivars Cabernet Sauvignon, Merlot, and Teran grape skin pomaces by comparing the data achieved by response surface methodology (RSM) and effects of sequential irradiation cycles, in terms of extraction time (Curko et al., 2019). An extraction yield of 8 mg GAE g^{-1} dry pomace has been reported by MAE application for 20 min by Brahim et al. (2014).

MAE was applied at 60 °C for 30 min in the olive pomace, and the total polyphenol extracted was 10.61 mg GAE g^{-1} raw material with the antioxidant activity of 10.40 mg Trolox g^{-1} (DW) (Chanioti and Tzia, 2017). By application of the MAE condition of microwave power 700 W over 10 min of extraction time in a closed vessel system and the solvent (20% ethanol), the higher amounts of hydroxytyrosol (1.2 g kg^{-1}) were obtained from olive pomace (Jurmanović et al., 2019).

The recovery of phenolic compounds in tomato pomace was subjected to MAE, at temperatures (25, 55, and 90 °C) and times of extraction (5 and 10 min). The average TPC was 53.12 g kg^{-1}, where the lowest value was obtained for samples extracted at 25 °C, while higher values were found in samples extracted at 55 and 90 °C. Kaempferol-3-*O*-rutinoside yield was in range of 8.5–142.5 mg kg^{-1}, *p*-coumaric acid ranged from 3 to 111.5 mg kg^{-1}, and chlorogenic acid derivative was 10.5–109 mg kg^{-1} (Bakić et al., 2019). Panzella et al. (2020) reported an extraction time of 20 min, at 180 °C, with 47% ethanol, SSR of 45 g L^{-1}, and 200 W resulted in extraction yield of 43.9 mg GAE g^{-1} and a total flavonoid content of 3.5 mg CE g^{-1} (Panzella et al., 2020).

In order to extract the phenolic parts of the spent coffee grounds (SCG), MAE was performed, and the optimum condition was reported as 16 cycles of 40 s, MP at 240 W, and solvent to SCG ratio of 6:1 using 20% ethanol. The phenolic yield ranged from 18.83 to 79.83% w/w (Ranic et al., 2014).

The recovery of hesperidin from citrus pomace has been reported by using 70% ethanol at 140 °C for 8 min, at SSR 100 g L^{-1}. After 24-h storage at 5 °C, about 48 mg g^{-1} hesperidin was collected (Inoue et al., 2010). The phenolic content of 12.20 mg GAE g^{-1} DW was reported under MAE condition (MP 500 W, and the temperature 135 °C, for 122 s and SSR 25:1 ml g^{-1}) (Dahmoune et al., 2013). With a slightly different MAE condition i.e., MP 400 W, T 123°C, SSR 28:1 ml, the total polyphenol obtained was 15.74 mg GAE g^{-1} DW (Londoño-Londoño et al., 2010).

The combined use of microwave-assisted and ultrasound-assisted extraction has also been developed for the extraction of phytochemicals. For example, it has been proposed the extraction of polyphenols from the orange peels in a solvent-free process (Papoutsis et al., 2017). The results showed that microwave pretreatment could significantly affect the total yield. The total phenolic content, total flavonoids, and proanthocyanidins, as well as the total antioxidant activity significantly increased as the microwave radiation time and power increased (e.g., 2.5-fold for phenolics, 1.4-fold for flavonoids, and 5.5-fold for proanthocyanidins). These findings indicate that microwave irradiation time and power may enhance higher levels of the phenolic compounds as well as the antioxidant capacity of the dried lemon pomace powder. However, higher power and longer time of irradiation may lead to a degradation of phenolic compounds and lower the antioxidant capacity of the dried lemon pomace (Papoutsis et al., 2017).

MAE has been applied to extract the phenolic compounds from citrus pomace, and different factors such as solvent composition and extraction time, microwave power, and extraction cycle were tested. The optimized condition was obtained at MP 152 W, T 49 s, SSR 16, and MeOH (66%) and the phenolic compound yield was 1,163.33 ± 9.65 μg g^{-1} DW, from which free phenolics (ferulic acid: 465.49 ± 2.58 μg g^{-1} DW, *p*-coumaric: 317.38 ± 5.13 μg g^{-1} DW, *p*-hydroxybenzoic: 34.81 ± 3.25 μg g^{-1} DW, and gallic acid: 137.94 ± 1.31 μg g^{-1} DW) were higher than other phenolic detected classes (Sharma et al., 2017).

Enzyme-assisted extraction

Phenolic compounds that are present in the insoluble form (in general phenolic acids) are covalently bounded to the cell walls, and mostly are embedded with cellulose or hemicellulose, pectin, or lignin structures in different plants. The efficiency of EAE is based on the fact that the enzymatic action can catalyze reactions in an aqueous solution that degrades cell walls and membranes, therefore, increases the permeability, releasing the desired compounds. Enzymes usually used are

including pectinases, tannases, and ligninases depending on the complexity of the material. Cellulases and hemicellulases largely hydrolyze larger carbohydrate subunits in plant, whereas pectinases are usually used in the fruit matrix. The efficiency of pectinolytic enzymes in the separation of anthocyanins from their glycoside in the grape pomace has been proved (Gligor et al., 2019). Cellulases and pectinases have widely been reported to extract the procyanidins and anthocyanins from grape pomace, while tannase application also was effective to extract the phenolics from grape by-products, as this enzyme catalyzes the esters links between tannins and gallic acid. Therefore, a combination of pectinolytic and cellulolytic enzymes may offer an increased yield of total phenolic compounds from GP (Martins et al., 2016). By using cellulase/tannase, the extraction of insoluble phenolic acids (gallic acid, *p*-coumaric acid, and caffeic acid) and malvidin was improved from the grape pomace (the total polyphenol content extracted was 0.75 g GAE 100 g^{-1} (Costa et al., 2020).

To accomplish the separation, enzymes are often used as a mixture to increase the extraction yield of bioactives; however, choosing proper enzymes and extraction condition as well as enzyme concentration, time, and temperature of treatment should be taken into consideration. Extraction time can be decreased to half by increasing the enzyme concentrations, which are an important factor, as the prolonged time/temperature may cause compounds degradation or oxidation. The influence of pH in this method has been confirmed, since cellulases work better in acidic pH, while the mixture of cellulase and pectinase showed better enzymatic activity at pH ranges 5.0–6.5 (Gligor et al., 2019).

The EAE method commonly occurs at low temperatures and shorter periods of time with respect to conventional methods, such as maceration or soxhlet. This procedure is based on prior treatment of the matrix with the corresponding enzyme followed by a process of extraction solvent and is widely used to improve the efficiency of the extraction of compounds from a plant matrix. This method is an environmentally friendly technology that can improve the yield of target compounds and solvent use reduction.

Enzyme-assisted extraction was used in multiple extraction (non-conventional) methods to recover phenolics from various biomasses. The combination of two methods of extraction, i.e., enzyme-assisted extraction (EAE) and high hydrostatic pressure (HHP), was evaluated on the phenolic recovery from grape pomace (GP). HHP was applied at different pressures and times (50, 100, and 200 MPa, 0–30 min). The results demonstrated that HHP increased by up to 16 times the activity of the enzymes used in the extraction. Treatments with HHP were more efficient than enzyme-assisted extraction (Cascaes Teles et al., 2020).

Enzyme-assisted extraction has been widely used to extract lycopene from tomato pomace; however, it can also improve the extraction of bound phenolic compounds since the enzyme hydrolyzes the cell compartments and augment the phenolic extraction yield (Catalkaya and Kahveci, 2019). Treatment with various enzymes at different conditions was performed, and the results demonstrated higher phenolic compounds and antioxidant activity with Celluclast–Viscozyme–Pectinex in ethyl acetate solution: TPC of 28.9 ± 3.13 mg GAE g^{-1}, DPPH of 12.7 ± 1.67 mg TEAC g^{-1}, and ABTS of 86.5 ± 8.10 mg TEAC g^{-1} (Table 3).

Pectinase-assisted extraction has been employed to extract the phenolic compounds from spent coffee grounds at various temperatures (0–100 min). The results revealed that the incubation time of 1 h gives better extraction of flavonoids and phenolic acid with higher antioxidant activity (58.30 ± 2.36 mg QE g^{-1}, 267.17 ± 26.69 mg GAE ml^{-1}, and 84.18 ± 7.01%, respectively) (Khairil Anuar et al., 2020). However, SCG treatment with cellulase over a longer time of extraction (24 h) was not effective to extract chlorogenic acid, possibly due to acid oxidization and degradation (Pinelo et al., 2007).

EAE has been combined with other chemical methods or instruments to increase enzymatic efficiency and extraction yields. The applications of microwave, ultrasound, pressurized liquids, and supercritical fluids are examples. The consequences can be described as shortening extraction time, utilizing non-toxic or non-flammable solvents within simpler steps. The effects come from better contact between enzymes and substrates which augment cell disruption, and rapid mass transfer occurrences.

The effects of enzymes pectinase, cellulase, tannase, and β-glucosidase were evaluated to screen the improvement of phenolics extraction from citrus by-products at various incubation times. Pectinase treatment could enhance the release of phenolic aglycones naringenin and hesperetin significantly ($p \leq 0.05$). This enzyme has been reported to be more effective to hydrolyze polysaccharides in grapefruit peels than cellulose, and therefore, in releasing phenols from glycones (Ruviaro et al., 2019). The highest yield of narirutin (47.5 ± 2.3 mg 100 g^{-1}) and hesperidin (255.2 ± 6.9 mg 100 g^{-1}) was gained by cellulase treatment at 6 h; pectinase treatment also resulted in higher hesperidin content (117.3 ± 1.6 mg 100 g^{-1}) but after 12 h treatment, while β-glucosidase treatment could extract higher hesperidin (129.4 ± 8.7 mg 100 g^{-1}). The efficiency of cellulose treatment was more evident on the release of large amounts of narirutin (∼4.7-fold increase with respect to the control) and hesperidin (∼2.4-fold increase). Increasing the incubation time to 24 h could not influence the amounts of aglycones, which might be due to the enzymatic inhibition created by cellobiose or glucose and even the liberated phenolic compounds in the medium following the enzymatic reaction (Ruviaro et al., 2019).

Tannase (T) treatment improved the naringenin and tangeretin extraction (22.6 ± 0.6 7 mg 100 g^{-1} and 1.7 ± 0.27 mg 100 g^{-1} after 12 h). The effects of Tannase on orange juice have been described in particularly through hydrolysis of ester bonds from naringenin, and therefore, enhancing its bioactivity (Ruviaro et al., 2019), while β-glucosidase

generally acts on various glycoside substrates and hydrolyze glycosidic links releasing glucose from flavonoid structures. Tangeretin, which was detected in lower amount after tannase and β-glucosidase, has demonstrated antioxidant and anti-inflammatory activities (Chen et al., 2017). Hesperetin, once again, was the main flavanone extracted by β-glucosidase treatment from citrus juice by-products. As it was discussed earlier, the incubation time is an important factor in aglycones production, following 24 h of enzyme reaction, the production of hesperetin was increased up to 110-fold with tannase, 111-fold with β-glucosidase, and 70-fold with pectinase (Ruviaro et al., 2019).

The synergism between enzymes was tested by their combination, and within the combined enzyme treatments, the enzymatic cocktail of β-glucosidase (B), cellulase (C), and pectin (P) seemed to be the most effective ones since it notably could increase the hesperetin concentration within all incubation times; however, following 24 h of incubation, its recovery was 1.5-fold higher than treating with TCP and 2.7-fold higher than with CP, although the results of each single enzyme treatment after 6 and 12 h indicated that, individually, tannase and β-glucosidase may be adequate to urge phenolic hydrolysis and conversion in citrus juice pomace (Ruviaro et al., 2019). This study confirmed that these enzymes (individually or in combination) could facilitate the hydrolysis of sugar residues linked to the phenolic aglycones, resulting in a release of the relative aglycone from their glycosylation, which in this chemical structure has proven the higher biological activity. It is noteworthy that the optimum condition for hesperetin and naringenin extraction was obtained after 24 h incubation with β-glucosidase (20 U g^{-1}) from the citrus juice by-products (Ruviaro et al., 2019). The importance of hesperetin and naringenin extraction as in aglycone form could be of high interest since many clinical properties have been attributed to them, and therefore, the citrus juice by-product can be considered as a commercial source through enzymatic processing.

In a recent study, the efficiency of EAE to extract flavanones hesperidin and naringenin from *Citrus* pomace with respect to the conventional hydroalcoholic methods was demonstrated (23.32 ± 1.46 to 0.54 ± 0.08 μg^{-1} mg DW, and 2.54 ± 0.15 to 0.14 ± 0.01 μg^{-1} mg DW, respectively, for hesperidin and naringenin), since tannase and β-glucosidase treatment were effective in hydrolyzing the rutinosides flavanone and caused the release of naringenin and hesperetin aglycones, in another word the EAE could promote the higher conversion of hesperidin than narirutin (95% to 45%, respectively), through the de-glycosylation of flavanones in the CP matrix during the extraction, which was also evident in the extraction of Diosmetin by EAE and not *via* the hydroalcoholic extraction (Barbosa et al., 2021).

To be summarized, enzymatic treatment has been considered as the most efficient method for citrus pulp processing, and an enzyme concentration of 1.5% (w/w of the peel sample size) has been reported as the optimum condition to obtain the highest phenolic acid extraction (Sharma et al., 2017).

The other advantages of EAE are the possibility of using plant material as a whole with only a few steps which results in extracting a greater number of bioactive molecules from a specific substrate. The quality and bioavailability of collected compounds are usually high since the amount of residue is relatively low. By the way, this method has some limitations: a) the enzyme application is relatively costly for processing large volumes of raw vegetal material, b) the currently available enzyme mixtures do not permit the complete hydrolyze of plant cell walls, cause in limiting extraction yields of bioactive compounds, c) it is difficult to be used for the industrial scale due to the distinct enzymes' behavior at different environmental conditions, such as the percentage of dissolved oxygen, temperature, and nutrient availability (Puri et al., 2012).

Subcritical fluids extraction, supercritical fluid extraction, and pressurized liquid extraction

Subcritical fluids extraction (SbFE) is a modern technique and is usually referred to as hot liquid solvents or highly pressurized liquid solvents, in which the temperature helps to increase solubility. Solvent such as methanol or ethanol has been used together with subcritical CO_2 fluid extraction (since it has been recognized as safe) to extract the phenols from winery by-products (Barba et al., 2016). The results showed a better recovery of anthocyanins up to 85% under the pressure of 100–130 bar, temperature 30–40 °C, pH of 2–4, and the ethanol as solvent (20–50 ml min^{-1} CO_2 flow). This method could also improve the recovery of gallic acid, catechin, and epicatechin (Barba et al., 2016). The advantages of SbFE method application are easy separation between solid and solvent and using non-toxic solvents; however, the extended time due to the low rate of diffusion of solute from a solid matrix and the requirement of a very specialized automated instrument are the disadvantages of this method (Ameer et al., 2017).

Aliakbarian et al. (2012) have reported the total phenolic content in grape pomace by subcritical water extraction application. The optimized conditions were obtained at 130 min in which the yield was 31.69 mg GAE g^{-1}dry material (Aliakbarian et al., 2012).

Supercritical fluid extraction (SFE) is a technology mainly used to gain a much purer extraction from both solid and liquid matrixes. Generally, CO_2 is used as the supercritical fluid, although it is not very efficient to extract the more polar phytochemicals because of the low polarity of CO_2; therefore, ethanol or methanol is being used as co-solvents (Zhou et al.,

2021). SFE has been widely used to recover anthocyanins and phenolic compounds such as resveratrol from vinery by-products (Barba et al., 2016).

SFE application on citrus pomace indicated higher antioxidant and antimicrobial activities for the extracted biomolecules, although the ultrasonic and soxhlet methods still give a higher yield of total phenolic compounds (Zhou et al., 2021).

Currently, the most important application of SFE in food industry is the extraction of caffeine from coffee and coffee residue. The subcritical fluid extraction was performed with water (SWE) at 100 bar and temperatures up to 220 °C to extract the phenolic compounds from spent coffee grounds. The results gave higher phenolic acids content (19.9 mg GA g^{-1}dry SCG), higher antioxidant activity (EC_{50} of 20.6 μg ml^{-1}) for samples heated up to 140 °C, whereas samples heated between 140 and 220 °C exhibited a total polyphenol content of 5.7 mg GA g^{-1} dry and antioxidant activity of EC_{50} of 132.2 μg ml^{-1}. Interestingly, these extracts were confirmed to have functionality effects such as antiaging and skin lightening by inhibiting elastase at 99% and 97.9%, respectively, also the tyrosinase activity by 78.6 and 92.1%, respectively (Ribeiro et al., 2018). Xu et al. (2015) applied subcritical water extraction (SWE) to extract the phenolic compounds from spent coffee grounds under extraction conditions of temperature 160–180 °C, extraction time of 38–55 min, and solid/solvent ratio (SSR) (g g^{-1}): 14.1 g L^{-1}. Under this condition, the phenolic yield was 86.2 mg GAE g^{-1} (Xu et al., 2015).

The pressurized solvent extraction (PLE) is a technique in which solvent extraction at temperatures (50–200 °C) and high pressures (1,500–2,000 psi) takes place causing the quick and efficient extraction of compounds from the solid matrix. In fact, the use of liquid solvents at high temperatures and pressures improves solubility and mass transfer. PLE is considered as a green extraction method when a non-toxic solvent is used. PLE could be carried out in static and dynamic modes. The advantages with respect to the conventional ones such as maceration or soxhlet extraction are the shorter operational time, higher yield, and lower solvent usage; however, since the high temperature can modify the structure of phenolic compounds this method is not very applicable for the temperature-sensitive molecules, such as phytochemical (Dhua et al., 2022).

PLE application on olive pomace was investigated (the tested factors were consisted of temperature: 65.0–185.0 °C, ethanol as the solvent: 8.0–92.0%, and solid/liquid ratio: 0.2–0.8 g ml^{-1}), and the optimized condition was defined as 184 °C, EtOH 90.0%, SSR = 0.8 g ml^{-1}, at which the hydroxytyrosol (HT) and tyrosol (TY) extraction increased by 5-fold and 3-fold (9.5 vs. 1.79 mg HT g^{-1} and 5.3 vs. 1.78 mg TY g^{-1} dry extract, respectively). Under this condition, the total polyphenol contents also doubled (340 instead of 180 mg GAE g^{-1} dry extract) (Katsinas et al., 2021).

Combining SFE and SbFE methods with pressurized liquid extraction has been investigated to extract phenolic compounds from grape pomace. The SFE was set using CO_2 plus 20% ethanol as co-solvent (100 bar, 55 °C, 20 g min^{-1} CO_2, 5 g min^{-1} ethanol for 3 h, and the PLE condition was 120 bar and 100 °C for 3 h). The results indicated an extraction yield of total anthocyanins content of 0.3–2 and 10.1–49.7 mg malvidin chloride g^{-1} dry grape pomace for SFE and PLE methods, and the total polyphenol yield was of 2.1–4.5 and 15.5–28.9 mg gallic acid equivalent g^{-1} dry grape pomace, respectively, for different variety of grape pomace (Otero-Pareja et al., 2015).

The effects of UAE, MAE, supercritical CO_2 extraction (SCE), and high pressure (HPE) extraction methods were applied to extract the polyphenol content and flavonoid from orange peels. The optimal conditions extraction was identified as UAE at 125 W at 35 °C for 30 min, MAE at 200 W for 180 s, SCE at 10 MPa and 80°C, and HPE at 50 MPa at 35°C for 30 min, although the optimal antioxidant activity was not gained with these conditions (M'hiri et al., 2015), whereas increasing the power and pressure up to 300 W and 100 MPa resulted in the highest antioxidant values for MAE and HPE; therefore, the SCE method showed the least effectiveness, regardless the green nature. They also explored the effect of these methods on individual phenolic compounds. The results demonstrated that the main flavonoids form (about 84%) were mostly neo-hesperidin (ranged 0.6–1.04 g 100 g^{-1} for MAE), and hesperidin (from 0.40 g^{-1} for SCE to 0.83 g 100 g^{-1} for UAE), indicating that the highest and the lowest extraction yield was obtained by MAE and SCE, respectively, even though, the conventional extraction methods again was reported as the best method to recover bioactive with the highest activity (M'hiri et al., 2017).

Pulsed electric field

This method is based on the use of short-span pulses (μs–ms) of controlled electric voltage (typically 0.5–20 kV cm^{-1}) between two electrodes to a matrix. Pulsed Electric Field (PEF) pretreatment has been reported to enhance the phenolic extraction from plant cells (Rocha et al., 2018; Arshad et al., 2021) since the electric voltage can disrupt the cell walls. The advantage of PEF pretreatment to conventional solvent extraction is the selective recovery of intracellular bioactives with no severe damages since the mild temperature increases onto the matrix structures. The efficacy of this technique is based not only on the processing factors but also on the solvent nature, sample composition such as size, shape, pH, conductivity, and the extracted component's size and position in the plant cell cytoplasm or vacuoles (Ranjha et al., 2021).

The extraction of phenolics from grape skin residue was performed. The PEF condition of 3 kV cm^{-1}, 3 s resulted in an increased value by 10-fold in anthocyanin content, while the electric field densities of 0.5–1.5 kV cm^{-1} for 10 μs could

improve the polyphenol and anthocyanin extraction by 20 and 75%, respectively (Thirumdas et al., 2020).

The potential of pulsed electric fields to extract the phenolic compounds from citrus by-products increased significantly up to 159% (orange peels) (electric field densities of 1 kV cm^{-1} and 7 kV cm^{-1}, t PEF = 60 μs, 20 pulses, f = 1 Hz). By increasing the electric field strength and the treatment duration, polyphenol extraction increased. In particular, the recovery yields of naringin and hesperidin increased 2- and 3-fold, respectively, in samples pretreated with PEF, as compared to the untreated samples (Putnik et al., 2017). The method was applied also in tomato and olive pomace, the PEF conditions were set up to 2 kV cm^{-1} and 700 pulses. The extraction of phenolic compounds increased up to two times (56.16 mg GA kg^{-1}) (Andreou et al., 2020). The olive pomace was pretreated with 1.0–6.5 kV cm^{-1}, 0.9–51.1 kJ kg^{-1}, and 15 μs pulse width. The results showed a significant increase in phenolic extraction up to 91.6% (Andreou et al., 2020).

Noteworthy, PEF has exhibited plausible extraction yields not only for phytochemicals from food processing industries but also for enzymes and nutrients from microorganisms, such as bacteria, yeast, and algae (Ranjha et al., 2021).

High voltage electrical discharges

High Voltage Electrical Discharges (HVED) have various applications such as extraction of bioactive compounds rather than water purification and is based on physicochemical process that occurs when electrical discharges contact with water. This process of dielectric breakdown is the result of ionization of liquid upon applying a high voltage (30–40 kV) and intensity (approximately 10 kA) pulse of short duration (μs–ms) between two electrodes (Nutrizio et al., 2021). The advantage of HVED method may is cellular structure destruction and mass transfer enhancement from the cell to the solution, thus greatly improving the yields of bioactive (Rocha et al., 2018).

The application of HVED has been reported in grape pomace that could enhance the polyphenol yield, not only for the fresh samples but also for the dried ones (Vorobiev and Chemat, 2013).

Boussetta has reported the extraction of polyphenols from grape pomace which was performed for about 20 h at 50–60°C. The optimization of electrically assisted extraction resulted in higher polyphenols content, and the most efficient extraction was obtained by 30% ethanol in water at 60°C for 30 min (28 mg GAE g^{-1} dry pomace) (Boussetta et al., 2011).

In olive by-products, HVED parameters were investigated for different green solvent types (water, ethanol). The treatment times were varied between 3 and 9 min, and gases such as nitrogen and argon, with voltages of 15, 20, and 25 kV were tested. The highest yield of phenolic compounds was obtained for the sample treated with argon/9 min/20 kV/50% (3.2 times higher as compared to conventional extraction) (Žuntar et al., 2019).

Although by HVED, the extraction yield usually increases, the extraction time is shortened, and the energy consumption is reduced, a contradictory large number of free radicals are produced during the high voltage discharge that can lead to oxidative cell damage and oxidizing the target phytocompounds and consequently decrease the final yield (Li et al., 2019).

Pulsed ohmic heating

Pulsed Ohmic Heating (POH) is an innovative electro-heating method in which the electrical energy provided to the heating cell is ideally used only for heat generation, and electrochemical reactions, that is, chemical reactions at electrode-solution interfaces induced by the current. POH may combine electrical and thermal treatments to give a more effective extraction method to extract the bioactive through mild temperatures (Ferreira-Santos et al., 2021; Junqua et al., 2021).

In grape pomace, both the normal and freezed samples were treated at POH criteria of electric field between 00 and 400 V cm^{-1}, and time of 2,000 μs was compared. The effects of electric field strength (E: 100–800 V cm^{-1}) and the percentage of ethanol in water (E/W: 0–50%) on polyphenols extraction were tested as well. The results indicated a better polyphenols extraction in water and in water–ethanol solution. The final yield of polyphenols in water after 60 min of extraction was 310 mg GAE 100 g^{-1} DM for the untreated grape pomace, 420 mg GAE 100 g^{-1} DM for the pomace treated at E0400 V cm^{-1}, and 540 mg GAE 100 g^{-1} DM for the pomace treated at E0800 V cm^{-1}. It assumes that the addition of ethanol can improve the polyphenol extraction efficiency (Boussetta et al., 2011; Pereira et al., 2020). The optimum temperature for better polyphenol extraction was yielded at 50 °C (El Darra et al., 2013).

POH was applied on tomato pomace at 70 °C for 15 min with ethanol 70%, and the results indicated a better recovery for Rutin (77%) than control samples (Coelho et al., 2019).

Ohmic heating

Recently, a thermal method has been developed to extract phenolic compounds. The principle of ohmic heating (OH) is based on electrical energy that generates heat within the material being extracted instead of transferring heat from a hot surface as in the conventional methods. This advantage facilitates heat distribution in multicomponent matrix and highly viscous materials. The benefits of using ohmic heating is that the uniform generated heat results in a reduced treatment time, less energy consumption and with no utilization of organic solvents (green extraction), giving a high recovery yield of anthocyanins and phenolic compounds from vegetable tissues

(Pereira et al., 2016; Rocha et al., 2018; Ferreira-Santos et al., 2019). The other advantage reported for OH is its suitability for bacterial inactivation in industry. Usually, bacterial inactivation which is performed by PEF needs high electric field strengths that increase power consumption extremely. Combining OH with high temperature within a short time, not only allows for a higher phenolic extraction yield but also provides the principal for bacterial inactivation; therefore, it has superiority to other bacterial inactivation treatments such as mechanical or enzymatic techniques in industrial applications (Pereira et al., 2016). In the study by Pereira et al., 2016, during OH the MEF applied was 0 V cm^{-1} (conventional heat exchange heating), 15 V cm^{-1}, and 30 V cm^{-1} (OH); for each MEF level, the temperatures selected were 30 °C (room temperature), 60 °C, and 90°C (corresponding to minimum and maximum blanching temperatures). The holding time was 0-, 5-, and 10-min samples were put in distilled water at 1:5 w v^{-1} and placed in an orbital shaker at 90 rpm, 20 °C). This condition allowed enhancing different classes of phytochemical extraction from colored potatoes, with lower power consumption (Pereira et al., 2016). Therefore, OH can provide fast and homogeneous internal heating which can be suitable for selective extraction of solutes from vegetal tissues in controlled temperatures. Condition of high frequency (25 kHz) and low electric field (30 V/cm) is usually reported as being well suited for industrial applications (Pereira et al., 2016). However, some disadvantages have been reported for ohmic heating: a) narrow band of frequencies, b) high cost of establishing ohmic heating systems, c) it is not applicable in matrixes with high-fat granules that do not permit the heat conduction due to lack of water, and d) the corrosion of the electrodes due to electrochemical reactions which consequently increasing the total cost (Junqua et al., 2021).

Deep eutectic solvent

Deep Eutectic Solvent (DES) is a method based on easy preparation by mixing a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD) at a suitable temperature. The advantages are low price, easy, and biodegradability with relatively low toxicity. Usually, choline chloride (ChCl) is used in DES since it is a cheap and non-toxic salt, and HBD are urea, ethylene glycol, glycerol, alcohols, amino acids, carboxylic acids, and sugars. The physicochemical characteristics of DES, such as freezing point, conductivity, density, viscosity, and polarity, normally depend on their composition; therefore, it is possible to modulate them by modifying the HBD and HBA components.

DES has been applied in grape pomace to extract the phenolic compounds. Panzella et al. (2020) has performed three trials in which citric acid–based DES were prepared as follows: A- citric acid/maltose (4:1 molar), B- lactic acid-sodium acetate (5:1 molar), and C- ChCl-oxalic acid (4:1 molar). The results emphasized longer extraction times (50 min, at 65 °C, with a solid-to-liquid ratio of 100 g L^{-1}) in the case of UAE using ChCl-oxalic acid as DES in presence of 25% water to extract phenolic compounds from grape skin, while A-citric acid/maltose resulted in higher total anthocyanin content (TAC), and lactic acid–sodium acetate was efficient for pigment extraction (Panzella et al., 2020).

In olive pomace, glycerol–glycine–water (at 7:1:3 molar ratio) were explored and the optimized parameters in terms of total polyphenol yield and antioxidant power were 80% in water (w/w) DES concentration and a solid-to-liquid ratio of 31 g L^{-1}, at 70 °C. Under these conditions, higher total polyphenol yield from leaves (+18–30%) was obtained compared to 60% aqueous ethanol, aqueous methanol, and water, used as reference solvents, which resulted in significantly higher antiradical activity and reducing power (Athanasiadis et al., 2018). Lactic acid–glucose 5:1 mol mol^{-1} implemented with 15% of water has also been proposed as a solvent for extraction of phenolic compounds from different by-products of olive oil industry, combined with 30–60 min UAE at 40°C, using a solid-to-solvent ratio of 75 g L^{-1} (Fernández et al., 2018). Roughly, the same condition was applied to extract the phenolic compounds from tomato pomace (Table 3), where rutin and catechin were extracted as the main phenolic compounds (Fernández et al., 2018).

In citrus pomace, optimal conditions for DES were found as 10% w/w of water, a temperature of 60 °C, a solid-to-liquid ratio of 100 g L^{-1}, and an extraction time of 100 min (Orange peel) (Ozturk et al., 2018).

Despite the advantages of this technique, the isolation of desired compounds after extraction by DES is difficult due to the density, viscosity, and low vapor pressure of solvents (Palos-Hernández et al., 2022).

Biological activity

Anti-inflammatory activity of agro-industrial phytochemicals: Mechanism of action

Inflammation refers to a series of body responses against external harms that can be injuries and infections or toxins (Abdulkhaleq et al., 2018). As a consequence, chemicals like cytokines are liberated from immune systems to protect the cells. Chronic inflammation occurs when the immune systems fail to combat the inflammation stimuli and the inflammatory status prolongs, which in turn reactive oxygen species (ROS) or reactive nitrogen species (RNS) are produced from the body immune response, causing numerous negative impacts on the cells and tissues. In addition, inflammation is associated with diseases, such as diabetes, cancer, cardiovascular, and neurodegenerative disease

(Blaser et al., 2016). Several gene expressions are in charge of the inflammatory responses that encode transcription factors, cytokines, chemokines, interferons, cellular adhesion molecules, and growth factors, as well as regulatory enzymes that prompt the phosphorylation/glycosylation to produce or remove generated free radicals.

As it has been discussed earlier in this review, different classes of phenolic compounds have been recovered from agro-industrial by-products and their mechanism of action as anti-inflammatory activities both *in vitro* and *in vitro* are described in detail in the following (Table 4).

Antioxidant enzymes modulations

The antioxidative activity of phenolic compounds within the cells is integrated through enzymatic redox systems (Mármol et al., 2021). These enzymes consist of superoxide dismutase (SOD), glutathione peroxidase (GPx), peroxiredoxins (PRXs), catalase (CAT), heme oxygenase-1 (HO-1), and glutathione reductase (GR) that act primarily as a defense mechanism to control the oxidative status. The activity of these enzymes is modulated by an important transcriptional factor, i.e., nuclear factor erythroid-related factor (Nrf)-2 (Zhang and Tsao, 2016). Generally, Nrf2 is delimited by Kelch-like ECH-associated protein 1 (Keap1). Polyphenols result in Nrf2 disassociation and its translocation from cytoplasm into nucleus where the transcription of several genes encoding the antioxidant enzymes, such as SOD, GPx, and CAT, initiates *via* antioxidant-responsive elements (ARE) regulation at the excessive cellular reactive oxygen species (ROS) levels. Releasing above mentioned antioxidant enzymes and endogenous antioxidant glutathione (GSH) is one of the most important mechanisms in maintaining oxidative stress. The Nrf2/Keap1 pathway is also essential as a defensive mechanism against reactive carbonyl compounds (RCC) that are accumulated in organs, such as blood, skin, kidney, and retina, and possibly are associated with many chronic diseases, such as arteriosclerosis, diabetes mellitus, and kidney disease. The effect of RCC has been proposed also on the central nervous system (CNS), involving neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease (Nishimoto et al., 2017). The contribution of Nrf2/Keap1 pathway as a detoxifying mechanism against RCC in neuronal cells has been reported (Nishimoto et al., 2017). Polyphenols are recognized as triggering the interaction between Nrf2 and aryl hydrocarbon receptor (AhR). Nrf2–ARE activators induce a battery of cell-protective genes that are critical for preventing oxidative damage, inflammation, and tumorigenesis, and this ability could be taken advantage of in antioxidant, anti-inflammatory, and anticancer agents.

Flavonoids, in particular, are AhR agonistic regulators mediating further inflammatory signaling events (Zhang and Tsao, 2016). It has been reported that many flavonoids such as quercetin, rutin, apigenin, chrysin, and luteolin and their derivatives act as AhR agonistic regulators to maintain the oxidative status. Flavonoids such as rutin, kaempferol, apigenin, catechin, chrysin, tangeretin, and luteolin have demonstrated antioxidative stress activities on various cell types *via* activation of AhR/Nrf2 pathway (Table 4). As it has been reported that these phenolic compounds are found at various concentrations in agro-industrial wastes reviewed in this work (Tables 2, 3).

Inflammatory cytokine expression regulation

Nuclear factor kappa B (NF-κB) family is one of the most important signaling pathways that control the immune responses and the development of inflammation, composed of five hetero- or homo-dimer members that modulate the transcription of target genes. The most important and abundant complex is p65/p50, which controls the expression of genes such as IL-1β, IL-6, IL-8, TNF-α, IFN-β, and iNOS. Irregular activation of these pathways results in inflammatory disease progress, causing autoimmune disease and cancer. The importance of NF-κB in inflammation regulation is not only inducing the expression of inflammatory cytokines/chemokines or adhesion molecules but also regulating the carcinogenesis process within the cells, such as proliferation, apoptosis, morphogenesis, and differentiation (Liu et al., 2017). Polyphenols have demonstrated strong efficiency to control this pathway at different phases. Many membrane-bound ligands such as Toll-Like Receptor (TLR) and interleukine-1 (IL-1) can activate this pathway, resulting in IκB phosphorylation [NF-κB Inactive form is bounded to an inhibitor (IκB)] and its degradation. Therefore, NF-κB translocates into the nucleus and initiates the upregulation of transcription genes that in consequence regulate cell survival/proliferation and inflammatory responses (Liu et al., 2017).

The other signaling pathway that controls cellular processes during the inflammatory status and modulates cytokine expression and inflammatory proteins expression is mitogen-activated protein kinase (MAPK). This signaling pathway includes different kinase classes: p38 MAPKs, extracellular signal-regulated kinases (ERK), and c-Jun NH2 terminal kinases (JNK), which mainly control the cell growth/survival and differentiation, and can be activated by different stimuli such as oxidative stress, inflammatory cytokines, and DNA damage (Zhang and Tsao, 2016).

Phosphatidylinositol 3-kinase (P13K/Akt) signaling is the other pathway that coordinates cellular processes in many cancers' progression. The pathway in particular regulates cell metabolism, motility, and proliferation over the protein transcription. P13K/Akt downregulation causes apoptosis and ceases cell survival. Natural or synthesized agents, such as

TABLE 4 Different class of phenolic compounds and their mechanism of action.

Class	Compounds	Concentration	Mechanism of action	By-products					Ref.
				OP	CP	GP	SCG	TP	
Hydroxybenzoic acids	Gallic acid	50 μmol L^{-1}	Modulating the phosphorylation of IkB-a in IL-1β treated Caco-2 cells			*	*	*	Romier et al., 2008
		0.1 mg ml^{-1} fruit extract	IL-6, IL-8 and MCP-1 concentrations significantly decreased $p < 0.001$						Hollebeeck et al., 2012
	Ellagic acid	50 μmol L^{-1}	Modulating the phosphorylation of IkB-a in IL-1β -treated Caco-2 cells			*		*	Romier et al., 2008
		50 μM	IL-6, IL-8 and MCP-1 concentrations significantly decreased $p < 0.001$						Hollebeeck et al., 2012
			Inhibition of NLRP3 inflammasome activation						Tang et al., 2015
	Vanillic acid	0.09 mg g^{-1}	Modulating IL-8 and PGE2 secretion			*		*	Martins et al., 2017
Hydroxycinnamic acids	Cinnamic acid	0.025–1 mg ml^{-1}	inhibition of cytokines, NO, PGE2, IL-6, IL-8, and TNF-α secretion			*		*	Kim and Kim, 2019
	Coumaric acids	2.62–21.3 mg g^{-1}	Inhibition on COX-2 expression & IL-8 secretion		*	*	*	*	Huang et al., 2015
									Chen et al., 2017
	Caffeic acids	0.5–2 mmol L^{-1}	Suppression IL-8 secretion in caco-2 cells		*	*	*	*	Shin et al., 2015
		2 mmol L^{-1}	IL-8 cytokine secretion reduced			*	*	*	Zhao et al., 2008
	Chlorogenic acids	0.5–2 mmol L^{-1}	Suppression IL-8 secretion. In caco-2 cells			*	*	*	Shin et al., 2015
		3.24 mg g^{-1}	Inhibition on COX-2 expression & IL-8 secretion						Huang et al., 2015
		0.2–2 mM CQA	increased the amount of Nrf2 protein in Caco-2 cells						Liang and Kitts, 2018 Zhao et al., 2008
	Ferulic acid		Reduced IL-1β secretion	*	*	*	*	*	Parizad et al., 2019 Chen et al., 2017 Villela-Castrejón et al., 2017
	Sinapic acid			*	*		*	*	Chen et al., 2017
Flavones	Apigenin		Reducing IL-1β secretion		*	*	*	*	Funakoshi-Tago et al., 2011; Zhang et al., 2014; Ali et al., 2017
	Luteolin				*				
	Diosmetin				*				
	Tangeretin	0.5–4 mg ml^{-1}	inhibit iNOS and COX-2 expression in LPS and IFN- γ induced Raw 264.7 cells		*				
	Nobiletin	0.5–4 mg ml^{-1}	inhibit iNOS and COX-2 expression in LPS and IFN- γ induced Raw 264.7 cells		*				
Flavonols	Kaempferol	3.11 mg g^{-1}	Inhibition on COX-2 expression & IL-8 secretion		*	*	*	*	Devi et al., 2015; Huang et al., 2015
	Quercetin	50 μmol L^{-1}			*	*	*	*	Romier et al., 2008
			Reducing IL-1β & IL-18						Wang et al., 2012

(Continued)

TABLE 4 (Continued)

Class	Compounds	Concentration	Mechanism of action	By-products					Ref.
				OP	CP	GP	SCG	TP	
		4.4–34.6 mg g^{-1}	Inhibition on COX-2 expression & IL-8 secretion						Huang et al., 2015
		0.58 mg g^{-1}	Modulating IL-8 and PGE2 secretion						Martins et al., 2017
		0–60 μM	Reducing IL-6, IL-1β, IL-8 and MCP-1 secretion						Chuang et al., 2010
			Reduced IL-1β secretion						Parizad et al., 2019
	Rutin	1.27 mg g^{-1}	Modulating IL-8 and PGE2 secretion		*	*	*	*	Martins et al., 2017; Mascaraque et al., 2014
			Reduced IL-1β secretion						Parizad et al., 2019
	Myrecetin	1.5 mg g^{-1}	Inhibition on COX-2 expression & IL-8 secretion			*		*	Huang et al., 2015
		0.33 mg g^{-1}	Modulating IL-8 and PGE2 secretion						Martins et al., 2017; Semwal et al., 2016
Flavanones	Naringenin	50 μmol L^{-1}			*	*		*	Romier et al., 2008
		2.43 mg g^{-1}	Inhibition on COX-2 expression & IL-8 secretion						Huang et al., 2015; Yilma et al., 2013; Patel et al., 2018; Raza et al., 2013
	Neohesperidin				*				
	Hesperidin	20–30 μM	The level of NO2 decreased iNOS protein gene expression suppressed in RAW 264.7 macrophage cells stimulated by LPS		*				Parhiz et al., 2015
		0.5–4 mg ml^{-1}	Inhibition of iNOS and COX-2 protein/mRNA expression in Raw 264.7 in a dose-dependent manner.						
	Hesperitin								
	Narirutin	50–100 μg ml^{-1}	Inhibit the release of NO, PGE2, IL-1β, and TNF-α in RAW 264.7 macrophage cells stimulated by LPS		*				Ha et al., 2012
		0.5–4 mg ml^{-1}	inhibition of iNOS and COX-2 protein/mRNA expression in Raw 264.7 in a dose-dependent manner cells were treatment with 50 ng/ml of LPS and 10 ng/ml of IFN-γ						
Flavan-3-ols	Catechin	50 μmol L^{-1}					*		Romier et al., 2008
		13.55 mg g^{-1}	Modulating IL-8 and PGE2 secretion						Martins et al., 2017
			Reduced IL-1β secretion						Parizad et al., 2019; Silvan et al., 2017; Chen et al., 2018a,b; Chen et al., 2017
	Epicatechin	50 μ mol L^{-1}				*	*		Romier et al., 2008
		7.14 mg g^{-1}	Modulating IL-8 and PGE2 secretion						Martins et al., 2017
			Reduced IL-1β secretion						Parizad et al., 2019; Silvan et al., 2017; Chen et al., 2017

(Continued)

TABLE 4 (Continued)

Class	Compounds	Concentration	Mechanism of action	By-products					Ref.
				OP	CP	GP	SCG	TP	
									Rodríguez-Ramiro et al., 2013
	Proanthocyanidin								Kramer et al., 2019
									Rodríguez-Ramiro et al., 2013
									McKenzie et al., 2009
stillbenes	Resveratrol	50 μmol L^{-1}				*		*	Romier et al., 2008
Catechol	Hydroxytyrosol			*					
	HT								Fuccelli et al., 2018; Bertelli et al., 2020
	Tyrosol			*					
	Oleuropein			*					
			Inhibition IL-1β, TNF-α, NLPR3, IL-6						Cheng et al., 2016; Song et al., 2016; Wang et al., 2017
									Panaro et al., 2012
		0–60 μM	Reducing IL-6, IL-1β, IL-8 and MCP-1 secretion						Ranjha et al., 2021
Chalcones	Chalcon naringenin				*			*	Yadav et al., 2011
Anthocyanins	Cyanidin		Reduced IL-1β secretion			*			Gessner et al., 2012; Taverniti et al., 2014; Jung et al., 2015; Kuntz et al., 2015; Ferrari et al., 2016; Zhang et al., 2016; Haggard et al., 2017; Parizad et al., 2019
	Delphinidin		Reduced IL-1β secretion		*	*			Zhang et al., 2016; Parizad et al., 2019
	Pelargonidin								Zhang et al., 2016, 2017
	Peonidin				*				Jung et al., 2015; Zhang et al., 2019
	Petonidin								Zhang et al., 2017
	Malvidin				*	*			Bognar et al., 2013; Decendit et al., 2013; Santos et al., 2013; Kuntz et al., 2015; Cheng et al., 2016; Dai et al., 2017; Huang et al., 2018

*Refers to the presence of phenolic compounds in the by-products.

phenolic compounds, that can modulate the activity of the PI3K/AKT pathway, may contribute to the development of therapeutic treatment of cancers (Fatima and Siddique, 2019). Polyphenols are recognized as inhibitors not only on P13K/Akt but also on kappa kinase/C-Jun amino-terminal kinases (IKK/JNK) and toll-like receptor (TLR) (Kopustinskiene et al., 2020).

Under cellular infections, oxidative stress or excessive pro-inflammatory response resulting from IL-1β have regulatory effects on NLRP3 inflammasome. Pyrin domain-containing protein 3 (NLRP3) is an intracellular sensor that in case of external danger forms NLRP3 inflammasomes, activates Toll-like receptor (TLR), and leads to releasing caspase 1-dependent (caps-1). Activation of TLR-1 by interleukine-1 results in NF-κB-activated and MAPK and generates a series of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, and IFN-g. (Swanson, 2019). These reactions, subsequently, initiate the extension of inflammatory status within the cells. NLRP3 regulatory property is important in the development of inflammatory metabolic disorders and degenerative diseases, such as type-2 diabetes and Alzheimer's disease (Milner et al., 2021). Recent *in-vivo* and *in-vitro* studies have demonstrated that phenolics such as procyanidins, apigenin, cinnamic acids, and stilbenes have anti-inflammatory effects by inhibiting the NLRP3 inflammasome activation and IL-1β secretion.

Polyphenols also have demonstrated regulatory properties on the activation of peroxisome proliferator-activated receptor (PPAR)-g. This nuclear receptor is important in regulating fatty acid breakdown and metabolism of glucose, so, controlling the lipid and glucose metabolism and the consequent inflammatory status. Therefore, this pathway is important in multiple diseases, such as obesity, diabetes, and hypertension (Salau et al., 2020).

Nonsteroidal anti-inflammatory drugs (NSAID) mechanism of action

Phenolic compounds are effective on arachidonic acid cascade enzymes, such as cyclooxygenase (COX) and lipoxygenase (LOX) enzyme inhibitors (Lončarić et al., 2021).

The exogenous inflammatory stimuli such as LPS, TNF-α, or tissue injuries affect phospholipase A_2 that modulate the arachidonic acid pathway and secretion of prostaglandins (PG) and thromboxanes (TX). In fact, COX inhibition has been recognized as the main mechanism for the anti-inflammatory activity of Non-steroidal Anti-inflammatory Drugs (NSAIDs). NSAIDs have also suppressive effects on NF-κB and inflammatory proteins expressions, such as cytokines, chemokines, and adhesion molecules. Many polyphenols such as gallic acid, quercetin, and resveratrol are recognized as COX inhibitors, whereas caffeic acid, quercetin, catechin, benzoic acid, ferulic acid, and kaempferol are good examples of LOX inhibitors (Lončarić et al., 2021). Since PGE2 synthesis is important in the development of cancer, polyphenols can be considered as complementary compounds to develop effective drugs for the treatment of the resilience of tumor cells and reducing the inflammatory processes.

Many of the phenolic compounds act on several simultaneously; however, some are limited just to one pathway. Hydroxybenzoic acids (HBAS), for example, act on the interleukin (IL-6) suppression in Caco-2 cell lines. HBAS comprises gallic acid (GA), Vanillic acid (VA), and syringic acid (SyA). Studies have reviled that a cocktail at a final concentration of 50 μM made from GA and Ellagic acid (EA) could significantly decrease the gene levels of inflammatory markers IL-6 and IL-8 ($p < 0.001$) in the intestinal cells (Hollebeeck et al., 2012). Ellagic acid that is mainly found in the grape pomace and to some extent in the tomato pomace had exerting antioxidative activity on inhibiting NLRP3 inflammasome signal pathway in animal model (EA concentration: 50 mg EA per kg body weight) (Tang et al., 2015). Grape pomace extracts (GPE) at 100 μg ml^{-1} concentration of phenolic compounds could suppress the IL-8 and PGE2 secretion in the Caco-2 cells pretreated with leukocyte IL-1β (1 ng ml^{-1}). HPLC analysis revealed that this extract was rich in flavonoids, in particular, catechin, epicatechin, and gallic acid. To evaluate the NF-κB complex activity, the p65 protein translocation was quantified and showed a moderate correlation ($r = 0.36$) with the cytokine IL-8 secretion ($p = 0.012$), although when the concentration of IL-1β were raised to 20 ng ml^{-1}, the NF-κB activity was improved by 223% with respect to the negative control, this activity was then suppressed at 27% by GPE at a concentration of 100 μg ml^{-1}. The prostaglandin E2 (PGE2) secretion was also decreased in cells treated with GPE at 200 μg ml^{-1} and was more correlated ($r = 0.85$) with the IL-8 secretion ($p \leq 0.0001$). The levels of cyclooxygenase-2 enzyme after treatment by IL-1β (20 ng ml^{-1}) increased by 228% after 6 h; however, grape pomace extract at 100 μg ml^{-1} was not able to decline it (Martins et al., 2017). The effects of Vanilic acid (VA) that have been found in other by-products except for SCG in minor quantities have been reported by Martins et al. (2017) on modulating IL-8 and PGE2 secretion at a concentration of 0.09 mg g^{-1} (Martins et al., 2017).

Resveratrol, which is the main representative of stilbenoids, in grape skins and consequently can be found in grape pomace, accounts as one of the main antioxidants in grape products (Singh et al., 2016). The anti-inflammatory properties of resveratrol have been described through different mechanisms. The inhibition of pro-inflammatory cytokines expression is mainly by inhibiting COX-2 and AP-1. This stilbenoid can also reduce nitric oxide (NO) production by inducible nitric oxide synthase (iNOS) inhibition. Resveratrol has shown inhibitory effects on MAPK *via* (ERK) 1/2 and p38 inhibition (Singh et al., 2016).

Hydroxycinnamic acid (HCCA) such as cinnamic acid (CA), ferulic acid (FA), caffeic (CA) and chlorogenic acids (Chl A) constructs the main part of phenolic acids in the agro-industrial by-products (Table 2). Cinnamic acid at a concentration between 0.025 and 1 mg ml^{-1} has demonstrated inhibitory activity on the NO, PGE2 production, and cytokines secretion such as IL-6, IL-8, and TNF-α (Kim and Kim, 2019). Tomato by-products have considerably high contents of cinnamic acid (Table 2). Coumaric acid (CoA) is the hydroxy derivative of cinnamic acid also found in tomato by-products and grape pomace in three various isomers forms (certainly depends on the origin and variety of material). CoA at a concentration of 2.62–21.3 mg ml^{-1} could inhibit both the COX-2 and IL-8 cytokine expression (Huang et al., 2015). Notable contents of *p*-coumaric acid have been also found in citrus pomace. Ferulic acid is a phenolic compound covalently bound to almost all plant cell walls, and therefore, usually present in plant-derived agro-industrial by-products in variable concentrations. Experiment in Caco-2 cells has demonstrated the anti-inflammatory properties of ferulic acid on IL-1β secretion (Parizad et al., 2019). Spent coffee grounds are the main source of caffeic acid and chlorogenic acid both at a concentration of 0.5–2 mmol L^{-1} have displayed strong suppression activity on the IL-8 cytokine secretion in caco-2 cells (Monente et al., 2015). ChlA at 10 μg ml^{-1} could inhibit the IL-cytokine expression by 78.5% vs. control (Abbasi-Parizad et al., 2021). Huang has reported that chlorogenic acids at 3.24 mg g^{-1} could inhibit the expression of COX-2 and cytokine IL-8 secretion (Huang et al., 2015); however, the caffeeolquinic acid (CQA) is more effective since lower concentration (0.2–2 mM) of that could reduce the inflammatory status. Treatment of the Caco-2 cells with CQA, downregulated cytokine IL-8 expression by 50%, further analysis revealed its capacity for upregulating the NFκB signaling cascade through reducing the p-38 in mitogen-activated protein kinases (MAPK) (Liang and Kitts, 2018).

Flavonoids are a large group of polyhydroxyphenols that can act not only on protein kinases such as protein kinase C (PKC), phosphoinositol kinase, phosphatidylinositol kinase (PIK), cyclin-dependent kinase-4, and tyrosine kinase but also on phosphodiesterases like cyclic adenosine monophosphate (cAMP) pathway that is involved in the numerous cellular signaling cascades such as cell differentiation and lipid metabolism besides affecting gene/protein expression in inflammation (Yokoyama et al., 2015). It has been evaluated that the flavonoid's chemical structure is responsible for their anti-inflammatory properties, in fact, number and position of hydroxy/methoxyl groups on the B-ring and a double-bonds in C2 = C3 improves the interaction between flavonoids and regulatory enzymes (Chen et al., 2018b).

Flavonoids quercetin, kaempferol, myricetin, and apigenin can inhibit serin/theronine protein kinases (PIK3/AKT) in a competitive manner (Lolli et al., 2012). These flavonoids have been reported for modulatory properties of transcription factors such as NF-κB (Choy et al., 2019). The main flavonols, kaempferol, myrecetin, quercetin, and its glycosylic form, rutin are found in relatively high concentrations in agro-industrial by-products (Martins and Ferreira, 2017). Both kaempferol and myrecetin were effective to suppress the interleukin-8 (IL-8) and cyclooxygenage-2 (COX-2) expression in the Caco-2 cells at 3.11 mg g^{-1} and 1.5 mg g^{-1}, respectively (Huang et al., 2015). Kaempferol decreased the expression of PGE2 and iNOS by inhibiting the p38 phosphorylation (Chen et al., 2018a,b). Martins et al. (2017) have illustrated that myrecetin at lower concentrations (0.33 mg g^{-1}) could affect PGE2 secretion (Martins et al., 2017). Quercetin, myrecetin, and kaempferol were found to be better lipoxygenase inhibitors than others. Quercetin showed the different mechanism of anti-inflammatory properties *via* the modulation of several signaling pathways. This flavonol by having an ortho-dihydroxy group on its B-ring had presented very effective both on antioxidant enzymes regulation such as Nrf2 and the inhibition of cytokine expressions *via* pathways of COX-2, p38-NF-kB, and MAPK. It also could attenuate the NO production by inhibiting the inducible nitric oxide synthase (iNOS); however, it has been proved that the anti-inflammatory activity of various flavonoids mightily depends on the de-conjugation of the glycosides to flavonoid aglycones (Chen et al., 2018b). Apigenin has been reported as an strong inhibitor for the IL-1β secretion in Caco-2 cells (Funakoshi-Tago et al., 2011; Zhang et al., 2014; Ali et al., 2017). Apigenin has demonstrated the different mechanism of action in various cell types on signaling pathways, resulted in reducing the expression of TNF-α and IL-6 *via* suppressing the phosphorylation of p65, and inhibiting the activation of MAPK, NF-kB, and iNOS. Naringenin belongs to the flavanones and is the main flavonoid found in tomato and citrus by-products (Belović et al., 2016). Recent *in-vitro* and *in-vivo* studies have illustrated a wide range of health benefits and its anti-inflammatory properties on the various inflammatory biomarkers (Yadav et al., 2011). The levels of COX-2 enzyme and cytokine IL-8 were reduced by treating with 2.43 mg g^{-1} of naringenin in Caco-2 cell line (Huang et al., 2015), and it also could decrease the gene expression of MCP-1 (monocyte chemoattractant protein-1). Naringenin chalcone is almost found in exclusive amounts in tomato peel, and therefore, is present in the tomato pomace (Table 2) (Belović et al., 2016). Anti-inflammatory properties of naringenin chalcone have been demonstrated through the downregulation of pro-inflammatory mediators MCP-1, TNF-α, and the iNOS expression. Although chalcones have an open C-ring but it seems that the presence of a double bond in conjugation with carbonyl group is responsible for their anti-inflammatory properties.

Catechin and epicatechin belong to the flavan-3-ols found principally in spent coffee ground and grape pomace (Table 2) (López-Linares et al., 2021). The concentration of 13.55 mg g^{-1} and 7.14 mg g^{-1} could modulate the secretion of inflammatory

cytokines, such as IL-8, IL-1β, and PGE2(Martins et al., 2017), while their strong anti-inflammatory property can be indicated by the unique chemical structural; in particular, the presence of the hydroxyl and galloyl groups in a stereochemitric pattern (Chen et al., 2018b).

Anthocyanin, a group of flavonoids, is greatly concentrated in grape pomace and red orange pomace. They have demonstrated modulatory properties on various cellular signaling pathways of inflammation including NF-kB, MAPK, and COX-2, and in consequence downregulating different gene expressions of inflammatory cytokines. Derivatives of cyanidin and malvidin in grape pomace are predominant anthocyanins. Studies on the anti-inflammatory properties of anthocyanins in Caco-2 cells demonstrated downregulation of IL-1β cytokine (Haggard et al., 2017; Huang et al., 2018).

The main flavanones detected in citrus pomace are eriocitrin, narirutin, naringenin, nobiltin, apigenin, and rutin. The flavones tangeretin, diosmin, and luteolin are mainly found in orange, lemon, and bergamot by-products (Barreca et al., 2020). Aglycone hesperetin is also found in citrus juice by-products to the inferior values (Ruviaro et al., 2019). Phenolic compounds from Clementine Mandarine could decrease the ROS significantly ($p < 0.05$) in Caco-2 cells stimulated with H_2O_2 (Fernández-Fernández et al., 2021).

To show the efficiency of flavanones mixtures on suppression of the inflammatory status, a mix of two rutinosides and two neohesperidosides plus hesperetin aglycone were prepared at 10 μM concentration and were tested in Caco-2 cells treated by IL-1β (25 ng ml^{-1}). The citrus by-products flavanones mix demonstrated a significant ($p < 0.001$) increase in IL-6 (∼7-folds), IL-8 (∼27-folds), and in NO release (∼2.5-folds) vs. control, which approves the synergism effect (Denaro et al., 2021). Narirutin has been reported the inhibition of NO and PGE2 release in the macrophages stimulated by LPS (Chen et al., 2017). The mechanism of action of these flavanones has been reported through the activation of NF-kB and mitogen-activated protein kinases (MAPKs).

By testing extract rich in flavone aglycone from citrus pomace at a concentration of 1.0 mg ml^{-1} in RAW264.7 cells stimulated by LPS, cytokine secretion was decreased by 30.7% and 43.4% for TNF-α and IL-6, respectively (Nakajima et al., 2017). When flavonol quercetin has been only detected in mandarin by-products (126 ± 18.2 mg kg^{-1} FW), quercetin 3-*O*-rhamnoside has been extracted from almost all citrus by-products (3.7 ± 0.65 to 150 ± 11.4 mg kg^{-1} FW). The concentration of hesperidin extracted from citrus by-products has been reported up to 377 ± 17.2 mg kg^{-1} FW (Multari et al., 2020). The anti-inflammatory effect of hesperidin is to target cytokines, such as IL-6, COX-2, iNOS, and TNF-α. It has been reported that hesperidin treatment could reduce PGE2 production significantly (Multari et al., 2020). It also could suppress the iNOS expression in the RAW 264.7 macrophage cells stimulated by LPS. The flavonoids mix of hesperidin and naringenin extracted from Korean orange could suppress the pro-inflammatory mRNA and cytokines, and the enzyme levels of COX-2 (Chen et al., 2018a). Hesperidin could also prevent scavenging ROS, thus reducing skin inflammation. The intercellular antioxidant activity of hesperidin and its aglycon hesperetin can be described through the ERK/Nrf2 signaling pathway (Zhu et al., 2020).

Citrus pomaces from Clemenule and Ortanique mandarin varieties and Navel and Valencia orange varieties demonstrated TPC and ABTS in the range of 10–25 mg GAE g^{-1} and 60–420 μmol g^{-1}, respectively, with naringin/narirutin content accounting for more than 71% of total phenolics (Fernández-Fernández et al., 2021), for which the mechanism of anti-inflammatory has been discussed earlier in this work.

Conventional extraction has revealed the total polyphenol content in the olive pomace of about 661 mg kg^{-1} of pomace (Yakhlef et al., 2018). Hydroxytyrosol (HT), tyrosol, and oleuropein are considered as the most abundant polyphenols in olive and olive by-products and have shown strong antioxidants and anti-inflammatory properties (Richard et al., 2011). The anti-inflammatory effects of these substances on different cytokines and chemokines have been evaluated in the macrophages stimulated by LPS (1 μg ml^{-1}). Hydroxytyrosol (HT) decreased the secretion of all cytokines tested (IL-1α, IL-1β, IL-6, IL-12, TNF-α) and chemokines (CXCL10/IP-10, CCL2/MCP-1), whereas the results demonstrated an IC_{50} of 11.4 and 19.5 μM for production of NO and PGE_2, respectively, that was inhibited by the hydroxytyrosol. Tyrosol and hydroxytyrosol also demonstrated great suppression efficiency on pro-inflammatory IL-8 secretion in Caco-2 cells (Di Nunzio et al., 2018). Further hydrolysis of oleuropein also results in hydroxytyrosol production that can be rapidly absorbed in the gastrointestinal tract and have modulating mechanism on the NF-κB signaling pathway. It has been observed in the cells stimulated by LPS and HT treatments a remarked diminish in I-κBα, NF-κB1 besides NF-κB49 and NF-κBp65 level of expression (Richard et al., 2011).

As a general consideration, the anti-inflammatory capability of the various extracts is in most cases higher than in similar extracts from similar sources, suggesting that activities in each extract may imply specific synergies between anthocyanins and other phenolics (Parizad et al., 2019).

Future perspectives and conclusion

The recovery of valuable compounds from food and agro-industrial wastes is an important challenge for the field-related scientists, though the commercial implementation is a complex approach depending on several parameters that should be considered. Apart from the methods reviewed above, research should manage to succeed scaling up without affecting the functional properties of the target compound to develop a

product that meets the manufacturer's high-quality standards for safety and features characteristics.

The growth of sustainable solutions for food and agro-industrial waste management depicts one of the main concerns in each society. The solutions could be presented by exploiting these precious resources of bioactive compounds to attain not only economic but also social and environmental benefits. Agro-industrial by-products have been generally considered as sources for the production of compost, bioplastics, biofuels, or for animal feeding, although, recently, their bioactive compounds recuperation has emerged as a new prospective. Most research studies have usually used entire pomace and bagasse sources rich in glycosylated phenolic compounds containing lower amounts of aglycone forms, although data evidence that the aglycone forms not only have higher antioxidant capacity but also demonstrate higher bioavailability; therefore, innovative extraction procedures giving extracts from low-cost sources such as agro-industrial wastes which represent both glycosyl and aglycon forms of polyphenols could be a more adequate composition. The added value of the recovered phenolic compounds from agro-industrial by-products resides in the fact that the presence of various classes of phenolic compounds (in both glycone and aglycone forms) obtained as a unique mixture may result in possible synergism effects that can amplify their biological activities. Since these bioactive compounds have the ability to modulate various signaling pathways contemporary in oxidative stress status, and therefore, inflammation condition, preventing chronic non-communicate diseases by anti-inflammatory mechanism, are of high interest for food/feed, beverages, cosmetics, and neutra/pharmaceutical applications, although the data on the effectual procedure, total yield, energy consumption, and economic perspectives should be taken into consideration.

Author contributions

PA-P: conceptualization, methodology, writing—original draft, and editing. PA-P, BS, RP, and PD: investigation. PA-P, AS, and FA: review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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