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Review

Resveratrol-based biorefinery models for favoring its inclusion along the market value-added chains: A critical review

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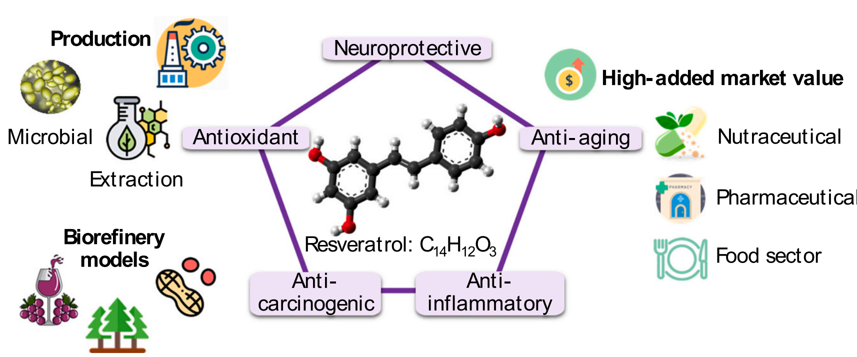
HIGHLIGHTS

- Resveratrol produced by agro-industrial waste valorization leads to more efficient and sustainable waste management.
- Green extraction and biosynthesis technologies for resveratrol are more effective and beneficial than conventional ones.
- Further analysis and optimization is needed for the effective and feasible scale-up of emerging technologies.
- Integration of resveratrol production on biorefinery schemes could enhance its penetration on the market value chains.
- Sustainability assessments are crucial to demonstrate the benefits of resveratrol industrialization and market penetration.

GRAPHICAL ABSTRACT



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ABSTRACT

Resveratrol, a natural organic polyhydroxyphenolic compound, has gained significant attention in the last years given its potential health benefits, including antioxidant, anti-cancer, and anti-inflammatory properties. It can be directly extracted from plants, vegetables, and related products and waste resources, but also chemically/enzymatically/microbially synthesized. However, certain process strategies have some limitations, such as high costs, reduced yield or high energy demand, thus implying significant environmental loads. In this context, the search for more sustainable and circular process schemes is key to the integration of resveratrol into the market value chain of the food, cosmetic and pharmaceutical sectors. The extraction of resveratrol has traditionally been based on conventional methods such as solvent extraction, but advanced green extraction techniques offer more efficient and environmentally friendly alternatives. This review analyses both conventional and green alternative extraction technologies, as well as its bioproduction through microbial fermentation, in terms of production capacity, yield, purity and sustainability. It also presents alternative biorefinery models based on resveratrol bioproduction using by-products and waste streams as resources, specifically considering wine residues, peanut shells and wood bark as input resources, and also following a circular approach. This critical review provides

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some insight into the opportunities that resveratrol offers for promoting sustainable development and circularity in the related market value chains, and thus provides some criteria for decision making for biorefinery models in which resveratrol is one of the targeted high value-added products. It also identifies the future challenges to promote the inclusion of resveratrol in value chains, with the scale-up of green technologies and its demonstrated economic feasibility being the most prominent.

1. Introduction

The first resveratrol isolation dates from 1939 using white hellebore as bioresource (*Veratrum grandiflorum* O. Loes) (Takaoka, 1939), which is classified as a species of poisonous perennial herbs of the *Melanthiaceae* spp.. Later, it was isolated from the roots of *Polygonum cuspidatum syn. Fallopia japonica*, also known as Japanese knotweed, a well-recognized plant given its high content of polyphenolic *trans*-resveratrol, being the highest bioavailable form of resveratrol that can be extracted and isolated from bio-based resources (Kaur et al., 2022; Suvarna et al., 2018).

Resveratrol can be found on various plants, fruits, and herbaceous species, but its functions can vary depending on the bioresource of extraction (Donnez et al., 2009). For example, grapevine, one of the most recognized raw materials for the extraction of resveratrol, provides a product with antifungal properties, while in berries and plant leaves, its main function is to respond to stress situations, acting as a phytoalexin, i.e. antimicrobials with protective functions belonging to the iso/flavonoid family of phenolic-based compounds (Tuladhar et al., 2021). Furthermore, resveratrol can be found in more wood-nature sources, in which its main behavior is to act as a phytoanticipin, a precursor of an antimicrobial compound against pathogens (Tiku, 2020). Given the benefits that resveratrol can provide, resveratrol bioavailability has been enhanced by encapsulation in nanoparticles or liposomes (Jayan et al., 2019; Davidov-Pardo and McClements, 2014), co-administration with adsorption enhancers as piperin, a compound that could be found on black pepper (Vesely et al., 2021; Johnson et al., 2011) or by the development of controlled and sustained release formulations (Chimento et al., 2019; Devi et al., 2019).

Interest in resveratrol has been increasing year after year, given its potential and interesting properties as an antioxidant, cardioprotective, cancer preventive agent, neuroprotective, anti-inflammatory, among others (Abo-Kadoum et al., 2022; Gugleva et al., 2020; Majeed et al., 2023; Zhang et al., 2022). However, one of its main drawbacks is that most commercial forms of resveratrol are produced chemically, as it is more economically viable and meets market demands (Lorena et al., 2018). Some of the commercial products are extracted from plants, but the procedures are not efficient, and the extraction yield is low. With this in mind, the introduction of biotechnological production processes and/or environmentally-friendly processes for extraction is key to increase their quality, natural nature and commercialization.

In this context, this critical review is developed to present the bioactive potentials of resveratrol, together with the main bio-based and waste resources that can be used for its extraction, followed by the description of the valorization technologies available for its extraction, as well as its bioproduction, with a special focus on the usage of renewable substrates. In addition, in order to provide a broader view and potential of resveratrol in the market value chain, alternative biorefinery scenarios are described. It is hoped that the information provided by this critical review can help researchers, policy makers, stakeholders and manufacturers to advance the recovery and biotechnological production of resveratrol from waste-related streams, seeking to provide more sustainable production pathways based on the comprehensive use of available resources.

2. Resveratrol: properties, uses and market trends

Resveratrol belongs to the polyphenol stilbenes group, concretely being a 3,5,4-trihydroxy-trans-stilbene, with an ethylene bridge in which two phenol groups are bonded. It has an average molecular weight of 228 g/mol, with 14 carbon skeletons (Thirumalaisamy et al., 2022). It has two geometric isomers, *cis*-resveratrol and *trans*-resveratrol, being the *trans* isomer the one associated with its biological functions and properties, and also the dominant geometrical structure (Salehi et al., 2018a, 2018b).

One of the most promising features of resveratrol is its antioxidant properties, which implies potential health benefits (Fraga et al., 2019). The antioxidant effects of resveratrol could be provided by various mechanisms, including its actuation as free radical scavenger (resveratrol donate electrons to superoxide anions, hydroxyl and peroxynitrite radicals, thus stabilizing them and avoiding cell damage), neutralization of reactive oxygen species (ROS), reaction with nitrogen free compounds (RNS) and it could also activate various antioxidant enzymes, as the cases of superoxide dismutase and catalase, which may also help to combat cellular oxidative stress and thus maintain cellular redox balance (Bononi et al., 2022a, 2022b; Heo et al., 2018). The latter case is known as “indirect antioxidant activity” as it could act as a regulator for these enzymes and thus enhancing the body defense system (Truong et al., 2018; Xia et al., 2017). Besides, resveratrol could also chelate metal ions, including iron and copper, which are known as important enhancers of high reactive free radicals by developing Fenton and Haber-Weiss reactions (Aaseth et al., 2021; Salehi et al., 2018a, 2018b). Another antioxidant effect of resveratrol is through the inhibition of lipid peroxidation, which is a chain reaction that also promotes cell damage, and mitochondrial protection in cellular respiration (a source of ROS) (Pinyaev et al., 2019; Gimeno-Mallench et al., 2019).

Apart from the antioxidant properties, resveratrol also stands out for its potential to provide antimicrobial functions (Abedini et al., 2021; Karamese and Dicle, 2022). It has been identified that it has activity against multidrug-resistant Gram-negative bacteria with a minimal inhibitory concentration between 32 μg/mL and 128 μg/mL, following an inhibition action analogous to that of efflux pump inhibitors (Inchingolo et al., 2022; Ma et al., 2018). Given this, resveratrol has the ability to rejuvenate the functionality of antibiotics against bacterial pathogens (Sharma et al., 2019). On the other hand, resveratrol could also induce the expression of antimicrobial peptides (AMPs), which are crucial proteins in the immune system for defense against pathogens and microbial infections (Lan et al., 2017). Besides, it positively modulates gut microbiota, considered as essential for the preservation of a balanced immune system (Wang et al., 2022; Inchingolo et al., 2022) and also it has demonstrated its good combination with other antimicrobial agents, thus enhancing microbial resistance (Liu et al., 2020; Skroza et al., 2019; Vestergaard and Ingmer, 2019). It has been demonstrated that resveratrol has the capacity to inhibit the replication and expression of rhinovirus, the cause of common respiratory diseases, as well as other illness related with high-fat diets, as hepatic steatosis or hyperglycemia, given the efficacy of resveratrol to reduce the amount of glucose, total cholesterol and triglycerides, among others (Su et al., 2022; Mastromarino et al., 2015).

But, it should be taking into account that, even with its benefits, the amount of resveratrol intake could be critic to human and animal organisms Jung et al. (2009).

There are some derivatives of resveratrol with slightly different molecular and functional properties, and mechanisms of action (Thirumalaisamy et al., 2022). Resveratrol can be found in a hydroxylated form (as dihydroxy stilbene) containing higher stilbene proportion and lower amount of hydroxyl groups, which leads to increased water solubility and pharmacological functionality but, at the same time, reduced bio-availability within oral intake (Arbo et al., 2020). It can also be found in a methoxylated structure (as pterostilbene or trimethoxy stilbene), commonly available on berries and grapes, which has enhanced oral absorption and stability, given the addition of a methoxy group on the resveratrol structure (Nagarajan et al., 2022).

On the other hand, to enhance natural resveratrol stability and water solubility, as well as bioavailability and prevention of enzymatic oxidation, the development of a glycosylation reaction has been demonstrated to be effective. It is based on the addition of glycosidic compounds (carbohydrates, such as sugars), commonly glucose, by the formation of an ether bond with the hydroxyl group of the resveratrol compound (Cole and Kramer, 2016; Lin et al., 2021). Another way to increase the bioavailability and water solubility of resveratrol for human intake is through its micro and nanoencapsulation in casein microparticles, as reported by Gani et al. (2022). For this encapsulation, resveratrol is dissolved with casein, phosphate buffer and 95 % ethanol, homogenized and ultrasonicated in periods of 5 min to avoid casein denaturation, ending with a lyophilization of the nanoparticles, which are then ready to be included in the formulation of food, pharmaceutical or cosmetic products (Arora and Jaglan, 2018; Gani et al., 2022). Other less common derivative forms are the aminated/amidated/iminated forms, based on reaction with an amine group, with enhanced antioxidant and neuroprotective properties, and the prenylated derivatives, obtained by the substitution of the hydroxy groups of the resveratrol molecule (Puksasook et al., 2017; Toume et al., 2015).

Regarding resveratrol use on the market value-chain, it is mainly applied for the production of nutraceuticals, cosmetics, pharmaceuticals and for drug formulation. The rationale behind its prominent use in the aforementioned applications is based on its bioactive properties, which are beneficial for preventing cancer, liver diseases, arthritis, oxidative stress, age-related illnesses, and skin-related problems, among others (Sharifi-Rad et al., 2022). Besides, it could also be used to enhance the quality and productivity on the agricultural sector, and thus increasing the food quality, an important value chain for the bioeconomy, as it could degrade some bacteria found on the soil, on the rhizosphere, thus reducing the detrimental effects of the chemicals over the soil properties and nutrients balance (Kurt et al., 2018).

Another important characteristic of resveratrol is that its properties do not alter with increasing storage time of the raw material used for its extraction. This has been the main conclusion reached when analyzing how the concentration of resveratrol varies in vine-related residues (such as shoots) or grapes stored after one, three, and six months, observing that not only its potential is maintained but increases (Cebrián et al., 2017). The rationale behind this fact could be explained given the influence of the environmental issues over the resveratrol content, mainly due to its polygenic trait (Guo et al., 2022). This fact also implies that even the same type of feedstock (e.g., vines or peanuts) could have a different content of resveratrol depending on the cultivated region or on the genotypes. For example, in the case of vines, the *V. labrusca* genotype has a much lower content in comparison to that of *V. vinifera*, and on peanuts, the variation in resveratrol composition could vary in the range of 125–1626 μg/kg of peanut, which is, indeed, a significant variance (Crăciun and Gutt, 2022).

In order to provide the main applications of resveratrol, the following Table 1 is included:

Table 1
Resveratrol applications and descriptions.

Application	Description	Reference
Antioxidant	Reduces oxidative stress	Bononi et al., 2022a, 2022b; Zhang et al., 2021a, 2021b, 2021c
Anti-inflammatory	Resveratrol reduces inflammation by modulating enzymes in order to produce mediators	Chowdhury et al., 2022; Udenigwe et al., 2008
Cardiovascular health	The antioxidant properties also provide increase on cardiovascular health given the decrease of the oxidation of low-density lipoprotein-cholesterol	Bhullar and Udenigwe, 2016; Das and Das, 2010
Neuroprotective functions	It has demonstrated neuroprotective functions to Aβ-related toxicity	Bastianetto et al., 2015
Anti-aging effects	Given the induction of sirtuin expression, as sirtuins are directly related with cellular response to oxidative stress.	Zhang et al., 2021a, 2021b, 2021c; Kaeberlein et al., 2005
Anti-cancer effect	Could promote the inhibit of cancer cell-growth and proliferation by modulating the transduction mechanisms.	Ren et al., 2021; Zhang et al., 2021a, 2021b, 2021c
Metabolic functions	Affect over insulin sensitivity and glucose regulation	Qiu et al., 2019; Liu et al., 2014
Increase skin health	By enhancing collagen synthesis and protecting against UV	Jang et al., 2015; Polonini et al., 2013; Zhang et al., 2012
Increase bone health	Resveratrol could promote osteoblast-mediated bone formation.	Li et al., 2021; Wong et al., 2020
Anti-viral	It has shown antiviral effects over some viruses related with respiratory infections	Van Brummelen and Van Brummelen, 2022; Filardo et al., 2020;
Cognitive function	Reduction on oxidative stress of brain cells enhances the protection of neurodegenerative processes	Tosatti et al., 2022; Zaw et al., 2021
Immune support	It could modulate the immune response of the body by the regulatory cell suppressive functions	Chen and Musa, 2021; Malaguarnera, 2019
Hormone regulation	Resveratrol could balance the hormone levels, mostly with estrogen.	Qasem, 2020; Gehm et al., 1997
Anti-depressant	The anti-inflammatory and neuroprotective effects of resveratrol promote a positive impact on mental well-being.	Chen et al., 2021; Zhu et al., 2019
Anti-hypertensive	It could lower blood pressure caused by hypertension by the production of an endogenous vasodilate, as nitric oxide	Theodotou et al., 2017; Movahed et al., 2016

On the other hand, according to the available reports on resveratrol market insights, it is expected to achieve an annual growth between 6.2 % and 8.4 % until 2031 (Future Market Insights, 2023a; Priya, 2021). The last data about the market size on resveratrol dates to 2022, with an amount of $118.60 million, with a projection to reach $131.0 by 2030 (Future Market Insights, 2023b; Priya, 2021). Another important fact is that there will be a significant difference between production trends between synthetic and natural resveratrol, being the latter the one that is going to increase and penetrate better on the market, and also the one with the highest growth. With respect to the applications of resveratrol, the huge market value is going to be appreciated for nutraceuticals and pharmaceuticals production, while its use on cosmetics will be lower. Considering the global scope of resveratrol, is North America the region with the higher production market, followed by Europe (Priya, 2021).

3. Sources for resveratrol extraction

Various plants, including vegetables, fruits and nuts, are good examples of food products containing resveratrol in their composition. Resveratrol can be found in more than 70 plant species, highlighting its higher composition in grapes (92–1759 mg/g fresh weight), peanuts (around 0.08 μg/g), berries (0.007–5.88 μg/g), apples (400 mg/g), pistachio (0.09–1.67 μg/g) and cocoa (around 1.85 μg/g) (Bolling et al., 2010; Weiskirchen and Weiskirchen, 2016). It is important to mention that the amount of resveratrol available in these biological sources could vary depending on several factors. Factors that could significantly alter the bioavailability of resveratrol are the growing conditions of the plants and vegetables, the processing of the food in manufacturing facilities, and food cooking at home.

Resveratrol has a reduced solubility in water, which affects its bioavailability, so its dissolution and absorption potential are low (Robinson et al., 2015). This implies that the main absorption occurs in the intestine and liver, where it is rapidly converted into primary metabolites (i.e., resveratrol sulfate and glucuronide) that are more easily excreted from the body, thus reducing the potential beneficial health effects (Pannu and Bhatnagar, 2019; Sergides et al., 2016). Another important aspect affecting the availability of resveratrol is the source used for its production, together with the amount of added dose, interaction with other substances (e.g., pharmaceuticals) and interindividual variation among consumers (Liu, 2022).

To give an overview of the amount of resveratrol present in the most common vegetables and food products, as well as it methods for extraction and quantification, Table 2 is provided.

Regarding the extraction technologies used, good recovery yields are attained with different techniques as summarized in Table 3. These techniques will be detailed in the next section.

4. From resources to product: main extraction techniques

There are several methods for obtaining resveratrol, considering its extraction from plants and/or food products with different bioprocessing or chemical reaction schemes. Both conventional methods, such as solvent extraction, or emerging technologies, such as supercritical, microwave-assisted or ultrasound-assisted extraction, could be used as efficient procedures. Each method has its advantages and disadvantages, and the selection of one or the other will vary depending on the quality required, the desired processing time, and/or the type of raw material or resource used. In this context, this section highlights the most used extraction methods, both conventional and emerging, for resveratrol recovery.

4.1. Conventional methods

Conventional extraction technologies have been used for resveratrol recovery from, for example, spruce bark. Diethyl ether was selected as the extraction solvent, with a solid-to-liquid ratio of 1:10, requiring an extraction time of 24 h. Then, as a subsequent step to purify resveratrol, a first washing step with 5 % sodium bicarbonate, elution in dichloromethane and methanol for a first HPLC analysis, followed by re-elution in dichloromethane and ethyl acetate for reverse-phase column chromatography, is necessary. Following this extraction scheme, an amount of 279.9 μg of resveratrol/g spruce bark is obtained, thus achieving a global resveratrol recovery of 84 % (Piyaratne et al., 2022).

Spruce species have also been used as feedstock for analyzing and identifying the best solvent to be used in the extraction of resveratrol compounds. This has been the main goal of Suprun et al. (2021) research, in which methanol, ethanol, ethyl acetate, acetone, hexane, and water were selected for resveratrol extraction (Suprun et al., 2021). Extraction temperatures, process time, and seasonal variation have also been evaluated, looking for the conditions that allow the highest possible extraction yield. The main results obtained showed that methanol is the most advisable solvent not only for resveratrol but also for other stilbene-based compounds (such as astringin, piceid, or piceatannol, among others). As for the operating conditions, 60 °C is the optimum temperature for resveratrol extraction from spruce bark, considering an extraction time of 6 h. Finally, as regards seasonal variation, it has been observed that the concentration of the target compound on the raw material really varies according to the harvesting season, detecting that, for resveratrol, autumn harvesting is the most suitable, whereas, when evaluating all the stilbene compounds, summer is the most recommended (Suprun et al., 2021).

4.2. Emerging methods

Pressurized liquid extraction (PLE) has been used as an extraction method to recover the bioactive compounds available on grapevine shoots. Quercetin and resveratrol are the bio-actives extracted in gross quantity, being its concentrations in the grapevine shoots of 10.6 mg/g and 1.9 mg/g, respectively (Serna-Loaiza et al., 2022). It should be mentioned that quercetin is available mostly in the leaves, while resveratrol is mostly present in the stem part of the grapevine shoots, thus both could be obtained separately. The best results of extraction correspond to the following conditions: 75 °C and 50 vol% of ethanol, 30 min, and a solid load of 1:11 *w*/w. Considering these conditions, the extraction yield of resveratrol amounts to 1.90 mg/g dry matter of grapevine shoots, while for the case of quercetin the yield increases to 10.69 mg/g (Serna-Loaiza et al., 2022). Furthermore, the highest antioxidant capacity is obtained, thus increasing the quality of resveratrol and quercetin. On the other hand, a liquid hot water treatment could be applied to separate sulfur-free lignin from the cellulosic and hemicellulosic fractions of the grapevine shoots which could be used as a source of fermentable sugars, being a more efficient process scheme that valorizes completely the feedstock used (Serna-Loaiza et al., 2022).

Another emerging green extraction technology that is considered for the extraction of stilbenes, such as resveratrol, is subcritical water extraction (SWE), requiring processing temperatures between 100 °C and 374 °C. The main advantage of this extraction alternative is that water at high temperature and pressure, acquires a dielectric constant similar to that of organic solvents, thus being able to extract the resveratrol within the same yield as the one achieved by ethanol. Vine pruning residue has been shown to be a relevant resveratrol source (Jesus et al., 2019, 2020). Jovanović Galović et al. (2022) have used SWE to extract *trans*-resveratrol from pruning waste of *V. vinifera* (vineyards) (Jesus et al., 2019), according to the following conditions: 200 °C, 30 bar, 18.27 min, addition of 1.55 of HCl, and a solid to liquid ratio of 1:10 g/mL (Jovanović Galović et al., 2022). Subsequently, a liquid extract was obtained with a flavonoid content of 2.91 g/100 g (dry weight, DW) and a phenolic content of 10.67 g/100 g (DW), with an amount of resveratrol extracted of 296.98 μg/100 mL of extract (Jovanović Galović et al., 2022).

Deep eutectic solvents have also been used as a green method for the extraction of resveratrol from different plant species, as Melinjo (*Gnetum gnemon* L.), a Gymnospermae with a promising composition of resveratrol. For the extraction, a NADES (natural deep eutectic solvent) has been prepared, for which various components are used: betaine:urea (1:11), betaine:lactic acid (1:1) and betaine:malic acid (1:1), 90 °C, 500 rpm and 90 min processing time. Afterward, the NADES is added to the Melinjo seed powder and ultrasound assisted extraction (UAE) is applied, with a solvent (water) to solid ratio of 1:10. Considering these aspects, the yield on resveratrol extraction amounts to 0.227 mg/g of powder, which is almost 50 % higher than using betaine-urea as extraction solvent and 70 % when using betaine-malic acid, which demonstrates the effectiveness of using NADES for the extraction of resveratrol (Aryati et al., 2020). A similar extraction procedure has been developed by Wang et al. (2021a, 2021b, 2021c), but using *Polygonum cuspidatum*, a Polygonaceae plant species, and using hydrogen bond donors for the formulation of the NADES, using glycerol and choline chloride/oxalic acid in a molar ratio of 1:1 and 75 °C. Afterward, NADES is mixed with *P. cuspidatum* powder in a ratio of 20 mg:1 mL and ultrasonicated for 80 min, prior to obtaining the final resveratrol product, within an extraction yield of 8.03 mg/g (Wang et al., 2021a, 2021b, 2021c). Chen et al. (2018a, 2018b) combined NADES with UAE for the extraction of resveratrol from peanut roots. The NADES is formulated considering choline chloride and 1.4-butanediol in a ratio of 1:3 g:g, requiring 55 °C, 40 min and a solid to liquid ratio of 1:30 g:mL. The UAE procedure requires energy (40 kHz and 400 W) to achieve a

Table 2
Resveratrol amount, extraction or quantification method and important features on bibliographic references about resveratrol.

Source	Technique used	Resveratrol amount	Other information	Reference
	Homogenization + HPLC	1.87 ± 0.64 mg/g	Digestibility: 52.45 ± 3.48	(Lee et al., 2020)
	Water extraction + HPLC	1.47 ± 0.26 mg/g	Digestibility: 51.08 ± 5.54	(Lee et al., 2020)
	Ethanol extraction + HPLC	1.97 ± 0.71 mg/g	Digestibility: 49.54 ± 3.47	(Lee et al., 2020)
Grapes	Freeze drying + HPLC	7.93 ± 2.05 μg/g	Red globe grape variety is the one with the higher resveratrol content	(Wijekoon et al., 2022)
	Ethanol extraction + HPLC	4.74 ± 3.57 mg/L	Variability on content considering from July to September, being July the month in which the grapes have higher content	(Căpruciu et al., 2022)
	Enzymatic hydrolysis with glycosidase and reverse-phase solid extraction	1.7 ± 1.3 mg/L	Variations on the concentration of resveratrol in function of the ripening stages, being 20°Brix the one presenting the highest content	(Genovese et al., 2021)
	Solid phase micro extraction	3.78 ± 1.79 mg/L	The average recovery obtained is 99.4 %	(Aresta et al., 2018)
	HPLC	0.1–0.7 mg/L	Resveratrol content in red wine improve insulin resistance and phosphorylation	(Brasnyó et al., 2011; Castaldo et al., 2019)
Red wine	HPLC	3.0 ± 0.6 mg/kg	*Negroamaro* red wine type (Salento)	(Ragusa et al., 2019)
	HPLC	2.4 ± 0.4 mg/kg	*Primitivo* red wine type (Salento)	(Ragusa et al., 2019)
	Reverse-phase HPLC	10.7 ± 7.0 mg/L	Decrease on an average of 76 % the resveratrol concentration during storage and wine ageing	(Naiker et al., 2020)
Red wine	Homogenization, liquid-liquid microextraction and disperse solid-phase extraction	8–322 μg/L	Resveratrol content analysis of wines from local markets, detected in 4 out of 6	(Lu et al., 2018)
	Solid phase micro extraction	0.74 ± 0.22 mg/L	The average recovery obtained is 94.9 %	(Aresta et al., 2018)
	Ultraviolet- C radiation and colorimetric analysis	CP:0.53 ± 0.06** OP:0.40 ± 0.05** CP-UV:0.50 ± 0.10** OP-UV:0.45 ± 0.05**	Comparison of traditional and organic productions, as well as UV post-treatment on resveratrol concentration (**mg/mL)	(Pinto et al., 2022)
Grape juice	Liquid-liquid[1], ultrasound[2] and microwave assisted extraction[3]	0.94 ± 0.06 mg/kg[1], ND[2], 7.59 ± 0.49 mg/kg[3]	For conventional liquid-liquid extraction resveratrol is only detected with ethanol, and for MAE also with ethyl acetate, but 7 times lower in comparison with ethanol solvent	(Pezzini et al., 2019)
	Folin – Ciocalteu colorimetric method	0.01 mg/ 100 g DW – 0.58 mg/100 g DW	Grape juice coming from red wine is the one with highest resveratrol content, and the one coming from white wine has the lowest resveratrol content	(Guler et al., 2022)
	Homogenization with HCl and methanol, and HPLC analysis	18.62 mg/kg	54 % of the antioxidant activity of raisins is coming from the content on resveratrol	(Roychev et al., 2020)
Raisins	HPLC	1.08 ± 0.17 mg/kg[4] and 0.40 ± 0.04 mg/kg[5]	Change on resveratrol content by raisins pre-treated with olive oil[4] and not-pre-treated with olive oil[5].	(Olivati et al., 2019)
	HPLC	236.4 ± 7.5 μg/g – 269.9 ± 5.7 μg/g	The variety of blueberry implies different resveratrol concentration, and its degradation is increased when exposed to light at room temperature	(Shanmuganathan and Li, 2009)
	HPLC	0.12 mg/100 g	DPPH radical scavenging activity increases with the increase in resveratrol content	(Song et al., 2014)
Berries	Oleogel systems of soybean and peanut oil containing blueberry extract	0.001–0.063 mg/ 100 g	Best inhibition rate for oxidation products achieved with soybean oleogel	(Qiu et al., 2021)
	Ultrasound extraction with methanol as solvent	38.13 ± 0.27 μg/100 g dry matter	The blueberry variety of "Windsor" is the one with higher resveratrol content, followed by "Millennia" variety	(Varo et al., 2021)
	HPLC with[6] and without[7] ultraviolet treatment	2.43 mg/g[6] and 7.53 mg/g[7] dry weight	Content of resveratrol on blueberry leaves, the UV irradiation increases the content of resveratrol	(Kim et al., 2020)
	Extraction with 80 % acetone and dissolution with formic acid and methanol, HPLC	830.5 ± 20.6 ng/ g of dry weight	The concentration of resveratrol increases with maturation, with compost cultivation treatment and with enriched CO_2 environment	(Wang et al., 2007)
	Botrytis inoculates to treat cocoa beans and treatment with UV light	7.0 g/g	Enhancement of resveratrol content by modifying the treatment of the cocoa beans for the production of related products	(Hurst et al., 2009)
	Extraction with ethanol/water for 10 min and 60 °C, analysis with HPLC	0.4 mg/kg in dark chocolate and 0.5 mg/kg in cocoa liquor	The antioxidant activity of cocoa and chocolate is more related to the procyanidin content than the composition of stilbenes	(Counet et al., 2006)
Cocoa & chocolate	Extraction with hexane, hydrolyzation with methanol/water acidified solution and rotatory evaporation before HPLC analysis	1.85 ± 0.43 g/ g in cocoa powder, 0.35 ± 0.08 g/g in dark chocolate, 0.10 ± 0.05 g/g in milk chocolate	The content of resveratrol on cocoa-related products varies according to the type of chocolate, the processing of the final product and the amount of contained sugar	(Hurst et al., 2008)
	Industrial processing of chocolate for producing cocoa-related products	11.4 g/kg before fermentation and roasting and 9.8 g/kg after fermentation and roasting	Fermentation and roasting processing stages imply a not significant reduction in the resveratrol content of cocoa-related products	(Salvador et al., 2019)
Peanut	Ultrasonic and magnetic stirring-assisted dissolution	175.51 mg/kg peanut oil	The resveratrol content of peanut oil helps to preserve its organoleptic and antioxidant properties, prolongs its shelf-life for 2 folds and improves its thermal stability.	(Li et al., 2022)
	Ultrasonic treatment and phenylalanine addition during peanut germination	36.99 g/g dry weight	The content of resveratrol by developing this alternative germination process increases 9.4 times	(Yu et al., 2016)
Peanut	Various methods for drying peanuts for further resveratrol extraction: hot-air drying, infrared radiation and microwave-freeze-drying	33.5 % of resveratrol extracted using infrared radiation and 40.9 % using microwave	The huge energy consumption of microwave-freeze-drying does not compensate the increased extraction capacity, being the infrared radiation the preferred drying method	(Zhu et al., 2022)

[*] CP: Conventional production, OP: organic production, UV: ultraviolet.

Table 3
Extraction technologies for resveratrol recovery. Acronyms: PLE (Pressurized Liquid Extraction), SFE (Supercritical Fluid Extraction), SWE (Supercritical Water Extraction), DES (Deep Eutectic Solvents), NADES (Natural Deep Eutectic Solvents), UAE (Ultrasound Assisted Extraction).

Method	Product(s)	Resource	Operation conditions	Recovery/yield	Reference
PLE	Resveratrol (RES) and ellagic acid (EA)	Blueberries	1500 psi 40 °C Methanol	91.85 % EA and 84.97 % RES	Seyhan et al., 2023
PLE	Trans-resveratrol	Grapes	40 atm 5 min 150 °C Water	2.33 mg trans-RES /kg grapes, 94.5 % trans-RES	Piñeiro et al., 2006
PLE	Resveratrol	Grape seeds	1.02 MPa 152 °C 25 min Ethanol 1:15 g/mL	91.98 %	Tian et al., 2017a, 2017b
High pressure and high temperature stirred reactor	Polyphenols	Grape skins	150 °C 270 min Methanol 1:5	45.4 mg /100 g DS	Casazza et al., 2012
SFE	Resveratrol	Grape skin	110 bar 40 °C 7.5 % ethane 15 min	100 %	Pascual-Marti et al., 2001
SWE	Resveratrol	Bark	190 °C and 3 mL/min water flowrate	23.18 μg/g dry weight	Chainukool et al., 2014
SWE	Resveratrol	Grapevine	160 °C 5 min 10 MPa	1.95 g/kg dry mass	Gabaston et al., 2018
DES	Resveratrol	*Polygonum cuspidatum*	80 °C 80 min 60 % v/v DES 4.5 % g/v HCl 40:1 g/mL	96.3 %	Sun et al., 2021
NADES (choline chloride/oxalic acid)	Resveratrol	*Polygonum cuspidatum*	1:50 75 °C 80 min 250 W ultrasonic powder	12.31 mg/g	Wang et al., 2021a, 2021b, 2021c
DES + UAE	Resveratrol	Peanut roots	1:3 g water:g DES 55 °C 40 min 1:30 g/mL	88.19 %	Chen et al., 2018a, 2018b
Maceration	Resveratrol	*Arachis repens*	1:40 g: mL methanol 30 min 25 °C 1 h	1.02 mg/L	Garcia et al., 2016
Solvent extraction	Resveratrol and its glycoside	Knotweed	35 °C 0.79 MPa 5 h Water	0.34 mg/g	Kanda et al., 2021
Solvent extraction	Resveratrol	Grape skin	Ethanol or methanol as solvent 1 h 1:10 80 °C 400 rpm stirring	72.4 mg/L MeOH and 71.3 mg/L EtOH, 82 % purity recovery	TRIFOI and ANCUTA, 2019
Solid-liquid extraction	Resveratrol and other phenolics	Milled grape canes	Ethanol/water (80:20 v/v) 30 min 83.6 °C 103.6 mg/L solvent to solid ratio	4.25 mg /g dw	Karacabey and Mazza, 2008
Solvent extraction	Trans-resveratrol	Vine pruning waste	4:1 ethanol:diethyl ether 1 g: 35 mL solid to liquid ratio 96 h 25 °C	174.14 mg/kg dw	Crăciun and Gutt, 2023
Liquid extraction	Resveratrol	*Polygonum cuspidatum*	2/3 v/v water/organic mixture 5 h 45 °C	81.10 %	Wang et al., 2021a, 2021b, 2021c

resveratrol extraction yield of 38.91 mg of resveratrol per kg of peanut roots used (Chen et al., 2018a, 2018b).

5. Resveratrol production

5.1. Chemical synthesis

The synthesis of resveratrol can be achieved following different reaction schemes (Tian and Liu, 2020). The Heck-reaction is one the most widely used, consisting of a heterogeneous catalytic reaction in which a C-C cross-coupling is developed between a halide compound and an activated oleofin (Andrus et al., 2003; Klotter and Studer, 2014). Other common alternatives are the Perkin-reaction, characterized by the synthesis of unsaturated aromatic acids through the condensation of aromatic anhydrides and aldehydes (de Lima et al., 2009; Grau et al., 2023), and the Wittig-reaction, which comprises an oleofin production by the reaction between an aldehyde or a ketone with a primary or secondary alkyl halide (Chalal et al., 2012; Kang et al., 2009). Several studies also recurred to the Horner-Wadsworth-Emmons reaction, an organic reaction based on the reaction of a carbanion phosphate and an aldehyde or ketone (Gester et al., 2005; Khan et al., 2017). However, biosynthesis could be considered as an alternative more sustainable scheme.

5.2. Microbial synthesis

Another valuable option that has attracted increasing interest among researchers is the microbial production of resveratrol. This has advantages over microbial-mediated conversion mainly due to the availability and cost of the resveratrol precursor. One example of such a process is the use of the bacteria *Bacillus safensis* to convert polydatin, a glucoside derivative of resveratrol, efficiently and rapidly to resveratrol, reaching a yield of 93.1 % in 8 h and 37 °C (Hu et al., 2019). Regarding resveratrol production, *Escherichia coli* and *Corynebacterium glutamicum* are, among bacteria, two of the most widely used hosts (Hong et al., 2020; Braga et al., 2018), while *Yarrowia lipolytica, Scheffersomyces stipitis,* and *Saccharomyces cerevisiae* are the most reported yeasts (Costa et al., 2021, 2022b; Kobayashi et al., 2021a, 2021b). Some strategies to increase the yield on resveratrol encompass protein engineering and mutagenesis of the microorganisms, increasing the overall efficiency and feasibility of the resveratrol production process.

5.2.1. Genetically modified strains

Genetically engineered strains have been developed to enable the capacity of producing resveratrol. The first reports on the biotechnological production of resveratrol relied on the supply of the expensive precursor *p*-coumaric acid, which hindered the feasibility of the biotechnological production of resveratrol (Beekwilder et al., 2006). Since then, many developments were accomplished and, in the last decade, several studies on *de novo* resveratrol production from carbon sources were reported. The production of resveratrol from cheap and simple carbon sources, such as glucose or ethanol, by fed-batch fermentation has been proposed (100 h) and *S. cerevisiae* as a strain, achieving 415.65 mg/L of resveratrol from glucose and 531.41 mg/L from ethanol, being 5.7 and 3.1-fold higher compared to batch cultivation (Li et al., 2015). In fact, resveratrol production by fed-batch fermentation strategies has often been explored. In another study using a recombinant strain of *S. cerevisiae*, an initial concentration of 20 g/L glucose was used, with a subsequent feeding of 3 g/L/h, leading to a significant increase in resveratrol titers up to a final concentration of 4.1 ± 0.2 g/L (Meng et al., 2023a, 2023b).

While most of the researchers focus on using glucose as a carbon source, given the extensive number of feedstocks that could be used as a source of fermentable sugars, other carbon sources have also been explored to produce resveratrol. Park et al. (2021) engineered an *E. coli* strain with the ability to produce 80.4 mg/L of resveratrol using glycerol as a carbon source. *S. stipitis*, which is capable of naturally metabolizing various carbon sources, has been used to produce resveratrol from carbon sources such as glucose, fructose, galactose, xylose, maltose, and the disaccharides cellobiose and sucrose, reaching a maximum concentration of 668.6 mg/L from 50 g/L of sucrose (Kobayashi et al., 2021a, 2021b). Costa et al. (2022a, 2022b) have reported the production of resveratrol from lactose and xylose using recombinant *S. cerevisiae* strains, achieving titers of 210 mg/L and 223.8 mg/L of resveratrol, respectively. A maximum titer of 388 mg/L of resveratrol was achieved when combining xylose (10 g/L) and glucose (50 g/L) in batch fermentation. The authors reported the valorization of different agro-industrial residues such as cheese whey (source of lactose) or vine pruning residue hydrolysate (source of xylose and glucose) as substrates for resveratrol production (Costa et al., 2022a, 2022b; Kobayashi et al., 2021a, 2021b).

5.2.2. Co-culture production processes

Other authors have also developed co-culture processes in order to enhance resveratrol production. Yuan et al. (2020) have developed a co-culture of *E. coli* and *S. cerevisiae*, based on an upstream process in which *E. coli* can excrete *p*-coumaric acid for being used in the downstream module, in which *S. cerevisiae* is placed, with the function of converting *p*-coumaric acid into resveratrol. In this strategy, both upstream and downstream modules are fed with glucose as a carbon source of fermentable sugars (Yuan et al., 2020). Considering this co-culture, using an inoculation ratio of 1:1, 33.5 °C, and a process time of 72 h, the maximum amount of resveratrol obtained was 36 mg/L, representing a productivity of 0.25 mg/L/h. Hong et al. (2020) reported a co-culture strategy using glucose as carbon source (20 g/L) and a single type microorganism, dividing this metabolic pathway in two *E. coli* strains. This co-culture was able to produce 55.7 mg/L of resveratrol after 30 h (Hong et al., 2020).

6. Examples of proposed biorefinery schemes

The increase on the demands of agroindustrial-based products have ended on an intense production of waste streams, that, if not properly managed at the end of the value chain, could entail significant effects over the sustainability of the value chains. In this context, the enhancement and penetration of integrated biorefineries could promote eco-friendly and economically profitable production chains (De Corato et al., 2018). Resveratrol could be part of this transition on the implementation of integrated biorefineries, given the possibility of extracting or bioproducing it from waste resources with high carbon (sugar) composition. To this end, some examples of valorization scenarios are presented in this section. It should be noted that the later scenarios only include the section necessary for the extraction of resveratrol, which is included as another stage of the production process, i.e., in the wine production process, the grape pomace stream is valorized for the recovery of resveratrol. The idea of this section is to give a broader view of how the integration of waste streams to resveratrol production could help in the development of cascade biorefinery approaches, thus promoting the integral use of available resources.

6.1. Scenario I. Winery biorefinery

The first stage of the winemaking process consists of destemming, in which the stems are removed from the grapes, thus being cataloged as the first waste stream obtained in the winemaking process with a significant concentration of resveratrol (0.08–5 mg/L) (Anastasiadi et al., 2012). This side stream could be considered as a potential bio-resource and two alternatives have been considered for providing an example of a biorefinery approach in the winery sector, depicted on Fig. 1.

One conventional extraction technique and one emerging technology have been proposed, concretely maceration and pressurized liquid extraction (PLE). Both alternatives require a pre-treatment to dry the stems and reduce their size through a crushing stage, before passing thoroughly to the extraction stage. In the case of maceration, a solid/liquid ratio of 1:100 *w/v* is required, using ethanol at 50 % as solvent. One of the main drawbacks in performing maceration is the extraction time required (24 h), somewhat decreasing the resveratrol productivity. Considering these operation conditions, and a constant temperature of 40 °C, the recovery of resveratrol amounts to 0.88 mg/g extract (Quero et al., 2021). In the case of opting for PLE, the solvent required is barely

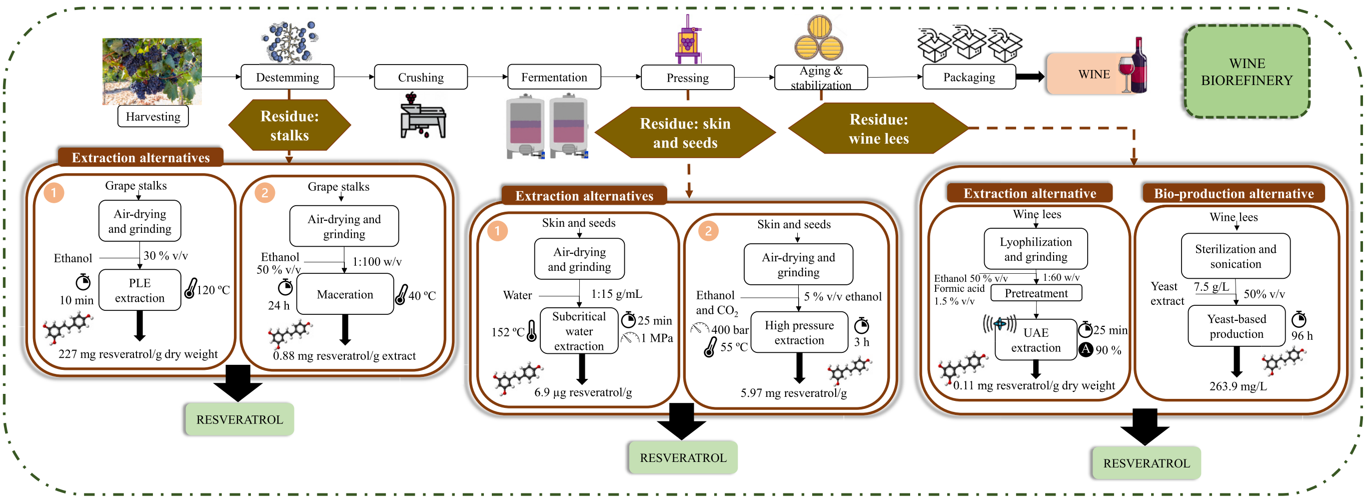

Fig. 1. Biorefinery alternatives for the valorization of wine production side-streams to resveratrol.

the same, considering in this case a ratio of 30 % *v*/v. The main difference observed on the extraction conditions relies on the extraction time (only 10 min), and on the temperature, which is significantly higher (120 °C). The amount of resveratrol obtained by the development of the PLE method is 227 mg/g of stalks (DW) going through the extraction reactor, thus being a potential valorization route for the residual stalks (Nieto et al., 2020).

Grape skins and pips are another by-product obtained in the industrial production of wine, with 120 kg of this waste stream being obtained per ton of grapes (Marqués et al., 2013; Rodrigues et al., 2022). Given this large amount of residual secondary flow produced, the recovery of the available bioactive compounds, such as resveratrol, could be considered as a viable and an appropriate strategy in search of a more sustainable wine production. In this regard, two main alternatives for resveratrol extraction have been included in Fig. 1.

One possible route for extracting the resveratrol from grape skin and seeds is through conventional extraction, using as solvent a mixture of methanol/HCl, requiring 30 min of process time, to be afterward centrifuged and filtered for further purification. Another alternative is an extraction procedure at high pressure, using as CO_2 and ethanol as solvents, requiring 400 bar and 55 °C. The main difference between both extraction technologies relies on the extraction yields and the concentration of resveratrol in the extract. While for the conventional extraction a yield of 0.9 mg resveratrol/100 g of dry sample and a concentration of 8.82 mg resveratrol/g extracted is obtained, by using a high pressurization system the yield increases to 19.2 mg resveratrol/100 g of dry sample and the concentration to 5.97 mg resveratrol/g extracted, thus enable a more efficient production process to be further scaled-up (Casas et al., 2010).

A similar result has been obtained by Monari et al. (2020), who also chose to compare a solvent extraction, in this case with ethanol, and a pressurized liquid extraction, with the latter showing a higher extraction yield. Another more emerging technology is the supercritical water extraction, requiring firstly an air drying and grinding pretreatment of the seeds and grape skin. It consists of a high pressure and temperature extraction procedure, amounting to 1 MPa and 152 °C, respectively, with a solid-to-liquid ratio of 1:15 g/mL, requiring an extraction time of 25 min. Bearing in mind these operation conditions, a total of 6.9 μg resveratrol/g extract was obtained, which is a lower quantity in comparison with the high pressure and temperature extraction method, though the process time is lower. Considering an analogous time for extraction, the total quantity of resveratrol that could be potentially extracted is 49.6 μg resveratrol/g (Tian et al., 2017a, 2017b).

Finally, the third residual stream obtained is the result of the aging and wine stabilization stage, being known as the wine lees, concretely defined by the EEC regulation No. 337/79 as "residue formed at the bottom of wine containers after fermentation, during storage or after treatments, as well as the one obtained after filtration or centrifugation of wine". The wine aging is the main stage of wine manufacturing responsible for the production of these residual streams and, in fact, this is a traditional technique that improves the quality of wines, as its lees are able to enhance the structure and color stability of the wine products (Jara-Palacios, 2019). Two strategies have been considered, the first one based on the extraction of resveratrol, and the second one based on the production of the resveratrol using a recombinant *S. cerevisiae* strain (Fig. 1).

Regarding the extraction procedure, the ultrasonic assisted extraction requires a pretreatment of the wine lees with ethanol 50 % (*v*/*v*) and formic acid 1.55 % (v/v) in order to enhance the productivity of the extraction stage and considering a solid to liquid ratio of 1:60 (*w*/*v*). Afterward, the pretreated wine lees undergo the extraction stage, requiring a ultrasonic power of 400 W and an amplitude of 90 %, for an extraction time of 25 min, to obtain a yield on resveratrol that amounts to 0.11 mg/g dry weight of wine lees (Dujmić et al., 2020). On the other hand, by considering a bioproduction process, sterilization and sonication of wine lees is required as pretreatment stage before introducing them into the fermenter. The concentration of yeast extract required for the fermentation process is 7.5 g/L, and the wine lees are dissolved in the fermentation media to achieve a concentration value of 50 % (*v*/*v*). After 96 h of fermentation time, the quantity of resveratrol obtained amounts to 263.9 mg/L, which could be considered as a potential alternative for resveratrol production, partly due to the avoidance of polluting solvents and the use of renewable biological resources for resveratrol production (Costa et al., 2022a).

6.2. Scenario II. Peanut skin biorefinery

Peanut skin is a by-product obtained from peanut processing, with a global average production of 46 million tons annually, and, for the moment, is a scarcely explored source of antioxidants of biological origin (Putra et al., 2023). Its commercialization in the market is not foreseen at the moment, given its high tannin content and low caloric level (Lorenzo et al., 2018). On the other hand, their high level of antioxidants and other bioactive compounds opens up a possibility for their valorization through recovery extraction processes (Sorita et al., 2020). One of the most commercialized products from peanuts, apart from its natural and roasted form, is peanut butter. For this section, a simple biorefinery flowchart is provided in the framework of integrating resveratrol recovery into the peanut butter processing line (Fig. 2).

Jin et al. (2020) have developed an extraction of resveratrol by the

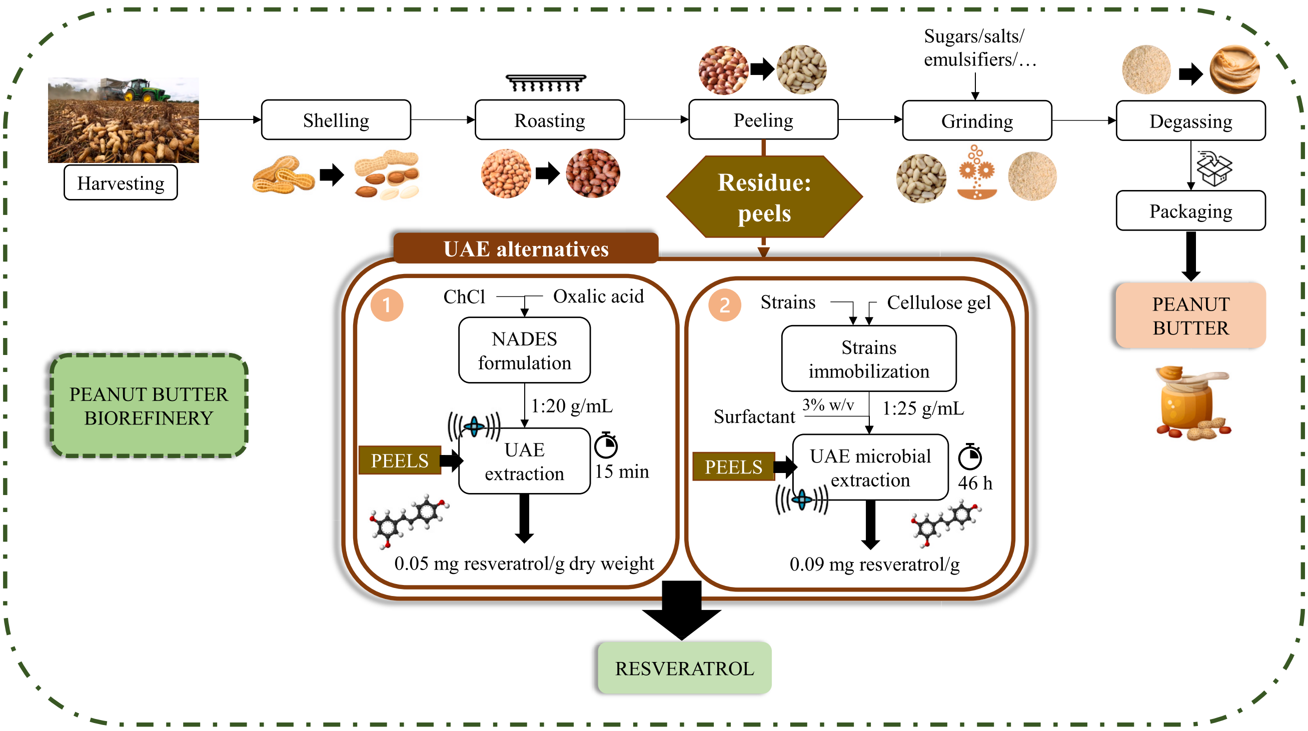

Fig. 2. Biorefinery alternative of peanut processing considering resveratrol extraction from peanut peels.

combination of ultrasound-assisted surfactant extraction and microbial immobilization using cellulose. A combined consortium of yeast and *Aspergillus* sp., namely, *Aspergillus oryzae* and *Aspergillus niger,* has been considered the best microbial combination to enhance the recovery of resveratrol from peanut skin wastes. In order to immobilize the microbial cells, a cellulose gel was prepared using sterile cotton, water, NaOH and urea, requiring soaking for 2 h at −20 °C, to be subsequently sterilized for use in the extraction step. Additionally, it is also necessary to add a surfactant, as it helps to maintain the stability of the enzyme, thus helping to achieve a higher extraction yield. In this case, the use of Triton X-114 is the one preferred, with a concentration of 3 % (*w/v*), a nonionic surfactant, non-toxic and cheap, leading to an extraction yield of 96.58 μg/g. Regarding the extraction conditions, a temperature of 30 °C, an ultrasonic power of 250 W, a ratio of 25:1 mL/g, and a process time of 36 h are the optimal conditions for achieving the highest amount of resveratrol (96.58 μg/g), which is 4-fold higher when compared to a traditional extraction method (Jin et al., 2020).

Syahdi et al. (2020) have used NADES in combination with ultrasound-assisted extraction (UAE) or microwave-assisted extraction (MAE) to obtain resveratrol, in order to compare the yields obtained with a conventional extraction technique, such as maceration, which requires a larger amount of solvent and a longer extraction time (Syahdi et al., 2020). Regarding the model of extraction used, the MAE requires the addition of 70 % ethanol as solvent, a processing time of 12 h at 23 °C, and a microwave power that amounts to 270 W. In the case of UAE, the NADES is prepared using choline chloride and oxalic acid, in a molar ratio of 1:1, as it is the combination that promotes the higher resveratrol extraction, and is used as the solvent for UAE, considering a solid to NADES ratio of 1:20 (g:mL) and 15 min of process time. By assessing those alternatives, the use of UAE combined with NADES is the one achieving a higher extraction of resveratrol of 0.049 mg/g dry weight (0.011 mg/g DW), but when compared to the conventional extraction method by maceration, the yield is significantly lower, reaching a total of 0.221 mg/g (DW). However, taking into account that maceration requires an extraction time of 24 h, the total amount of resveratrol produced amounts to 4.70 mg, being thus significantly higher (Syahdi et al., 2020). Therefore, it can be concluded that UAE-NADES is an efficient and more sustainable technology for the recovery of resveratrol from peanut skin waste and is a potential alternative to be integrated in a biorefinery.

<Fig. 2 to be included here>

6.3. Scenario III. Wood bark biorefinery

The commercialization and production of wood-based products, such as wood panels or furniture, has increased intensively in the last decades (Arias et al., 2022). The main residual stream obtained from the production process is the bark, as debarking is one of the first stages required for wood-based panels and related wood products, including the pulp and paper industries. In this regard, it is estimated that millions of cubic meters of bark are annually managed as residues (Gomes et al., 2021). The valorization strategies of these waste streams are usually based on energy production, through their combustion, but prior to this end-of-life management strategy, the extraction of the valuable compounds could be considered in the arena of circular economy (Andersone et al., 2018). Given its composition on resveratrol, wood bark could be considered as a potential bio-based resource for the development of an integrated biorefinery producing resveratrol as a side-product (Fig. 3). In addition, this extraction could be integrated with the simultaneous valorization of the remaining bark to biofuels (Romaní et al., 2019).

Regarding the extraction alternatives for resveratrol recovery, Ferreira-Santos et al. (2020) have considered developing a conventional solid-to-liquid extraction to extract the phenolic compounds available in the bark, including resveratrol (Ferreira-Santos et al., 2020). The extraction conditions require 115 min of process time, 82 °C and with a solid-to-liquid ratio of 0.15 g/mL, using ethanol 70 % (*v/v*) as solvent, thus obtaining a concentration of resveratrol that amounts to 18.9 mg/L (Ferreira-Santos et al., 2020). Jyske et al. (2022) have reported the extraction of resveratrol from spruce bark by developing a conventional hot extraction method, based on using a solution of acetone:water 95:5 (v/v) as solvent, with a concentration of 0.2 mg/L, in an ultrasonic batch for 30 min, thus obtaining a concentration of resveratrol that amounts to 22 mg/g of dry weight (Jyske et al., 2022).

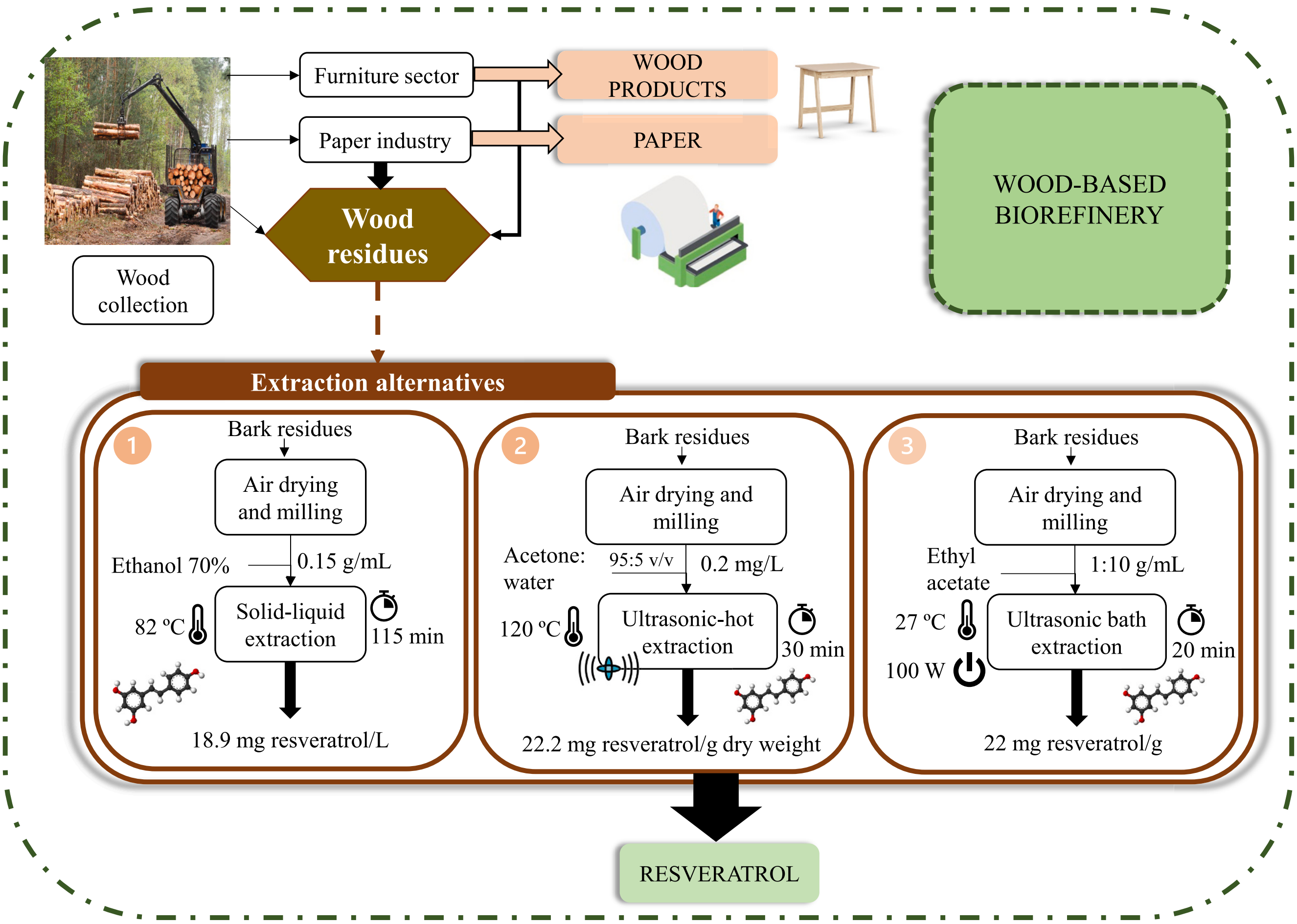

Fig. 3. Biorefinery alternative for resveratrol extraction from wood-bark residues.

Another possible alternative is considering an ultrasonic bath extraction (100 W), using as solvent ethyl acetate in a solid-to-liquid ratio of 1:10 g/mL for an extraction period of 20 min and 27 °C. Considering all these conditions, a total recovery of 22 mg resveratrol/g of extract could be obtained (Pinheiro et al., 2022).

7. How could resveratrol production support sustainable development and circular economy?

The extraction and production of resveratrol could certainly help and contribute to more circular and sustainable production schemes, by reducing waste, thus minimizing environmental impacts, improving recovery strategies, and thus promoting resource efficiency, by improving the use of alternative technologies and process schemes for its formulation or extraction, and also by its use in consumers' daily lives, thus endorsing the consumption of natural and sustainable products (Sirohi et al., 2020). Some examples of how resveratrol could be embedded in more sustainable and circular practices are described and discussed below:

(1) The antimicrobial properties of resveratrol could be useful for the development of biodegradable active packaging for preserving food and beverages, thus extending the shelf life of products by avoiding the use of synthetic preservatives, that has been demonstrated that could vary the organoleptic properties of the food products and thus reducing its quality. In this regard, a double benefit could be obtained, firstly given the promotion of a natural-based preservation agent and, secondly, avoidance of the use of plastic packaging that entails significant environmental and waste management problematic issues.

There are different methods to incorporate resveratrol into a biodegradable packaging. In the research report developed by Huang et al. (2021), a low methoxyl pectin composite films were activated by incorporating resveratrol in a fish gelatin, previously dissolved by using ethanol, with a composition of 0.05 % (*w/v*) to be afterward used for fatty food packaging. The results obtained show that the composite film composition is adequate to favor the resveratrol release for the preservation of the packaged food and its encapsulation on the fish gelatin facilitates its slow release from the films, thus favoring an increase on the shelf life of the food being stored (Huang et al., 2021). Another strategy has been developed by Busolo and Lagaron (2015), through the development of an active low-density polyethylene composite in which the resveratrol is immobilized in a polymeric matrix, with the ability to migrate from the film to the stored food in a level of 0.01 mg/kg.

Apart from polyethylene-based films, also polypropylene packaging has been used to incorporate resveratrol. Glaser et al. (2019) incorporated resveratrol in chitosan nanoparticles, providing a reduction of 90 % in the proliferation of *Staphylococcus aureus* and of 77 % in *E. coli* in comparison to the inactive packaging films, and also an increase over 10-fold on the antioxidant activity of the stored food was obtained, thus increasing its quality and health functions (Glaser et al., 2019). Chitosan nanoparticles have also been used by Abdalbeygi et al. (2022) to evaluate how integrating resveratrol could be beneficial for chicken meat packaging films, achieving also better results in comparison to a common food packaging, in both antioxidant, preservative, and microbial quality.

(2) Since most resveratrol is obtained from agricultural and forestry residues, such as prunings, bark, peanut shells, and grape pomace, among others, its recovery leads to a more efficient waste management and the promotion of sustainable agricultural practices, reducing waste and maximizing the use of resources (Aliaño-González et al., 2022; Martins et al., 2023; Michalaki et al., 2022; Mir-Cerdà et al., 2023).

(3) In the scope of farming activities, resveratrol could be used as an antioxidant and anti-inflammatory natural product for animal feeding. In this sense, a more sustainable livestock farming is also achieved, since the use of synthetically produced antibiotics is avoided in order to preserve the health of livestock (Alagawany et al., 2015; Yeung et al., 2019).

(4) The presence of resveratrol not only promotes soil health and avoids the extensive use of chemical and synthetic fertilizers, but also reduces irrigation needs by reducing water losses in the soil (Rätsep et al., 2021). Santos Wagner et al. (2022) has demonstrated that the use of resveratrol as natural crop protector and growth promoter is beneficial for the stimulation of vegetables growth, as lettuce, as it aids to increase the photosynthesis efficiency and the content on some metabolites (as galactose, nucleotides, amino acids, etc.) that contribute to diminish the presence of free radicals, thus reducing the oxidative damage and promoting a more efficient rate of growth (Santos Wagner et al., 2022).

(5) The production or extraction of resveratrol from natural resources promotes the reduction of dependence on synthetic products, its bioactive properties are suitable for use in the development of health supplements and everyday products that could contribute to the reduction of health costs, environmental burdens and improved well-being (De Luca et al., 2022; Pereira et al., 2022).

8. Main conclusions and future challenges

Although resveratrol production and extraction routes from bio-based resources and waste streams appear promising, it is important to evaluate them from a critical point of view, including sensitivity analyses around environmental and techno-economic variables. So far, no life cycle assessment (LCA) or techno-economic assessment (TEA) are available in the literature to evaluate the full-scale potential of resveratrol production processes, which would be essential to deciding on one extraction methodology or another (for example, the emerging technologies of microwave or ultrasound-assisted extraction allow for a higher resveratrol recovery. However, these technologies are highly energy-demanding, which may represent an important environmental contribution, as well as a significant contribution to the economic costs and profitability of the process when compared to other more conventional methods such as solvent extraction). Therefore, this gap in the lack of sustainable-related assessment could be identified as a future challenge for this research field.

The overall conclusion of the review article can be summarized in the potential of resveratrol to be incorporated into the market value chain, given its widely demonstrated bioactive properties with high applicability in the food, pharmaceutical and cosmetic sectors. However, a bio-based production route should be sought, using organic waste streams, beyond its synthesis by chemical methods, as this would promote more sustainable and circular production models.

CRediT authorship contribution statement

A.A.: Methodology, Formal analysis, Investigation, Writing-original draft, Writing-review & editing. CE.C: Formal analysis, Investigation, Supervision, Writing-review & editing. MT.M: Supervision, Writing-review & edition. G.F.: Supervision, Writing-review & edition. L.D.: Conceptualization, Validation, Supervision, Writing-review & editing.

Declaration of competing interest

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

Data availability

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

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