Future Foods 12 (2025) 100710

Contents lists available at ScienceDirect

Future Foods

journal homepage: www.elsevier.com/locate/fufo

Valorization of grape by-products: Insights into sustainable industrial and nutraceutical applications

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ARTICLE INFO

Keywords:
Grape by-products
Antioxidant properties
Therapeutic potential
Sustainability

ABSTRACT

Grapes and their by-products are also considered abundant sources of protein, fatty acids, and a range of phytochemicals, e.g., resveratrol, quercetin, anthocyanins, procyanidins, catechin, kaempferol, etc. Indeed, researchers revealed several therapeutic advantages of grapes and their constituents, including the ability to fight oxidative stress, maintain heart health, lower inflammation, retard aging processes, and provide antimicrobial and blood sugar-lowering effects. Grapes and its derivatives are also being utilized in preparation of widely consumed products like wine, grape juice, raisins, fermented milk, jam etc. Owing to these benefits, its natural preservatives are gaining traction as a sustainable alternative to synthetic chemicals, contributing to cleaner and greener product formulations across industries. However, existing studies rarely emphasise all aspects of grapes and their by-products, especially its potential application in different sectors. This review integrates various new facets of grapes and their byproducts, highlighting their nutritional and phytochemical abundance while elucidating their therapeutic potential and numerous applications. By elucidating these advantages, the importance of grape derivatives and their role in fostering a healthier and more sustainable future can be emphasised. Accordingly, isolating additional bioactive compounds from grape derivatives holds significant potential to boost the economic value of grape cultivation, foster sustainability, and enhance public health through the advancement of novel therapeutic products.

1. Introduction

Grapes (*Vitis vinifera L.*), belong to the Vitaceae botanical family, has been cultivated for over 7500 years, proving themselves as the leading horticulture crops globally, owing to their extensive cultivation and adaptability (Moldovan et al., 2020). With the total of approximately 7.4 million hectares worldwide is now used for vineyard grapes and are cultured across several regions, with the largest concentrations found in Spain (13.1%), China (11.5%), France (10.7%), and Italy (9.6%) (Kandylis et al., 2021). Beyond their global cultivation, grapes are valued for their distinct uses, covering culinary, pharmaceutical and healing applications, which highlight their considerable nutritional and therapeutic benefits. Although they have vast potential, grapes and their derivatives are yet to be explored in novel fields such as food production, cosmetics, pharmaceuticals and preservatives. In this review, the nutritional potential and therapeutic values of grapes and their derivatives are discussed emphasizing their multifaceted applications and promising future prospects.

In fact, grapes are famous for their therapeutic compounds, such as polyphenols, which include flavonoids, flavonols, and anthocyanins (Di Lorenzo et al., 2019). Specifically, grapes are nutritionally rich, containing about 12–18% carbohydrates, 0.5–0.6% protein, 0.3–0.4% fat, and 82% water (Khan et al., 2020). Beyond a fruit, grape seeds and leaves are widely utilized in herbal remedies and nourishing supplements, further emphasizing their health benefits (Liperoti et al., 2017), valuing across several manufacturing units, involving food, cosmetics, pharmaceuticals and preservative industries (Chen et al., 2020). Besides, fatty acids, primarily linoleic acid (70–75%), along with oleic and palmitic acids, extracted from grape pomace (GP) and grape seeds (GS) are exhibited beneficial for the cosmetic industry due to their moisturizing and softening action on skin. For instance, these oils contain minimal linolenic acid, which enhances their stability and avoids unpleasant

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https://doi.org/10.1016/j.fufo.2025.100710
Received 12 January 2025; Received in revised form 8 June 2025; Accepted 3 July 2025
Available online 4 July 2025

odors, making them ideal for cosmetic formulations. Apart from the mentioned benefits, GP and GS oils are abundant in Vitamin E, which includes various tocopherols and tocotrienols (α, β, γ, δ), which offer antioxidant properties valuable for both cosmetic and food applications (Durazzo et al., 2019; Keen and Hassan, 2016). Coming to grape leaves, they have been found useful in extending food shelf life and playing a vital role in cosmetics, further showcasing the versatility of grape by-products (Singh et al., 2023a).

While much of the existing literature emphasis on the antioxidant properties and health benefits of grapes, there is less focus on the comprehensive nutritional composition and bioactive compounds of these derivatives, which are abundant in phenolic compounds, vitamins, and carotenoids (Zhou et al., 2022). For example, grape seeds, which contain high levels of proanthocyanidins, provide high antioxidant activity, platelet control, immune function assistance, and vasorelaxation through nitric oxide (NO) release, yet their complete role in cardiovascular wellness is not fully explored (Ma and Zhang, 2017; Varzakas et al., 2016). Likewise, grape leaf polyphenols have been shown to enhance endogenous antioxidants and reduce oxidative stress, but their diverse composition in different grape varieties has not been studied fully (Uddin et al., 2020; Dresch et al., 2018). Additionally, resveratrol, a critical component in grape skin, assists in defense against environmental stresses such as UV radiation and fungal infection. Although, its potential applications, especially in anti-aging and skincare, are not yet well covered. This research gap presents a promising opportunity to delve deeper into the unexamined advantages of grape derivatives.

Referring to these gaps, the present review makes a specific contribution by presenting a comprehensive evaluation of the nutritional content and bioactive potential of grapes and their derivatives, one that is frequently underrepresented in contemporary literature It presents a comprehensive comparison of the nutritional contents between different grape varieties and their derivatives, reflecting their diverse therapeutic benefits, such as antioxidant activity, cardiovascular protection and immunoenhancing effects. This review also explores the uses of grape derivatives like seeds, pomace, leaf and skin, finding their uses in the food, cosmetic, pharmaceutical and preservatives industry. Furthermore, it identifies new applications of grape by-products in food, ranging from their use in hard and soft drinks to bakery foods and functional foods, fields that have been given scant attention in earlier research. In addition, a specific emphasis is found in the application of such derivatives as natural preservatives, highlighting their value as a safer and more sustainable source of substitute additives for the food industry. By targeting these key issues, this research offers new perspectives into the multifunctional uses of grapes and secondary products, giving better insight into their health-improving effects as well as industrial uses. Based on this, this review delves into the nutritional, bioactive and therapeutic qualities of grapes and their derivatives, including seeds, pomace, leaf and skin. It also highlights the health promoting properties of grape-derived compounds like resveratrol and flavonoids in managing chronic conditions like diabetes, heart disease, obesity and cancer. Moreover, the paper discusses new applications of grape derived products in functional foods, nutraceuticals, cosmetics and dietary supplements with a major focus on their role in sustainable product development. This review also emphasizes the ways in which grape by-products can enhance nutrient bioavailability and enhance the health benefits of many food and beverage products. Ultimately, it analyzes the economic potential of these derivatives, showcasing their ability to support growth in industries such as food processing and cosmetics.

2. Review methodology

To carry out this review, systematic literature search was carried out through Google Scholar, Scopus, PubMed and Web of Science with articles published between the period of 2010 to 2025. The keywords applied for literature searching were: "grape by-products, " "grape pomace, " "grape seeds, " "grape skin, " "grape leaf, " "valorisation, " "bioactive compounds, " "nutraceutical applications, " "therapeutic potential" and "industrial utilization." Peer-reviewed articles, review publications, and scientific studies on nutritional content, phytochemical status, health implications, and industrial uses of grape and its by-products were taken as priority choices. Articles were filtered for relevance to the subject and availability through open access or institutional access. Duplicate and foreign language articles were removed. The collected literature was subsequently critically appraised to retrieve data, ascertain areas of knowledge gaps, and collate key findings for this review.

3. Nutritional composition

The nutritional profile of grapes and its by-products covers several attributes including proximate compositions, dietary fiber, vitamins and minerals as depicted in Table 1. Being a nutrient dense fruit with rising health benefits, the grapes and its derivatives are seeing a surge in demand within society (Kandylis, 2021). The bar chart highlighting the nutrient content of various grape by-products Fig. (1).

3.1. Grapes

Grapes are considered a rich source of vital nutrients, comprising approximately 12–18% carbohydrates, 0.5–0.6% protein, 0.3–0.4% fat and 82% water (Khan et al., 2020). To analyse carbohydrates, specific grape variety is exhibited to constitute varied glucose concentrations, i.e., purple grapes range from 25.9 to 28.5 μg/mL, concord grapes from 9.3 to 11.3 μg/mL, green grapes from 23.5 to 28.5 μg/mL, and red grapes from 23.0 to 27.8 μg/mL (Callaghan et al., 2013). Similarly, research on other grape varieties observed the *Trakya Ilkeren* (red) variety to possess utmost carbohydrate content and the *Cardinal* (red) variety to hold lowest carbohydrate but the highest protein content (Doğan and Uyak, 2022). Additionally, grapes are attributed to contain more than 50% dietary fibre. Besides, the proximate composition of grapes comprises of 9 percent moisture, modest lipid content, nominal energy value, and a neutral flavor (Karovičová et al., 2015). Moving further, the oil attained from *Temascaltepec* grapes exhibited remarkable quality indicators persuaded by their unsaturated fatty acid content. These indicators comprised of iodine (57.9 g/100 g), soapy number (170.7 mg/g) and the peroxide value (30 mEq/kg). However, despite the eminent unsaturated fatty acid content, the smoking point (211 °C) of this oil remains unchanged due to the existence of palmitic and stearic acids (Mora et al., 2015). Besides, grapes provide considerable amount of minerals, including potassium (0.1–0.2%), phosphorus (0.08–0.01%), followed by calcium (0.01–0.02%). Moreover, grapes provide significant amounts of vitamins including vitamin C (0.01–0.02%), and vitamin A (0.001–0.0015%) that help in boosting the immune system, maintaining healthy skin and supporting vision (Acquadro, 2020).

3.2. Grape seeds

Being a valuable source of significant nutrients, grape seeds have engrossed remarkable interest for utilization of various food and supplement products (Al Juhaimi et al., 2017). They are packed with numerous compounds, including, dietary fiber (48.53%), carbohydrates (27.77%), protein (9.17%), oil (11.72%) ash (2.81%) and moisture (5–7%) (Salama, 2007). The ash content of grapes seeds is exhibited to emphasize their mineral richness (Odabaşioğlu and Gürsöz, 2022). Also, the carbohydrate composition in grape seeds, based on their chemical nature, i.e., monosaccharides, disaccharides and trisaccharides is proved to be 13.5–19.4, 70.2–73.8 and 7.1–16.3%, respectively. Also, the water-soluble saccharides in grape seeds are shown in the range of 3.6–6.3% (Ovcharova et al., 2015). Moreover, the amino acids content of grape seeds was higher than that of cereals and oil seeds, hence a great food supplement for cattle (Dhillon et al., 2016). Additionally, grape

Table 1
Nutritional composition of Grapes and its by- products.

Components	Grape	Grape seed	Grape pomace	Grape leaf	Grape skin
Proximate composition (%)					
Moisture	81–85	5–7	65–75	85–90	8–10
Protein	0.6–0.8	6.0–8.0	2.0–4.0	4.0–5.0	2.5–3.0
Ash	0.5–1.0	3.0–5.0	2.0–4.0	2.0–3.0	2.0–3.0
Fiber	0.5–1.0	22–28	10–15	2.5–3.0	8–10
Carbohydrates	17–20	10–12	15–20	8–10	15–20
Minerals (mg/100 g)					
Potassium	200–250	250–300	150–200	500–600	300–350
Calcium	10–20	70–100	40–60	250–300	50–70
Iron	0.3–0.5	5.0–8.0	3.0–5.0	2.5–4.0	3.0–5.0
Magnesium	10–15	60–80	30–50	50–70	20–30
Vitamins (mg/100 g)					
Vitamin C	10–15	1.0–2.0	5.0–8.0	25–30	15–20
Vitamin A	0.01–0.05	0.02–0.05	0.05–0.10	1.0–1.5	0.1–0.3
Vitamin K	0.01–0.05	0.1–0.2	0.05–0.1	1.0–1.5	0.2–0.3
References	(Khan et al., 2020) (Karovičová et al., 2015) (Yadav et al., 2009)	(Ovcharova et al., 2015) (Felhi et al., 2016) (Özcan et al., 2017) (Abdrabba and Hussein, 2015)	(Sousa et al., 2014) (Spinei and Oroian, 2021) (Mohamed Ahmed et al., 2020)	(Oganesyants et al., 2018) (Rana et al., 2022)	(Mendes et al., 2013) (Aghazadeh et al., 2022)

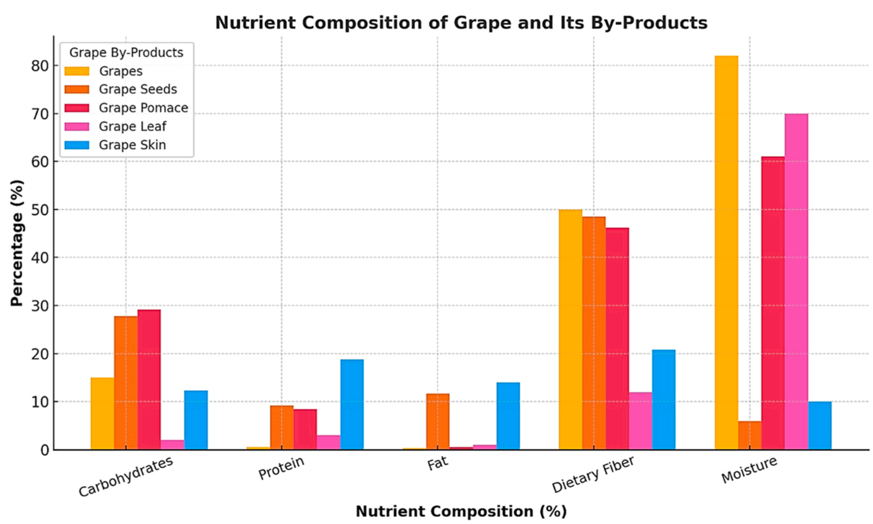

Fig. 1. Bar chart highlighting the nutrient content of various grape by-products.

seeds are a great source of polyunsaturated fatty acids, which are good for the treatment and management of most diseases (Lucarini et al., 2019). Furthermore, grape seeds are rich in critical macro-minerals — potassium (K), calcium (Ca), phosphorous (P), magnesium (Mg), sulphur (S) and sodium (Na) — in the amounts ranging from 56 to 8042 mg/kg (Özcan et al., 2017). Grape seeds are rich in vitamin C (ascorbic acid) and vitamin E (tocopherols) that together may have a synergistic effect of keeping the heart healthy and may assist in alleviating Type II diabetes symptoms (Gupta et al. 2020).

3.3. Grape pomace

Grape pomace, a by-product of winemaking, is regarded as a nutritionally beneficial derivative of grapes due to its significant therapeutic benefits (Pereira et al., 2020). Moisture composition in grape pomace differs extensively (50–72%), depending on grape variability and ripeness (Spinei and Oroian, 2021). Additionally, grape pomace contains an average carbohydrate level of 29.2 g/100 g, though, distinguishes with an enormously high total dietary fiber content of 46.17 g/100 g (Machado et al., 2024b; Iuga and Mironeasa; 2020). However, this higher fiber content, especially in red grape pomaces, is overlooked by insoluble fibers like cellulose and hemicellulose (Antonić et al., 2020). Conversely, the fiber content is analysed considerably minimal in white grape pomaces. Moreover, lignin, another component of dietary fiber in grape pomace, varies from 16.8% to 24.2% ((Spinei and Oroian, 2021).

Furthermore, grape pomace flour holds 8.49 g/100 g of protein content, making it a reasonable source of plant-based protein (Gularte et al. 2022). Besides, grape pomace is remarkably valued for its prominent content of polyunsaturated fatty acids (PUFAs), specifically linoleic acid, with minimal content of saturated fats (Vašeková et al., 2020). Additionally, grape pomace is considered as a beneficial source of essential minerals for instance potassium (K), phosphorus (P), manganese (Mn), iron (Fe), and zinc (Zn). Notably, numerous varieties of grape pomace showcase varying mineral composition, i.e., *Antepkarası* is exhibited abundant in potassium and phosphorous, *Büzgülü* is remarked rich in calcium and *Marcaş* comprises a rich source of manganese (Mohamed Ahmed et al., 2020). *Rebo* grape pomace, too, is vitamin-rich: Vitamin A averages 639 mg/kg, followed by vitamin B1 with ascorbic acid (vitamin C) and B-complex vitamins B2, B3, B5 and B7 (Tikhonova et al., 2021). This non-animal by-product encourages diversity while being rich in fibre, fatty acids, minerals, and vitamins. Grape pomace is a highly nutritious product with great potential as a food ingredient and as a pharmaceutical raw material, possessing immense health benefits.

3.4. Grape leaf

The grape leaves are a remarkable source of macronutrients and essential trace elements, and also dietary fibers that can be useful for overall health and wellbeing as it's highly chemically complex, making it a therapeutic product (Rana et al., 2022; Zakirova et al., 2013). They provide 13 kcal but are dense in fibre and, due to their low glycaemic index, regulate blood sugar (Rana et al., 2022). They also have 2% sugar and other organic acids (Atakulova, 2021). Also present in grape leaves is potassium, calcium, sodium, magnesium, iron, aluminium, zirconium, silicium, phosphorous, sulphur and chlorine, all of which are particularly vital for cardiovascular and cellular metabolism (Karimi et al., 2021). Red grape leaves are considered as high in calcium (3.3% of the total dry weight), silicon (0.71%), magnesium (0.42%) and potassium (0.25%) all of which are crucial for physiological functions (Oganesyants et al., 2018). Moreover, a cup of juice made from grape leaves contained 51 mg of calcium for bone development and iron for transporting and circulating oxygen. In addition to it, they are packed with vitamins C, A, K, and B, which boost immunity, reinforce nerve health, and enhance cognitive function. Specifically, vitamin B6 enhances brain function and may lower the chance of dementia (Rana et al., 2022). Hence, the significant nutrient profile of grape leaves with their abundance of key vitamins, minerals, and fiber, makes them a convincing addition to a healthy intake.

3.5. Grape skin

The majority of the beneficial phytonutrients in grapes are concentrated in their skin (Abdiev et al., 2023). Being the most abundant components, the structure of grape skin is largely made up of polysaccharides comprising of cellulose (20.8%) and hemicelluloses (12.5%). Following these, protein content in grape pomace makes up to18.8%, while sugars - mainly glucose and fructose – contribute for 12.3%. Additionally, aliphatic compounds such as fatty acids, wax and cutin accounts for 14%, and the remaining 7.8% consists of ash. Remarkably, no lignin is found in grape skins (Albuquerque et al., 2020). Besides, researchers exhibited a decrease in the steady-state moisture level of grape skins with a rise in its temperature. In contrast, the moisture composition of grape skins increases with a reduction in the net isosteric heat. Additionally, the highest equilibrium moisture content was found to be highest at 20 °C and lowest at 60 °C (Aghazadeh et al., 2022). Based on these nutritional observations, grape skin extract can be used along with inulin and fructo-oligosaccharides, to produce various food products, exhibiting therapeutic properties (Kandylis, 2021).

4. Bioactive compounds

Grapes and its derivatives are considered an excellent source of significant biologically active compounds, including phenolic acids, anthocyanins, flavonoids, stilbenes, tannins (hydrolysable and the nonhydrolyzable or condensed tannins), xanthines and lignans (Fig. 2) (Alfaia et al., 2022). This section focuses on different significance of various bioactive substances present in grapes and its derivatives as illustrated in Table 2 and Fig. 3.

4.1. Grapes

Grapes are regarded as an abundant source of bioactive compounds, such as proanthocyanidins, anthocyanins, flavonols, phenolic acids and stilbenes (Almatroodi et al., 2020). However, withering of grapes have demonstrated an increase in the concentration of anthocyanins, proanthocyanidins, especially stilbenes, mainly because of the natural weight loss that occurs after drying of the grapes (Rosso et al., 2016).

Besides, ozone (O3) serves as an abiotic stressor for boosting the bioactive compounds in grapes. Also, it promotes the biosynthesis of phenolic and aromatic compounds by initiating defense mechanisms at the transcriptional, genetic and biochemical levels within plant tissues (Modesti et al., 2021). Additionally, the bioactive substances present in grapes, polyphenols is exhibited to endow a diverse array of biological effects, including antioxidant, antimicrobial, anti-inflammatory, anticancer and cardioprotective (Zhou et al., 2022). Moreover, the interest in grape polyphenols has grown predominantly among researchers and food manufacturers due to their antioxidant activity and substantial presence in the diet (Brenes et al., 2016). Furthermore, grape extracts at doses of 100 mg/kg and 200 mg/kg have been exhibited to specify extensive cardioprotective effects, thus, increasing the recovery of ventricular function following ischemia and decreasing the degree of heart tissue injury. Furthermore, in vitro experiments indicate that grape extracts efficiently neutralize damaging superoxide and hydroxyl radicals produced during the re-establishment of blood flow following ischemic incidents (Almatroodi et al., 2020).

Moving further, *V. labrusca* variety of grape, particularly Bordô and Concord grapes widely developed in the southern Brazil, exhibited maximum antioxidant potential, leading to the higher content of bioactive substances (da Silva et al., 2022). Moving further, flavonols, another class of natural compounds observed in all Vitis species and help differentiate grape varieties due to their unique profiles. They are rich in white grapes and closely associated with anthocyanins in red grapes. Flavonol content is influenced by sunlight, and notably affect grape quality and are also worthy as dietary antioxidants (Flamini et al., 2013). Consequently, the varied bioactive compounds in grapes,

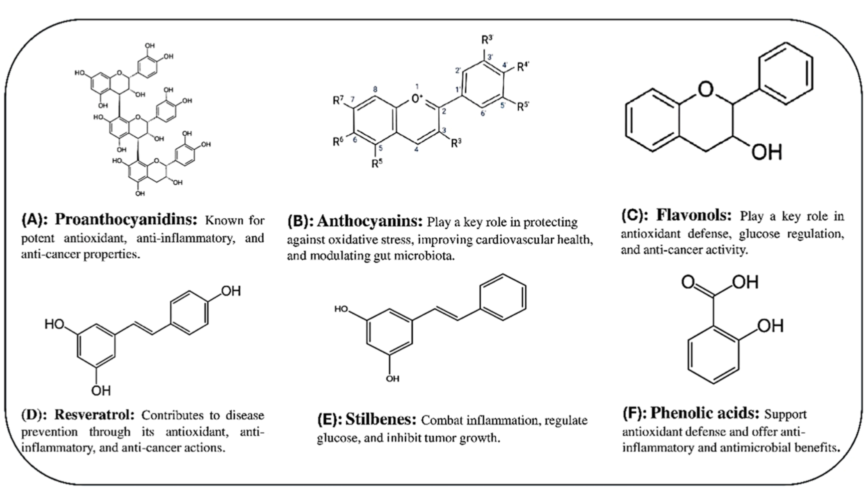

Fig. 2. Chemical structures of bioactive compounds in grapes and their by-products.

Table 2
Bioactive components of grapes and its derivatives.

Bioactive Components	Grape	Grape seed	Grape pomace	Grape leaf	Grape skin
Antioxidants					
Total Phenolic Content (mg GAE/100 g)	200–300	400–600	300–500	250–350	600–800
Flavonoids (mg/100 g)	50–100	150–200	100–150	80–120	200–250
Ascorbic Acid (mg/100 g)	3–5	0.2–0.5	1–3	2–4	5–8
Resveratrol (mg/100 g)	0.3–0.6	0.5–1.0	0.8–1.2	0.2–0.5	1.5–2.0
Proanthocyanidins (mg/100 g)	50–70	300–500	200–400	30–50	100–200
Anthocyanins (mg/100 g)	25–50	10–20	50–70	10–20	100–150
Tannins (mg/100 g)	15–20	50–100	60–80	30–50	80–120
Other Bioactive Compounds					
Saponins (mg/100 g)	1–2	5–10	4–8	2–5	6–10
Catechins (mg/100 g)	5–10	20–30	15–25	10–15	25–35
Lignans (mg/100 g)	0.5–1.0	2–3	1.5–2.5	0.8–1.5	3–5
Stilbenes (mg/100 g)	0.2–0.5	0.8–1.5	1–2	0.3–0.6	1.5–2.5
Quercetin (mg/100 g)	1–1.5	2–3	2–4	1.5–2.5	3–5
Gallic Acid (mg/100 g)	1–2	5–8	6–10	4–6	8–12
References	(Liu et al., 2018) (Singh et al., 2016) (da Silva et al., 2022)	(Ma and Zhang, 2017) (Machado, 2017) (Farhadi et al., 2016)	(Mohamed et al., 2020) (Peixoto et al., 2018) (Tikhonova et al., 2021)	(Moldovan et al., 2020) (Banjanin et al., 2021) (Goufo et al., 2020)	(Ricci et al., 2017) (Pugajeva et al., 2018) (de Andrade et al., 2021) (Zhou et al., 2022)

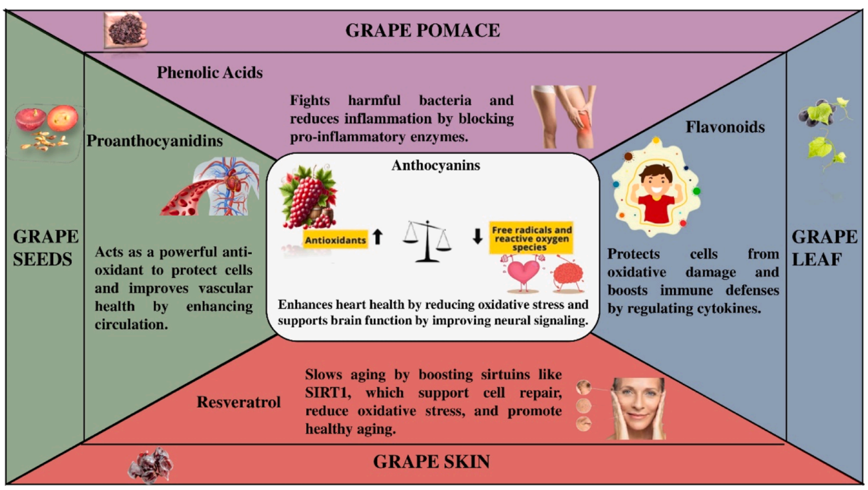

Fig. 3. Health benefits of bioactive compounds present in grapes and their by-products.

especially polyphenols and flavonols, promote considerable therapeutic benefits, making a beneficial addition not only to research but also to dietary practices.

4.2. Grape seeds

Grape seeds are regarded as an abundant source of phytochemicals, making them worthy source of dietary supplements with substantial antioxidative properties. Grape seeds contain key phenolic compounds, primarily flavonoids, like flavan-3-ols, comprising of catechin, epicatechin and epicatechin-3-O-gallate monomers along with their polymersized forms (Ashour et al., 2023). Besides, grape seed extracts are the heterogeneous blend of proanthocyanidins (3532 mg/100 g), encompassing monomers (5–30%), oligomers (17–63%), and polymers (11–39%). However, proanthocyanidins, being the main compounds in these extracts, have been exhibited to scavenge superoxide radicals, highlighting their antioxidative potential (Ma and Zhang, 2017). Formed from flavanol monomers, they are among the most common phenolics in plants after lignin. Interestingly, their antioxidant activity has been reported to be as high as 20 times that of vitamin E and 50 times that of vitamin C (Ashour et al., 2023).

Moving further, grape seeds hold much greater quantities of total flavonoids, as much as ten times higher than the skin, highlighting their worth. Among the flavonoids present, quercetin and kaempferol by-products are considered the most significant one whereas luteolin and dihydrofisetin derivatives are demonstrated the most ordinary flavones (Lucarini et al., 2018; Pasini et al., 2019). The elementary anthocyanin found in grape seeds is cyanidin-3-glucoside, with concentrations varying from 0.058 to 0.840 mg/g of fresh weight (Machado, 2017).

Additionally, phenolic acids in grape seeds include hydroxybenzoic and hydroxycinnamic derivatives, with gallic and protochatechuic acid being the most prominent varying from 6.5 to 224.0 and 2.0 to 10.0 μg/g dry weight, separately (Silva et al., 2018). The levels of other essential phenolic substances, such as gallic acid, catechin, epicatechin and quercetin differ between 67–91 μg/g, 122–156 μg/g, 103–167 μg/g, 25–38 μg/g, respectively (Farhadi et al., 2016). Hence, grape seeds serve as a rich source of numerous phenolic substances, remarkably proanthocyanidins and flavonoids, making them a significant by-product with noteworthy antioxidant and health-promoting benefits.

4.3. Grape pomace

Grape pomace, which is a winemaking by-product, is full of healthy compounds like anthocyanins, phenolic acids, flavonoids and stilbenes, and hence has numerous culinary and medical uses. In laboratory experiments, hydroalcoholic grape pomace extracts are also more antioxidant than aqueous extract because they contain more of these bioactive compounds (Caponio et al., 2022). Additionally, grape pomace has significantly more insoluble fiber than soluble fiber (Antoni et al., 2020).

Even still, anthocyanins, flavonoids and stilbenes are abundantly present in the grape pomace because they aren't extracted from the wine (Mohamed et al., 2020). *Marcas* grape pomace has the highest overall phenolics (147.51 mg GAE/100 g) and antioxidant (98.47%) among all the varieties and phenolics are closely related to antioxidant activity (Mohamed et al., 2020).

Ggrape pomace flours (GPF) have also been found highly productive for anthocyanins when produced using 25% of the grape variety *'Niagara Rosada'*. This blend resulted in reducing allergenicity with an increase in levels of rutin and caffeic acid, without altering its antioxidant capacity (Monteiro et al., 2021). *Saperavi* grape pomace was also found to be richer in 3-O-glycosides, an anthocyanin, than *malvidin, petunidin, cyanidin, peonidin* and *delphinidin* grape variety (Tikhonova et al., 2021). Moreover, red grapes *('Maximo', 'Bordo', 'Violeta')* are still the most concentrated anthocyanin source and are therefore ideal material for food preservatives due to their strong antioxidant capacity (Monteiro et al., 2021)..

The methanol-water extracts derived from grape pomace and seeds contain flavan-3-ols, another potent family of phenolic molecules. These included D-catechin – a potent antioxidant – in high levels in the pomace of the *Merlot* and *Rebo* grapes respectively at 522 mg/kg and 611 mg/kg, individually (Peixoto et al., 2018; Tikhonova et al., 2021). All of this makes grape pomace an attractive, large-scale bioactive source with multiple functional effects.

4.4. Grape leaf

Grape leaf has also identified as a rich source of health-promoting bioactive compounds – quercetin, resveratrol, caffeic acid, kaempferol, gallic acid, phenolic acids and flavanols such as isorhamnetin and myricetin which are both free and glycosylated and act as powerful antioxidants (Singh et al., 2023b). As it happens, the most abundant constituents of grape leaves are quercetin-3-O-glucoside and quercetin-3-O-galactoside, with myricetin-3-O-glucoside present only in small quantities. Remarkably, red grape varieties tend to have higher amounts of phenolic substances than whites (Fernandes et al., 2013). Moreover, studies have demonstrated *Vitis Vinifera* leaf extracts containing 16.75 mg/g of total flavonoids and 6.39 mg/g of caffeic acid derivatives (Moldovan et al., 2020).

Parallelly, another review suggests organic vine leaf extract to contain more resveratrol than regular vine leaf extract, indicating the variability in phytochemical substances, thus influencing the therapeutic efficacy of vine leaves (Rana et al., 2022). Consequently, the wide-ranging bioactive compounds of grape leaves make them a promising subject for further research, exclusively in development of functional foods and nutraceuticals that leverage their convincing antioxidant and therapeutic properties (Singh et al., 2024).

4.5. Grape skin

Grape skin is observed to be rich in numerous bioactive molecules, including proanthocyanidins, anthocyanins, flavonols, resveratrol, phenolic acids and stilbenes which alter significantly based on processing conditions (Zhou et al., 2022). A study demonstrated that heating grape skin at the temperatures of 40 °C and 60 °C without using ultrasound-assisted extraction (UAE) can indicate a significant increase in total polyphenols by 260 and 287 percent, respectively. Additionally, anthocyanins — pigments that dissolve in water — are mostly found in the skins of pigmented grape varieties like red and purple, and are usually lacking in white grape varieties (Zhou et al., 2022). Studies have shown that the levels of anthocyanins, particularly malvidin-3, 5-di-O--glucoside, differ significantly from 118.8 to 324.5 mg per 100 g (de Andrade et al., 2021). Table 3 – illustrates different grape by-products, their chemical components, extraction methods and corresponding health effects.

Further research was conducted on *syrah* grape skin residue that resulted a high amount of total phenolic compounds and a bioactive compoundstotal flavonoid content ranging from 196 to 733.7 mgGAE/100 g and 9.8–40.0 mgQE/100 g, respectively. These skins also indicate high antioxidant and antibacterial activity with notable free radical scavenging activity (16.0–48.7 mg/100 mL, as EC50) and its inhibition of microbial growth (0.16 mg/mL, as EC50 for *S. aureus*, and 0.04 mg/mL, as EC50 for *Escherichia coli*) in UAE-processed extracts (de Andrade et al., 2021). Moreover, studies have proved that the skin residue of the BRS magna grape variety, in particular, retain an elevated concentration of bioactive compounds and antioxidant activity. The effectiveness of these bioactive compounds is also influenced by the drying method. Conventional drying has been directed to yield higher concentrations of phenolic acids, which are mostly accountable for antioxidant activity, whereas freeze-drying is further valuable in maintaining thermolabie anthocyanins (Silva et al., 2020).

5. Health benefits

Grapes offer a versatile range of health benefits, including their ability to modulate gut microbiota, protect the heart, manage diabetes, and fight cancer (Zhou et al., 2022) as depicted in the Table 4 and Fig. 4. These effects are discussed further in the provided section.

5.1. Grapes

5.1.1. Anti-diabetic

Diabetes mellitus, being a long-term metabolic condition, impacts blood sugar regulation, however certain foods like grapes can play a supportive role in managing it (Gupta et al., 2020). This is attributed to the glycaemic index of grapes, i.e., around 50, leading to moderate rise in blood sugar level (Mullie et al., 2016). Besides, dietary polyphenols – naturally occurring compounds in grapes, have been observed effective

Table 3
Different grape by-products, their chemical components, extraction methods and corresponding health effects.

Grape and their by-products	Major bioactive compounds	Common extraction methods	Reported health effects	References
Grapes	Resveratrol, quercetin, anthocyanins, catechin, kaempferol, organic acids, vitamins	Solvent extraction, ultrasound-assisted extraction (UAE), Supercritical fluid extraction (SFE), and Pressurized liquid extraction (PLE)	Antioxidant, anti-diabetic, anti-inflammatory, cardioprotective, anti-cancer, neuroprotective	(Castro-López et al., 2016)
Grape Seeds	Proanthocyanidins, catechins, epicatechins, linoleic acid, vitamin E	Cold pressing, Soxhlet extraction, ultrasound-assisted extraction (UAE)	Antioxidant, anti-aging, cardiovascular protection, anti-cancer	(Yuzhu et al., 2024)
Grape Pomace	Polyphenols, dietary fiber, flavonoids, anthocyanins, organic acids	Solid–liquid extraction (SLE), UAE, supercritical fluid extraction (SFE), enzymatic methods	Antimicrobial, anti-inflammatory, anti-obesity, antioxidant, prebiotic effect	(Constantin et al., 2024)
Grape Leaves	Flavonols (quercetin, kaempferol), phenolic acids, vitamins A, C, E	Decoction, infusion, solvent extraction	Antioxidant, anti-hypertensive, antimicrobial, anti-inflammatory	(Singh et al., 2023b)
Grape Skin	Anthocyanins, flavonoids, tannins, phenolic acids, carotenoids	Enzyme-assisted extraction (EAE), microwave-assisted extraction (MAE)	UV-protective, anti-diabetic, anti-inflammatory, antioxidant	(Sochorova et al., 2020)

Table 4
Health benefits of Grapes and its by- products along with the mechanism, specific clinical trial types, number of participants, intervention details, and dosage.

Ingredients	Health Benefits	Mechanism	Clinical Trial Type	Number of Participants	Intervention Details	Dosage	References
GRAPES	**Antioxidant effect**	Rich in resveratrol and flavonoids; scavenges free radicals, decreasing oxidative stress.	Randomized Controlled Trial (RCT)	60	Grape extract supplementation vs. placebo	500 mg/day	(Rasines-Perea et al., 2017) (Sato et al., 2020) (Unusan et al., 2020) (Imran et al., 2017) (Gupta et al., 2020) (Moodi et al., 2021) (Sarkhosh-Khorasani et al., 2021)
	Antidiabetic effect	Resveratrol increases insulin sensitivity and regulates glucose metabolism.	RCT	50	Resveratrol supplementation for 12 weeks	1 g/day	
	Anticancer effect	Reduces cancer cell proliferation via apoptosis induction and angiogenesis suppression.	In vivo & In vitro	–	Preclinical animal models & cell line studies	–	
	Anti-inflammatory effect	Decreases inflammation by regulating NF-κB signaling and cytokine release.	Clinical Study	30	Grape polyphenol intake for 8 weeks	800 mg/day	
	Anti-obesity effect	Controls lipid metabolism and suppresses adipogenesis.	RCT	40	Grape seed extract supplementation	300 mg/day	
	Cardioprotective effect	Improves endothelial function and lowers LDL oxidation.	RCT	70	Grape juice intervention for 12 weeks	250 ml/day	
GRAPE SEEDS	**Antioxidant effect**	Contains proanthocyanidins; neutralizes free radicals and improves antioxidant defense.	RCT	55	Grape seed extract vs. placebo	200 mg/day	(Li et al., 2020) (Sochorova et al., 2020) (Gupta et al., 2020) (Unusan, 2020) (Mojiri-Forushani et al., 2022) (Zhang et al., 2016)
	Antidiabetic effect	Improves glycemic control by increasing pancreatic β-cell function.	RCT	40	Grape seed polyphenol supplementation	400 mg/day	
	Anticancer effect	Proanthocyanidins inhibit DNA damage and prevent tumor growth.	In vitro & Animal Study	–	Laboratory-based tumor inhibition studies	–	
	Anti-inflammatory effect	Proanthocyanidins control inflammatory mediators such as TNF-α and IL-6.	Clinical Study	25	Grape seed extract in metabolic syndrome patients	250 mg/day	
	Anti-obesity effect	Polyphenols hinder fat accumulation and enhance lipid metabolism.	RCT	30	Grape seed extract supplementation	300 mg/day	
	Cardioprotective effect	Proanthocyanidins lower cholesterol and enhance vascular health.	RCT	50	Grape seed extract vs. statins	500 mg/day	
GRAPE POMACE	**Antioxidant effect**	Rich in polyphenols; lowers oxidative stress by inhibiting ROS formation.	RCT	65	Grape pomace extract supplementation	400 mg/day	(Kato-Schwartz et al., 2020) (Perdicaro et al., 2017) (Almanza-Oliveros et al., 2024) (Nirmala et al., 2017) (Ramos-Romero et al., 2020) (Machado et al., 2024a)
	Antidiabetic effect	Polyphenols improve glucose uptake and decrease insulin resistance.	Clinical Trial	45	Grape pomace supplementation for 10 weeks	600 mg/day	
	Anticancer effect	Polyphenols demonstrate cytotoxic effects on cancer cells and inhibit metastasis.	In vitro & Animal Study	–	Cell-line and animal models	–	
	Anti-inflammatory effect	Phenolic compounds inhibit COX-2 and decrease inflammation markers.	Clinical Study	40	Grape pomace extract for inflammatory conditions	800 mg/day	
	Anti-obesity effect	Contains dietary fiber and polyphenols that promote weight loss.	RCT	35	Grape pomace intake for weight reduction	500 mg/day	
	Cardioprotective effect	Polyphenols protect against atherosclerosis by decreasing inflammation.	RCT	55	Grape pomace extract supplementation	450 mg/day	
GRAPE LEAF	**Antioxidant effect**	Contains phenolic compounds; shields against oxidative cell damage.	Clinical Study	30	Grape leaf extract for oxidative stress reduction	600 mg/day	(Mohammed et al., 2020) (Devi and Singh, 2017) (Abdel-Khalek and Mattar, 2022) (Saadaoui et al., 2020) (Schön et al., 2021) (Nayak et al., 2019)
	Antidiabetic effect	May inhibit α-glucosidase enzymes, lowering postprandial glucose levels.	RCT	45	Grape leaf extract for diabetes management	300 mg/day	
	Anticancer effect	Contains compounds that decrease cancer risk by inhibiting cell signaling pathways.	In vitro & Animal Study	–	Preclinical studies on carcinogenesis inhibition	–	
	Anti-inflammatory effect	Rich in quercetin and flavonoids that inhibit pro-inflammatory cytokines.	Clinical Study	40	Grape leaf extract in inflammatory conditions	500 mg/day	
	Anti-obesity effect	Rich in compounds that lower lipid accumulation and promote fat oxidation.	RCT	30	Grape leaf extract supplementation	400 mg/day	
	Cardioprotective effect	Quercetin and flavonoids enhance cardiovascular health by reducing cholesterol.	RCT	50	Grape leaf extract vs. placebo	500 mg/day	

(*continued on next page*)

Table 4 (*continued*)

Ingredients	Health Benefits	Mechanism	Clinical Trial Type	Number of Participants	Intervention Details	Dosage	References
GRAPE SKIN	**Antioxidant effect**	Rich in anthocyanins and resveratrol; decreases lipid peroxidation.	RCT	60	Grape skin extract supplementation	500 mg/day	(Sochorova et al., 2020) (Sabra et al., 2021)
	Antidiabetic effect	Anthocyanins and resveratrol improve insulin secretion and glucose metabolism.	RCT	50	Grape skin extract for diabetes management	400 mg/day	(Zhou and Raffoul, 2012) (Bhise et al., 2014)
	Anticancer effect	Anthocyanins and tannins inhibit oxidative DNA damage and induce apoptosis.	In vitro & Animal Study	–	Preclinical studies on tumor growth inhibition	–	(Paller et al., 2018)
	Anti-inflammatory effect	Resveratrol and anthocyanins decrease inflammation through cytokine modulation.	Clinical Study	30	Grape skin extract in inflammatory conditions	450 mg/day	
	Anti-obesity effect	Resveratrol improves fat metabolism and suppresses adipocyte differentiation.	RCT	35	Grape skin extract supplementation	400 mg/day	
	Cardioprotective effect	Anthocyanins and resveratrol enhance heart health by lowering oxidative stress.	RCT	70	Grape skin extract for cardiovascular support	500 mg/day	

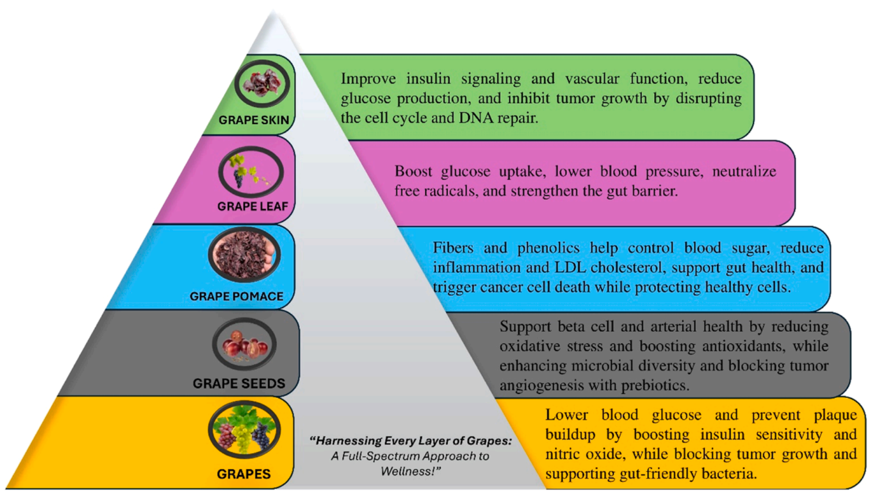

Fig. 4. Health benefits of grapes and their by-products, including seeds, pomace, leaves, and skin, showcasing their role in anti-diabetic, cardioprotective, anti-cancer activities, and gut microbiota modulation.

in controlling diabetes by protecting the pancreatic cells against glucose toxicity, inhibiting the enzymes that digest starch, improving insulin sensitivity and preventing the formation of harmful composites identified as advanced glycation end products (AGEs) (Rasines-Perea et al., 2017). Moreover, phenolic compounds present in grapes possess insulinotropic property, leading to an increase in insulin secretion by 2–8 folds. This is considered crucial as pancreatic beta cells, responsible for insulin secretion, play major role in reducing obesity and lowering blood sugar concentration. Interestingly, grape procyanidin also regulates the growth and death of pancreatic beta cells, thus enhancing glucose uptake under high blood glucose concentrations (Singh et al., 2023b).

Furthermore, studies demonstrated whole grapefruit with significantly higher insulin response than grape juice alone, indicating glucose in grapes more effective in stimulating insulin compared to oranges and apples. This is credited to the existence of fiber and glucose concentration in whole fruits that influences the plasma insulin response (Murphy et al., 2017). Consequently, grapes demonstrate strong anti-diabetic activity by inhibiting key enzymes like amylase and α-glucosidase, which play a critical role in breaking down complex carbohydrates and retarding the release of glucose to the bloodstream (Shang et al., 2022), henceforth, supporting pancreatic health, improving insulin sensitivity and making grapes a valuable component in diabetes prevention and management (Zhou et al., 2022).

5.1.2. Cardioprotective activity

Grapes are rich in variety of polyphenol molecules, comprising flavonoids, phenolic acids, and resveratrol, thus, playing an important role in heart health. For instance, grape extracts, such as those from the *chardonnay* variety (white wine grape variety) have demonstrated the ability to increase nitric oxide (NO) production in endothelial cells, thus, improving blood vessel function and lower blood pressure. Likewise, studies on rats exhibited grape extract to alleviate hypertension by initiating specific pathways in the body, like the endothelial nitric oxide synthase and PI3K/Akt signalling mechanism (Sato et al., 2020). Similarly, one notable study also explored resveratrol, a key polyphenol in grapes, as a potential treatment for atrial fibrillation (AF). Additionally, supplementation of a daily dose of polyphenol-rich grape juice (225 mL) to hyperlipidaemic rabbits exhibited a decrease in platelet aggregation and atheroma by 30% over 96 days. Analogous effects were also observed in hamsters, where catechin, quercetin, or resveratrol reduced aortic fatty streaks by up to 84% (Baczkó and Light, 2015). Moreover, grape powder demonstrated a reduction in blood pressure by enhancing arterial relaxation, and lowering heart strain in hypertensive rats, thus, indicating its potential as a pharmacological treatment for hypertension (Singh et al., 2015). Moreover, incorporating grapes into one's routine alongside other heart-healthy habits—like following a calorie-controlled diet and avoiding smoking—can further enhance protective benefits for the heart. (Zhou et al., 2022).

5.1.3. Anticancer activity

Grapes and their bioactive compounds, primarily proanthocyanidins, have exhibited considerable anticancer properties, showing effectiveness against numerous carcinogenic disorders including hepatic, vesical, prostate, and cervical cancer (Unusan, 2020; Gupta et al., 2020; Wu et al., 2023). In a model of prostate cancer using Pten-deficient mice, grape powder aided in its prevention by reducing inflammation, improving prostate cell health, and suppressing cancer-promoting pathways like Akt and androgen receptors (Joshi et al., 2020).

Additionally, resveratrol, a well-known polyphenol in grapes, has been demonstrated to slow down cancer-related blood vessel formation and inhibit tumor growth in models like the chick chorioallantoic membrane, as well as in fibrosarcoma tumors in mice (Imran et al., 2017). Nonetheless, high dosage of grape powder (100 μg/mL) has been analysed to efficiently reduce cell viability in contrast to the lower doses (1.5–15 μg/mL), that was observed to reduce colony formation and wound healing, thus, leading to cancer progression (Kumar et al., 2018). Besides, in cancer chemoprevention, long-term administration of phytochemicals from grapes may help delay or prevent cancer development by reducing harmful reactive oxygen and nitrogen species that can damage irreversible DNA (Averilla et al., 2019). Such anti-proliferative and anti-genotoxic effects are especially notable in red wine pomace, containing hydroxybenzoic acids and hydroxycinnamic acids, compounds exhibited to protect colon cells from cancerous changes (Del Pino-García et al., 2017).

5.1.4. Gut microbiota modulation

Grape extracts have been exhibited to counteract the adverse consequences of a lipid-rich diet on gut bacteria. Researchers evaluated grape extract to boost the balance of gut-friendly microbes, namely, *Firmicutes* and *Bacteroidetes* and enhance specific bacteria such as *Bifidobacteria, Clostridia*, and *Akkermansia*, leading to a healthier gut function (Han et al., 2020). Based on a recent research, consumption of 46 g grape powder daily for the consequent four weeks by the subjects lead to a significant increase in gut microbiota diversity along with an enrichment of beneficial bacteria, namely, *Akkermansia* and *Lachnospiraceae_UCG-010*, and a decline in potentially problematic bacteria like *Bifidobacterium* and *Dialister*. (Yang et al., 2021). Additionally, polyphenols in grapes, specifically tannins are exhibited to reinforce gut health by stimulating beneficial bacteria like *Bifidobacterium, Lactobacillus,* and *Enterococci* along with inhibiting harmful bacteria *Clostridium histolyticum* (Wang et al., 2022). Besides, grape flavonoids, on absorption, demonstrates anti-inflammatory effects by transforming into an active form that circulates to different areas of inflammation. Moreover, oleanolic acid, another grape compound, validates to reduce inflammation by stimulating the cholic acid receptor, TGR5 (Santa et al., 2019). The therapeutic advantages of grapes and their derivatives, including seeds, pomace, leaves, and skin, showcasing their role in anti-diabetic, cardioprotective, anti-cancer activities, and gut microbiota modulation.

5.2. Grape seeds

5.2.1. Anti-diabetic

Grape seed proanthocyanidins show promising potential in diabetes prevention by regulating key enzymes like α-glucosidase and lipase, reducing inflammation, lowering post meal blood glucose levels, and enhancing insulin sensitivity and pancreatic function. These effects are also associated with beneficial changes in gut bacteria, such as increase in Clostridium XIVa, Roseburia, and Prevotella (Unusan, 2020). In animal studies, rats on fructose-rich diet provided with 1 percent grape seed extract (GSE) experienced significant reductions in blood sugar and insulin levels, demonstrating that GSE enhance glucose metabolism and assist in preventing insulin resistance caused by excessive fructose intake (Nowshehri et al., 2015). Besides, monomeric and oligomeric flavanols, isolated from grape seeds, have been exhibited to hold a positive impact on patients with microalbuminuria, improving kidney function in individuals with diabetes mellitus (Rashid et al., 2018). Scientists also discovered that feeding diabetic nephropathic mice grape seed extract significantly reduced kidney damage and increased kidney function. Western blot analyses had identified grape seeds as one that regulates milk fat EGF-8 globule levels in kidneys and consequently suggested a hypothesis on pathogenesis of diabetic nephropathy (Sochorova et al., 2020). Grape seed extract was found to have produced diabetic nephropathic mice with considerably low levels of kidney damage and enhanced kidney function. Using Western blot examination, grape seeds-maintained milk fat EGF-8 globule levels in kidneys constant, resulting in new hypotheses regarding diabetic nephropathy procedure (Sochorova et al., 2020). In addition, grape seed extract was shown to reverse pancreatic damage and improve the form and function of pancreatic islets in streptozotocin-deceived diabetic rats, a chemical that kills insulin-producing cells (Irak et al., 2018). Vitamin supplements enriched with virgin grape seed oil also lowered insulin resistance, with the polyphenols in the oil thought to be responsible (Li et al., 2020).

5.2.2. Cardioprotective activity

GSPs control lipid metabolism, transferring cholesterol and excreting through bile. Researchers reported that high dosages of GSPs highly reduce plasma triglycerides and apolipoprotein B and consequently reduce cardiovascular risk in healthy rats (Unusan, 2020). GSPs also defend against peroxynitrite damage in endothelial cells and dilate the arterial wall to uphold enhanced cardiovascular wellness (Sochorova et al., 2020). In a specific clinical trial, 400 mg of GSP extract per day for 12 weeks decreased systolic blood pressure by 13 mmHg in middle-aged pre-hypertensives. GSPs were able to help the heart recover after myocardial infarction by guarding heart cells through PI3K/Akt pathway, promoting the function and structure of the cardiac tissue in mice (Ruan et al., 2020). Also, GSP extracts suppressed oxidative stress after high-fat diets. The 300 mg decreased lipid hydroperoxides and increased HDL-linked serum paraoxonase (PON) activity by augmenting antioxidant levels in plasma that decelerates the breakdown of LDL (Kwatra, 2020). In ischemic reperfusion research, 100 mg/kg GSPs reduced free radicals by 75% in rats, showing they have strong potential to reverse oxidative damage during ischemia (Liu, 2018).

5.2.3. Anticancer activity

Grape seed extract (GSE) is rich in phenolics that possess strong anticancer activities by acting on tumour cells without damaging normal cells. The drugs induce the synthesis of pro-angiogenic factors such as angiopoietins and vascular endothelial growth factors, along with inhibiting the PI3K/PBK signalling cascade, leading to the apoptosis of cancer cells (Gupta et al., 2020). Proanthocyanidins, for example, attach to signalling molecules and exert cytotoxic action, killing cancer cells. They also regulate MAPK and NF-B gene expression, thus preventing the cell's ability to migrate and spread cancer (Unusan, 2020).

Chemotherapy works, but it tends to damage the cells that have recovered. Studies demonstrated that GSE at a dose of 25 g/ml mitigates this damage, decreasing apoptosis rates by 50 % in healthy liver cells when used in combination with Idarubicin and 4-hydroxyperoxycyclophosphamide, thus indicating its curative activity (Leigh, 2003). In colorectal cancer experiments, GSE prevented lung metastasis and demonstrated its ability to slow down cancer proliferation (Derry et al., 2014). Moreover, in epidemiological studies from 2002 to 2009, increased intake of flavonoids and proanthocyanidins were associated to a decreased risk of advanced prostate cancer, though this effect was not measured at late stages (Bagchi et al., 2014).

One of the most potent ingredients, Procyanidin B2 3, 3″-di-O-gallate, has shown effective results against prostate cancer cell proliferation. It suppresses colony growth, kills cells and arrests cell cycles in many prostate cancer cell lines (Zhu et al., 2015). Additionally, GSE polyphenols regulate apoptosis, a process used to inhibit uncontrolled cell growth that contributes to cancer and neurodegenerative disease

(Bhise et al., 2014). So, phenolic compounds and proanthocyanidins are a multidisciplinary approach to treating cancer – by inducing the death of tumour cells, defending normal cells, and preventing cancer growth and dissemination.

5.2.4. Gut microbiota modulation

Grape seed proanthocyanidins (GSPs) are highly digested by gut microbiota, increasing their beneficial effects on the colon. Most GSPs are not assimilated through the small intestine, and only a very small percentage enduring glucuronidation (Unusan, 2020). These studies emphasize that grape seed and grapefruit extracts rich in proanthocyanidins are antioxidant protection for the GI tract by reducing oxidative stress on intestinal walls. Massive amounts of these extracts have been exposed to counteract reactive oxygen species (ROS) produced by poor diets, in particular by fasting animals (Sochorova et al., 2020). Grape seed extract has antioxidant qualities and also aids in controlling gastrointestinal health. According to Zhao et al. (2021), rats with colon infections caused by the carcinogen PhIP can benefit from its ability to sustain *Lactobacillus* levels, which in turn improves gut health. Additionally, GSE aids in intestinal flora regeneration in mice fed a fat-rich diet and given antibiotics (Lu et al., 2019). Additionally, Vislocky and Fernandez (2010) found that GSE and doxorubicin improved immunity in mice (S180), which are animals affected by sarcoma. Proanthocyanidins improved metabolic health indices in female rats when derived from grape seed extract from France. In this way, they can induce metabolic diseases (Casanova-Marti et al., 2018).

Interestingly, GSPs also elevate levels of the hormone glucagon-like peptide-1 (GLP-1), a hormone that induces feelings of fullness. This relationship has led numerous studies to investigate how GSPs influence entero-hormone synthesis and gut microbial populations (Averilla et al., 2019).

5.3. Grape pomace (GP)

5.3.1. Anti-diabetic

There has been a rise in incidence of bioactive chemicals present in plants as possible natural methods of diabetes control. One possible alternative could be blocking compounds, which consist of essential carbohydrate-digesting enzymes such as glucosidase and amylase (Almanza-Oliveros et al. 2024). Citrus pomace contains the highest amount of these phenolic compounds, such as peonidin-3-O-acetylglucoside, catechin, quercetin-3-O-glucuronide, and isorhametin-3-O-glucoside; these chemicals inhibit the -amylase enzyme (Kato-Schwartz et al., 2020). Compared to the commonly employed diabetic drug acarbose, grape pomace juice inhibited the enzymes at 56 % for α-amylase and 98 % for α-glucosidase (Huamán-Castilla et al., 2021). In the same vein, it has been established that type II diabetic mice with enhanced insulin resistance and blood sugar control were administered a mixture of grape pomace and Omaja fruit extract. In later studies, researchers indicated that red grape pomace extracts had high levels of phenolic compounds and flavonoids, which suppressed gut α-glucosidase, reducing postprandial hyperglycemia by as much 35 % in diabetic mice, comparable to the classical synthetic drug (Wang et al., 2024).

5.3.2. Cardioprotective activity

Products containing Grape Pomance (GP) have proven beneficial in lowering cardiovascular risk and multiple studies have demonstrated the same. Taking into consideration how human intervention trials have shown that blood pressure drops 3–8 % in patients with metabolic syndrome, and up to 14.5 % in hypersensitive patients after GP supplementation (Taladrid et al., 2023). In animal models, 15% GP combined with cholesterol decreased liver and serum cholesterol by 50–70% while enhancing HDL by 26% (Yu & Ahmedna, 2013). More studies also showed that GP was cardioprotective, suppressing platelet formation, modulating lipid levels, and relaxing blood vessels. Such effects, however, did not depend on grape variety but were strongly affected by extraction solvent selection. The anti-aggregation effects were strongest for ethanolic extracts (Muñoz-Bernal et al., 2021; Choleva et al., 2019). The cardiovascular advantages of grape polyphenol are believed to be caused by a range of compounds, such as flavonoids, non-flavonoids, and anthocyanins (Perdicaro et al. 2017). Examples of such compounds are catechins and malvidin-3-O-glucoside. When these polyphenols are given to rats, they boost antioxidant defense and reduce indicators of oxidative stress, thereby guarding the heart (Balea et al., 2018).

5.3.3. Anticancer activity

Current research suggests the anti-cancer activity of GP polyphenols, showing efficacy against several cancer cells (Almanza-Oliveros et al., 2024). Polyphenolic extracts from GP varieties, such as Chardonnay and Syrah, have been shown to reduce the viability of metastatic melanoma cells (B16F10) by 25–50%, depending on dosage, extract form, and treatment duration (Spissu et al., 2022).

In addition, the stabilization of AuNPs by grape pomace extract of Vitis vinifera improved antitumor activity. The process achieves this by inhibiting cancer cell proliferation, increasing ROS production, and interfering with mitochondrial membrane disruption (Nirmala et al., 2017). Investigations in colorectal cancer also support this, showing that aqueous extracts of GP inhibited cell viability and inflammation through reduced vital inflammatory markers and increased antioxidant enzyme expression (Recinella et al., 2022). Interestingly, GP extracts showed strong antiproliferative activity towards colon cancer cells (HT29 and SW480) in simulation models of intestinal digestion, implicating that GP may increase the bioactivity of polyphenol (Caponio et al., 2022). Solid-state fermentation of grape pomace can also extend these anticancer activities by adjusting the phenol content and may further improve the anticancer property of GP on different cancers (Miškovíc-Špoljaríc et al., 2023; Šelo et al., 2023).

5.3.4. Gut microbiota modulation

Grape pomace (GP) obtained from *V. vinifera cv. Negroamaro* has shown to support the development of beneficial prebiotics, particularly *Lactiplantibacillus plantarum* 12A and PU1, *Lacticaseibacillus paracasei* 14A, and *Bifidobacterium breve* 15A. The results confirmed that grape pomace (GP) also significantly improved bacterial cell density to levels of more than 9.0 CFU/g and improved survival under simulated conditions of digestion by one cycle log compared to starting cell density (Campanella et al., 2017).

Similarly, another research conducted investigated the role of supplementing GP from *V. labrusca cv. Isabel* to goat yogurt on the growth and metabolic activity of *Lactobacillus acidophilus* La-05, *Lacticaseibacillus casei* LAFTI L-26, and *Bifidobacterium animalis* subsp. *lactis* Bb-12. Over 48 h, the GP-enriched yogurt boosted bacterial growth, attaining microbial survival rate beyond 7 log CFU/mL, however boosting bacterial metabolic activity, demonstrated by a drop in pH levels (Silva et al., 2022).

Further studies also reported structural benefits in the gut, such as increased villus length and enhancing the balance between villus height and crypt depth ratio in various sections of the intestine, including the jejunum, ileum and colon of animals. GP was also useful in lowering colonic lesions and shortening in rats under DSS and TNBS-induced stress. These effects were attributed mainly to the plant-based fiber and fiber-associated polyphenols in GP, which were more valuable than free polyphenols (Taladrid et al., 2023).

5.4. Grape leaf

5.4.1. Anti-diabetic

Numerous studies highlighted the anti-diabetic potential of grape leaves, involving various proteins and enzymes in managing glucose. Tests suggest that *Vitis Vinifera* leaf extracts, directed at 100 mg/kg and

200 mg/kg doses over 12 weeks, may safeguard prediabetic individuals from peripheral changes, though they do not significantly alter glucose homeostasis or nerve fiber length (Rana et al., 2022). Besides, the alpha-amylase inhibition mechanism by grape leaf compounds, particularly flavonoids, remains complex. Findings suggest that flavonoids in the stomach interact with dietary starch and saliva-derived nitrous acid, then inhibit alpha-amylase activity and form complexes in the intestine, reducing starch digestion. In addition, the tannins' inhibit alpha-amylase via hydrogen bonding, and flavonoids rich foods may lower diabetes risk by regulating glucose and insulin (Mohammed et al., 2020). Further studies support numerous plant-based flavonoids to serve as plant-based blockers of both α-amylase and α-glucosidase (Alara et al., 2018b). Consequently, grape leaves, rich in beneficial flavonoids, offer promising anti-diabetic effects by regulating glucose metabolism through multiple pathways.

5.4.2. Cardioprotective activity

Studies show that water and methanol based extracts derived from red grape (*Vitis vinifera*) leaves can help reduce body weight while improving lipid profiles by lowering LDL and raising HDL levels, indicating potential anti-hypercholesterolemic effects (Devi and Singh, 2017). Interestingly, a notable pharmaceutical product, Antistax®, derived from the aqueous extract of red wine leaves, is widely used to alleviate chronic venous insufficiency (CVI) symptoms. Besides, clinical trials demonstrate this extract to enhance blood circulation in skin capillaries and boosts oxygen supply. Additionally, oral administration of red *Vitis vinifera* leaf extract has been demonstrated to improve blood flow in patients with chronic venous insufficiency (CVI), potentially increasing oxygen levels compared to placebo groups, decreasing leg edema, and reducing ankle circumference (Maamoun, 2022).

Furthermore, grape leaf extract was examined in women with lower limb plexopathy undergoing long-term hormone therapy. After a 12-week treatment, it reduced calf and ankle circumference, decreased great saphenous vein (GSV) diameter, alleviated venous issues and improving patients' quality of life. Its antioxidants boost nitric oxide production, improving blood flow (Rana et al., 2022).

5.4.3. Anticancer activity

Grape leaf (*Vitis vinifera L.*) extracts are regarded as a valuable source of phenolic-rich material and exhibits strong antioxidant activity. Recent investigations revealed grape leaf extracts to possess bioactive phenols with considerable antioxidant and antiproliferative effects. At a concentration of 1.98 mg/mL, methanol and water-based extracts inhibited 90.20% and 77.78% of DPPH* radicals, individually. Furthermore, these extracts, at the concentrations of 1.136, 2.27, and 4.54 mg/mL over 72 h, reduced the growth of melanoma A375 and SK-MEL cells (Selma et al., 2021). Likewise in another research, the cytotoxic effects of methanolic extracts from irradiated grape leaves, grape seeds, and mulberry leaves was observed at 5.0 kGy on colorectal carcinoma cell lines (HCT116). All tested samples reduced the growth of HCT116 colorectal cancer cells in a dose-dependent manner, substantially lowering cell viability compared to untreated controls (Abdel-Khalek and Mattar, 2022).

5.4.4. Gut microbiota modulation

Hydroxy methanolic extracts from grape leaf varieties "*Nefza-I*" and "*Marsaoui*" have shown encouraging gastroprotective properties, remarkably in inhibiting ethanol-induced gastric mucosal damage by neutralizing free radicals. These extracts help alleviate oxidative stress and enhance blood flow, improving the gastric mucosal barrier and lowering the severe lesions and blood vessel damage often affected by ethanol. In rat studies, initial treatment with grape leaf extract at doses of 100 mg/kg and 200 mg/kg evidenced more effective in avoiding gastric lesions than the standard drug, omeprazole, demonstrating its potential as a protective agent for gastrointestinal health (Saadaoui et al., 2020). Besides, grape leaf extracts show anti-inflammatory effects. For instance, in cases of *E. papillate*-induced infection, the extract lowered oocyst production, supported normal goblet cell counts, and enhanced antioxidant levels, all of which aided to healthier jejunal tissue in mice (Murshed et al., 2023).

Rich in flavonoids, polyphenols, polysaccharides, and tannins, grape leaves also possess antimicrobial properties that improve the fermentation process of lactic bacteria. Table 5 – depicts the major bioactive compounds present in grape by-products and their associated health effects on gut microbiome. When used as a prebiotic in yogurt, grape leaf powder can help release phenolic acids, which maintain milk stability and decrease harmful intestinal flora, signifying grape leaves as a valued addition to functional yogurt products with potential therapeutic benefits (Djilali et al., 2021).

5.5. Grape skin

5.5.1. Anti-diabetic

A recent study investigated the potential of grape skin extract to protect pregnant and wild-caught rats against diabetic oxidative stress and kidney damage. High dose of grape skin extract (4 g/kg) has been exhibited to effectively counter the disruptive effects on different organs. This indicates that grape skin extract shows promise as an antioxidant in the clinical setting, especially for maintenance of kidney function in diabetes and pregnancy (Sochorova et al., 2020).

5.5.2. Cardioprotective activity

Studies have revealed that rats with SHR treated with grape skin extract for 12 weeks were able to prevent the development of hypertension. In treated spontaneously hypertensive rats (SHRs), the antihypertensive action was attributed to an increase in superoxide dismutase activity, decreased oxidative stress, and reduced triglyceride and cholesterol levels (Sabra et al., 2021). They also concluded that a non-alcoholic extract of grape-skin from *Vitis labrusca*, called GSE, greatly decreased blood pressure in hypertensive Wistar rats. It also promoted vasodilation in distant blood vessels, which requires healthy endothelial cells. GSE was antioxidant too as it inhibited liver microsome lipid peroxidation (De Moura et al.,). These results highlight grape skin extract's potential as a natural aid in controlling hypertension.

Table 5
Key bioactive compounds and their health effects on Gut microbiome of grapes by-products.

Grape and their by-products	Key bioactive compounds	Observed effects on gut microbiome	References
Grapes	Polyphenols, flavonoids, resveratrol	Increases microbial diversity; regulates gut barrier and inflammatory response	(Santa et al., 2019)
Grape Seeds	Proanthocyanidins, catechins	Increases the richness of helpful bacteria (e.g., Lactobacillus, Bifidobacterium)	(Xu et al., 2024)
Grape Pomace	Polyphenols, fiber, tannins	Increases SCFA (short-chain fatty acid) production; aids gut homeostasis and richness of microbes	(Mezhibovsky et al., 2021)
Grape Leaves	Flavonoids, phenolic acids	Possible prebiotic activity by polyphenol-microbiota interactions	(Zorraquín et al., 2020)
Grape Skin	Anthocyanins, resveratrol	Encourages Healthy gut microbes; could suppress growth of disease-causing bacteria; enhances microbiota ratio	(Mokrani et al., 2022)

5.5.3. Anticancer activity

Grape skin anthocyanidins, also known as anthocyanin aglycones, have a much lower binding affinity to the estrogen receptor ERα—about 10, 000 to 20, 000 times ineffective than the natural estrogen estradiol. Conversely, when used at concentrations of 10–20%μmol/L on MCF-7 breast cancer cells, these compounds still demonstrated a mild but statistically noteworthy estrogenic effect. This suggests that, even though their estrogenic activity is uncertain, grape skin anthocyanidins may still influence estrogen-receptor interactions (Zhou and Raffoul, 2012).

6. Applications of grapes and its by-products

Many food, cosmetic, and pharmaceutical applications of grapes and its derivatives have been recounted, since they act as versatile ingredients or additives in distinct domains of industry (Kalli et al., 2018) as depicted in Table 6. The various value-added products of grapes and their by-products and its applications in food, cosmetics, pharmaceuticals, and preservatives are presented in and Fig. (5).

6.1. Food industry

6.1.1. Alcoholic beverages

Around 50 % of harvested grapes are used in wine production, making it a major agro-industrial sector worldwide. In 2019, global wine consumption reached 244 million hectolitres, highlighting its popularity as the second most consumed alcoholic beverage after beer (Chedea et al., 2021). Resveratrol, one notable compound, found in grape skins has been linked to the "French paradox, " where moderate wine consumption correlates with lower coronary heart disease rates along with managing conditions like cancer, obesity, and neurological disorders (Benbouguerra et al., 2021). Additionally, inclusion of grapevine leaves in Shiraz wine production, i.e., 500 g of leaves per batch during fermentation enhanced the carotenoid content of wine and contributed to higher levels of flavor compounds like C_6 alcohols and β-damascenone (Capone et al., 2021). On the other hand, vinegar is a valuable product made through the fermentation of agricultural liquids like wine or cider. The type of raw material, such as grapes for wine vinegar or apples for cider vinegar, determines the vinegar's classification (Singh et al., 2023). Together, wine and vinegar showcase the versatility of grapes and their by-products in creating diverse, beneficial products.

6.1.2. Non-alcoholic beverages

Grape pomace extract, encapsulated in alginate or chitosan-based microparticles, has been used to develop a health-enhancing coconut water beverage without altering its aroma or flavor. Even after digestion, bioactive compounds remained largely intact, and refrigeration at 4 °C slowed the degradation of phenolics and anthocyanins. The beverage also exhibited antimicrobial properties against gut pathogens due to its elevated phenolic and anthocyanin content (Costa et al., 2021). Similarly, another non- alcoholic beverage, fruit teas are gaining popularity due to their antioxidant properties and pleasant taste. Enhancing natural aromas derived from grape pomace further boosts their demand (Ferrer-Gallego and Silva, 2022). Majorly, *Vitis labrusca* grapes are commonly used for preparation of beverages. However, these varieties often lose their distinct taste during thermal processing, unlike American grape varieties, which preserve their characteristic taste in

Table 6
Applications of different grape by-products in different industries.

Industry	Grape by-product	Applications	Key benefits	References
Food Industry	Grapes	Vinegar production	Used as a preservative, adds taste, and offers health benefits	(Singh et al., 2023b)
		Fruit-based spreads	Offers a natural, nutrient-dense alternative to processed jams	(Morelli and Prado, 2012)
	Grape Skins, Seeds, Pomace	Wine production	Rich in resveratrol, associated with cardiovascular health benefits	(Chedea et al., 2021); (Benbouguerra et al., 2021)
	Vine Leaves	Enhancing wine flavor and carotenoid content	Enhances flavor profile and nutritional value	(Capone et al., 2021)
	Grape Pomace Extract	Functional beverage formulation	Enhances antioxidant activity, preserves bioactives, antimicrobial activity	(Costa et al., 2021)
	Grape Pomace, Seeds	Bakery products (bread, biscuits, cakes, muffins)	Enhances nutritional profile, boosts antioxidant content	(Ferhi et al., 2019); (Jridi et al., 2019); (Yalcin et al., 2022)
	Grape Skin Flour	Pasta, dairy products (yogurt, kefir)	Enhances flavor and probiotic activity	(Gaita et al., 2020); (Kandylis et al., 2021)
Cosmetics	Grape Leaf Extract, Seed Extract, Grape Water	Skin care (moisturizers, anti-aging creams)	Anti-inflammatory, antioxidant, enhances skin hydration	(Singh et al., 2023b); (Serra et al., 2023)
	Grape Stem Extract	Anti-aging formulations	Reduces wrinkles, redness, and firms skin	(Soto et al., 2015)
	Red Grape Anthocyanins	Melanoma treatment	Inhibits melanoma cell growth without damaging normal cells	(Diaconeasa et al., 2017)
	Grape Polyphenols, Pomace	Sunscreens, anti-pigmentation creams	Reduces melanin synthesis and pigmentation	(Malinowska et al., 2024);(Kalli et al., 2018)
	Grape Seed Oil	Moisturizers, acne treatment	Non-greasy, hypoallergenic, enhances hydration	(Martin et al., 2020)
Pharmaceuticals	Grape Extract, Grape Seed, Red Wine Powder	Dietary supplements	Antioxidant, blood-sugar-reducing, cholesterol-reducing activity	(Weseler and Bast, 2017)
	Red Vine Leaf Extract	Treatment for chronic venous insufficiency (CVI)	Anti-inflammatory, antioxidant activity	(Azhdari et al., 2020)
	Grape Seed Proanthocyanidin Extract (GSPE)	Diabetes management	Anti-oxidative stress protection of retina	(Sun et al., 2016)
	Grape Pomace Microemulsions	Drug delivery systems	Improve topical drug absorption	(Kumar et al., 2014)
	Grape Extracts	Athletic performance enhancement	Reduce oxidative stress, raise hemoglobin	(Elejalde et al., 2020)
Preservatives	Grape Leaf and Stem Extracts	Natural food preservatives	Antimicrobial, antioxidant activity in juice and ready-to-eat fruits	(Badr et al., 2021)
	Grape Seed Extract	Meat preservation	Decrease nitrite residues, increase shelf life	(Zhou et al., 2020)
	Grape Seed Extract	Seafood preservation	Prevent microbial growth, spoilage	(Kim et al., 2018)
	Grape Peel Powder	Bakery product preservation	Increase stability of lipids, decrease peroxide activity	(Ukom et al., 2022)
	Grape Leaf Extract	Anti-browning agent for fresh produce	Rich in resveratrol, associated with cardiovascular health benefits	(Singh et al., 2023b)

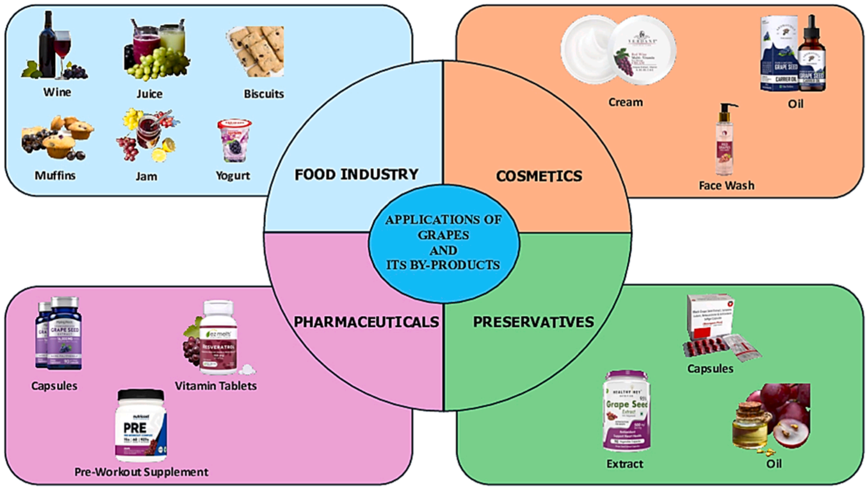

Fig. 5. Value-added products of grapes and their by-products: applications in food, cosmetics, pharmaceuticals, and preservatives.

juice (Cosme et al., 2018).

6.1.3. Bakery products

A series of studies revealed the incorporation of grape by-products into baked products, thus, enhancing their nutritional and sensory properties. The incorporation of grape leaf extract (GLE) in biscuits revealed it to slightly reduce moisture content and increase ash content. Nonetheless, GLE-enhanced biscuits received positive feedback for their color, texture and taste (Ferhi et al., 2019). Likewise, incorporation of grape leaf powder (GLP) to pistachio calissons enhanced the antioxidant activity, preserved color, and improved taste of the product, particularly, at addition of 3% GLP (Jridi et al., 2019). Additionally, muffins fortified with grape seed flour (GSF) resulted in higher nutritional value and antioxidant capacity. These baked products were quite different in texture and colour, likely due to the flour used and the breakdown of anthocyanins in the oven (Yalcin et al., 2022). GP in breads and cakes had potential, for one. In particular, 6% GP breads and 4% GP cakes had the best sensory properties (Boff et al., 2022; Nakov et al., 2020).

6.1.4. Other products

Several foods could use these uses of grape extracts. For example, it was discovered that the inclusion of 3% and 6% GP skin flour in pasta enhanced its taste over traditional pasta (Gaita et al. 2020). Yogurt, kefir, and other fermented milk products have long been utilized as probiotic sources and have experienced enhanced functionality through the inclusion of grape-derived ingredients such as extracts, skin flour and pomace. This maintains their probiotic quality as well as boosts their nutritional potency (Kandylis et al., 2021). Aside from wine, grape fruits like jams are non-alcoholic products that combine fruit, sugar, pectin and citric acid to offer a delicious, nutrient-rich year-round supplement to the diet (Morelli and Prado, 2012).

Furthermore, new advancements in additive manufacturing (AM) have brought forth innovative methodologies such as three-dimensional food printing (3DFP) to foster food personalization and sustainability. 3DFP, particularly using extrusion-based printing, makes it feasible to fabricate intricate food structures by depositing food material layers (Pant et al., 2023). This technology has created new avenues for the inclusion of food processing by-products as functional components in printable food formulations. Experiments have demonstrated the possibility of utilizing soy protein-based hydrogels with gelatin and agar production residues for 3D printing. The rheological behavior, printability, and structural stability of the end-products were investigated for these formulations and correlated their mechanical and physicochemical properties with residue content (Uranga et al., 2023).

In this regard, valued grape by-products like pomace—constituting a high dietary fiber, polyphenol, and natural color content—may present potential bio-ingredients in 3DFP. Their high fiber content would enhance texture and shape retention, while their bioactive constituents impart additional nutritional and functional benefits. Incorporating grape by-products in 3D-printed food may contribute towards the production of sustainable, healthy, and sensorially attractive foods. Yet, more research is required to assess their printability, their compatibility with current food matrices, and acceptability by consumers.

6.2. Cosmetics

The products of *Vitis vinifera* such as grape leaf extract, grape seed extract and grape water were found to be perfectly safe for cosmetic use (Singh et al., 2023). The soothing and free-radical fighting properties of grape stem extracts diminishes fine lines, wrinkles, and redness while keeping the skin luminous and youthful. They are viewed as a building block of environmentally responsible, natural beauty products (Serra et al., 2023).

Anti-aging grape compounds, such as phenolics, help to combat the aging process and strengthen the skin's antioxidants. Skin-care products containing these phyto-compounds offer the dual benefit of photo-protection and skin-renewing (Soto et al., 2015). Moreover, anthocyanins from red grapes have been reported to suppress the growth of melanoma cells while leaving healthy skin cells unaffected (Diaconeasa et al., 2017). Grape polyphenols, such as stilbenoids are known to counter skin pigmentation by reducing melanin and suppressing pigmentation. Grape Pomace and seeds are also antibacterial and anti-fungal in nature, and can therefore be used in skincare products (Malinowska et al., 2024 ;; Kalli et al., 2018). *Vitis Vinifera* Seed Oil, a popular ingredient in moisturizers, satisfy due to its non-greasy feel, hydrating and hypoallergenic nature. It replenishes linoleic acid to rehydrate, diminishes swelling to firm skin, and improves the health of the skin, especially beneficial to people with acne (Martin et al., 2020).

6.3. Pharmaceuticals

US nutritional supplements contain vine extract, grape seed and wine powder, each valued for their antioxidant, blood-sugar-lowering and cholesterol-lowering properties. Extracts of grape seeds have been used therapeutically in Europe for decades. Physicians often use Oligomeric Proanthocyanidins (OPCs) in the range of 50–200 mg/day as a complementary therapy to traditional treatments (Weseler and Bast, 2017). Likewise, flavonolic red vine leaf extracts are known to heal endothelial cells and decrease inflammation, oxidative stress and swelling, thus decreasing CVI symptoms (Azhdari et al., 2020).

Grape-based supplements have significant efficacy in controlling hyperglycaemia. Grape seed proanthocyanidin extract (GSPE), for example, was shown to help shield the retina from excessive blood sugar through decreasing oxidative stress through the Nrf2-mediated signalling (Sun et al., 2016). Furthermore, technologies such as grape pomace microemulsions are already under the microscope in the pharmaceutical field as viable drug carriers. These microemulsions enable topical medications such as antivirals, anti-inflammatories, antioxidants and anaesthesia to absorb better, leaving consumers with a safer and more natural alternative (Kumar et al., 2014). Grape pomace extracts have also been shown to regulate post-meal blood sugar elevation by preventing the production of -glucosidase, which is essential for carbohydrate digestion and glucose absorption, demonstrating their utility as a natural diabetic management agent (Fontana et al., 2013). Furthermore, grape extracts may benefit athletes. A study of 20 top handball players reported that, after one month of daily use of 400 mg of flavanol-standardized grape extract, antioxidant defences were enhanced, oxidative stress was lessened and physical performance increased. It also decreased Plasma Creatine Kinase (CK) and increased haemoglobin levels, suggesting better cellular defense against high-intensity exercise (Elejalde Caravaca et al., 2021).

6.4. Preservatives

Vine leaf and stem extracts show strong antioxidant as well as antimicrobial properties due to their richness in phenolic compounds like epicatechin and quercetin. These extracts, when microencapsulated, improve shelf life and protect bioactive components, making them effective natural preservatives for food products like juices and ready-to-eat fruits (Badr et al., 2021). Likewise, grape seeds are valuable for food preservation. In Japan, grape seed extracts have been used as additives, showing high reducing power and antioxidant activity at specific concentrations. For instance, at 100 ppm, these extracts achieved 65–90% antioxidant activity, highlighting their effectiveness in maintaining food quality (Ma and Zhang, 2017). Grape seed extract has also proven to be effective in meat preservation. A combination of grape seed extract and smoked sausages in Western style helped not only make them look better but extend their shelf life by eliminating the nitrite residues and removing the potentially cancer-causing N-nitrosamine (Zhou et al., 2020). Likewise, grape seed extract's shelf-life effects were evaluated on fresh shrimp in refrigerator storage. The combination of chitosan and alginate essential oil coatings inhibited microbial growth, halted melanosis, and slowed total volatile basic nitrogen (TVB-N), thereby preserving the freshness of the shrimp without very much change in sensory quality (Kim et al., 2018).

Furthermore, extracts from nature, including powdered grape peels, have proven effective when used to make baked goods, especially cakes. Cakes baked with this powder had lesser- peroxide, yeast, mould, lipase activity, which made the lipids more stable. Even after storage for 7 days, the cakes retained their texture and flavor (Ukom et al., 2022). Alternatively, grape leaf extract (GLE) prevented the enzymatic browning of freshly-cut lettuce quite effectively. The heat-treated GLE reduced the levels of polyphenol oxidase (PPO) that would have browned the lettuce and prevented it from being too heavy to store. Because of its low price, and non-toxic properties, GLE presents an amazing opportunity as a natural anti-browning agent but requires further studies to optimize its utilization in food manufacturing (Singh et al., 2023).

7. Innovative approaches in the valorisation of grape by-products

Grape derivatives, especially grape pomace, have been the subject of recent innovations into a range of value-added applications in several sectors. One emerging use is the utilization of grape pomace in functional animal feed, where bioactive compounds could enhance meat quality and offer key nutrients including fiber and protein. However, it remains a largely underused resource, with only about 3% of grape pomace worldwide being used in this way (Arend et al., 2022). For the biofuel industry, the prospect of utilizing grape pomace as a renewable feedstock is currently being considered. The property of grape pomace that has been credited as being wrong for these activities is that it contains a high proportion of organic matter appropriate for anaerobic digestion while simultaneously providing a beneficial avenue of waste disposal and clean energy generation with a reported yield of biogas in the range of 8.7 kJ/100 g (Wang et al., 2024). Parallelly, the cosmetic and pharmaceutical industries could also provide promising outlets for grape by-products. Importantly, extracts with powerful antioxidant properties including gallic acid have been reported to inhibit enzymes like collagenase and elastase involved in skin aging. Increasingly, these natural compounds are being considered as safer substitutes for synthetic chemicals associated with irritation or health concerns (Tapia-Quirós et al., 2022; Ferreira and Santos, 2022). Consequently, all these valorisation strategies reduce the load on the environment and provide a route for circular economy models by turning grape waste into functional feed, fuel, and health-related products.

8. Grape by-products: limitations, regulations, and economic feasibility

Despite its nutritional and therapeutical benefits, the widespread utilisation of grape by-products is still facing various challenges. One of the major concerns is related to the controlled disposal of grape residues such as the skin, seeds, stem and pomace after juice extraction. For instance, the disposal of such wastes to land and water bodies causes ground water contamination as well as generate unpleasant odour (Bhise et al., 2014). The variabilities in quality caused by climatic conditions and post-harvest treatments are another complication in the standardisation of grape by products in food products, pharmaceutical and cosmetic (Vega-Vega et al., 2013; Padilla-González et al., 2022). Additionally, there are limitations in large scale extraction of bioactive compounds from grape by products like polyphenols and flavonoids. This can be attributed to the low water solubility, chemical instability and less bioavailability of those compounds. While nano-emulsion-based systems are promising in terms of enhanced delivery and stability, their actual commercial viability is hampered by high production costs (Davidov-Pardo and McClements, 2015). Another constraint in grape by product management is the economic feasibility, as logistical and storage facilities in remote regions without processing units are expensive. Even though decentralised valorisation units in grape growing areas will minimize such issues, advanced development and commercialisation of grape waste-based value-added products requires considerable investments (Wang et al., 2024). Another limitation is the use of hexane for solvent extraction in food industry. However, alternatives such as ethanol and supercritical CO2 are considered safe to use, but its effect on food grade standards are yet to be explored (Taifouris et al., 2023).

Regulatory barrios are another challenging concern in managing grape by product waste from industries. The legal frameworks regarding safety and commercialization of any grape based products are different in every region. For instance, grape by products based functional foods and nutraceuticals must withstand clinical trials and toxicological profiling to make claims about health (Assmann et al., 2014; Granato et al., 2020). In the EU, the EFSA carries out extensive documentation, expressing concerns regarding products like 'dry grape extract 60–20' due safety concerns (Bampidis et al., 2020). Also, in order to be legally sold as nutraceuticals or functional foods, grape by-products need to comply with strict regulatory standards such as free access without a prescription, scientifically proven health benefits, and pre-approved food labelling statements. Moreover, adhering to regulatory agencies like ANVISA (Brazil), EFSA (EU), and FDA (USA) is critical to achieve legal endorsement (Brown et al., 2018; Lenssen et al., 2018). Therefore, the creation of a harmonized regulatory framework is required for facilitation and safe commercialization of products derived from grape by-products.

9. Unlocking potential: future research and biotechnology in grape by-product utilization

With an increasing focus on resource depletion and environmental degradation, the world is now shifting towards more sustainable methods. In accordance with the United Nations' Sustainable Development Goals—particularly with the target to diminish food loss by 50% by 2030—there is a growing interest in utilizing agro-industrial waste such as grape by-products for value-added applications (Ardra and Barua, 2022). Here after, future studies need to concentrate on developing eco-friendly extraction procedures and bioprocesses capable of recovering more bioactive components from grape pomace, seeds, skins, and leaves (Ilyas et al., 2021). Though, traditional processes like solid–liquid extraction (SLE) and ultrasound-assisted SLE (US-SLE) are already in practice and provide good results if optimized. Likewise, novel environment-friendly technologies like supercritical fluid extraction (SFE) and accelerated solvent extraction (ASE) have produced similar or superior results (Kalli et al., 2018). However, these new techniques need more tests on a large scale to validate their cost-effectiveness, efficiency, and suitability for commercialization. Besides, future research must also examine process modelling and simulation for better understanding and facilitating the scaling up of operations seamlessly.

In addition, innovation in fermentation technology exhibits the incorporation of grape pomace to enhance aroma and polyphenolic content in wines such as *Pinot Noir*, rendering them both palatable and healthy (Wimalasiri et al., 2022). Furthermore, nanotechnology is emerging as a valuable tool in the use of grape waste—especially for production of bioactive food packaging, wound healing products and drug delivery systems. Though, it's important not to overlook the potential risks of these nanomaterials. Further studies are needed to explore the long-term impacts of antimicrobial particles that are emitted into the environment or migrating into foods, thus, damaging the gut health or organs such as the brain—mainly with materials such as silver or gold nanoparticles (Samaddar et al., 2018). The potential future application of grape derivatives relies on an integrated approach with environmentally friendly technologies, biotechnology, and comprehensive safety evaluations. Moreover, additional research must also be directed towards the discovery of lesser-known plant constituents and their testing for health benefits, as well as overcoming regulatory, economic, and consumer acceptance hurdles. Interdisciplinary collaboration among food science, biotechnology, environmental science, and medicine experts will be crucial to comprehend the complete value of grape waste for application in wellness, nutrition, and sustainable industries.

10. Conclusion

Grapes are among the most abundant and widely eaten fruits globally and have many polyphenols in them, including proanthocyanins, anthocyanins, and resveratrol. These substances account for most of the health effects found in grapes, such as their anti-inflammatory, anticancer, anti-diabetic and antimicrobial effects. In addition to its bioactive qualities, grapes (and their seed, pomace, leaf and skin products) are also an abundant source of dietary fibre, minerals, carbohydrates, and protein. This multi-nutrient mix renders grapes and their by-products highly valuable raw materials for food and non-food processing. Given these benefits, this research focuses on the nutritional content, and bioactive elements in grapes and their various residues. For purposes of nutritional value, grapes and grape products contain high concentrations of resveratrol and flavonoids, which have potent antioxidant and anti-inflammatory effects. Therapeutically, grape residues offer promise for prevention of diseases such as diabetes, heart disease, obesity, and cancer. One of their many roles is to modulate inflammation and oxidative stress, two of the major engines of many health functions. On the commercial level, grape juice is used in vitamins and cosmetics, wine, jam and fermented milk. Their potential extends to functional foods and nutraceuticals, providing health benefits beyond basic nutrition. Finding the exciting opportunities for research to identify bioactive compounds and understanding its mechanism. It would be ideal to work on formulation and better clinical trials for the same, to ensure full usage of the foods within finished goods. Moreover, we can make operations more environmentally friendly by industrialising them. The eco-friendlier the entire production remains; the more market adoption will occur. If there can be possible co-ordination of efforts over these concerns, a cleaner, more resilient future for humans and Earth is within our grasp.

Funding

Funding Project No TKP2021-NKTA-32 has been implemented with support from the National Research, Development and Innovation Fund of Hungary, financed under the TKP2021-NKTA funding scheme.

Ethical statement - studies in humans and animals

The present study does not involve any human or animal study.

Ethics approval consent

Not applicable

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Not applicable

CRediT authorship contribution statement

Mitali Bhutani: Writing – review & editing, Visualization, Software, Methodology, Formal analysis, Writing – original draft, Validation, Resources, Investigation, Data curation. **Supriya Singh Gaur:** Writing – review & editing, Validation, Resources, Methodology, Formal analysis, Visualization, Supervision, Project administration, Investigation, Data curation. **Rafeeya Shams:** Writing – review & editing, Validation, Software, Methodology, Funding acquisition, Visualization, Supervision, Project administration, Investigation, Formal analysis. **Kshirod Kumar Dash:** Writing – review & editing, Visualization, Supervision, Resources, Methodology, Funding acquisition, Data curation, Writing – original draft, Validation, Software, Project administration, Investigation, Formal analysis, Conceptualization. **Ayaz Mukarram Shaikh:** Visualization, Software, Funding acquisition, Validation, Resources, Formal analysis. **Kovács Béla:** Visualization, Supervision, Project administration, Writing – review & editing, Validation, Software, Funding acquisition.

Declaration of competing interest

The authors have no competing interests to declare that are relevant to the content of this article.

Availability of data and materials

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

Data availability

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

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