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Review

Unveiling the Utilization of Grape and Winery By-Products in Cosmetics with Health Promoting Properties

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Abstract: Winemaking by-products, such as grape pomace and grape seed oil, provide sustainable and eco-friendly resources for cosmetics and are rich in bioactive compounds like phenolic bioactives, proteins, and lipids (i.e., unsaturated fatty acids, bioactive polar lipids, and carotenoids). These compounds, extracted using advanced techniques such as ultrasound, microwave, and enzyme-assisted methods, exhibit antioxidant, antimicrobial, anti-aging, and anti-inflammatory properties. In vitro and in vivo studies on keratinocytes and fibroblasts demonstrate their efficacy in enhancing skin hydration, elasticity, and UV protection while reducing oxidative stress and inflammation through pathways like SIRT1 and HSP47. Encapsulation techniques further improve their stability and bioavailability. The aim of this review is to investigate in detail the advanced techniques for the extraction of bioactive compounds from winemaking by-products and to evaluate their effectiveness in the isolation of phenolic compounds, proteins, and lipids. At the same time, it focuses on the application of the extracted compounds in the cosmetics industry, highlighting their contribution to products with antioxidant, anti-aging, antimicrobial, and anti-inflammatory properties. Finally, special emphasis is given to encapsulation techniques to improve their stability and bioavailability, with the aim of developing innovative and sustainable cosmetic products.

Keywords: grapeseed; grape pomace; bioactive compounds; winery by-products; cosmetics; skin health; fibroblast; keratinocytes

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1. Introduction

Grape cultivation is one of the most lucrative and traditional crops in the world and is known for its beneficial effects on human health [1]. With an annual production of more than 70 million tons, grapes are among the fastest-growing fruit crops worldwide (OIV, 2018) [1]. The International Organization of Vine and Wine (OIV) estimates that there were about 7.6 million hectares (mha) of vines worldwide in 2017, while 20 million tons of wine by-products are generated each year, corresponding to 30% of the total quantity of vinified grapes [1]. However, the winemaking process, along with the pressing and maceration of the grapes, produces not only wine but also a large volume of organic waste. This waste includes the grape seeds, which account for the largest proportion of the waste (62%), but also the lees (14%), stems (12%), and dehydrated sludge [2,3]. For many years, these by-products have mainly ended up in landfills, but in recent years there

have been several attempts to introduce them into various industries, one of which is the cosmetics industry [3]. These efforts have become imperative, as grape by-products present significant environmental problems, mainly due to their low pH and high content of phenolic compounds. These compounds are resistant to biodegradation since they have phytotoxic and antibacterial activity. Grape seeds contain a high percentage of organic carbon (31–54%), which contributes to water pollution and the emission of unpleasant odors. In addition, the parasites and tannins found in these grape residues, together with other compounds, can negatively affect the flora and fauna of the area [3,4]. The importance of the circular economy of the by-products of oenology becomes even more significant when considering the rate of disposal of oil pomace, which constitutes seven million tons per year [1].

This is because, in the context of the circular economy, these by-products are not treated as waste, but as secondary raw materials that can be used to produce new value-added products. This model aims to reduce waste, maximize the use of resources, and create sustainable industrial processes [5].

The by-products of winemaking support the circular economy model, with applications in various sectors beyond the cosmetics sector. In the food industry, they increase the antioxidant activity and shelf life of products [5]. In the energy sector, they play an important role in the circular economy, as they are transformed from waste into valuable sources of biofuels. Their use for the production of biodiesel, bioethanol, and biogas reduces dependence on fossil fuels and minimizes the environmental footprint [6–8]. In the agricultural sector, they can improve soil fertility and reduce pollution. Their high polyphenol content ensures the controlled release of nutrients [9] and helps in decontamination from chemical pollutants [10]. These applications support sustainable agricultural practices and reduce the environmental footprint.

Research on the by-products of winemaking should focus on optimizing the extraction parameters to achieve maximum yield and quality of bioactive compounds. Advanced extraction techniques, such as supercritical fluid extraction (SFE), have already proven to be more efficient than traditional methods, as they require fewer solvents, reduce processing time, and are more environmentally friendly [11–13].

At the same time, it is necessary to focus on improving the bioavailability of extracts so that bioactive compounds can be absorbed and utilized more efficiently by the human body or maintain their stability in cosmetics and food. Encapsulation techniques, for example, can protect compounds from degradation and increase their shelf life and future research should prioritize enhancing these techniques to improve the stability, bioavailability, and targeted delivery of bioactive compounds, ensuring their maximum efficacy in industrial applications [14].

In addition, the development of sustainable treatment techniques that ensure both efficiency and environmental friendliness is required. These technologies must reduce environmental impacts, minimize the waste generated, and be economically viable for industrial scale [12,15].

Finally, addressing regulatory gaps and creating clear standards is necessary for the wider use of grape by-product extracts in industrial applications. In the European Union, their use in food and cosmetics remains limited, as there are no clear guidelines on permitted limits and safety procedures [16,17].

Depending on the geographical location, climate, temperatures, and soil type, different grape varieties are grown, resulting in a variation in bioactive molecule content between different grape varieties, especially between red and white grapes [3]. However, several studies have shown that in most varieties the bioactive components of grapes remain after the vinification process in the by-products, i.e., in the grape seeds [1]. Thus, grape

pomace, which is a mixture of seeds, stems, and skins, has been found to be rich in valuable compounds such as fatty acids, proteins, carbohydrates, and polyphenols [3].

With proper processing, these compounds present in the core of grapes can offer a wide variety of beneficial properties to the health and appearance of the skin, as they offer antioxidant, antifungal, and antimicrobial action [3]. Polyphenols, including proanthocyanidins and resveratrol, have been shown to modulate critical cellular pathways involved in skin health [18]. In keratinocytes, these compounds reduce oxidative stress and inflammation by lowering reactive oxygen species (ROS) and pro-inflammatory cytokine levels, while also protecting DNA from UV-induced damage. Similarly, in fibroblasts, polyphenols enhance the expression of genes like SIRT1 and HSP47, which are linked to anti-aging processes, promoting skin elasticity and hydration [18–20].

These properties also make grape by-products particularly useful in cosmetic products, especially in anti-aging and skin-whitening products. They can be used to improve skin hydration and softness, reducing roughness, wrinkle depth, redness, and hyperpigmentation. They also protect the skin from oxidative stress and UV damage, acting as photo protectants with a high sun protection factor. In addition, they can inhibit the activity of proteinase, collagenase, and elastase, which are important for the degradation of collagen and elastin in the skin, thus providing firmness and elasticity. Because of these, grape by-products are active ingredients in cosmetics aimed at improving the texture, appearance, and general health of the skin, making it more youthful and resistant to environmental aggressions [3].

This paper aims to provide a comprehensive overview of the use of grape by-products as active ingredients in cosmetics, based on the latest available literature. It focuses on bioactive compounds, such as phenolic compounds and unsaturated fatty acids, and their benefits for skin health and appearance. Furthermore, it highlights advanced extraction techniques that enhance their stability and bioavailability. The innovation of this review lies in associating these bioactive ingredients with molecular mechanisms of action, including the SIRT1 and HSP47 pathways, offering a sustainable and natural alternative to synthetic additives in the cosmetics industry.

2. Methods and Materials

For the preparation of this literature review, a systematic search was conducted across various electronic databases, including PubMed, Scopus, Science Direct, Web of Science, and Google Scholar, with the aim of thoroughly studying the existing literature on the utilization of bioactive compounds derived from grape by-products. The following terms and keywords were used for the search: “grapeseed”, “grape pomace”, “winery by-products”, “bioactive compounds”, “by-products”, “cosmetics”, “extraction methods”, “human fibroblast”, “human keratinocytes”. The titles and abstracts of the articles were carefully reviewed to select the relevant publications during the preparation of this review. This process helped in the initial filtering of sources to ensure that the information contained was pertinent and aligned with the subject matter. The search had no publication date restrictions for the main review. However, in the chapter “Grape Pomace: Active Ingredients in Cosmeceuticals”, the search was limited to the period 2018–2024.

3. Chemical Composition and Properties of Grape Pomace

Vitis vinifera is the species most frequently used for wine production. The health advantages of wine were first recognized in the 1990s because of the “French paradox”, which postulates that despite conventional intake of high levels of sugar and saturated fats, the high consumption of red wine in France decreased the prevalence of coronary heart

disease [21]. Research suggested that the phenolic chemicals found in wine were the cause of this contradiction [22].

The grape industry produces a large number of solid residues, such as liquid filtrate, pomace oil, and stems, which, depending on the type of waste, grape variety, and processing technique, are rich in nutrients and bioactive compounds [23]. The core of grapes has long been underestimated despite its industrial importance as waste. It is usually used to produce distillate, fertilizer, or animal feed. However, interest in alternative uses has increased, and especially for the phenolic content present in these by-products [24].

The core of the grape, the solid waste that remains after the alcoholic fermentation of wine, is particularly rich in phenolic compounds due to the inefficiency of the extraction process during vinification [25]. Ribeiro et al. (2015) [26], found that the highest percentage of phenolic content is found in grape seeds (60–70%), followed by peel (28–35%), and pulp (10%). The main components of grape seeds are fiber, proteins, essential oils, and phenolic substances such as tannins. Grape strains contain tannic chemicals with significant potential in nutritional and medicinal applications, while grape skins are a rich source of anthocyanins with antimutagenic and antioxidant properties [27]. According to Mattos et al. (2017), hydrobenzoic and hydrocinnamic acids, flavonols, stilbenes, and anthocyanins are common phenolic chemicals that have been identified in grape pomace [28].

4. Grape Pomace: Constituents with Health-Promoting Properties

Plant polyphenols are powerful antioxidants. The highest concentrations of phenolic grape compounds are found in stems, peels, and seeds. In general, phenolic compounds of grapes are classified into three main groups: (1) phenolic acids (mainly benzoic and hydroxycinnamic acids); (2) simple flavonoids (catechins, flavonols and anthocyanins); and (3) tannins and proanthocyanidins (Figure 1) [29]. In fact, Feringa et al. (2011) described grape seed extract as a rich source of phenolic compounds, particularly proanthocyanidins (≈90%). Grape seed and bark extracts obtained from pomace contain significant amounts of flavanols and anthocyanins, as well as hydroxycinnamates that are also present in the flesh [30]. According to Yusuf Yilmaz (2004), grape seeds and skins also contain monomeric flavonols and phenolic acid, which contribute to their antioxidant capacity [31]. Muscadine seeds have the highest concentration of gallic acid, while Chardonnay seeds have higher concentrations of gallic acid, catechin, and epicatechin than Merlot seeds. These compounds are lower in grape by-products/waste. Most of the antioxidant capacity in grape seeds is attributed to procyanidins. The grape seeds or skins, in decreasing order, were resveratrol > catechin > epicatechin = gallocatechin > gallic acid = ellagic acid [31].

The functional properties of proanthocyanidins are poorly understood. Since 1983, studies have been conducted on antioxidant functions, preventive actions in diseases during the use of proanthocyanidins. The antioxidant activity of proanthocyanidins was found to be much stronger than vitamin C or vitamin E in water bodies. The mechanisms for its antioxidant actions have been shown to include radical binding, quenching, and enzyme inhibition actions [32]. According to Dr. Qingwang Lian (2016) [33], in vivo experiments showed significant enhancements in cognitive and spatial memory ability and improvements in the pathology of Alzheimer's disease; the results showed that proanthocyanidin GSPA from grape seeds may be a new therapeutic strategy for the treatment of Alzheimer's disease, or may, at least, improve patients' quality of life [33].

4.1. Flavonoiods and Poplyphenols

Flavonoids are polyphenols (phenolic compounds with more than one hydroxyl group attached to an aromatic ring) that are found in most plants. Currently, more than 8000 flavonoid structures have been identified [34]. Anthocyanins are water-soluble pig-

ments (flavonoids) that are present in many edible plants and fruits, particularly berries and pomegranates. They are responsible for red, blue, and purple colors and possess powerful antioxidant, anti-inflammatory, and cardioprotective activities. The stability of anthocyanins depends on light, pH, and temperature, as well as their color [35,36]. The main anthocyanins present in grape skin are 3-monoglycosides, followed by three caffeoylglycosides—peonidine, cyanidin, and delphinidine. The skin of the grape accounts for about 65% of the total grape core. However, the final yield depends on the winemaking process, which has an impact on the final phenolic content of the pomace husks [37].

Phenolic acids and stilbenes are non-flavonoid compounds that are present in GP. Hydroxybenzoic and hydroxycinnamic acids are further subdivided from phenolic acids. Gallic, p-hydroxybenzoic, and syringic acids are examples of hydroxybenzoic acids, whereas caffeic, p-coumaric, ferulic, and synaptic acids are the most prevalent hydroxycinnamic acids in GP. Two aromatic rings enclosed by the ethylene radical combine to generate stilbenes. Resveratrol is the most well-known and researched stilbene. Stilbenes have also been found to be present in wine and grapes in addition to GP as depicted in Figure 1 [38].

4.2. Resveratrol

Resveratrol can be found in various plant sources, including grapes, berries, and nuts. Several studies have shown that resveratrol has multiple health benefits, including antioxidant, anti-inflammatory, and anti-cancer properties [39,40]. Because of its potential health benefits and antioxidant properties, resveratrol has gained increasing attention among researchers and consumers. However, obtaining resveratrol from these sources is often expensive and can cause negative environmental impacts. Finally, grape pomace is an important source of resveratrol and various methods have been developed to isolate it [41]. However, Kunová and Simona (2019) [42] used six bacterial strains to evaluate the antibacterial properties of pure resveratrol and grape pomace extracts of the Blue Frankish variety. The results show that they have very good antimicrobial activity against Gram-positive bacteria compared to Gram-negative bacteria and yeasts [42].

4.3. Lipid Vitamins and Bioactive Fatty Acids and Polar Lipids

Grape seed, an important byproduct of grape processing, is also extremely rich in vitamin E, containing significant amounts of tocopherols and tocotrienols, ranging from 10 to 530 mg of vitamin E per kilogram of oil. In addition, a-tocopherol, the most potent and widespread isoform of vitamin E in biological systems, acts as a powerful biological antioxidant. In cosmetics, vitamin E is commonly used in day and night creams for its antioxidant properties, which help counteract oxidative stress. In addition, tocopherols play a critical role in protecting polyunsaturated fatty acids from oxidation caused by free radicals [43]. Furthermore, grape seed oil, which mainly contains unsaturated fatty acids, is considered an important cosmetic ingredient, with moisturizing properties for the skin. In addition, grape seed oil exhibits high levels of linolenic acid [44]. However, Sara M. Ferreira and Lúcia Santos (2022) [45], observed that the use of oils and extracts from grape pomace (GP) and grape seed (GS) in cosmetics have comparable benefits to those of synthetic antioxidants such as butylated hydroxytoluene (BHT) [45].

The incorporation of extracts and oils derived from wine industry by-products in cosmetic composition facilitate the development of a sustainable cosmetic product that satisfies the circular economy cycle. However, some phenolic compounds are susceptible to oxidation and thus may deteriorate within the product. Thus, the resultant extracts should ideally be microencapsulated to prevent this unfavorable oxidative transformation. The

stability of the creams containing extracts and extract-containing microparticles should then be compared [45].

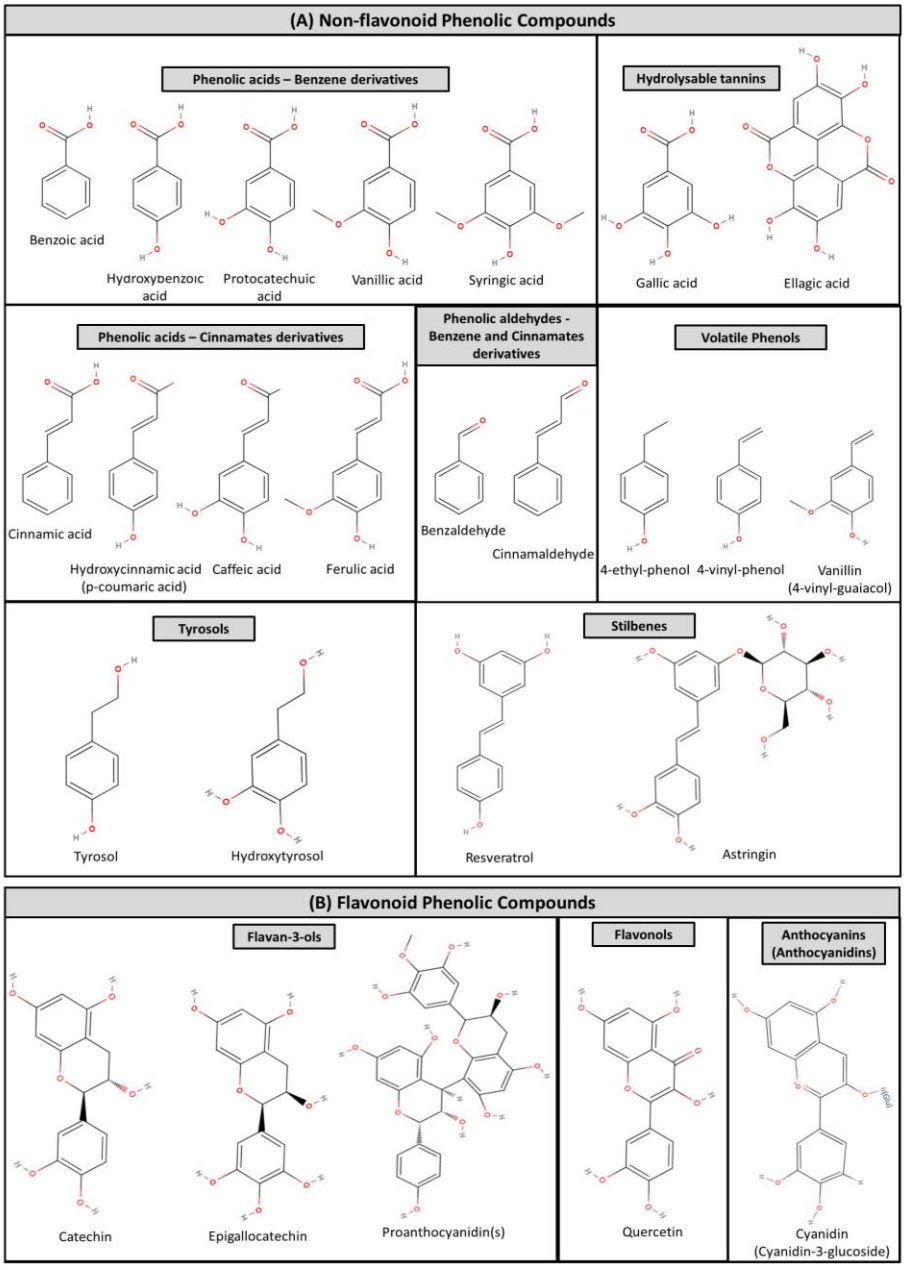


Figure 1. Illustration of different classes of phenolic bioactives of grape and winery by-products [46].

Moreover, grape pomace and grape seeds are also a valuable source of bio-functional lipids, such as unsaturated fatty acids (UFA), especially the monounsaturated fatty acid (MUFA) oleic acid (OA; 18:1), the omega-6 (n6) polyunsaturated fatty acid (PUFA) linoleic acid (LA; 18:2n6), and the omega 3 (n3) PUFA alpha linolenic acid (ALA; 18:3n3), as well as bioactive polar lipids (PL) and important lipid-soluble vitamins (A, D and E) for cosmetics as shown in Table 1. In combination with the high phenolic content of these winery by-products, this further emphasize their potential for applications with various health-promoting activities, including antioxidant, anti-inflammatory, antiplatelet, anti-cancer, and general anti-aging properties [46]. Because many of these compounds are inexpensive and readily available in large quantities from sustainable, reusable sources used by wineries, their recovery and valorization are both economically and environmentally

feasible, especially in light of consumers' preference for natural over synthetic substances and growing awareness of agricultural sustainability [46].

Table 1. Chemical composition and bioactive constituents of grape by-products.

Chemical Compositions (Content in g/100 g)	Representative Bioactive Constituents (Content in g/100 g)	References
Phenolic Acids (0.5–0.9 g/100 g) and Stilbenes (0.0003–0.0005 g/100 g)	Gallic acid (0.03–0.05 g/100 g), p-hydroxybenzoic acid (0.01–0.02 g/100 g), syringic acid (0.1–0.2 g/100 g), caffeic acid (0.0005–0.001 g/100 g), p-coumaric acid (0.02–0.04 g/100 g), ferulic acid (0.002–0.003 g/100 g), resveratrol (0.03–0.05 g/100 g)	[24,42,47]
Flavonoids (0.05–0.1 g/100 g) and Polyphenols (0.5–0.9 g/100 g)	Catechin (0.03–0.04 g/100 g), epicatechin (0.01–0.02 g/100 g), quercetin (0.01–0.02 g/100 g), anthocyanins (malvidin-3-O-glucoside 0.005–0.006 g/100 g)	[2,29,31,47]
Vitamin E (0.02–0.05 g/100 g) and Tocopherols (0.02–0.05 g/100 g)	α-tocopherol (0.02–0.05 g/100 g), tocotrienols (0.02–0.2 g/100 g)	[45,47]
Unsaturated Fatty Acids (UFA) (30–35 g/100 g)	Linoleic acid (30–35 g/100 g), oleic acid (10–12 g/100 g), alpha-linolenic acid (12–13 g/100 g)	[41,46,47]
Bioactive Polar Lipids (0.5–1.5 g/100 g)	Phospholipids (0.5–1.5 g/100 g), glycolipids (0.3–1.0 g/100 g)	[46,47]

5. Methods of Extraction of Bioactive Substances from Grape and Winery By-Products

The extraction of bioactive compounds from grape and winery by-products is currently not standardized due to variations in techniques and conditions. For example, there are five main types of techniques to extract bioactive substances from grape pomace, including but not limited to traditional solvent extraction, supercritical fluid extraction, microwave or ultrasonic extraction, and solid–liquid extraction. Often used in the extraction of bioactive chemicals, microwave-assisted extraction and ultrasonic-assisted extraction offer fast sample preparation along with a lower solvent requirement. However, the need for environmentally friendly extractions has led to the increased study of enzyme-assisted extraction techniques [48]. In this review, the types of extractions mentioned above will be discussed in detail.

5.1. Solid–Liquid Extraction (SLE)

Solid–liquid extraction (SLE) is based on the selective solubility of one or more of the components of the solid in the liquid solvent. There are many ways to perform the SLE process. The "shake filter" approach based on stirring is one of the most popular. In addition, there are many other methods for extracting solids from liquids, including heating (Soxhlet). Soxhlet extraction involves repeatedly washing the matrix with a new solvent, which increases the analyte's potential solubility because a heated solvent is used. These are the primary benefits of this method over traditional maceration, which allows for cost savings in terms of time, energy, and subsequent financial inputs. On a medium or large scale, Soxhlet extraction can be transformed from a batch process to a continuous process on a huge scale [49].

To extract a component from a solid, there are two fundamental processes. These include mixing the solid with the solvent and separating the liquid from the solid phase. However, there are also some intermediate stages concerning the solubilization of the compounds, the movement of the solution from the inside of the solid mass to the surface,

and finally, the movement of the extracted compounds from the inner surface of the solid to the volume of the solution. Finally, changes in concentration gradients, diffusion coefficients, or the boundary layer might increase the extraction efficiency, depending on the sample's properties and the molecules being targeted. The extraction technique, solvent type, temperature, extraction duration, particle size, and matrix composition can all affect these characteristics [50].

Alessandro A. Casazza et al. (2011) focused on optimizing traditional organic solvent extraction for Pinot Noir seeds, investigating various extraction times and solid–liquid ratios. The results indicated that the seeds contained high levels of total polyphenols (73.66 mg GAE/g dry weight) and flavonoids (30.90 mg CE/g dry weight), with an optimal extraction time of approximately 19 h. This study also found a significant correlation between the concentration of polyphenols and their antioxidant capacity, suggesting that careful manipulation of extraction parameters can enhance yield and efficacy [51]. Ana Bucić-Kojić et al. (2007) examined the influence of temperature, particle size, and solid–liquid ratios on the extraction kinetics of total polyphenols from grape seeds. The findings indicated that extraction yields were positively influenced by increased temperature and smaller particle sizes, with most polyphenols being extracted within 200 min. This study employed a modified Peleg's model to describe the kinetics of extraction, which could aid in optimizing the extraction process [52].

5.2. Ultrasound Assisted Extraction (UAE)

Ultrasound assisted extraction (UAE) is a convenient alternative to conventional (SEL), increasing extraction efficiency in a single step. Ultrasonic irradiation is simple, inexpensive, and efficient, reducing extraction time without high temperatures or long shaking times. Its efficiency is due to sonication, which enhances hydration and fragmentation processes [53].

The phenomenon of acoustic cavitation answers the basic principle of ultrasound. In the process, when a sound wave meets a liquid medium, longitudinal waves are generated that lead to expansion in the molecules of the medium. In this way, bubbles, negative pressure, and heating are created. To achieve dynamic equilibrium, the ultrasonic intensity must be maintained constant during bubble formation and collapse. After collapse, jets are created due to pressure and high temperature, causing shock waves to be driven towards the solid. In this way the solvent penetrates towards the solid and the mass transfer rate increases [54]. The benefits of UAE include ease of application, reduction of extraction costs through the technique of ultrasonication, and shortened processing times. In addition, the method is more environmentally friendly since it uses small amounts of sustainable solvents, requires less energy, and is carried out at a lower temperature [55].

Anđelković et al. (2014) [55], conducted research to optimize ultrasound-assisted extraction (UAE) for maximizing extraction yield, total phenolic content (TPC), and individual phenolic compounds from grape pomace seeds. The study utilized response surface methodology (RSM) to analyze the effects of extraction temperature, time, and the liquid-to-solid ratio. The results indicated that UAE provided higher TPC values and stronger antioxidant activity compared to conventional solvent extraction, achieving a 23.76% increase in extraction yield and 34.54% stronger antioxidant activity. This highlights UAE as a promising technique for extracting phenolic compounds suitable for food and pharmaceutical applications. Minjares-Fuentes et al. (2014) focused on optimizing the ultrasonic-assisted extraction of pectins from grape pomace using citric acid. The research employed a Box–Behnken design to determine the optimal conditions, leading to high yields of pectin with a significant molecular weight and degree of esterification. The study found that the use of citric acid in combination with ultrasound

increased extraction efficiency, resulting in a yield that was 20% higher than those of non-ultrasonic methods [56].

5.3. Microwave-Assisted Extraction (MAE)

Microwave-assisted extraction belongs to the green methods for extracting bioactive substances without loss of stability. Microwave heating works mainly with non-ionizing electromagnetic waves, increasing the isolation and extraction of phytocomponents that are antioxidants. The operational viability and capability of MAE have been demonstrated in studies, with anthocyanin and proanthocyanidin yields varying based on factors such as extraction time/temperature, solvent type, microwave power, and solvent volume. MAE is a valuable process for commercialized polyphenol extraction [57]. The principle of operation of MAE includes the direct effects of microwave energy on the molecules of the material—their heating due to dielectric energy. This energy corresponds to the polarity of the medium, creating a rotary dipole and ion migration. This creates heat and collisions between molecules, increasing the energy of the medium. The whole process of microwave extraction is based on the interaction of the solid matrix with the solvent [58,59].

MAE is used for the extraction of bioactive compounds from grape by-products. Tania Garrido et al. (2019) examined the feasibility of MAE at room temperature to extract polyphenols from Chardonnay grape marc. The optimization process involved RSM to determine the effects of solvent concentration, solid mass, and extraction time. The study found that optimal conditions included 48% ethanol, 10 min of extraction time, and 1.77 g of solid mass. The resulting extracts exhibited a high level of antioxidant activity, demonstrating potential applications as bioactive additives in food and pharmaceutical formulations [60]. Also, Mariana Spinei et al. (2022) explored the extraction of pectin from two grape pomace varieties (Feteasc̆ă Neagră and Rară Neagră) using microwave-assisted extraction. The study aimed to optimize the process, evaluating parameters such as microwave power, pH, and extraction time. Optimal conditions were established at 560 W, pH 1.8, and 120 s. The extracted pectin was characterized by its yield, galacturonic acid content, degree of esterification, and molecular weight, revealing that grape pomace is a viable and unconventional source of high-quality pectin [58]. Cassiano Brown da Rocha et al. (2020) investigated the extraction of bioactive compounds from grape juice residue using microwave-assisted extraction (MAE) and UAE with an acidic aqueous solution. The study aimed to recover phenolic compounds while minimizing environmental impact. It was determined that MAE at 1000 W for 10 min effectively recovered 45% of anthocyanins, demonstrating that both UAE and MAE are effective in extracting valuable compounds while adhering to green chemistry principles [61].

5.4. Supercritical Fluid Extraction (SFE)

De Campos et al. (2008) analyzed the effect of extraction methods on antioxidant potential in GPE, comparing conventional SLE, Soxhlet, and SFE with CO_2 and CO_2 with ethanol as a co-solvent. The results showed that the addition of a co-solvent such as 15% ethanol enhances yield and antioxidant activity due to proportional changes in the characteristics of the solvent mixture. However, the antioxidant activity and total phenolic yield (TPC) of the extracts obtained were significantly lower than those achieved using other extraction methods. SFE was best for non-polar compounds such as fatty acids and was able to extract important compounds not detected in conventional extracts [62]. SFE is a new technique for extracting target analyzers from solid matrices using supercritical fluids. A supercritical fluid is a substance above critical temperature and pressure, located at a borderline between liquid and gas, exhibiting high solubilizing power, high effusivity, low viscosity, and low marginal surface tension, allowing rapid mass transfer and efficient

extraction. SFE is an environmentally sustainable alternative to conventional solvent extraction as it avoids toxic solvents and is fast, automated, and selective [63]. The goal of SFE is to use non-toxic organic solvents, minimize pollution, achieve quick extraction periods, and be extremely selective. SFE is faster, automated, more selective, and less harmful to the environment than traditional solvent extraction. Coordinated solvent density must be attained and excessive use of hazardous solvents must be avoided. Furthermore, the breakdown of active chemicals is restricted throughout the extraction process due to the lack of light and air [64].

Also, Daniela A. Oliveira et al. (2013) aimed to evaluate the use of different extraction methods, including supercritical fluid extraction (SFE), using CO_2 and CO_2 with co-solvents, to obtain extracts from Merlot and Syrah grape pomace. The study compared the global extraction yield and antibacterial activity of the extracts. Although SFE yielded lower amounts of extract, it effectively inhibited the growth of various microorganisms, particularly Gram-positive bacteria, demonstrating its potential as an efficient method for obtaining antimicrobial compounds from grape pomace [65]. Marko Z. Andjelković et al. (2014) focused on optimizing a supercritical fluid extraction method that employs a liquid trap instead of a solid trap for polyphenol extraction from grape marc. The research aimed to maximize extraction efficiency while avoiding organic solvents. The study optimized key variables, including CO_2 modifier content and extraction time, achieving successful extraction of polyphenols with significant biological activity, highlighting the potential for profitable use of grape marc as a source of bioactive compounds [66]. Fikret Pazir et al. (2020) investigated the supercritical extraction of anthocyanins from grape pomace, utilizing ethyl alcohol as a co-solvent. The study aimed to maximize anthocyanin yield while evaluating the effects of extraction time on yield and total antioxidant capacity (TAC). The results indicated effective extraction of anthocyanins, with the total monomeric anthocyanin content (TMAC) recorded at 1932.1 mg/kg dry matter. While the yield was lower than traditional methods, the research emphasized the need for further optimization to enhance economic viability and extraction efficiency for anthocyanin-rich materials [67].

5.5. Enzyme-Assisted Extraction

Kammerer et al. (2005) improved the enzymatic hydrolysis of GP extracts using pectinolytic and cytolytic enzymes. After pre-extraction, 70.1% of phenolic acids, 75.2% of flavonoids, and 1.7% of anthocyanins were recovered, while after enzymatic processing, the two-step process yielded 98.1% phenolics, 96.8% flavonoids, and 2.9% anthocyanins. The success was explained by a reduced inhibitory effect on enzymatic digestion, because phenolics were partially extracted during the first stage. However, from the presented data, even pre-extraction did not significantly improve anthocyanin recovery [68]. Enzyme-assisted extraction is also a valuable tool for extracting nutrients from waste and agricultural by-products. It offers faster extraction, higher recovery, reduced solvent use, and lower energy consumption compared to non-enzymatic methods. It also showed the ability to operate under mild treatment conditions in aqueous solutions. This technique increases extraction yields and improves process kinetics while maintaining bioactive properties. Enzymes are catalysts that contribute to the extraction, modification, or synthesis of complex bioactive compounds of natural origin. Their application is particularly associated with the processing of plant material before conventional extraction methods [69].

Aline Soares Cascaes Teles et al. (2021) aimed to evaluate the extraction of phenolic compounds, particularly proanthocyanidins, from grape pomace using high hydrostatic pressure (HHP) combined with enzyme-assisted extraction (EAE). Four extraction conditions were tested: EAE without HHP, EAE with pre-treated enzymes, simultaneous EAE

and HHP, and HHP alone. Results showed that HHP increased enzyme activity by up to 16 times, with the best inhibitory α-amylase activity in treatments E3 and E1. This study concluded that combining HHP and EAE effectively extracts valuable bioactive compounds from grape pomace [70]. Ivana Tomaz et al. (2015) sought to optimize the enzyme-assisted extraction of flavonoids from grape skins using oenological enzymes. A Box–Behnken design was employed to analyze the effects of enzyme dosage, temperature, extraction time, pH, and enzyme type on flavonoid yield. Optimal conditions were found using Lall zyme EX-V at 45 °C for 3 h, pH 2.0, and 10.52 mg/g enzyme dosage. This method is cost-effective and environmentally friendly, suitable for both laboratory and industrial applications, allowing for immediate HPLC analysis without solvent removal [71]. Ioanna Drevelegka and Athanasia M. Goula (2020) used alternative techniques to examine the yields of phenolic extraction from grape kernels following enzymatic treatment. Following the enzymatic procedure, UAE had the highest phenolic component extraction efficiency as compared to MAE. The study concluded that improved mass transfer led to increased solvent penetration into enzymatically treated cell components [72].

5.6. Limitations of Extraction and the Use of Bioactive Components

The entire process, from extraction to the use of bioactive molecules of grape and winery by-products, has been well improved. However, it has naturally presented challenges and limitations as summarized in Table 2, most of which are related to the extraction of bioactive compounds and their exploitation on an industrial scale [73]. Examples from studies indicate that the lack of universally applied processes and methods, the high demands and high costs of equipment, the environmental impact of the use of certain techniques, and consumers' suspicion of products containing such bioactive substances are a sample of these limitations [73]. Some proposals to address a part of these limitations include using more advanced analytical techniques to standardize the bioactive constituents of grape by-products, as well as finding and using more sustainable extraction techniques. The utilization of various enzymes or the use of water as a solvent make extraction techniques safer, more attractive for use in cosmetic products, and more trustworthy for consumers [74].

Table 2. Advantages and disadvantages of extraction methods.

Extraction Method	Advantages	Disadvantages	References
Solid-Liquid Extraction (SLE)	• Simple and widely used • Scalable to medium or large processes • Compared to maceration, Soxhlet improves analyte solubility and efficiency	• Particle size, temperature, and solvent type affect extraction • Time-consuming	[48,51,69]
Ultrasound-Assisted Extraction (UAE)	• Fast and efficient • Environmentally friendly with low solvent and energy needs	• For effectiveness, you must create a stable temperature and ultrasound intensity	[52–54,64]
Microwave-Assisted Extraction (MAE)	• High efficiency and operational viability • Green method • Effective for polyphenol extraction	• Restriction to polar solvent application • Optimization needed to avoid compound degradation	[56–60]
Supercritical Fluid Ex-traction (SFE)	• Environmentally friendly with no toxic solvent needs • High selectivity for substances • Cost-effective • Fast and efficient	• Increased control and equipment requirements • Restrictions on the use of specific solvents • Sensitivity to parameter settings	[61–66]
Enzyme-Assisted Extraction (EAE)	• High yields by breaking down complex structures • Operates under mild conditions • Reduced solvent and time requirements	• Expensive method • Pretreatment may not significantly improve some compound extractions	[67–71]

6. Grape and Winery By-Products: Active Ingredients in Cosmeceuticals

6.1. Anti-Aging and Anti-Wrinkle Properties

The anti-aging effect of grape and winery by-products has been demonstrated by several studies, due to their ability to inhibit the action of enzymes associated with aging [75,76]. It seems that grape and winery by-products have a positive impact on the action of tyrosinase, collagenase (MMP-1), and elastase, which are involved in the skin aging process [75–77].

Specifically, it has been demonstrated that different grape-related products such as grape by-products, extracts of wine lees from alcoholic fermentation, wine lees from vinification, and red grape pomace are evaluated for their antioxidant capacity and their ability to combat hyperpigmentation [75].

Wine lees extracts, rich in phenolic compounds and anthocyanins, were evaluated for their anti-aging and cosmetic properties as depicted in Table 3. The extracts showed strong inhibition of elastase and MMP-1 enzymes, with activity strongly linked to their phenolic content and specific compounds like caftaric acid, malvidin, peonidin-3-O-glucoside, myricetin, and quercetin. Additionally, the extracts inhibited tyrosinase, the key enzyme for melanin synthesis, highlighting their potential use in cosmetic products against hyperpigmentation [75].

Another study conducted on six different grape by-product extracts revealed the anti-aging activity of these extracts. Their anti-aging activity was calculated by tyrosinase inhibition assays and elastase inhibition. The results, although having significant differences between the six extracts, showed that they have greater effect on elastase inhibition than on tyrosinase inhibition. This study also demonstrates the value of grape by-product extracts for cosmetics aimed at reducing wrinkles [76].

A study in vitro [78] examined the effect of grape extract (*Vitis vinifera* L.) on human dermal fibroblasts exposed to ultraviolet radiation (UVA) stress. The results showed that the extract promotes the expression of SIRT1 and HSP47 genes, which are associated with anti-aging of the skin, under both normal and UVA conditions [79,80]. At the same time, it modifies DNA methylation in the promoters of these genes, enhancing their gene expression. In addition, the extract improved cell viability by increasing intracellular ATP levels and provided protection against the damaging effects of oxidative stress caused by UVA radiation. Overall, grape extract shows strong protective and anti-aging propositions, making it a promising raw material for the creation of cosmetics [78].

In addition, one more study evaluated the anti-aging properties of *Vitis vinifera* L. leaf extract (a grape by-product) on human keratinocytes (HaCaT). The findings demonstrated that the extract offers protection against UVA-induced damage by reducing oxidative stress through antioxidant mechanisms, such as lowering ROS levels and protecting DNA, as assessed by the Comet assay and γ-H2AX markers. Additionally, it enhanced apoptosis, acting as an anti-mutagenic factor. Although protection against UVB was limited at low doses, the results highlight the extract's potential in developing products with anti-aging and protective properties [20].

Table 3. Anti-aging and anti-wrinkle properties.

Hypothesis–Intervention	Study Design-/Parameters Examined	Main Findings	Year of Study	Ref.
In this study, extracts of wine lees from alcoholic fermentation, wine lees from vinification, and red grape stems are evaluated for their antioxidant capacity and their ability against hyperpigmentation.	• TPC and TAC were measured by Folin–Ciocalteu (FC) method. • The compounds were analyzing HPLC-DAD-MS/MS. • Anti-aging activity was evaluated by elastase inhibition and MMP-1, and tyrosinase for hyperpigmentation.	• High levels of phenolic compounds and anthocyanins were found in the wine lees extracts. • The vinasse extracts are superior in elastase and MMP-1 inhibition.	2019	[75]
This study aims to evaluate extracts of grape by-products from six different grape varieties for their anti-aging and anti-pigmentation capacity.	• The phenolic composition was analyzed by HPLC. • The anti-aging and anti-pigmentation capacity was evaluated by measuring the inhibition of elastase and yyrosinase.	• In all the extracts of the different varieties, catechin was the main compound. • The extracts showed abilities to inhibit both elastase and tyrosinase, with higher rates of inhibition on elastase.	2020	[76]
This study investigates the protective and anti-aging effects of grape leaf extract (*Vitis vinifera* L.) on human dermal fibroblasts under ultraviolet (UVA) stress.	• Gene expression of SIRT1 and HSP47 was analyzed for anti-aging effects. • DNA methylation of SIRT1 and HSP47 promoters was examined for epigenetic changes. • Cellular viability was measured by ATP levels in fibroblasts treated with grape extract.	• Grape leaf extract boosted SIRT1 and HSP47 expression, particularly under UVA stress. • DNA methylation changes in SIRT1 and HSP47 promoters suggest influence on gene expression. • Grape extract increased ATP levels, improving fibroblast viability under stress.	2020	[78]
Vitis vinifera L. leaf extract protects human keratinocytes from ultraviolet radiation damage, reducing oxidative stress.	• The antioxidant and protective properties of DNA were measured using the Comet assay, γ-H2AX markers for DNA damage and ROS quantification. • Cellular effects were examined by apoptosis, cell cycle progression, and cytotoxicity assays.	• The extracts significantly reduced ROS and UVA-induced DNA damage while promoting apoptosis as an anti-mutagenic effect. • No significant protection was observed against UVB-induced damage under the tested conditions.	2020	[20]

6.2. Antioxidant

Many studies as demonstrated in Table 4, have shown that grape by-products contain large amounts of polyphenols, substances that act as powerful antioxidants [81,82]. These antioxidant molecules play a key role in maintaining good skin condition and preventing many skin diseases and disorders. Their main protective mechanism lies in their ability to bind free radicals, which are responsible for cellular damage and the aging process. Through this mechanism, the antioxidants contained in grape by-products ensure the repair of DNA damage, the regulation of gene expression associated with cell proliferation, metabolism, and cell survival, and the enhancement of antioxidant defenses [83,84].

Consequently, grape by-products are a natural source of antioxidants, making them ideal for use in cosmetic formulations. Their incorporation in cosmetic products not only provides a high added value, but also significantly enhances the effectiveness of these products in protecting the skin from oxidative stress, DNA damage, and premature aging.

A recent study on phenolic extracts, but also on grape seed and seed kernel oils, through their interaction with the free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), demonstrated their antioxidant capacity [85]. This ability is due to the efficiency of the transfer of a hydrogen atom from the hydroxyl group attached to their aromatic ring. This process helps to neutralize free radicals by breaking the chain of oxidative reactions. Phenolic extracts showed greater free radical inhibition than oils, since the antioxidant activity of the latter was due only to the presence of tocopherols and tocotrienols.

Also, the antioxidant activity of grape pomace extracts was higher than that of grape seed extracts, which can be explained due to the composition of grape pomace consisting of grape seeds and grape skin in addition to seeds [86]. The next step was to utilize such grape seed by-products for the preparation of a facial moisturizer base and nine formulations with extracts and/or oils with a composition of 0.1% [45]. These formulations were evaluated for stability gradually over 35 days and for lipid oxidation by measuring absorbance with a UV-Vis spectrophotometer, with the results being positive for the replacement of synthetic antioxidants in the cosmetic formulations with the extracts and oils of grape by-products [45].

Meanwhile, another study [87] investigated the efficacy and safety of grape pomace as an antioxidant raw material for cosmetics. Initially, HPLC analysis confirmed the presence of ellagic acid as a bioactive compound. Grape pomace extract was compared in terms of its ability to inhibit DPPH radical with the synthetic antioxidant butylated hydroxytoluene (BHT). The results showed that the extract exhibited higher antioxidant activity than BHT, but this difference was statistically insignificant. In addition, grape pomace extract was proven to be non-cytotoxic in a range of concentrations even under oxidative stress. These results were confirmed by scanning electron microscopy (SEM) [87].

The antioxidant activity of grape seed extracts from five different varieties (Marselan, Syrah, Obeidi, Asswad Karech, and Cabernet Franc) was evaluated in another study for incorporation into cosmetic creams [3]. After the extraction, which used glycerin as a base, the extracts were analyzed for their total phenolic content (TPC) using the Folin–Ciocalteu method. The results indicated higher levels of phenolic compounds in the extracts from the Marselan and Syrah varieties. Similarly, the proanthocyanidin content was assessed using the 4-dimethylaminocinnamaldehyde reaction. The phenolic compounds in each extract, including gallic acid, catechins, chlorogenic acid, caffeic acid, and p-coumaric acid, were identified and quantified using HPLC. Gallic acid, a well-known antioxidant [88], was found in high concentrations (883.05 ± 98.59 µg/g of dry matter) in the extract of the Obeidi variety. Catechins, which also exhibit antioxidant activity [89], were present in varying amounts across the extracts, with the Marselan variety showing the highest concentration. Similarly, other antioxidants such as chlorogenic acid, caffeic acid, and p-coumaric acid were most abundant in the Marselan extract.

Table 4. Antioxidant properties.

Hypothesis–Intervention	Study Design-/Parameters Examined	Main Findings	Year of Study	Ref.
The purpose of this research was to formulate a facial moisturizing cream containing phenolic extract and oils from grape pomace and grapeseeds, and to evaluate its antioxidant and its stability	• The antioxidant capacity was determined by the DPPH method. • Stability tests (pH, viscosity, spreadability, thermal stability, and skin compatibility) were carried out gradually over 35 days. • Lipid oxidation tests were carried out by measuring the absorption using a UV-Vis spectrophotometer.	• Both extracts and oils show antioxidant properties, with extracts showing higher levels. • Grape pomace extracts showed higher antioxidant activity than grape seed extracts. • Stability tests and lipid oxidation tests have shown that extracts and oils can replace synthetic antioxidants in cosmetic formulas.	2022	[45]
This study investigated the efficacy and safety of grape pomace for application as an antioxidant raw material in cosmetics	• The composition of the extracts was determined by HPLC. • The antioxidant capacity was evaluated by the DPPH method and compared with the synthetic antioxidant butylated hydroxytoluene (BHT). • The extracts were tested in cell line 3T3 (fibroblasts) with cytotoxicity. • Study of the cytoprotective effect of the extract at a lower concentration. • Analysis of SEM.	• HPLC analysis confirmed the presence of ellagic acid. • The DPPH method showed significant antioxidant activity, compared to BTH. • The extracts were safe at high concentrations. • There was significant cytoprotection from oxidative damage in fibroblasts.	2018	[87]
The aim of this study was to examine and evaluate seed extracts of different grape varieties for application in cosmetics with antioxidant activity	• TPC was measured by the Folin–Ciocalteu method and proanthocyanidins were identified by the 4-dimethylaminocinnamaldehyde reaction. • HPLC was used for the quantification and identification of phenolic compounds in the extracts. • The antioxidant capacity of the extracts was determined by three methods: DPPH, CUPRAC, and FRAP. • Various percentages of an extract were incorporated into cosmetic creams and stability tests were carried out for 4 months.	• Phenolic content and proanthocyanin content were higher in two of the varieties. • High levels of polyphenols (gallic acid, catechins, chlorogenic acid, caffeic acid, and p-coumaric acid) were found in some of the varieties.	2022	[3]
The study examines the capacity of grape pomace polyphenols to mitigate oxidative stress	• In vitro tests exposing cells to reactive oxygen species and measuring the reduction of oxidative stress. • Enzyme measurement evaluating levels of antioxidant enzymes such as SOD, CAT, and GPx. • Dose–response tests observing the effects of polyphenols at different concentrations.	• Polyphenols reduced reactive oxygen species (ROS) in cells. • They activated antioxidant enzymes (SOD, CAT, GPx), enhancing defense against oxidative stress. • A dose-dependent effect highlights the importance of optimizing polyphenol levels.	2022	[90]

The antioxidant capacity of the extracts was evaluated using three methods: DPPH (2,2-diphenyl-1-picrylhydrazyl), CUPRAC (cupric ion reducing antioxidant capacity), and FRAP (ferric reducing antioxidant power). As anticipated, the Marselan extract demonstrated the highest antioxidant activity, correlating with its elevated levels of phenolic compounds and proanthocyanidin [3].

Another study investigated the antioxidant properties of grape pomace polyphenols through a series of in vitro experiments. Grape pomace extracts were tested on cellular models exposed to reactive oxygen species (ROS), revealing a significant reduction in oxidative stress. Antioxidant enzyme activity, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), was evaluated, demonstrating an upregulation in response to GP polyphenols. Dose–response experiments confirmed that the antioxidant effect was concentration-dependent, with higher doses yielding enhanced ROS scavenging and enzyme activation. These findings highlight the potential of grape pomace polyphenols as a natural therapeutic agent for managing oxidative stress-related conditions, paving the way for future applications in nutrition and cosmetics [90].

6.3. Antimicrobial Properties

The addition of antimicrobial agents to cosmetic products is important to ensure their microbiological purity and therefore consumer safety. Improper use of cosmetics, as well as inappropriate storage and handling conditions, can lead to microbial contamination, which is associated with serious health consequences such as eye infections, corneal ulcers, dermatitis, phlebitis, and bursitis [91].

Contamination can occur at any stage of production, packaging, or use of products, and their high water, organic, and inorganic content creates an ideal environment for the growth of pathogenic microorganisms [92]. For this reason, the incorporation of effective and natural antimicrobial agents in cosmetic formulations is essential to ensure the quality, safety, and efficacy of the final products.

Therefore, grape by-products, thanks to their unique chemical composition and high content of phenolic compounds and bioactive molecules, are a good solution for enhancing antimicrobial protection in cosmetic products as shown in Table 5.

A study reported on the antioxidant activity of grape seed, seed kernel extracts, and oils also evaluated their antimicrobial activity [85]. In particular, the Kirby–Bauer disc diffusion test method was used to study the antimicrobial activity and to assess the sensitivity or resistance of microbes to the extracts. The assessments were carried out against Gram-negative bacteria (*Escherichia coli*) and Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*). Grape pomace and grape seed extracts showed efficacy against Gram-positive bacteria but had no inhibitory activity against Gram-negative bacteria. This is expected, as polyphenolic extracts are generally more effective against Gram-positive bacteria due to their structure. Using the Kirby–Bauer disc diffusion method, no antimicrobial activity was observed for the oils. However, alternative testing methods might reveal inhibitory effects against Gram-positive bacteria, potentially due to the oils' lipid composition [85].

Table 5. Antimicrobial Properties.

Hypothesis–Intervention	Study Design-/Parameters Examined	Main Findings	Year of Study	Ref.
The aim of the present study was to formulate a moisturizing face cream containing phenolic extract and oils from grape seeds and grape seeds, and to evaluate its antimicrobial activity.	• The antimicrobial property was determined by the Kirby–Bauer method.	• Phenolic extracts exhibit antimicrobial activity, inhibiting the growth of Gram-positive microorganisms.	2022	[85]
This study aims to evaluate extracts of grape by-products from six different varieties as antimicrobial agents.	• The antimicrobial activity of the extracts was evaluated using the disc diffusion assay and the minimum inhibitory concentration (MIC) method	• The extracts have shown that they can inhibit the growth of Gram-positive bacteria.	2020	[76]
The study examines *Vitis vinifera* L. extracts for microbiome regulation and antimicrobial action on the skin.	• In vitro, in vivo, and clinical trials conducted. • Focus on antimicrobial effects of Vitis vinifera extracts. • Parameters: microbial growth inhibition, biofilm disruption, and skin barrier restoration.	• Strong antimicrobial effects against Staphylococcus aureus and Cutibacterium acnes. • Inhibited microbial growth and biofilm while preserving beneficial microbiota. • Reduced inflammation and restored skin microbial balance.	2024	[93]

Another study evaluated the antimicrobial activity of grape by-product extracts from six different varieties. Specifically, the extracts were tested against Gram-positive bacteria (*Staphylococcus aureus*, *Enterococcus faecalis*) and Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*) using the disc diffusion method and the minimum inhibitory activity (MIC) method. The results were significant, as some of the extracts showed higher inhibitory activity against bacteria even compared to specific antibiotics. The inhibition of bacterial growth was due to the phenolic compounds contained in the grape by-products. It was also observed that the extracts in this study also acted effectively against Gram-positive bacteria; phenolic compounds showed effective activity against Gram-positive bacteria compared to their activity against Gram-negative bacteria. This is due to the resistance conferred by the lipopolysaccharides of the outer membrane of the negative bacteria against the phenolic compounds [76].

Another study examined *Vitis vinifera* L. leaf extracts and highlighted their significant antimicrobial activity, particularly against pathogens such as *Staphylococcus aureus* and *Cutibacterium acnes*. The extracts were effective in inhibiting microbial growth and biofilm formation while preserving the balance of the skin microbiome. In vitro experiments, using microbiological and molecular methods, demonstrated reduced microbial viability and disruption of biofilms. In vivo studies showed a decrease in inflammatory markers and restoration of microbial balance in dysbiotic skin models. Clinical trials confirmed these findings, reporting significant improvements in symptoms of inflammation and bacterial infections, underscoring the potential of *Vitis vinifera* by-products as natural, sustainable solutions for managing infectious and inflammatory skin conditions [93].

6.4. Anti-Inflammatory Properties

Inflammation is directly related to oxidative stress. Essentially, oxidative stress stimulates inflammatory molecules, which in turn activate the inflammatory response through cytokines, chemokines, and lymphokines [94,95]. This process leads to the development of vascular inflammation. In Table 6, studies have shown that polyphenols, such as resveratrol found in grape seeds, have strong anti-inflammatory properties achieved through various biochemical pathways [94,96,97].

By focusing on this polyphenol and taking into account the above information, the anti-inflammatory properties of resveratrol are revealed through various pathways, such as the targeting of nuclear factor-kB (NFkB), the expression of proinflammatory cytokines, such as interleukin 6 (IL6), and various others. In addition, various skin diseases, as well as many other diseases, are due to the body's inability to heal wounds. This dysfunction, in turn, is due to the improper functioning of the pathways associated with wound healing. At this point, we will refer again to resveratrol, as research shows that its involvement in regulating possible inflammation of the body can also help in wound healing. In particular, the way resveratrol works is more related to its interaction with epidermal growth factor (EGFR). The beneficent action of free radicals comes second. Cosmetic products with grape by-products as their main ingredient will provide solutions in cases of inflammation and irritation, utilizing the anti-inflammatory properties of their bioactive ingredients [98].

More specifically, a recent study reports the anti-inflammatory effect of an extract derived from a grape variety (GSE-Ov) [99]. This study is based on the comparison of microdispersion with embedded GSE-ov extract with the licensed microdispersion. The comparison relates to the production of the pro-inflammatory cytokines IL-1a and IL-6, which are derived from keratinocytes that have been exposed to air particles of various urban areas. The results showed that IL-1a expression decreased from 16.1 to 5.1 pg IL-1α mg^{-1} protein, at a GSE-Ov concentration of 0.1 mg/mL. IL-1a expression decreased from 16.1 to 8.1 pg IL-1α mg/mL protein, at a concentration of GSE-Ov-loaded microdispersion

equal to the highest concentration (2 mg/mL). For GSE-Ov microdispersion, only the most concentrated samples (2 mg/mL) were able to reduce the amount of cytokine (from 16.1 to 8.1 pg IL-1α mg/mL protein). On the other hand, the expression of IL-1a was not affected by the license microdispersion. IL-6 expression decreased slightly to a GSE-Ov concentration of 0.1 mg/mL. However, none of the samples showed any noticeable anti-inflammatory effect on the production of the IL-6 protein. The main conclusion is the anti-inflammatory effect of GSE-Ov extract, affecting the expression of IL-1a, which is associated with skin inflammation. However, the results show some specificity of the extract in skin care, since it inhibits IL-1α, a cytokine specifically linked to skin inflammation [99].

In addition, another recent study focusing on the anti-inflammatory effect of grape shoot extracts was based on the report of Queiroz et al. (2017). The following six different grape sprout varieties were used for this study: Tinta Roriz, Touriga Nacional, Castelão, Syrah, Fernão Pires, and Arinto. Grape sprout extracts possess significant anti-inflammatory properties, which were measured by the reduction of nitric oxide (NO) production in cell cultures. In the study, grape sprout extracts caused a decrease in NO production, ranging from 16.52% to 35.25%, depending on the variety and concentration of the extract. The Arnito and Syrah varieties demonstrated the highest effectiveness, with reductions of 35.25% and 32.99%, respectively. These results are attributed to the presence of different phenolic compounds in the grape sprout extracts [76].

The anti-inflammatory and anti-aging properties of grape pomace have found applications in several anti-UV cosmetic products [100]. Contrary to earlier beliefs, daily exposure to sunlight is not as harmless as once thought. UVA and UVB radiation have significant impacts on human health, causing skin-related inflammatory issues such as hyperpigmentation, dermatitis, premature aging, erythema, and sunburn, which are some of the most common conditions. Additionally, the incidence of irreversible diseases, including several types of skin cancer such as basal cell carcinoma, melanoma, and squamous cell carcinoma, has been increasing [100–103].

Sunscreens enriched with natural bioactive compounds from grape pomace, such as flavonoids, stilbenes, phenolic acids, and lipid bioactives (including unsaturated fatty acids, phospholipids, and vitamins), have shown great potential in enhancing skin protection. These natural ingredients work alone or together to boost the antioxidant and photoprotective properties of sunscreens. By leveraging their anti-inflammatory, antioxidant, anti-thrombotic, and anti-cancer properties, these formulations offer improved defense against the harmful effects of UV radiation, making them a promising addition to modern skincare solutions [100].

However, several limitations exist, such as the difficulties in incorporating lipophilic compounds and/or amphiphilic phenolics into cosmetic formulations. For example, the delivery of phenolic bioactives of winery by-products into the body system is limited due to their poor water solubility, bioavailability, and chemical stability [104,105]. With the use of different encapsulation techniques as an approach, the delivery of such bioactives may be achieved. Emulsion-based delivery methods are one such potential encapsulation method. Lipophilic bioactive substances can be contained inside the hydrophobic core of lipid droplets, preserving them from destruction while allowing them to be released after consumption [106]. The value of an encapsulation technique for stabilizing bioactive chemicals derived from winemaking by-products was also shown in a study, where crude extract polyphenols were observed to degrade faster than encapsulated ones [46].

Table 6. Anti-inflammatory Properties.

Hypothesis–Intervention	Study Design-/Parameters Examined	Main Findings	Year of Study	Ref.
This study examines the anti-inflammatory activity of an extract derived from a single grape variety (GSE-Ov) of the microdispersion with embedded GSE-ov extract, and of the licensed microdispersion.	• The comparison relates to the production of the pro-inflammatory cytokines IL-1a and IL-6, which are derived from keratinocytes that have been exposed to air particles of various urban areas. • In addition, cytokine production was tested for various concentrations of the extract.	• GSE-Ov extract reduced the expression of IL-1α, which is associated with skin inflammation, while microdispersion of GSE-Ov showed a similar effect at higher concentrations. In contrast, licensed microdispersion did not affect IL-1α expression	2024	[99]
This study evaluated how grape stem extracts affected nitric acid (NO) production in cell cultures. Control of their anti-inflammatory properties in various concentrations, presence, and absence of lipopolysaccharides (LPS), which promote the overproduction of nitric acid (NO).	• Incubation of cells with extracts from six different grape stem varieties • Use of Griess colorimetric method to measure NO production • Control of cellular toxicity for each GSE species to ensure maintenance of cell viability • Comparison of results related to NO production, between cells incubated with GSE and control cells, presence, and absence of LPS.	• Extracts of all varieties caused a notable reduction in NO production, in a concentration-dependent manner.	2020	[76]

The formulation of cosmetic emulsions using grape oil and diluted wine in the aqueous phase offers significant benefits. Specifically, it enables the direct inclusion of natural antioxidants, as well as aromatic and color compounds that enhance the organoleptic properties of the products (e.g., fragrance, color, and texture) [107]. Additionally, a reduction in the activity of proteolytic enzymes related to skin aging, such as collagenase and elastase, was observed; this is attributed to the higher availability of hydrophilic polyphenols, including low-molecular-weight phenolic acids like gallic acid [108].

Furthermore, these polyphenols demonstrated the ability to cross the blood–brain barrier, reduce oxidative stress by lowering reactive oxygen species (ROS) levels, and prevent the accumulation of α-synuclein fibrils. These effects restored cell viability in an in vitro model of Parkinson's disease, highlighting their potential applications in both dermatology and neurodegenerative diseases [46,109].

In another nanoemulsion, grape seed oil and grape skin extract were combined to encapsulate resveratrol, thus creating a stable delivery system for resveratrol, with minimal damage against UV-light isomerization and degradation, which reduced oxidative damage [110]. Moreover, the synergistic effect of a sunscreen system containing UV filters and grape pomace extract on improving antioxidant activity and UVB protection derived from this winery by-product has also been observed. Specifically, sunscreens containing up to 10.0%grape extract were considered safe, while a sample formulation containing UV filters + grape pomace extract was more efficient in protecting skin against UVB radiation, taking approximately more time for UVB to induce erythema compared to the extract-free control [46,111].

6.5. Limitations of the Application of By-Products in the Cosmetisc Industry

The majority of the beneficial ingredients found in grape offal are sensitive to light, oxygen, and heat. This makes cosmetic products containing them unstable and limits their shelf life. This hinders the strengthening of consumer confidence in these products. The utilization of nanocapsules, microparticles, liposomes, etc., can contribute to increasing the shelf life of cosmetic products, due to the controlled and gradual release of their active ingredients. In addition, one of the challenges we usually encounter in the cosmetics industry is the various kinds of possible allergic reactions caused by some active ingredients, as well as compliance with legislative and regulatory frameworks. In conclusion, in order to develop more accurate and effective clinical and toxicological studies, collaboration between researchers and legislative and regulatory authorities will be an important step in the safer and more reliable use of grape by-products in the cosmetics industry [112].

7. Conclusions

Grape cultivation and winemaking, one of the world's oldest and most significant crops and processes, produce large amounts of by-products, with the main being grape pomace. These by-products, comprising seeds, skins, and peels, are rich in bioactive compounds such as phenolic bioactives, flavonoids, stylbenes like resveratrol, and polyphenols like tannins, proanthocyanidins, and anthocyanins. as Additionally, they contain lipid bioactives like polar lipids, unsaturated fatty acids, carotenoids, and lipid vitamins, which exhibit strong antioxidant, anti-inflammatory, and anti-aging properties. Modern extraction techniques, such as enzymatic, microwave, ultrasound, and supercritical fluid methods, have enhanced the efficiency and sustainability of recovering these valuable compounds.

Studies have demonstrated that grape pomace extracts can significantly improve skin health, acting as natural tyrosinase inhibitors to reduce wrinkles and hyperpigmentation, while polyphenols and resveratrol lower inflammatory cytokines and nitric oxide production. These properties make grape-derived extracts particularly effective in protecting

against UV-induced skin damage and aging. Their incorporation into sunscreens and other skincare formulations has shown enhanced anti-inflammatory and antioxidant effects.

In vivo studies further confirm these findings. Research on human keratinocytes and fibroblasts has shown that grape extracts improve skin hydration, elasticity, and resistance to oxidative stress. They also modulate key anti-aging pathways, such as SIRT1 and HSP47 expression, while reducing ROS and pro-inflammatory cytokine levels, reinforcing their potential to promote healthier, more resilient skin.

The utilization of bioactive compounds from grape by-products aligns with circular economy principles, enabling the development of environmentally friendly and innovative cosmetics. Continued research and development are essential to overcome current challenges and maximize the industrial application of these natural resources, benefiting not only the cosmetics sector but also related industries such as food and medicine.

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