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Review

Grape By-Products in Sustainable Cosmetics: Nanoencapsulation and Market Trends

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Abstract: The largest human organ, the skin, serves a variety of essential functions including protection, preservation of water and electrolytes, regulation of body temperature, and fat storage. Its maintenance and preservation are supported by cosmetic products, whose functions include cleaning, protection, and modulation. The market for these products is predicted to increase from 100.13 billion USD in 2021 to 145.82 billion USD in 2028. Recently, it has been suggested that grape by-products (totalling 14.5 million tons per year just in Europe) has a great potential to be used in the creation of new cosmetic products. In this regard, this article aims to provide a comprehensive overview of the current state of knowledge regarding the bioactive compounds in grape pomace, the advantages of applying them to the skin, and the main cosmetic products already on the market incorporating these bioactives. Most of these compounds are derived from the *Vitis vinifera* L. species, and exhibit several biological properties, such as antioxidant, antimicrobial, anti-inflammatory, inhibition of skin degrading enzymes, protection from UVA damage, increased cell viability, and skin whitening effect. On the other hand, nanoencapsulation techniques can provide a significant improvement in the stability of grape-derived bioactive compounds, in particular of resveratrol, and this issue is also addressed in a critical manner in this review.

Keywords: cosmetic(s); grape(s); grape by-product(s); skincare; anti-ageing; circular economy; encapsulation

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1. Introduction

The worldwide use of biomass, fossil fuels, metals, and minerals is forecasted to double in the next four decades, while waste generation is estimated to increase by 70% by 2050 [1]. Proper waste management is crucial as it may lead the way for circular economy implementation [2]. Currently, there are numerous descriptions (around 114) for circular economy: Kirchherr et al. [3] defined as "an economic system that replaces the 'end-of-life' concept with reducing, alternatively reusing, recycling, and recovering materials in production/distribution and consumption processes". The shift to a regenerative growth model that gives back more to the world than it takes must be accelerated, thus maintaining resource use within planetary limitations. In fact, scaling up the circular economy from early investors to the main economic players will make a significant contribution to reach climate neutrality by 2050, as aimed by the European Union (EU), and detach economic development from excessive resource consumption [1]. Agro-industrial residues are one of the most significant waste flows, and their improper handling has major environmental consequences [4]. This awareness has boosted many research studies into the potential transformation of several agro-industrial wastes and by-products, including wineries [2,5]. Globally, the transition to a circular economy system will be profound and transformative. It will necessitate the alignment and collaboration of all stakeholders at all levels—"*EU*, *national*, *regional and local*, *and international*" [1].

In this review, we will focus on providing an overview into what is presently known about the application of grape by-product-derived ingredients to cosmetic formulations and their main biological potentialities and expected benefits on skin. Moreover, the market expression of cosmetic products which incorporate those ingredients will be considered and analysed throughout the paper. Additionally, the incorporation of nano-delivery systems and the use of nano encapsulation techniques to enhance the stability and the skin permeation of grape-derived bioactive compounds will be discussed.

A search was made regarding the number of papers published in PubMed concerning the following entry words: (1) "((grape) AND (cosmetics)) NOT (grapefruit)"; (2) "((grape) AND (nano)) NOT (grapefruit)"; (3) "((grape) AND (cosmetics) AND (nano)) NOT (grapefruit)". The word "grapefruit" was deleted from every search. In addition, the introduction of the word "grape" on its own aimed to include all kinds of by-products possible. The search results are presented in Figure 1. From the data collected, it is possible to notice an increasing interest across the years in topics involving grape, and cosmetics or nano techniques-related research. Nevertheless, if we consider the combination of the three subjects together, the number of papers is low, with a total of 10 since 2012. Of these, only one is a review, which focuses exclusively on the application of gallic acid (found in most plants) in cosmetics and nanocosmeceuticals. Therefore, this review presents a broad perspective of the potential of several grape by-products for cosmetic application, along with a detailed description of nanoencapsulation techniques used to facilitate the delivery and preservation of this compounds. The current year of 2023 was not included.

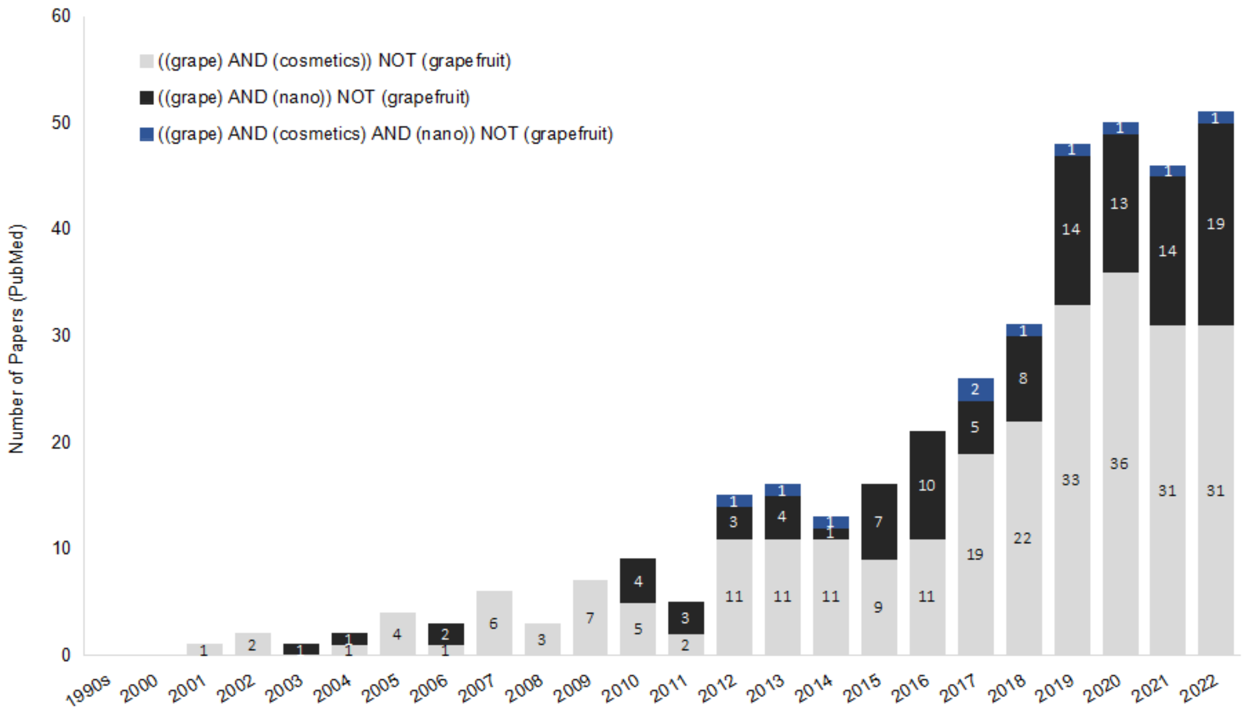

Figure 1. Number of papers included in PubMed database related to grapes, cosmetics, and nano-delivery and -encapsulation, according to the presented search words.

2. Skin: Anatomy, Functions, and Ageing

The skin is the largest organ of the human body with approximately 2 m^2. Regarding its weight, there are different descriptions among the literature. For instance, it is described as representing more than 10%, and approximately 16% of total body weight, and also as weighing approximately 3.6 kg in adults, the double of the weight of the brain [6–8]. This organ is composed by two layers—epidermis (the external layer) and dermis (underneath the epidermis) [7,9], and has an intricate arrangement of structures (appendages), such as sebaceous, sweat, and apocrine glands, hair follicles, and nails [6–8,10]. The skin enables the body to interact with its environment, providing an essential interface, and carrying out important functions, which can be broadly divided into three categories: sensorial, protective, and homeostasis maintenance. These comprise protection against trauma, solar radiation, toxins, and infections; preservation of water and electrolytes; thermoregulation; and water, vitamin D, and fat storage. Furthermore, the skin plays a major role in blood pressure control and in excretory physiological function [6,8].

The alterations that take place in the skin over time depend more on how the skin interacts with its environment than with genetic predisposition. Thus, it can be concluded that personal lifestyle has a bearing on how the skin ages [11]. Ageing is the process by which the body's capacity to adjust to the physiological and psychological environment gradually declines and eventually results in death [12]. This process is induced by both intrinsic (chronological) and extrinsic (environmental) factors, all leading to reduced structural integrity and loss of physiological function. Typical intrinsic factors are cellular senescence (decreased cell dividing ability), increased expression of skin-degrading enzymes, irregular hair growth, and decreased sebum production, which affect all skin areas [13,14]. These factors turn into ageing signs typically around the age of 30, when cell renewal is not as fast, and the hormone production undergoes changes [11]. On the other hand, usual extrinsic factors are solar radiation (exposure without protection), cigarette smoke or other pollutants, low air humidity, poor diet, and excess alcohol intake. For instance, photoageing accounts for more than 80% of facial ageing, and photo-aged skin is characterised by deep wrinkling, loss of elasticity, dryness, laxity, rough texture appearance, telangiectasia, and pigmentation disorders. These factors intensify the intrinsic ageing, and, in most cases, can be reduced by changing one's behaviour [11,13,14]. In addition, it has been reported that aged skin has an altered barrier function. The skin degradation by UV radiation is a cumulative process and its rate depends on the frequency, duration, and intensity of solar exposure, and on the natural protection offered by skin pigmentation [14]. We highlight that the impact of both types of ageing factors is especially concerning when oxidative stress is present [15].

3. Cosmetic Products and Markets

The term "cosmetics" is described in the literature as having several origins. For instance, Chaudhri and Jain [16] reported that Roman slaves whose job was to perfume men and women were the first to use the term "cosmetae", and that men and woman in Egypt began using scented oils and ointments to clean and soften their skin, as well as to conceal body odour, as early as 10,000 BC. On the other hand, Halla and colleagues [17] report that the term is originally derived from the Greek "Kosm tikos", which means 'having the power to arrange, skilled in decoration'.

In this line, cosmetic product is defined by the Council of European Union Regulation as "any substance or mixture intended to be placed in contact with external parts of the body (epidermis, hair system, nails, lips, and external genital organs), or with the teeth and the mucous membranes of the oral cavity, with a view to clean, perfume, protect, change the appearance, or correct body odours". Cosmetic products can be classified based on their use, application, function, form of preparation, consumer's age, or gender as: (1) personal cleansing (soaps, shampoos); (2) skin, hair, and integument care (toothpastes); (3) embellishment (perfumes, lipsticks); (4) protection (solar and anti-wrinkle products); (5) correction (beauty masks, hair dyes); (6) maintenance (shaving cream); and (7) active cosmetics (antiseptics, fluoridated toothpastes) [17].

Why is the skin's appearance so relevant? Human skin is the body's outermost tissue. Because of this, people are very sensitive to, and aware of, its appearance [18]. With the improvement in human living standards, more attention is paid to skin ageing. Cosmetics and medications for the prevention and treatment of skin ageing account for a sizeable portion of the regular expenses of many people, particularly among women [12], but, more recently, also among men. Skin with brighter complexion and smoother surface is typically regarded as healthier, more attractive, and linked to a fresher appearance [18]. The enormous demand for this aesthetic is what fuels ongoing research into anti-ageing strategies for the skin, among others [12].

According to a study performed by Fortune Business Insights, the global cosmetics market size was 277.67 billion USD in the year 2020. However, the demand across all regions has witnessed a negative impact during the COVID-19 pandemic period. Based on this study, the global market exhibited a decrease in growth of 10.57% in 2020, when compared to the average growth between 2017 and 2019. Still, the market is projected to grow from 287.94 billion USD in 2021 to 415.94 billion USD in 2028, corresponding to a compound annual growth rate (CAGR) of 5%. This rise in CAGR is the consequence of the market's demand and growth, returning therefore to pre-pandemic growth levels [19].

Segmenting the cosmetics market by categories, skincare products have a prominent share [19]. As expected, and just like the global cosmetics market, the skincare market was also negatively impacted during the pandemic. According to another study by Fortune Business Insights, skincare market growth suffered a 29.43% decline in 2020 (beginning of the pandemic), when compared to the average yearly growth during 2017–2019. This market is also projected to grow from 100.13 billion USD in 2021 to 145.82 billion USD in 2028 at a CAGR of 5.52% [20]. According to Transparency Market Research Inc., this growth trend is confirmed with the market projected to grow from 101.34 billion USD in 2021 to 154.7 billion USD in 2031, with a CAGR of 4.8% [21]. Thus, the main determining factors for the expected growth of this industry are the increased attention to personal care in all age groups, the increased demand for sustainable products, the increasing willingness of men to incorporate skincare products in their daily routine [20], the rapid ageing of the population [21], and increased investment in research and development of new products. Moreover, the flourishing of the e-commerce sector is anticipated to boost market growth further [22].

4. Grape By-Products and Their Environmental Impact

Grapevine (*Vitis vinifera* L.) is a perennial woody fruit crop used for the production of wine, juice, dried fruit, and distilled liquor, and for fresh consumption (table grapes) [23]. Grapes are one of the world's biggest fruit crops, being one of the most popular fruits consumed worldwide, with approximately 80% of its production being destined for winemaking [24,25]. High levels of organic waste are produced during the winemaking process, which primarily entails pressing and macerating grapes. Those wastes are primarily made up of grape pomaces (62%), lees (14%), stalks (12%), and dewatered sludge [26], reaching approximately 14.5 million tons per year in Europe [27]. In line with this, a significant amount of these by-products (Figure 2) is produced in a short amount of time, posing ecological issues, since 35.9 million tons of grapes are pressed worldwide each year to make wine. Grape pomace is composed of 25% seeds, 25% stalks, and 50% skins [28]. The main applications of these by-products have been composting and applications on agriculture and animal feeding; however, relevant quantities are still dumped in landfills. As an agro-industrial by-product, grape seeds may be responsible for environmental problems, when improperly managed [26,29], due to the low pH and high concentration of phenolic compounds, which can resist biological degradation [26], having the potential to unbalance the ecosystems, by modifying organic compound pathways and nutrients cycle [28]. In addition, the high organic carbon content of pomace, between 31 and 54%, can cause water pollution and bad odours.

Notwithstanding, it is possible to effectively valorise these wastes by means of extraction of their bioactive compounds, especially antioxidant phenolic molecules, but also vitamin E and fatty acids, using a safe, green, and environmentally friendly extractive medium (i.e., water–glycerol solution) [26,29].

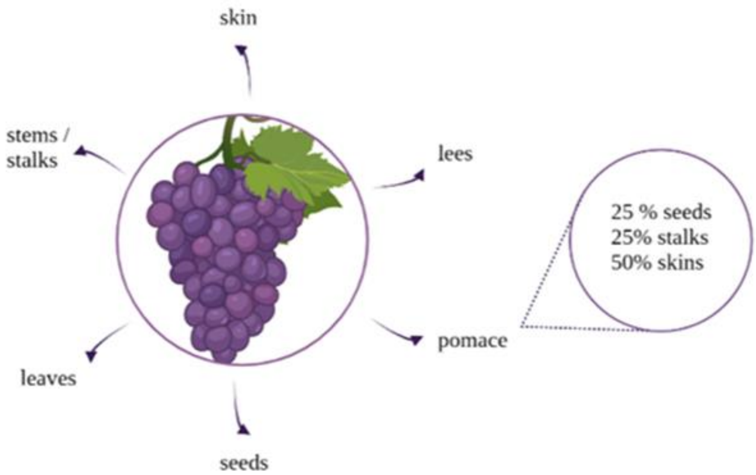

Figure 2. Grape by-products.

Phenolic compounds are secondary plant metabolites that can be used as adjuvant treatment for a number of illnesses, including diabetes, diseases associated with the ageing of the brain, and hypertension [30]. Structurally, they have an aromatic ring with one or more hydroxyl groups, and are mainly found in fruits, vegetables, nuts, seeds, and cereals. In particular, the phenolics produced by grapevine range from structural cell wall compounds, such as lignin and tannins, to specialised ones such as phenolic acids and flavonoids, exhibit several properties such as antioxidant, anti-inflammatory, antibacterial, anticarcinogenic, antidiabetic, and cardioprotective effects, having great potential for several industries, in particular the nutraceutical and cosmetic ones [23,30,31].

5. Grapes and Their By-Products for Cosmetic and Skincare Applications

5.1. Identified Skincare Biological Activities

As mentioned before, there are several types of grape by-products exhibiting potential health benefits. Since these ingredients are biodegradable and have therapeutic and functional qualities that are of value, they have an advantage over synthetic compounds [29]. In Table 1, a list of studies regarding these by-products and their skincare biological effects can be seen. In most of the presented cases, the grapevine variety used is *Vitis vinifera* L., and the explored by-products comprise extracts from seed and oil, pomace and oil, grape skins, shoot, lees stalk and stem, and seed paste. Nonetheless, other studies tested the biological activities of other grapevine varieties, such as *Vitis labrusca* L. [32]. Moreover, several other cultivars, such as *Mamaia*, *Carignano*, *Tempranillo*, *Touriga Nacional*, *Touriga Francesa*, and *Tinta-roriz*, have been explored [29,30,33,34].

Table 1. Grape by-products and their potential skincare biological effect.

Grapevine Variety	Grape By-Product	Type of Study	Biological Effect	Reference Source
——	Seed extract	Human Dermal Fibroblasts	Increased cell viability, UVA protection	[35]
Vitis vinifera L.	Seed extract	In vitro	UVA photoprotection, antioxidant activity	[36]
Vitis vinifera L.	Seed extract	In vitro	Antioxidant activity	[26]
Vitis labrusca L.	Pomace	In vitro	Antioxidant activity	[32]
Mamaia	Pomace extract	In vitro	Antioxidant activity	[30]
Carignano	Skins extract	In vitro	Antioxidant activity	[34]

Table 1. *Cont.*

Grapevine Variety	Grape By-Product	Type of Study	Biological Effect	Reference Source
——	Seed extract	In vitro	Antioxidant activity, sun protection factor (SPF) booster	[37]
Touriga Nacional, *Touriga Francesa*, and *Tinta-roriz*	Pomace/seed extract and oil	In vitro	Antioxidant and antimicrobial effects	[29]
Vitis vinifera	Shoot extract	In vitro, in vivo	Antioxidant and anti-ageing effects	[38]
Tempranillo	Lees extract	In vitro, keratinocyte and fibroblast cell cultures	Antioxidant, anti-tyrosinase, -elastase, and -collagenase activities; cellular protective effect against oxidative damage	[33]
Red grape	Seeds and stalks extract	In vitro, keratinocyte and fibroblast cell cultures	Antioxidant activity, cellular protective effect against oxidative damage	[39]
Vitis vinifera L.	Stems extract	In vitro	Antioxidant, anti-elastase and -tyrosinase activities, antimicrobial activity against *Staphylococcus aureus*, anti-inflammatory, and anti-ageing effects	[40]
Vitis vinifera L.	Seed extract	In vivo (Guinea pigs skin)	Tyrosinase inhibition (whitening effect)	[41]
Vitis vinifera L.	Seed paste	In vitro enzymatic assay	Anti-tyrosinase, -elastase, and -collagenase activities	[42]
Vitis vinifera	Seed extract	In vivo	Skin whitening, anti-ageing, and anti-acne effects	[43]
Vitis vinifera L.	Pomace extract	In vitro enzymatic assays, human embryonic kidney HEK293 cells ATCC	Tyrosinase and elastase inhibition, anti-inflammatory activity	[44]
Vitis vinifera	Pomace	In vivo	Anti-inflammatory activity	[45]
——	Seed extract	Raw 264.7 macrophages		[46]

Since many ingredients in the formulation of cosmetics are prone to oxidation, the presence of antioxidant agents, as the ones present in the grape by-products, is essential for their functionality and maintenance, extending their quality and shelf life.

5.1.1. Grape Seeds: Extract, Oil, Powder, and Paste

Several studies report important biological effects coming from grape seeds. For instance, grape seed extract is reported to increase cell viability, to protect against UVA damage, and to exert antioxidant activity [26,35–37,39]. Additionally, it is reported to have anti-tyrosinase, anti-ageing, anti-acne, and anti-inflammatory activities [41,43,46]. Grape seed extract is also reported to have anticaries, antidandruff, antifungal, antibacterial, and antioxidant properties, and to have light stabilizing and sunscreen applications. In addition, grape seed powder is reported to function as an abrasive and exfoliant by-product [47,48]. In the case of grape seed oil, it has been associated with antioxidant and antimicrobial activities. The oil was extracted using n-hexane as solvent for a solid–liquid extraction process with the following conditions: 5:1 (v/w) solvent–sample ratio, for 105 min at

70 °C. The solvent was then evaporated with a rotary evaporator at a bath temperature of 35 °C [29]. Moreover, grape seed paste was described as exhibiting anti-tyrosinase, -elastase, and -collagenase activities [42].

5.1.2. Pomace: Extract and Oil

As discussed before, grape pomace consists of a mixture containing seeds, stalks, and skins (Figure 2), and it has been described as a source of antioxidant and anti-inflammatory compounds [30,32,44,45] and also as a tyrosinase and elastase inhibitor [44]. Moreover, both the grape pomace extract and the oil present antimicrobial activity, the latter being equally associated with antioxidative protection [29].

5.1.3. Grapevine Shoot and Grape Stems/Stalks

In addition to grape pomace, vine shoot, which results from the pruning of vineyards during winter [49], has also been studied for its biological effects. Cornacchione et al. [38] describes vine shoot as having antioxidant and antimicrobial properties. Regarding grape stems or stalks, which are the skeletons of grape clusters or bunches [50,51], they have been reported to exert antioxidant, anti-elastase and -tyrosinase activities, antimicrobial action against *Staphylococcus aureus*, anti-inflammatory, and anti-ageing effects [39,40].

5.1.4. Others

Furthermore, there are other examples of grape by-products, which have been explored for its biological potentialities. For instance, wine lees were reported by Matos et al. [33] to have antioxidant, anti-tyrosinase, -elastase, and -collagenase activities, and to protect the cells against oxidative damage. This by-product is defined according to the European regulation EEC No. 337/979 as "the sediment/residue formed at the base of the deposit or barrel containing wine after fermentation, during storage or after performing authorised treatments to the product, as well as residues obtained from the filtration or centrifugation of said product" [52,53]. It consists of microorganisms (especially yeasts), tartaric acid, colloids, phenolic compounds, ethanol and inorganic matter [53,54]. Another example are grape skins, whose extract has been associated with antioxidant activity [34].

5.2. Market Expression

According to Cosmetics Europe—The Personal Care Association, the vast majority of Europe's 500 million consumers use, on a daily basis, a wide variety of cosmetic products such as soaps, shampoos, deodorants, perfumes, skincare products, and make-up, among others [55]. As it is one of the basic features in this field, over the last 20 years, the innovation in the cosmetic industry has been enormous, resulting in a wide range of different products. Moreover, the consumers are getting more concerned about their appearance, trying to accept the new social paradigms and with great enthusiasm and interest for natural trends and eco-friendly products. These tendencies have been increasing the use of bio-based extracts as active ingredients, leading to the development of new green compounds, which tend to be obtained according to sustainable principles [25,56,57].

In this section, we will focus on products which have grape related ingredients in their composition. In this line, as observed in Table 2, products containing by-products such as crushed grape seeds, seed oil, seed extract, and powder, grape water and juice, and resveratrol are presented. Among them, resveratrol, which is a natural polyphenol synthesised by plants, such as grapevine, in response to various stressful conditions (e.g., UV radiation exposure), has been one of the most explored bioactives in cosmetic industry. This compound has several biological effects, including antioxidant and anti-inflammatory properties [58,59]. It is found in both *cis* and *trans* versions, with the *trans* thought to be the active form [60], being more thermo- and photostable than the *cis* form, which is very unstable [61]. The biological effects on skin of some of these by-products were described in the previous section, and, in most cases, they are considered as key ingredients in the respective topical formulations. Some of the companies commercializing the products are

TheraVine™, CAUDALIE®, DVINE Skin, Vinoble Cosmetics, BIOLAVEN and KORRES©, and the claims made include removal of dead skin surface cells, skin smoothing, turning the skin more receptive to other active ingredients, and skin texture uniformization, among others. The products' commercial unit price, with variable unit volume, range from 7.60 to 199 EUR, depending on the ingredient composition and target claims as well as on the brand. Table 2 summarises the different products commercially available, employing grape-derived ingredients, along with its target claims and potentialities.

Table 2. Commercialised cosmetic products containing grape-derived ingredients.

Type of Cosmetic	Application Site	Company/Brand	Designation	Ingredients	Claims	Price	Reference Source
Scrubs	Face	TheraVine™	Grape seed Facial Exfoliator	Crushed grape seed beads *, grape seed oil *	Removes dead cells; more radiant, refined, and youthful skin	——	[62]
		CAUDALIE®	VINOCLEAN Gentle Buffing Cream	Grape seed oil *	Removes dead cells; cleans and purifies the face; clean, smooth, and radiant skin	21 EUR (75 mL)	[63]
		DVINE Skin	Light Harvest Facial Exfoliator	Grape seed powder *, grape seed extract *	Removes dead cells l; cellular renovation improvement; uniform skin texture	22.40 EUR (125 mL)	[64]
		Vinoble Cosmetics	Cleansing scrub	Grape seed oil *	Removes dirt, sebum, and excess skin cells; skin protection; cooling effect	129 EUR (200 mL)	[65]
			Enzyme scrub	Grape seed extract *	Frees the skin from dander; makes the skin more receptive to the following active ingredients	56 EUR (50 mL)	[66]
	Body	TheraVine™	Grape seed Body Exfoliator	Crushed Pinotage grape seeds *	Lift impurities and dead surface skin cells	——	[67]
		Vinoble Cosmetics	Salt & grape seed scrub	Grape seed extract *	Loosens dead skin cells and smooths the skin; detoxifying and purifying	22 EUR (100 mL)	[68]
		The Body Shop®	Spa of the World™ French grape seed scrub	Grape seed oil, grape seed powder	Helps to invigorate, exfoliate, and refine the skin; smoother and softer skin	15.88 EUR (100 mL)	[69]
		CAUDALIE®	Crushed Cabernet Scrub Vinosculpt	Grape seed oil *, grape seed powder	Gently eliminates dead cells; reduces skin irregularities; smoother skin	28.90 EUR (225 g)	[70]
Masks	Face	CAUDALIE®	Glycolic peeling mask Vinoperfect	Grape seed oil, grapevine shoot extract	Anti-tyrosinase, anti-blemishes	25.50 EUR (75 mL)	[71]
			Hydrating cream mask Vinosource-Hydra	Grape water *, grape seed oil *, grape seed extract, grape juice	Hydrates, soothes, antioxidant effect	23.90 EUR (75 mL)	[72]
		Vinoble Cosmetics	Regenerating & detoxifying mask	Grape seed oil *, grape flower cell extract, vine extract	Regenerates and purifies	199 EUR (50 mL)	[73]
		TheraVine™	HydraVine™ Chardonnay Grape tissue Mask	Grape seed Extract *	Soothes, desensitises and hydrates	——	[74]

Table 2. *Cont.*

Type of Cosmetic	Application Site	Company/Brand	Designation	Ingredients	Claims	Price	Reference Source
Creams	Face	dieNikolai	Grapeseed Oil Darling	Grape seed oil *, grape skin extract	Moistures and strengthens skin	69 EUR (50 mL)	[75]
		BIOLAVEN	BIOLAVEN Day Face Cream	Grape seed oil *	Hydrates and softens	7.60 EUR (50 mL)	[76]
		Schaf Skincare©	Restore	Grape seed oil	Balances skin's moisture barrier	95.52 EUR (30 mL)	[77]
Sun protection	Hair	KORRES©	Red Vine Hair sun protection	Grape seed extract	Water-resistant UV filters	15.50 EUR (150 mL)	[78]
Eye care	Eye	Patchology©	SERVE CHILLED™ ROSÉ EYE GELS	Resveratrol *	Calms inflammation	33.76 EUR (15 units)	[79]

* key ingredient.

6. Nanoencapsulation Trends

In the last decades, the delivery of grape by-product-derived compounds in micro or nanocarriers has been suggested as an innovative and effective way to enhance their stability, bioavailability, and biological activity at the target areas [2]. Nanomaterial-based cosmetics have distinct advantages over micro-scale cosmetics, since they have a wider contact surface, allowing for more effective and long-lasting effects [80]. Having said that, obtaining or producing natural bioactive compounds from such by-products through eco-friendly techniques and increasing their efficacy by utilizing nano-delivery systems is a growing trend [34], since "*Nano Delivery Systems consist of techniques where materials in the nanoscale range are employed to deliver therapeutic agents to specific targeted sites in a controlled manner*" [81]. Moreover, according to clinical studies, resveratrol and grape seed extract are very effective on a variety of skin conditions such as ageing, wounds, acne vulgaris, and redness, among others. In line with this, well-designed clinical research, particularly with nanoformulations, appears to be promising and is needed [61]. Among the several nanocarriers designed for different activities, particularly tailored for skin delivery, liposomes have been the favoured option since they protect the encapsulated compound, prevent its degradation, and are able to transport and release it more effectively on the targeted layers of the skin. On their own, liposomes are also beneficial since they repair the skin's protective barrier [34,82]. A schematic representation of different nanoencapsulation techniques is presented in Figure 3. Given the restricted number of available articles referencing the encapsulation/loading of other grape-derived by-products, the examples presented in the sections below will focus mainly, but not only, on the encapsulation/loading of resveratrol.

6.1. Liposomes and Nanovesicles

A liposome, Figure 3, consists of a spherical nanovesicle composed primarily of phospholipids that form a bilayer structure when dispersed in water [82]. Perra et al. [34] developed liposomes and phospholipid-based nanovesicles, modified with glycerol, or Montanov 82®, or a combination of the two, as carriers for grape pomace skin extract. The antioxidant activity of the extract was slightly boosted when placed into the vesicles, which were biocompatible and capable of protecting fibroblasts against oxidative stress. In a study conducted by Joraholmen et al. [83], chitosan-based liposomes successfully loaded resveratrol (0.1 and 0.2% in distilled water (*w*/*v*)) with an encapsulation efficiency of ca. 75% for topical treatment of vaginal inflammation and infections. Park et al. [84] also reported the development of chitosan-coated liposomes for transdermal delivery of resveratrol (0.1%), allowing to increase the proportions of resveratrol that permeate the skin from 96.85 $\mu g/cm^2$ with non-coated to 126.93 $\mu g/cm^2$ with coated liposomes, which may help delay the skin ageing process. In another study, PEG–resveratrol liposomes were shown to be more stable than simple resveratrol liposomes. In the PEG-based liposomes, no significant physical alterations (e.g., mean particle size) and no significant vesicle migration and aggregation were observed, and there was a constancy of the PI (polydispersity index) [85]. Moreover, Manconi et al. [86] combined a grape pomace extract (4 or 5% (*w*/*v*)) in small-sized sodium alginate (SA)- or arabic gum (AG)-based liposomes with good encapsulation efficiency, potentiating its applicability in the nutraceutical industry. Depending on the used extract concentration, the encapsulation efficiencies were 91 and 53% when using SA, and 84 and 52% when using AG, for 4 and 5% concentration, respectively. Caddeo et al. [87] evaluated an integrated resveratrol- and quercetin-loaded liposomal formulation, made from Lipoid S75, oleic acid, and ATX Tris buffer, in an animal model of cancer-mediated skin tissue injury, leading to the enhancement of human dermal fibroblasts viability (from 20 to 60% at 400 μM), presumably via reducing intracellular reactive oxygen species (ROS) levels. In 2008, Caddeo et al. [88] developed resveratrol-loaded liposomes, made from enriched soy phosphatidylcholine (P90G), diacetyl phosphate (DCP), cholesterol, or lecithin alone, stable up to 60 days, without significative differences in particle size, zeta potential, loaded resveratrol quantity and no signs of *trans*/*cis*-isomerisation, thus increasing the efficacy of the treatment and prevention of skin disorders caused by excessive UV radiation exposure. Castangia [89] created an in vitro formulation of propylene glycol liposomes and simple liposomes, both stabilised with grape–silver nanoparticles and loaded with grape pomace extract. The mixture was shown to be effective in removing several pathogens (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) and free radicals, as well as in protecting fibroblasts and keratinocytes against oxidative stress, suggesting a suitable formulation for topical treatment of skin lesions. In agreement with the last study, Vitonyte et al. [90] showed that resveratrol and gallic acid co-loaded (0.5% (*w*/*v*) each) into phospholipid liposomes were able to protect fibroblasts and keratinocytes from oxidative stress and from pathogenicity (antimicrobial activity boost). Another study focused on ultra-deformable liposomes (UDL), composed of 3ß-[N-(N′, N′-dimethylaminoethane)-carbamoyl] cholesterol hydrochloride (DC-Chol), cholesterol, and sodium deoxy cholate (SDC), and loaded with resveratrol and psoralen (from 2.5% to 10% (*w*/*w*), with respect to the lipids weight), highlighted their potential for vitiligo treatment. The procedure consisted of the administration of two doses of the liposomes, significantly increasing tyrosinase activity ca. 1.70-fold for both doses, and melanin concentration by 1.69 and 2.12 for first and second drug delivery moments, respectively. Interestingly, liposomes loaded only with resveratrol did not show significant improvements for these parameters [91].

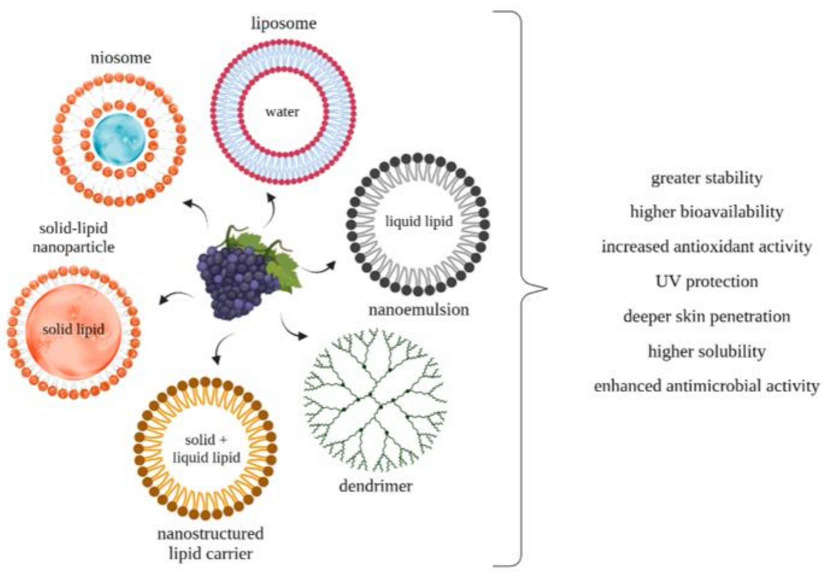

Figure 3. Nanoencapsulation techniques and their respective advantages.

6.2. Niosomes

Niosomes, Figure 3, are non-ionic surface-active compounds with a bilayer structure composed of surfactants and cholesterol [92]. A study by Pando et al. [93] focused on resveratrol-loaded niosomes made from Span 80 or a Span 60-cholesterol mixture. In this work, Span 80 niosomes were very stable but showed low entrapment efficiency (13.66% in the best-case scenario). Span 60-cholesterol niosomes had the opposite results (better entrapment efficiency, 40.96% in the best-case scenario, and lower stability), releasing resveratrol at a slower rate than the Span 80 niosomes. In another study, Pando et al. [94] showed that smaller niosomes for topical use, made from Gelot 64 and either oleic or linoleic acid, and exhibiting a size range of 299–402 nm, were more effective in maintaining the stability of resveratrol and in enhancing its entrapment efficiency. With nutraceutical purposes, Schlich et al. [95] prepared resveratrol-loaded niosomes, made of Tween 20/Span 60 (surfactants) and cholesterol, which exhibited minimal cytotoxicity for intestinal cells, indicating their safety for potential oral intake. A niosome-based hydrogel made from cholesterol and Span 80 was developed by Negi et al. [96] for the delivery of resveratrol. These delivery systems were able to increase the resveratrol biological half-life, as well as decrease its T_{max} (time until maximum cutaneous concentration is obtained).

6.3. Nanoparticles

Nanoparticles, Figure 3, are colloidal solids that can be branched or spherical in shape [97]. For instance, Rigon et al. [98] synthesised solid lipid nanoparticles (SLNPs), which are constituted by solid lipids and surfactants [99], made of stearic acid, poloxamer 407, soy phosphatidylcholine, and an aqueous phase, for transdermal delivery of resveratrol. These particles showed a diameter inferior to 200 nm and were more effective than kojic acid in inhibiting tyrosinase. Moreover, they showed the particles to be non-toxic in HaCat cells and allowed a resveratrol permeation through the skin up to 45% after 24 h. Furthermore, Imran et al. [100] created a dual drug-loaded nanostructured lipid carrier (NLC) gel, based on a 1% binary lipid mixture (Labrafil M 2125CS and Labrafil M 2130CS) and an aqueous phase (5% Cremophor RH40 in distilled water), containing resveratrol and quercetin for improved disposition in dermal and epidermal layers, obtaining a resveratrol encapsulation effectiveness close to 90%. When compared to traditional gel, the NLC results showed a rise in the resveratrol maximum concentration in skin ($C_{skin\ max}$, μgcm^{-2}) and in the area under the curve (AUC_{0-8h}, $\mu gcm^{-2}h$) from 0 to 8 h. Simonetti et al. [101] created novel poly(lactic-co-glycolic) acid nanoparticles, with 50 and 150 nm of diameter, to boost the antifungal efficacy of grape pomace extract against *Candida albicans*, reducing biofilm formation and maturation by 63% and 50%, respectively. Another study showed that NLCs and SLNPs are suitable carriers for the cutaneous delivery of resveratrol, providing a long-lasting antioxidant effect [102]. Very similar outcomes were reported by Gokce [103], where resveratrol-loaded NLCs and SLNPs, prepared with Compritol 888ATO, Myglyol, Poloxamer188, and Tween 80, were shown to improve its antioxidant activity. In addition, ex vivo studies showed that NLCs were more effective than SNLPs for epidermal deep penetration. Furthermore, Felippi et al. [104] observed that the administrations of lipid nanoparticles (NanoAging Reverse®; Inventiva, Brazil) carrying grape seed oil, among other antioxidants, resulted in a significant reduction in wrinkle intensity. Friedrich et al. [105] developed lipid-core nanocapsules (LNC), made with poly(ε-caprolactone), sorbitan monostearate and grape seed oil, which improved resveratrol photostability and enhanced its skin penetration and absorption, providing a solution for continuous polyphenol administration, for application in the treatment of skin disorders, such as sunburns. Moreover, a study by Shrotriya et al. [106] showed that resveratrol-loaded SLNPs, formulated with Precirol ATO5, Tween 20, and Span 80 combined into a carbopol gel, with a mean size less than 100 nm, had an encapsulation efficiency of 68–89%. They also provided a controlled drug release up to 24 h and no skin irritation. Polysorbate 60 and poloxamer 188 are also reported as surfactants for the development of cetyl palmitate- and stearic acid-based SLNPs, with encapsulation efficiency of 70% and 89%, respectively [107,108]. The gel demonstrated controlled release up to 24 h without causing skin irritation. Additionally, Teskač and Kristl [109] reported that SLNPs prepared with Compritol 888 ATO, Phospholipon 80H, and Poloxamer 188, of less than 180 nm, can go through keratinocytes membranes without causing significant alterations in cell morphology and function. Suktham et al. [110] developed sericin protein-based nanoparticles, which encapsulated resveratrol with a 71–75% efficacy, proving to be non-cytotoxic for dermal fibroblasts, and allowing a continuous drug release for 72 h.

6.4. Nanoemulsions

Nanoemulsions, Figure 3, are nano-scaled simple emulsions that can be utilised to create new functional compounds that improve water dispersibility and thermal stability and are able to preserve bioactive compounds in the active form during storage, among other qualities [111]. Tsai et al. [112] developed resveratrol-loaded nanoemulsions based on Caproyl 90 or isopropyl myristate as oil phase, and propylene glycol and ethanol as cosurfactants. The particles had a range from 23.4 to 422.2 nm of diameter and allowed an increase in transdermal penetration and deposition of resveratrol in the skin, by 896.2- and 10.2-fold after 24 applications, respectively, comparing to the drug solution group. Additionally, in an in vivo study, plasma concentration of resveratrol was shown to be maintained at high levels for a long time after topical delivery of the emulsions. Pangeni et al. [113] synthesised a resveratrol nanoemulsion using vitamin E and sefsol as the oil phase, and Tween 80 and Transcutol P as surfactants. The obtained drug release was ~88% in 24 h. Resveratrol nanoemulsions, created using Sefsol 218® as oil, PEG 400 as co-surfactant, Tween 80 as surfactant and water as aqueous phase, were also capable of improving the permeability and antioxidant activity of resveratrol against UV-related skin damage [114]. In another work, grape seed oil was used as one of the oil phase components of nanoemulsions, designed for resveratrol encapsulation. Orange oil was used as the other component of the oil phase and Tween 80 was selected as surfactant. In this case, resveratrol stability was improved after UV-light exposure, and the nanoemulsion allowed an 88% retention of resveratrol, compared to 50% when using dimethylsulphoxide (DMSO) [115].

6.5. Dendrimers

A dendrimer, Figure 3, is a hyperbranched spherical polymer composed of a hydrophobic central core, branched monomer, and functional peripheral groups [116]. A study by Pentek et al. [117] showed that the application of polyamidoamide dendrimer enhanced resveratrol solubility and stability in water and semisolid dosage forms. Moreover, the dendrimer allowed higher efficiency in resveratrol loading and skin penetration. In another study, Shi et al. [118] used glucan-based dendrimers to encapsulate resveratrol, showing that its bioactivity and bioavailability were significantly improved. For instance, its solubility increased about 9.1 times when compared to the raw resveratrol solution. Furthermore, the antioxidant activity of encapsulated resveratrol was significantly higher (from about 30% of DPPH radical scavenging activity with raw resveratrol to 94.1% when encapsulated), its apparent permeability coefficient (Papp, cm/s) was slightly higher (2.12×10^{-6} cm/s) than those of common permeable compounds (1×10^{-6} cm/s), while the resveratrol uptake by cells was markedly enhanced, raising from 3.47 nmol with raw resveratrol to almost 6 nmol with the dendrimer encapsulation technique. Table 3 summarises the different reported studies related to nano-delivery systems incorporating grape-related bioactive compounds with applications in cosmetics.

Table 3. Nano-delivery systems used for the delivery of compounds from grape by-products in cosmetics and their advantages/applications.

Nano-Delivery System	Material	Loaded Compound	Advantages/Application	Reference Source
Liposomes/Nanovesicles	Glycerol, Montanov 82®, or a mix	Grape pomace skin extract	Boosted antioxidant activity	[34]
Liposomes/Nanovesicles	Chitosan	Resveratrol	Ca. 75% encapsulation efficiency; Topical treatment of vaginal inflammation and infections	[83]
Liposomes/Nanovesicles	Chitosan	Resveratrol	Increased amount of resveratrol that permeates skin	[84]
Liposomes/Nanovesicles	PEG	Resveratrol	Improved liposome stability	[85]
Liposomes/Nanovesicles	Sodium alginate or Arabic gum	Grape pomace extract	Good encapsulation efficiency; applicability in nutraceutical industry	[86]
Liposomes/Nanovesicles	Lipoid S75, oleic acid and ATX Tris buffer	Resveratrol and quercetin	Enhanced human dermal fibroblasts viability	[87]
Liposomes/Nanovesicles	P90G, DCP, cholesterol or lecithin alone	Resveratrol	Good liposome and resveratrol stability; Increased efficacy of the treatment of UV-caused skin disorders	[88]
Liposomes/Nanovesicles	Propylene glycol; grape–silver nanoparticles for stabilizing the liposomes	Grape pomace extract	Antimicrobial activity against *S. aureus* and *P. aeruginosa*; Antioxidative stress effect	[89]
Liposomes/Nanovesicles	Phospholipid	Resveratrol and gallic acid	Antimicrobial activity boost; antioxidative stress effect	[90]
Liposomes/Nanovesicles	DC-Chol, cholesterol, and SDC	Resveratrol and psoralen	Increased tyrosinase activity and melanin production; potential for vitiligo treatment	[91]
Niosomes	Span 80 or Span 60-cholesterol mix	Resveratrol	——	[93]
Niosomes	Gelot 64 and oleic acid/linoleic acid	Resveratrol	Enhanced stability and entrapment efficiency	[94]
Niosomes	Tween 20/Span 60 (surfactants) and cholesterol	Resveratrol	Minimal cytotoxicity	[95]
Niosomes	Span 80 and cholesterol	Resveratrol	Increased biological half-life; decreased time until maximum cutaneous concentration	[96]
Nanoparticles	SLNPs: Stearic acid, poloxamer 407, soy phosphatidylcholine and an aqueous phase	Resveratrol	Enhanced tyrosinase inhibition (better than kojic acid); non-toxic for HaCat cells; best drug permeation	[98]
Nanoparticles	NLC: 1% lipid mix (Labrafil M 2125CS and Labrafil M 2130CS); Aqueous phase (5% Cremophor RH40 in distilled water)	Resveratrol and quercetin	Improved disposition in dermal and epidermal layers; resveratrol encapsulation close to 90%	[100]
Nanoparticles	Poly(lactic-co-glycolic) acid	Grape pomace extract	Boosted antifungal efficacy against *C. albicans* (reduced biofilm formation and maturation)	[101]
Nanoparticles	Compritol 888ATO, Myglyol, Poloxamer188, and Tween 80	Resveratrol	Improved antioxidant activity; NLCs more effective than SNLPs for epidermal deep penetration	[103]

Table 3. *Cont.*

Nano-Delivery System	Material	Loaded Compound	Advantages/Application	Reference Source
Nanoparticles	NanoAging Reverse® (Inventiva)	Grape seed oil	Significant reduction in wrinkles	[104]
	Poly(ε-caprolactone), sorbitan monostearate and grape seed oil	Resveratrol and curcumin	Improved photostability; enhanced resveratrol penetration and skin absorption; treatment of sunburns	[105]
	Precirol ATO 5 (lipid), Tween 20 (Hydrophilic surfactant) and Span 80 (Lipophilic surfactant)	Resveratrol	Encapsulation efficiency of 68–89%; controlled drug release up to 24 h; no skin irritation	[106]
	SLNPs: cetyl palmitate and Polysorbate 60 (surfactant) NLCs: cetyl palmitate, Polysorbate 60 and miglyol-812		Encapsulation efficiency of 70%	[107]
	SLNPs: stearic acid and poloxamer 188 (surfactant)		Encapsulation efficiency of 89%; controlled drug release up to 24 h	[108]
	Compritol 888 ATO (lipid); Phospholipon 80H (emulsifier) and Poloxamer 188 (surfactant)		Trespass keratinocytes membranes without causing alterations in cell morphology and function	[109]
	Sericin protein		Encapsulation efficiency of 71–75%; non-toxic for dermal fibroblasts; continuous drug release up to 72 h	[110]
Nanoemulsions	Caproyl 90/isopropyl myristate (oil phase); Propylene glycol and ethanol (cosurfactants)	Resveratrol	Increased transdermal and deposition in skin;	[112]
	Vitamin E and sefsol (oil phase); Tween 80 and Transcutol P (surfactants)		ca. 88% drug release rate	[113]
	Sefsol 218® (oil phase); PEG 400 (co-surfactant); Tween 80 (surfactant) and water (aqueous phase)		Improved permeability and antioxidant activity	[114]
	Grape seed oil and orange oil (oil phase); Tween 80 (surfactant)		Improved stability after UV exposure; enhanced drug retention	[115]
Dendrimers	Polyamidoamide	Resveratrol	Enhanced solubility and stability; more efficiency in loading and skin penetration	[117]
	Glucan		Improved bioactivity, bioavailability, and solubility; higher antioxidant activity and cellular uptake	[118]

Na—Not applicable.

7. Future Challenges of Nanotechnology in Cosmetics

Nanotechnology is a relatively new and promising area that has witnessed tremendous improvements and broad use in cosmetics, dermatology, and biological applications in recent years [80]. The cosmetics industry was one of the pioneers in considering nanotechnology-based products, and it is now a global leader in the inclusion of nanotechnologies in the development of new products [119]. For instance, up to 13% of 1000 registered nano-based products on the global market were referred as cosmetic ones [120].

Despite the growing interest in nanocarriers due to their unique features, they also raise concerns related to consumer's health [119]. We have an incomplete knowledge of its interactions and implications. These problems must be addressed [121] and lead to the need of regulation over the incorporation of nanomaterials/nanotechnologies in cosmetic products. However, this raises another problem, as each country or world region follows its own legislation [119]. In the European Union (EU), the Regulation (EC) nº 1223/2009 establishes the legal basis for all manufactured or sold cosmetic products [80]. For example, according to this document, each nanomaterial must be properly identified in the list of ingredients, using the word "nano" (in brackets) as a suffix to the material's name [119,122], which, due to the misinformation of the general public, may cause some reluctance to purchase products incorporating such materials. A good example of that was the distrust of a significant part of the world population towards the COVID-19 vaccines, which was partly due to the alleged incorporation of nanotechnologies in their formulations. In contrast to the EU, the United States Food and Drug Administration (FDA) does not require manufacturers to expressly state on the label that their products include nanomaterials since it is believed that particle size is not always connected to the toxicity profile and that labelling may consequently mislead customers. Moreover, in Brazil and India, there are no special regulations concerning the safety of cosmetics that include nanomaterials [119,123]. Thus, there is still a long way to go when it comes to the challenges of using nanotechnologies in cosmetics, to ensure success both in the desired efficacy of the product and in the safety of its use.

Furthermore, nanomaterials may also have an adverse effect on the environment. For example, they may be released into water, air, and soil, posing major environmental dangers [122]. On this note, concepts such as "green nanotechnology" emerge, where the production of nanomaterials that do not harm the environment or poses questions on human health is prioritised. For instance, green nanotechnology can design and build eco-friendly, safe metal nanoparticles without the use of harmful chemicals in the synthesis process by combining the principles of green chemistry and green engineering [124]. Moreover, researchers should promote the manufacturing of creative and sustainable cosmetic products, by using natural nanomaterials derived from renewable by-products (e.g., grape), selecting procedures with few operating stages, and opting for formulations that prevent or reduce the use of harmful solvents, among others [80,125].

8. Conclusions and Future Perspectives

Grape by-products (seeds, water, juice, among others) have been widely explored for cosmetic applications, due to the related health benefits, such as antioxidant, antimicrobial, and anti-inflammatory activities. These biological effects of grape by-products have been thoroughly studied and explored. Furthermore, considering that these wastes can have a negative impact on the environment, the continuous efforts to explore them can be included in the ongoing driver for a sustainable industry development. In addition, nanoencapsulation techniques allow to surpass some of the difficulties faced with the extracts from grape by-products, such as low solubility, susceptibility to photodegradation, and low bioavailability, exhibiting great potential for cosmetic applications.

To this day, nanotechnology-based formulations are not yet supported by clinical trial data. Therefore, prior to product promotion, there is a need to address several issues such as the reproducibility of the synthesis process or even the need to scale these solutions from pilot to industrial scale. Looking forward to these developments, it seems wise to consider that future well-designed clinical trials employing nanoformulations seem hugely promising [61,99].

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