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Review

Valorization of Wine-Making By-Products' Extracts in Cosmetics

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Abstract: The increased demand for conscious, sustainable and beneficial products by the consumers has pushed researchers from both industries and universities worldwide to search for smart strategies capable of reducing the environmental footprint, especially the ones connected with industrial wastes. Among various by-products, generally considered as waste, those obtained by winemaking industries have attracted the attention of a wide variety of companies, other than the vineries. In particular, grape pomaces are considered of interest due to their high content in bioactive molecules, especially phenolic compounds. The latter can be recovered from grape pomace and used as active ingredients in easily marketable cosmetic products. Indeed, phenolic compounds are well known for their remarkable beneficial properties at the skin level, such as antioxidant, antiaging, anti-hyperpigmentation and photoprotective effects. The exploitation of the bioactives contained in grape pomaces to obtain high value cosmetics may support the growing of innovative start-ups and expand the value chain of grapes. This review aims to describe the strategies for recovery of polyphenols from grape pomace, to highlight the beneficial potential of these extracts, both in vitro and in vivo, and their potential utilization as active ingredients in cosmetic products.

Keywords: cosmetics; grape pomace; phenolic compounds; antioxidants; extracts; natural active ingredient; sustainable development

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1. Introduction

Valuable phenolic compounds can be recovered from several edible fruits and vegetables, but also from different food by-products such as citrus fruits, orange peels [1–3], lemon peels, pomelo peels [3], grapefruit peels [4] and olive leaves [5–7]. in addition to pomegranate fruits peels and seeds [8–10], peach pomace [11] and viticulture by-products, in particular vine shoots [12–17] and winemaking by-products, especially grape pomace [18–22].

Grape by-products derived from the winery wastes consist mainly of vine stems, grape pomace and wine lees. Grape pomace is one of the most important residues, constituting between 20 and 25% of the initial grapes' weight and composed of 25% seeds, 25% stalks and 50% skins [23,24]. Grape pomace is generated during the winemaking process, after the fermentation step in the case of red grapes, and prior to it in the case of white grapes (Figure 1) [25]. Considering that 35.9 million tons of grapes are pressed yearly worldwide to produce wine [26], a large amount of such by-products is generated in a limited period of time causing ecological problems. In fact, polyphenols have a potential to alter the

equilibrium of the ecosystem, by modifying organic compound pathways and the nutrients cycle [27].

Figure 1. Grape pomace derived from the wine making process.

Given that, its exploitation and valorization by means of phenolic compounds' extraction is an attractive strategy aiming to recover functional compounds and, at the same time improve the lifecycle of grape production and use by reducing the environmental impact of its by-products [28]. Although considered as a waste, grape pomace still contains a high amount of valuable phenolic compounds. Those are characterized by the presence of at least one benzene ring with one or more hydroxyl substituents in their chemical structure [29].

Phenolic compounds can be divided into different groups: phenolic acids, flavonoids, tannins, lignans and neolignanes, stilbenes, coumarins and phenyl ethanol derivatives, (Figure 2) [30]. These molecules are naturally produced by the majority of plants as a strategy to protect and defend themselves against environmental aggressions and pathogens such as bacteria, fungi, etc. [31]. At the same time, and when properly used, these secondary metabolites may exert beneficial and protective activities for the human body. Indeed, they can be used as active ingredients in pharmaceutical, food and cosmetic products [32–35].

The aim of this work is to examine the extraction methods used for the recovery of bioactive polyphenols and their effective potential as functional ingredient in cosmetic applications. The novelty of this review resides in its waste-to-market approach. It analyses the effects of the extraction methods and parameters on the diversity and quality of the recovered phenolic compounds and their stability when incorporated in cosmetic products. The activity of the extracts studied in vitro, and/or incorporated in cosmetic products and evaluated in vitro and/or in vivo was also presented. The purpose of the review is to give a wide view of the life cycle of *Vitis vinifera* by-products starting by the extraction process of phenolic compounds and their characterization, passing through their in vitro study to finally reach the cosmetic application and the in vivo validation in clinical trials (Figure 3).

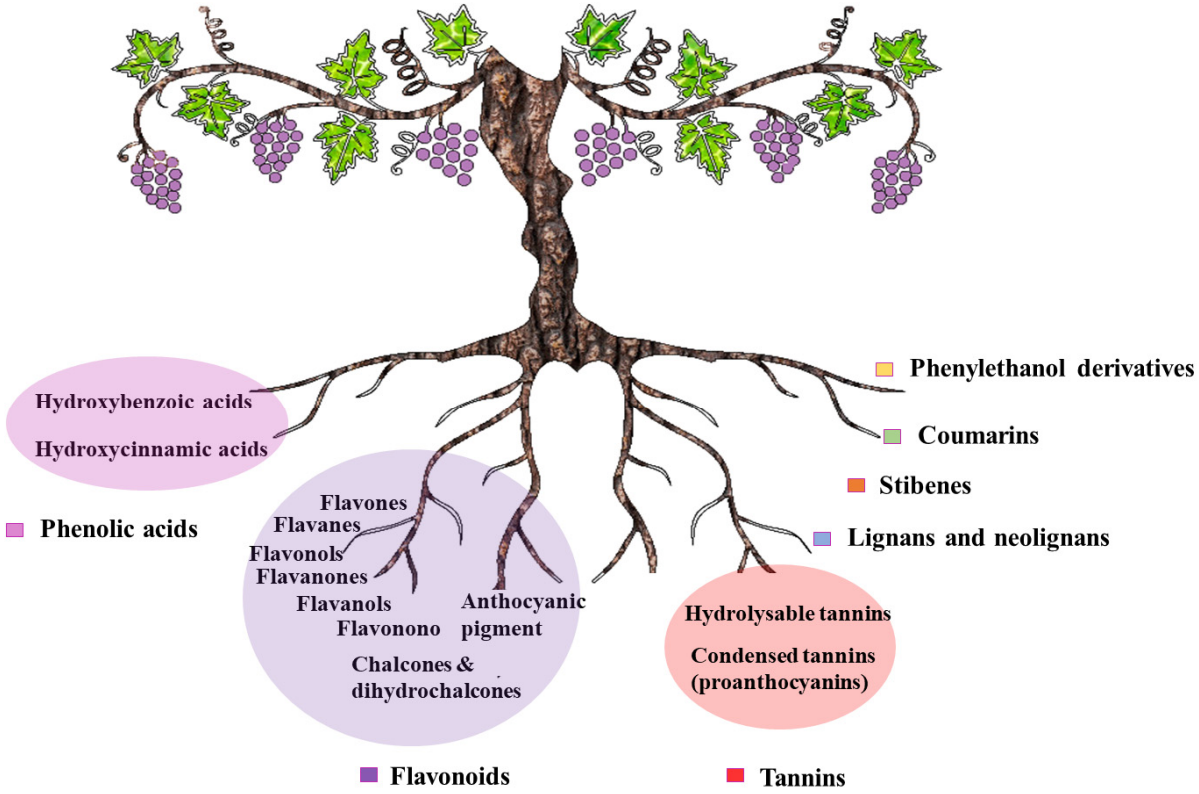

Figure 2. Schematic representation of phenolic compounds' groups.

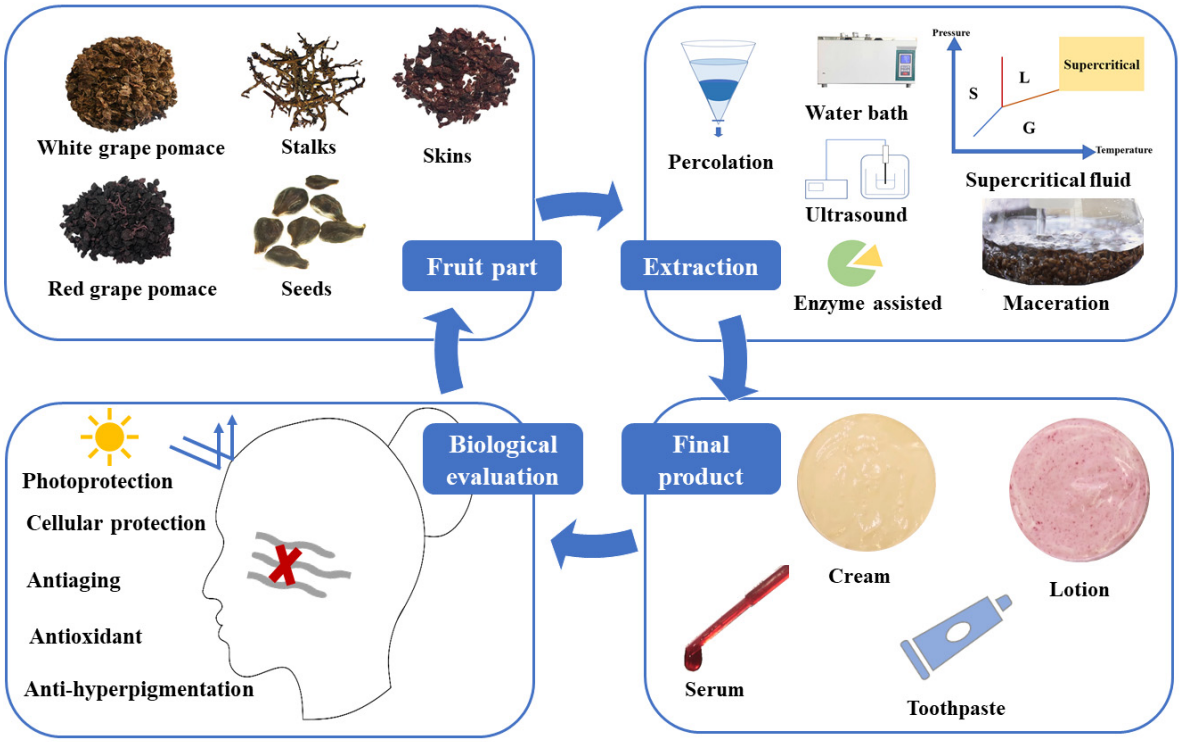

Figure 3. Schematic representation of the life cycle of *Vitis vinifera*, starting by the studied by-product, then the extraction technique, the cosmetics products in which polyphenols were formulated and finally the acquired biological activities.

2. Extraction of Phenolic Compounds from Grape By-Products

The extraction process is the first key step towards the recovery of phenolic compounds. The effectiveness of the process relies on the matrices used, the experimental conditions, the type of phenolic compounds to be extracted and the applied method [36]. Aiming to improve the extraction efficacy of polyphenols from grape by-products, different treatment techniques, extraction parameters and solvents have been used and several combinations of polyphenols were recovered. Table 1 gathers data about the extraction methods, parameters and solvents used for the different studied activities of the grape by-products' extracts used in cosmetics.

The overall reported procedure of the obtainment of functional ingredients from grape by-products consisted of an optional pre-treatment step (e.g., grinding), followed by an extraction process (e.g., ultrasound), a separation and concentration step (rotary evaporation), and finally a dehydration step (e.g., freeze drying).

The majority of the pre-treatment of the grape by-products consist of grinding. This mechanical reduction of particle size improves the extraction rate by reducing the distance the solute has to diffuse from the solid to the solvent [19].

Some innovative technologies such as microwave irradiation can be used in both pre-treatment or treatment processes. Matos et al. suggested that a short (60 s) microwave irradiation pre-treatment (80 °C) of the grape pomace led to targeting an enhanced selective extraction of anthocyanins compared to untreated samples. In fact, microwaves allow rapid heating of water molecules in the grape pomace, thus accelerating the extraction of the valuable compounds [37].

Besides the role of pre-treatments, like grinding or microwaves, in enhancing the recovery of phenolic compounds from the matrices, they are also used to eliminate undesired compounds. For example, in order to avoid the stickiness of the grape skin extract during freeze drying, it was pre-treated by suspending it in water for 24 h at 25 °C to reduce its sugar content [38].

After the pre-treatment process, many extraction methods are used to recover phenolic compounds from grape by-products. For example, ultrasound [39,40], supercritical fluid [40], maceration [22,41–43], enzyme-assisted extraction [44], percolation [45] and traditional solid liquid extraction [37–39,46,47] are mentioned. Solid liquid extraction remains the most commonly used and accessible technique in the studies of polyphenol extraction for application in cosmetic products.

The majority of the extraction processes were performed by using organic solvents, in particular ethanol and water blends. Indeed hydroethanolic mixture solvents facilitate the solubility of the phenolic compounds and enhance their extraction [38]. Maluf et al. compared the efficiency of polyphenol extraction from *Vitis labrusca* L. pomace using different solvent mixtures. Acetone:water (75:25) provided the highest yield (190 $mg \cdot g^{-1}$) of polyphenols, compared to methanol:water (75:25, 100 $mg \cdot g^{-1}$), acetone (100%, 90 $mg \cdot g^{-1}$), ethanol (100%, 50 $mg \cdot g^{-1}$), ethanol:water (75:25, 20 $mg \cdot g^{-1}$), and methanol (100%, 20 $mg \cdot g^{-1}$) [47].

Recently, the user-friendly COSMOtherm tool was suggested to design tailor-made GREEN and GRAS deep eutectic solvents. The latter can be used for an environmentally friendly recovery of polyphenols from grape pomaces to be used in subsequent cosmetic applications. This software is expected to save time and reduce the experimental costs of the solvent selection process [48].

After the extraction process, the exhausted solid pomace is mainly separated from the liquid extract by filtration or centrifugation and the organic solvent is then mainly regenerated by rotary evaporation. The concentrated aqueous remaining extract is either used as it is in cosmetic applications or transformed into a powder by freeze drying (Table 1).

The majority of studies have used spectrophotometry (Folin-Ciocalteu) and/or chromatography (HPLC) to identify and quantify the main phenolic compounds. The main components detected in grape pomaces by HPLC were gallic acid, catechin, epicatechin and quercetin (Table 1). Moreover, this identification was sometimes linked to the skin

biological activity. For example, quercetin and gallic acid have the highest capacity to inhibit the tyrosinase activity and are therefore expected to decrease the hyperpigmentation activity in human skin [44]. The ultimate goal of Table 1 is to link the extraction techniques to the quality (selectivity, polarity, etc.) and quantity of the obtained polyphenols and subsequently to their biological activities on the skin.

Some papers analyzed only the in vitro biological activities of the crude grape pomace extracts [22,37,38,40,44,46,47] (Table 2). Meanwhile others incorporated those extracts (liquid or powder) into cosmetic products and studied their in vitro [39,41,42,45,49,50] and/or in vivo effects [39,43,45,51] (Table 3).

Table 1. Grape variety, pre-treatment, extraction parameters, extract treatment, analytical methods and identified compounds for the corresponding studied activities in cosmetics.

Grape Variety/Fruit Part	Pre-Treatment	Extraction Parameters (Method; Solvent; Solid to Liquid Ratio; Time; Temperature)	Extract Treatment	Spectrophotometric Methods	Chromatographic Methods	Identified Phenolic Compounds	Analysis on Extract In Vitro	Incorporation in Product		Studied Activity	Ref
								In Vitro	In Vivo		
***Vitis vinifera*L./seeds**	Drying	Solid liquid extraction EtOH: H_2O (95:5 v/v) 7 days	Concentration under rotavapor (40 °C) Filtration	DPPH and FRAP assays	HPLC	Catechin, epicatechin, gallic acid, epicatechin gallate, and procyanidin dimers (B-1, B-2 and B-3)	Yes	No	Yes	Antiaging	[49]
***Vitis vinifera*L. Grechetto/skin and seeds**	-	Homogenizing by UltraTurrax T25 (3 min, 30,618 g) or ultrasound bath (5 min) EtOH: H_2O (60:40 v/v) or H_2O (100%) 1:2	Centrifugation (21,074× g, 15 min, 4 °C)	Proanthocyanidins, Folin-Ciocalteu and DPPH assays	Reversed phase—HPLC	Quercetin glucoside	No	Yes	No	Antioxidant	[39]
	Freezing under liquid nitrogen Grinding	Solid liquid extraction EtOH (100%) 1:3 1 h 20 °C	Centrifugation (21,074× g, 15 min, 4 °C) Concentration under rotavapor (4 °C) Freeze drying								
***Vitis vinifera*L. Cabernet Sauvi-gnon/seeds**	Freezing under liquid nitrogen Grinding	Solid liquid extraction EtOH: H_2O (60:40 v/v) or H_2O (100%) 1:10 1 h 20 °C	Centrifugation (21,074× g, 15 min, 4 °C) Concentration under rotavapor (4 °C) Freeze drying	Folin-Ciocalteu assay	-	-	No	Yes	Yes		
Carignano/skins	Freeze drying Grinding	Solid liquid extraction and sonication at scheduled times by high-intensity ultrasonic disintegrator (1000 s, 200 cycles, 5 on, 5 off, 15 µm of probe amplitude) EtOH: H_2O (70:30 v/v) 1:32 48 h 25 °C	Centrifugation (8000 rpm, 30 min, ×2) Concentration under rotavapor Freeze drying Loading into vesicles (liposomes, montanov-glycerosomes, glycerosomes and montanov-liposomes)	Folin-Ciocalteu and DPPH assays	HPLC-ESI-TOF-MS	Both samples contained: Catechin isomers, fisetin, quercetin, myricetin, quercetin hexoside, syringetin hexoside, quercetin-3-methyletere, apigenin-6,8-di-C-arabinoside and apigenin-6,8-di-C-arabinoside Sample not pre-treated: Syringic acid and myricetin hexoside Sample pre-treated: Epicatechin gallate	Yes	No	No	Antioxidant Cellular protection	[38]
	Suspension in distilled water (constant stirring, 24 h, 25 °C, 1:40) Filtration Freeze drying Grinding										

Table 1. *Cont.*

Grape Variety/Fruit Part	Pre-Treatment	Extraction Parameters (Method; Solvent; Solid to Liquid Ratio; Time; Temperature)	Extract Treatment	Spectrophotometric Methods	Chromatographic Methods	Identified Phenolic Compounds	Analysis on Extract In Vitro	Incorporation in Product		Studied Activity	Ref
								In Vitro	In Vivo		
***Vitis vinifera*/seeds paste**	Cold pressing of seeds Defatting of the seed pastes	Ultrasound extraction EtOH and EtOH: H_2O (1:1 *v*/*v*); 1:3 20 min	Evaporation to dryness	Folin-Ciocalteu and DPPH assays	HPLC-DAD and LC-HRMS	Gluconic acid, tartaric acid, citric acid, gallic acid, glucogalli, catechin, epicatechin, epicatechin gallate, dimer and trimer and tetramer proanthocyanidins, dimer and trimer proanthocyanidins gallate	Yes	No	No	Antioxidant Inhibition activity against collagenase, elastase and tyrosinase enzymes	[40]
		Supercritical fluid extraction (300 bar) CO_2 at 15 g/min with 10% EtOH and CO_2 at 15 g/min with 20% EtOH *w*/*w*	-			Gluconic acid, tartaric acid, citric acid, gallic acid, glucogalli, catechin and epicatechin					
Grape/seeds	Grinding	Maceration extraction EtOH: H_2O (95:5 *v*/*v*) 1 week	Filtration (Whatman grade 1 size) Concentration under rotavapor (40 °C)	-	HPLC	Catechin and epicatechin	Yes	Yes	No	Photoprotection	[41]
***Vitis vinifera*L. *Cabernet Sauvignon*/pomace**	Drying Pulverizing	Percolation extraction EtOH: H_2O (70:30 *v*/*v*)	Concentration (ascending film evaporator) Homogenization Freeze drying	-	-	-	No	Yes	Yes	Photoprotection	[45]
***Vitis vinifera*L. Red varieties: Tinta Roriz, Touriga Nacional, Castelão and Syrah/stems White varieties: Arinto, and Fernão Pires/stems**	Grinding	Solid liquid extraction MeOH: H_2O (70:30 *v*/*v*) 0.4:15 30 min Room temperature	Centrifugation (10,000 rpm, 15 min, at 4 °C) Filtration (0.45 µm PVDF filter)	ABTS, DPPH, and FRAP assays	Reversed phase-HPLC-DAD	Gallic acid, protocatechuic acid, catechin, epicatechin, *trans*-cinnamic acid, caftaric acid, quercetin-3-*O*-rutinoside, resveratrol, ε-viniferin, malvidin-3-*O*-galactoside, malvidin-3-*O*- glucoside	Yes	No	No	Antioxidant and inhibition activity against elastase and tyrosinase enzymes	[46]

Table 1. *Cont.*

Grape Variety/Fruit Part	Pre-Treatment	Extraction Parameters (Method; Solvent; Solid to Liquid Ratio; Time; Temperature)	Extract Treatment	Spectrophotometric Methods	Chromatographic Methods	Identified Phenolic Compounds	Analysis on Extract In Vitro	Incorporation in Product		Studied Activity	Ref
								In Vitro	In Vivo		
***Tempranillo* /pomace**	With and without microwaves irradiation (80 °C for 60 s)	Solid liquid extraction EtOH: H_2O (50:50 *v*/*v*) 60 °C	Concentration under rotavapor	Folin-Ciocalteu, total monomeric anthocyanin pigment content, ORAC, HOSC and HORAC assays	HPLC-DAD-MS/MS	Gallic acid, 2-S-glutathionylcaftaric acid, procyanidin dimer and trimer, caftaric acid, catechin, epicatechin, delphinidin-3-*O*-glucoside, quercetin-3-*O*-glucoside, coutaric acid, cyanidin-3-O-glucoside, visitin A, petunidin-3-*O*-glucoside, myricetin-3-*O*-glucoside, malvidin-3-*O*-glucoside, peonidin-3-*O*-glucoside, quercetin-3-*O*-glucuronide, delphinidin-3-*O*-6″-*p*-acetylglucoside, 10-carboxypyranomalvidin-3-6″-*p*-coumaroylglucoside, syringetin-3-*O*-glucoside, myricetin, cyanidin-3-*O*-6″-*p*-coumaroylglucoside, petunidin-3-*O*-6″-*p*-coumaroylglucoside, quercetin, malvidin-3-*O*-6″-*p*-coumaroylglucoside, peonidin-3-*O*-6″-*p*-coumaroylglucoside, kaempferol	Yes	No	No	Inhibition activity against elastase, tyrosinase and MMP-1 enzymes Antioxidant activity	[37]
Grape/seeds	Crushing	Maceration extraction EtOH: H_2O (95:5 *v*/*v*) 1:3 1 week	Filtration Concentration under rotavapor (40 °C)	Folin-Ciocalteu, total monomeric anthocyanin content, DPPH and FRAP assays	-	-	Yes	Yes	No	Photoprotection	[42]

Table 1. *Cont.*

Grape Variety/Fruit Part	Pre-Treatment	Extraction Parameters (Method; Solvent; Solid to Liquid Ratio; Time; Temperature)	Extract Treatment	Spectrophotometric Methods	Chromatographic Methods	Identified Phenolic Compounds	Analysis on Extract In Vitro	Incorporation in Product		Studied Activity	Ref
								In Vitro	In Vivo		
Red grape/seeds Red grape/stalks	Freeze drying Grinding	Maceration extraction EtOH 1:5 48 h Room temperature (25 °C)	Centrifugation (8000 rpm, 30 min, ×2) Freeze drying Loading into vesicles (liposomes, hyalurosomes and transfersomes)	DPPH assay	HPLC-DAD	Seeds: catechin, epicatechin, epicatechin gallate Stalks: gallic acid, epigallocatechin gallate, quercetin, quercetin 3-glucoside and malvidin-3-glucoside	Yes	No	No	Antioxidant Cellular protection	[22]
***Vitis vinifera*/seed**	Grinding	Maceration extraction MeOH: H_2O (70:30) 1:5 72 h Room temperature	Filtration (16 folds of muslin cloth and Whatman grade 1 size) Concentration under rotavapor (40 °C)	-	-	-	No	No	Yes	Antiaging Skin depig-menting	[43]
***Vitis labr-usca*L./pomace**	Drying (60 °C, 2 h) Grinding	Ace: H_2O (75:25), MeOH: H_2O (75:25), Ace (100%), EtOH (100%), EtOH: H_2O (75:25) and MeOH (100%)	-	-	-	-	-	-	-	-	[47]
		Solid liquid extraction Ace: H_2O (75:25) 1:5 120 min <60 °C	Filtration (pore filtre membrane 0.22 µm) Freeze drying	Folin-Ciocalteu and DPPH assays	HPLC-PAD	Ellagic acid	Yes	No	No	Antioxidant Cell protection and cyto-toxicity	

Table 1. *Cont.*

Grape Variety/Fruit Part	Pre-Treatment	Extraction Parameters (Method; Solvent; Solid to Liquid Ratio; Time; Temperature)	Extract Treatment	Spectrophotometric Methods	Chromatographic Methods	Identified Phenolic Compounds	Analysis on Extract In Vitro	Incorporation in Product		Studied Activity	Ref
								In Vitro	In Vivo		
Mix of *Vitis vinifera* L. Trebbiano & Verdicchio (60:40)/pomace	Wet pomace: Grinding and addition of distilled water (1:5 g/mL) Dried pomace: Drying at 60 °C for 24 h; grinding then hydration (1:5 g/mL for 1 h)	Enzyme-assisted extraction H_2O (100%) and EtOH: H_2O (95:5 *v*/*v*) Overnight 24 °C	-	Folin-Ciocalteu, flavonoid and flavanol content assays	HPLC-DAD	Catechin, epicatechin, epigallocatechin gallate, epicatechin gallate, epigallocatechin, gallic acid, *cis*-piceid, *cis*- resveratroloside. Catechin, epicatechin, epigallocatechin gallate, epicatechin gallate, epigallocatechin, gallic acid, protocatechuic acid, chlogenic acid, *cis*-piceid, *cis*-resveratroloside, quercetin	Yes	No	No	Anti-tyrosinase Anti-elastase	[44]
Grape/seeds	-	Purchased extract	-	-	-	-	Yes	Yes	No	Photo-protection	[50]
Grape/seeds	-	-	-	DPPH assay	-	-	Yes	No	Yes	Antiaging	[51]
***Vitis vinifera*L./seeds**	-	Purchased extract	-	Folin-Ciocalteu assay	-	-	No	Yes	No	Skin penetration	[52]
Muscat Hamburg/seeds	Grinding	Sonication MetOH: H_2O: 1 M HCl (70:29.5:0.5) 1:5 15 to 20 min	Filtration (Whatman grade 1) Concentration under rotavapor Filtration	-	-	-	No	No	Yes	Skin depigmenting Moisturizing Antiaging	[53]

DAD: Diode Array Detector; ESI: Electrospray Ionization; HPLC: High Performance Liquid Chromatography; HRMS: High-Resolution Mass Spectrometer; LC: Liquid Chromatography; MS: Mass Spectrometry; PAD: Photodiode Array Detector; TOF: Time Of Flight.

Table 2. In vitro assays conducted on grape pomace extracts with their corresponding studied and effective concentrations as well as their observed effects.

Grape Variety/ Fruit Part	Studied Activity	Type of Assay	Sample	Studied Concentrations	Effective Concentration	Observed Effect	Ref
Carignano/skins	Antioxidant activity	DPPH assay	Extract in dispersion	-	30 mg/mL	84% reduction of DPPH radicals	[38]
			Extract loaded vesicles (montanov-glycerosomes)	-	30 mg/mL	86% reduction of DPPH radicals	
			Extract-loaded vesicles (glycerosomes)	-	30 mg/mL	88% reduction of DPPH radicals	
			Extract-loaded vesicles (montanov-liposomes)	-	30 mg/mL	89.5% reduction of DPPH radicals	
			Extract-loaded vesicles (liposomes)	-	30 mg/mL	90% reduction of DPPH radicals	
	Cellular protection in the presence of H_2O_2	Fibroblast cell culture	Extract in dispersion	0.3, 3 and 30 and µg/mL	0.3 µg/mL	Increased viability of fibroblasts to 70%	
			Extract-loaded vesicles (liposomes, montanov-liposomes, montanov-glycerosomes and glycerosomes)		0.3 µg/mL	Increased viability of fibroblasts ≥83%	
			Positive control (treated cells with H_2O_2)	-	-	Reduction of the viability of fibroblasts to 50%	
***Vitis vinifera*/ seeds paste**	Anti-tyrosinase activity	Enzymatic assay	Ultrasound extract in EtOH	20, 150 and 500 µg/mL	500 µg/mL	Up to 75% decrease of tyrosinase activity	[40]
			Ultrasound extract in EtOH: H_2O (1:1)	20, 150 and 500 µg/mL	500 µg/mL	Up to 72.4% decrease of tyrosinase activity	
			Supercritical fluid extract (10% EtOH)	20, 150 and 500 µg/mL	500 µg/mL	Up to 10% decrease of tyrosinase activity	
			Supercritical fluid extract (20% EtOH)	20, 150 and 500 µg/mL	500 µg/mL	Up to 15% decrease of tyrosinase activity	
			Positive control: kojic acid	-	7.1 µg/mL	Up to 52% decrease of tyrosinase activity	

Table 2. *Cont.*

Grape Variety/Fruit Part	Studied Activity	Type of Assay	Sample	Studied Concentrations	Effective Concentration	Observed Effect	Ref
***Vitis vinifera*/ seeds paste**	Anti-elastase activity	Enzymatic assay	Ultrasound extract in EtOH	30, 150 and 300 µg/mL	300 µg/mL	Up to 91.3% decrease of elastase activity	[40]
			Ultrasound extract in EtOH: H_2O (1:1)	30, 150 and 300 µg/mL	300 µg/mL	Up to 83.2% decreasing of elastase activity	
			Supercritical fluid extract (10% EtOH)	30, 150 and 300 µg/mL	300 µg/mL	Up to 30% decrease of elastase activity	
			Supercritical fluid extract (20% EtOH)	30, 150 and 300 µg/mL	300 µg/mL	Up to 35% decrease of elastase activity	
			Positive control: Elastatinal	-	0.5 µg/mL	Up to 51.3% decrease of elastase activity	
	Anti-collagenase activity	Enzymatic assay	Ultrasound extract in EtOH and EtOH: H_2O (1:1)	50, 200 and 600 µg/mL	200 µg/mL	Up to 100% decrease of collagenase activity	
			Supercritical fluid extract (20% EtOH)	50, 200 and 600 µg/mL	600 µg/mL	Up to 90% decrease of collagenase activity	
			Supercritical fluid extract (10% EtOH)	50, 200 and 600 µg/mL	600 µg/mL	Up to 80% decrease of collagenase activity	
			Positive control: Phosphoramidon	-	16 µM	Up to 46.4% decrease of collagenase activity	
Grape/seeds	Cytotoxicity	MTT assay on fibroblast cell culture	Extract	0.1 to 31.25 µg/mL	31.25 µg/mL	Dose-dependent and significant increased fibroblast viability by up to 132%	[41]
	UV protection	MTT assay on irradiated fibroblasts with UVA (20 $J.cm^{-2}$)	Extract	0.1 to 25 µg/mL	25 µg/mL	Improved cell viability by up to 68%	

Table 2. *Cont.*

Grape Variety/Fruit Part	Studied Activity	Type of Assay	Sample	Studied Concentrations	Effective Concentration	Observed Effect	Ref
***Vitis vinifera* L. Red varieties: Tinta Roriz, Touriga Nacional, Castelão, Syrah/stems White varieties: Arinto, and Fernão Pires/stems**	Anti-tyrosinase activity	Enzymatic assay	Extract	-	1 mg/mL	Inhibition ranging from 41.47% to 53.83%	[46]
	Anti-elastase activity	Enzymatic assay	Extract	-	1 mg/mL	Inhibition ranging from 67.98% to 98.02%	
	Antioxidant activity	DPPH assay	Extract	-		Capacity ranging from 0.15 to 0.64 T/g dw	
		ABTS assay	Extract	-		Capacity ranging from 0.35 to 0.84 T/g dw	
		FRAP assay	Extract	-		Capacity ranging from 0.35 to 1.03 mmol T/g dw	
Grape/seeds	Antioxidant activity	DPPH assay	Extract	1 to 100 µg/mL	33.17 µg/mL	50% reduction of DPPH radicals	[42]
			Vitamin E acetate	1 to 1000 µg/mL	12.23 µg/mL		
			Trolox		6.08 µg/mL		
			BHT		206.81 µg/mL		
		FRAP assay	Extract	1 to 100 µg/mL	1 mg/mL equivalent to: 4.17 mM of vitamin C and 0.73 of Trolox	Reduction of Fe^{+3}	
	Photoprotection	UV absorption spectrum	Extract	1%, 3%, and 5% (*w/v*)	3% and 5% *w/v* More effective than 1% *w/v* of extract	UVA (320–400 nm) and blue light (400–495 nm) absorption	

Table 2. *Cont.*

Grape Variety/Fruit Part	Studied Activity	Type of Assay	Sample	Studied Concentrations	Effective Concentration	Observed Effect	Ref
***Tempranillo*/pomace**	Anti-tyrosinase activity	Enzymatic assay	Extract without irradiation	Increasing concentration	4.03 ± 0.14 mg/mL	50% reduction of tyrosinase activity	[37]
			MW irradiated extract		4.00 ± 0.14 mg/mL		
	Anti-elastase activity		Extract without irradiation		0.87 ± 0.03 mg/mL	50% reduction of elastase activity	
			MW irradiated extract		3.43 ± 0.11 mg/mL		
	Anti- MMP-1 activity		Extract without irradiation		1.08 ± 0.08 mg/mL	50% reduction of MMP-1 activity	
			MW irradiated extract		1.16 ± 0.06 mg/mL		
	Antioxidant activity	ORAC assay	Extract without irradiation	-	-	481 ± 30 µmol TE/g Extract	
			MW irradiated extract			448 ± 31 µmol TE/g Extract	
		HOSC assay	Extract without irradiation			746 ± 49 µmol TE/g Extract	
			MW irradiated extract			441 ± 34 µmol TE/g Extract	
		HORAC assay	Extract without irradiation			305 ± 28 µmol CAE/g Extract	
			MW irradiated extract			198 ± 19 µmol CAE/g Extract	
	Cellular protective effects against oxidative damage (TBHP)	keratinocyte cell culture	Extract without irradiation	0.25 mg/mL to 2 mg/mL	0.25 mg extract/mL	Cell viability increased to 60%	
			MW irradiated extract			Cell viability increased to 45%	
		Fibroblast cell culture	Extract without irradiation			Cell viability increased to 50%	
			MW irradiated extract			Cell viability increased to 20%	

Table 2. *Cont.*

Grape Variety/Fruit Part	Studied Activity	Type of Assay	Sample	Studied Concentrations	Effective Concentration	Observed Effect	Ref
Red grape/seeds Red grape/stalks	Antioxidant	DPPH assay	Extract in dispersion	-	40 μg/mL	78% reduction of DPPH radicals	[22]
			Extract loaded vesicles (liposomes, transfersomes, hyalurosomes, hyalo-transfersomes)	-	40 μg/mL	88% reduction of DPPH radicals	
	Protection in the presence of H_2O_2	Fibroblast and keratinocyte cell culture	Extract in dispersion	-	2 μg/mL	Viability of keratinocytes and fibroblasts increased to 88 and 92%	
			Extract loaded vesicles (liposomes, transfersomes, hyalurosomes, hyalo-transfersomes)	-	2 μg/mL	Viability increased >100% in both cell lines	
			Positive control (exposed to H_2O_2 and untreated with extract)	-	-	Viability of keratinocytes and fibroblasts reduced to ∼65 and 70%	
***Vitis labrusca*L./pomace**	Antioxidant	DPPH assay	Extract	0.5 to 25 μg/mL	6.9 μg/mL	50% reduction of DPPH radicals	[47]
			BHT	0.11 to 19 μg/mL	7.6 μg/mL	50% reduction of DPPH radicals	
			Quercetin	0.75 to 15 μg/mL	4.5 μg/mL	50% reduction of DPPH radicals	
	Cytotoxicity	Fibroblast cell culture	Extract	0.5 to 200 mg/mL	No statically significant difference	Maintained cell viability	
			Control (without extract)	-			
	Cytoprotecting in the presence of H_2O_2 (600 μM)	Fibroblast cell culture	Freeze dried extract	0.73 to 3.65 mg/mL	0.73 mg/mL	Maintained cell viability and protecting against H_2O_2 damage	
			Positive control (without extract)	-	-	Cell viability reduced to 60%	

Table 2. *Cont.*

Grape Variety/Fruit Part	Studied Activity	Type of Assay	Sample	Studied Concentrations	Effective Concentration	Observed Effect	Ref
Mix of *Vitis vinifera* L. Trebbiano & Verdicchio (60:40)/pomace	Anti-tyrosinase	Enzymatic assay	Ethanol extract	-	Aliquots of 0.3 mL	79% decrease of tyrosinase activity	[44]
			Water extract			Up to 71% decrease of tyrosinase activity	
	Anti-elastase	Enzymatic assay	Extract	1 mg/mL	-	From 67.98% to 98.02 inhibition	
Grape/seeds	Antioxidant	DPPH assay	Extract	-	6.87 µg/mL	50% inhibition of DPPH radicals	[50]
			Positive control: Ascorbic acid	-	4.40 µg/mL	50% inhibition of DPPH radicals	

CAE: caffeic acid equivalents; dw: dry weight MW: microwaves; TE: Trolox equivalents.

Table 3. Formulation of the incorporated grape extracts in different cosmetic products, evaluation and effects.

Grape Variety/Fruit Part	Product	Product Evaluation			Effect	Ref
		Stability	In Vitro	In Vivo		
***Vitis vinifera*L./seeds**	**Emulsion:** Propylene, paraben, paraffin oil, Abil-EM 90, distilled water, methylparaben, olive oil, lemon oil, grape seed extract (5%)	Rheological studies Macroscopic observations	-	Skin evaluation Parameters: skin moisture content, Sebum content, elasticity, and SELs (scaliness, wrinkles, roughness) 40 females 12 weeks Cheeks	Reduce: roughness (14%), scaliness (13%), winkles (21%) and sebum content (26.13%) Enhance: elasticity (45.3%) and hydration (29.85%)	[49]
	Emulgel: Propylene, paraben, paraffin oil, Abil-EM 90, distilled water, methylparaben, olive oil, Carbapol 940, Triethanolamine, lemon oil, grape seed extract (5%)				Reduce: roughness (55%), scaliness (26%), winkles (23.9%), and sebum (30.3%) Enhance: elasticity (50%) and hydration (32.2%)	
***Vitis vinifera* L. Grechetto/skin and seeds**	**Toothpaste:** 2% or 10% ethanol skins extract added into commercial toothpaste.	-	Total polyphenols content	-	No significant difference of polyphenol content between 2% and 10% samples.	[39]
	Toothpaste: 2% or 10% ethanol seeds extract added into commercial toothpaste.				Significant increase of polyphenol content in the 10% sample	
***Vitis vinifera* L. Cabernet Sauvignon/seeds**	**Toothpaste:** 2.5% or 5% of ethanol extract added into commercial toothpaste.	-	Shelf life evaluation (after 2 and 4 months, at ambient temperature) by evaluating: Total polyphenols content and antioxidant activity	Acceptability of the toothpaste was evaluated by 10 consumers	Increase in total polyphenol content after 2 months, and persisted after 4 months. Better preservation action in ethanol than in water.	
	Toothpaste: 5% or 10% of water extract added into commercial toothpaste.				Decrease in in total polyphenol content after 2 months and 4 months. Highest antioxidant activity in 10% sample. Most appreciated clinically in 5% sample.	

Table 3. *Cont.*

Grape Variety/Fruit Part	Product	Product Evaluation			Effect	Ref
		Stability	In Vitro	In Vivo		
Grape/seeds	**Cream:** Mineral oil (5%), cetomacrogol 1000 (7%), cetyl alcohol (2%), octyl methoxycinnamate OMC (7%), grape seeds extract **(3%),** xanthan (1%), glycerine (5%), phenoxyethanol (0.5%), purified water q.s. to 100% *	-	Photoprotection efficacy: measurement of UV emissions before and after exposure to UV light using PMMA plates and Transpore tapes	-	SPF 9.92 on PMMA plates after UV exposure SPF 13.64 on Transpore tapes after UV exposure	[41]
***Vitis vinifera* L. *Cabernet Sauvignon*/pomace**	**Cream:** Ammonium acryloyldimethyltaurate/VP copolymer, trilaureth-4 phosphate, rapeseed oil sorbitol esters, mineral oil and isopropyl palmitate (4%), ammonium acryloyldimethyltaurate vinylpyrrolidone (0.5%), propylene glycol (5%), ethyl alcohol (2.5%), disodium EDTA (0.1%), grape pomace extract (10%), water purified q.s. to 100%, butylmethoxydibenzoyl methane (2.5%), ethylhexyl methoxycinnamate (5%), ethylhexyl dimethyl PABA (4%), butylated hydroxy toluene (0.1%), mixture of phenoxyethanol and parabens others (0.75%) *	Evaluation of organoleptic properties by aspect, color, and odor and the pH value.	Design of Experiment DPPH assay SPF measurement using PMMA plates	Primary and cumulative cutaneous irritability and sensitization tests 60 males and females 6 weeks Application on the back skin Phototoxicity and Photosensitization test 30 males and females 5 weeks Applications on the back skin	Antioxidant activity (40.10%) Absence of irritation and dermal sensitization *In vitro* SPF: 16.33 *In vivo* SPF: 12.30	[45]
Grape/seeds	**Cream:** Mineral oil (16.07%), span 80 (3.93%), Tween 80 (3.07), triethanolamine (0.4%), Carbopol 940 (0.5%), glycerin (5%), propylparaben (1%), q.s. water to 100%, grape seeds extract (3%) *	Evaluation for texture profiles, viscosity and pH: at 25 °C & 4 °C before and after heat cool cycling (6 cycles) for 12 h	SPF and PA measurement	-	UV protection booster: SPF 1.29 PA 1.19	[42]

Table 3. *Cont.*

Grape Variety/Fruit Part	Product	Product Evaluation			Effect	Ref
		Stability	In Vitro	In Vivo		
Grape/seeds	**Lotion:** Anisotriazine (8%), titanium dioxide (12%), silicone DC 5562 (5%), sorbitan monostearate (1%), cremophore A6 (2%), cremophore A25 (1.5%), cetyl alcohol (0.8%), beeswax (0.8%), isopropyl myristate (2.4%), disodium EDTA (0.2%), glycerin (1%), propylene glycol (2%), methyl paraben (0.1%), propyl paraben (0.02%), polysorbate 60 (1%), q.s. to water 100%, grape seeds extract (1%) *	Evaluation for the physical characteristic of pH and viscosity after freeze-thaw condition (4 °C, 45 °C, 24 h) for each condition (6 cycles)	SPF measurements DPPH assay	-	SPF booster up to 53.58 Antioxidant activity (84.04%)	[50]
Grape/seeds	**Cream:** ABIL-EM 90 (cetyl dimethicone copolyol), paraffin oil, distilled water, grape seeds extract (3%),methyl paraben, glycerin, lemon oil, triethanolamine solution	Evaluation at 8 °C, 25 °C, 40 °C for 12 weeks for stability, color and pH	-	Study of the moisture content, pH value, sebum content, elasticity and average pore size of skin Questionnaire subjective evaluation 20 females 12 weeks Application on cheeks	Stable product Antiaging effects: Reduction of size pores (56.8%) Reduction in roughness (18.98%) Increase in skin elasticity (47.95%) Increase in sebum content (93.85%) Increase in hydration (47.56%).	[51]
***Vitisvinifera*/seed**	**Cream:** Paraffin oil (16%), abil-EM 90 (4%), distilled water q.s. to 100%, grape seeds extract (4%), rose oil (2 to 3 drops)	Evaluation at 8 °C, 25 °C,40 °C for 12 weeks for pH, centrifugation, electrical conductivity, phase separation, organoleptic and physical characteristics	-	Study of skin microrelief parameters, elasticity, moisture contents and melanin 11 males 12 weeks Application on cheeks	Stable product Antiaging effects Skin depigmenting effects	[43]

Table 3. *Cont.*

Grape Variety/Fruit Part	Product	Product Evaluation			Effect	Ref
		Stability	In Vitro	In Vivo		
***Vitis vinifera*L./seeds**	**Liquid gel-based serum:** Grape seeds extract phytosome (10%), carbopol ultrez 30 (0.5%), triethanolamine (TEA) (0.4%), propylene glycol (10%), methylparabene (0.18), propylparaben (0.02%), sodium metabisulfite (0.075%), demineralized water q.s. to 100% *	Physicochemical evaluations: Organoleptic test (color, odor, syneresis), homogeneity, pH, viscosity and rheology	Penetration test (18 h)	-	Increasing the penetration of the phytosome into membrane	[52]
Muscat Hamburg/seeds	**Cream:** Liquid paraffin (16%), abil EM 90 (4%), grape seed extract (2%), distilled water (98%)	-	-	Patch test Study the effects of the formulations (containing or not the extract) on melanin content, erythema, moisture, elasticity and sebum 110 Males 8 weeks Application on cheeks	Absence of skin sensitive cases Safe application Decrease of skin melanin content (~18%) Increase in skin elasticity (~13%) Decrease in skin sebum content (15%) Increase skin moisture (data not indicated)	[53]

q.s.: quantity sufficient; *: formulation was selected amongst others.

3. Potential In Vitro Cosmetic Applications of Grape Pomace Extracts

The first step towards the assessment of an extract to be hypothetically used in cosmetic applications as an active ingredient is to conduct some in vitro tests. Those are a quick and cost-effective way to evaluate the potential use of grape pomace extracts in a specific biological activity prior to their incorporation in cosmetic formulas and the testing of their in vivo effectiveness in clinical trials. Grape pomace polyphenol extracts mainly exhibited promising antioxidant, antiaging, anti-hyperpigmentation and UV-protecting activities with in vitro testing (Table 2).

3.1. Antioxidant Activity

Antioxidants are valuable compounds that interrupt radical chains and protect cells from the damage caused by reactive species [54]. Among others, polyphenols are potent antioxidants capable of protecting human cells and tissues from oxidative stress [55]. Their presence in grape pomace extracts confers them a great antioxidant activity, as previously reported by several authors [22,37,38,42,46,47,49,56,57]. *Vitis labrusca* L. pomace [47], grape stems [56], *Tempranillo* red grape pomace [37], grape pomace [57], Carignano pomaces skins [38] and red grape seeds and stalks extracts [22] have all been tested to be used as an active ingredient in cosmetic formulations due to their antioxidant activity.

The antioxidant capacity of the grape seeds extract was evaluated in comparison to vitamin E acetate, Trolox and BHT using a DPPH assay. Natural grape seed extract only showed a better antioxidant activity than BHT. Its ability to scavenge free radicals (IC_{50} 33.17 µg/mL) was 6.23-fold lower than the synthetic molecule (IC_{50} 206.81 µg/mL) [42]. Likewise, Maluf et al. detected significant antioxidant effect (EC_{50} 6.9 µg/mL) of the *Vitis labrusca* L. pomace extract, suggesting it as a natural alternative for the synthetic antioxidant ingredient BHT (EC_{50} 7.6 µg/mL). This antioxidant activity was attributed to ellagic acid that was identified by HPLC [47].

On another note, the antioxidant activity of untreated red grape pomace extract was higher than the one obtained after a microwave irradiation pre-treatment (80 °C for 60 s). The same tendency was observed with three different chemical assays: ORAC (481 and 448 µmol TE/g Extract), HOSC (746 and 441 µmol TE/g Extract) and HORAC (305 and 198 µmol CAE/g Extract). The results of the chemical assays were in accordance with the total phenolic (TPC), and the total anthocyanin (TAC) contents. In fact, TPC was 1.82-fold higher in the untreated extract than that of the pre-treated one, but the TAC was 1.58-fold higher in the treated extract compared to the untreated one, indicating that the microwaves irradiation selectively enhanced anthocyanin extraction leading to an antioxidant activity of this class only and not the other phenolic subclasses. Moreover, the cellular antioxidant activity of MW-treated and -untreated extracts was conducted on two cell lines: keratinocytes and fibroblasts. In concordance with the previous results, the unirradiated extract had better cellular protective effects against induced oxidative damage compared to the MW irradiated extract in both keratinocyte and fibroblast cell models respectively. In conclusion, it is important to validate the antioxidant cellular activity of the chemical assays in cellular cultures and biological environment to be able to better assess and confirm the results [37].

The antioxidant capacity of the grape pomace extracts was also shown to be dependent of the carrier system. Red grape seeds and stalks extracts (40 µg/mL) showed a higher antioxidant activity (reduction 88% of DPPH radicals) when incorporated into vesicles (liposomes, transferosomes, hyalurosomes, hyalo-transferosomes) compared to extracts in dispersion (reduction 78% of DPPH radicals) [22]. The extracts (2 µg/mL) loaded into these vesicles also provided protection from the H_2O_2-induced oxidative effect on the keratinocytes and fibroblasts in cell culture. Results showed an increased cell viability of both cell lines by up to 100% with extract loaded vesicles, compared to 88% and 92% of viability increase of keratinocytes and fibroblasts, respectively, when the extract is in dispersion [22]. Likewise, Perra et al. reported that the extract-loaded vesicles can enhance

the cellular protection effects against hydrogen peroxide by up to 83% compared to 70% when the extract is in an aqueous dispersion [38].

Furthermore, the cytoprotective effect of the extracts was reported [22,37,38,47]. For example, Maluf et al. demonstrated that the lyophilized *Vitis labrusca* L. pomace extract studied at the lowest concentration (0.73 mg·mL^{-1}) was capable of effectively protecting fibroblasts from the damages caused by the treatment with H_2O_2 (600 µM) [47]. On that note, *Tempranillo* red grape pomace extracts (0.25 mg·mL^{-1}) also revealed their protective effects on both keratinocytes and fibroblasts that were co-incubated with a stressor, *tert*-butyl hydroperoxide (TBHP) [37].

3.2. Anti-Hyperpigmentation Activity

The pigmentation of the skin is associated with the accumulation and the production of melanin that is synthetized by tyrosinase enzyme. It is well known that phenolic compounds have structural analogies with the substrate of that enzyme and can thus inhibit melanin production (Figure 4) [37].

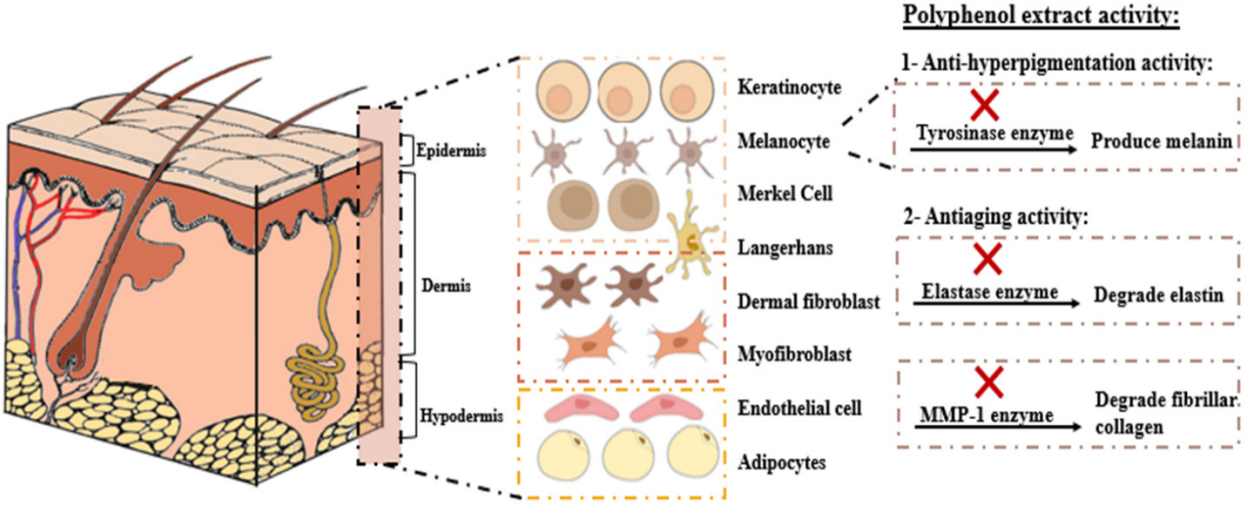

Figure 4. Effects of phenolic extracts on the skin anti-hyperpigmentation activity by inhibting tyrosinase enzyme as well as on the antiaging property by inhibting elastase and MMP-1 enzymes.

Red and white grape by-products have been studied for their inhibitory activities of tyrosinase enzyme. Results are likely to show the potential cosmetic application of polyphenols as active ingredient against hyperpigmentation [37,40,44,46].

Matos et al. detected the in vitro inhibitory capacity of the tyrosinase enzyme by treating cells with *Tempranillo* red grape pomace extracts. Almost the same IC_{50} of 4.00 mg/mL was found for the untreated and the MW pre-treated samples. Although both extracts showed the same inhibiting capacity for the tyrosinase enzyme, the untreated extract had 2 times more TPC (83.9 mg GAE/g extract) than the MW pre-treated one (45.9 mg GAE/g extract). However, the MW pre-treated extract had 1.5 times more TAC (2.7 mg malv-3-O-gl/g Extract) than the untreated extract (1.7 mg malv-3-O-gl/g Extract). Moreover, HPLC analysis showed that the flavonols content was higher in the MW pre-treated extract than the untreated one. This means that the tyrosinase inhibiting activity does not depend only on the phenolic compounds' quantity but also their overall quality and diversity [37].

Ferri et al. used solvent based extraction process in H_2O (100%) and EtOH: H_2O (95:5 *v*/*v*) for the mixture of white grapes (Trebbiano and Verdicchio) pomaces. The hydroethanolic solvent was 1.5 times more efficient than water in terms of polyphenol quantity. Moreover, the drying pre-treatment of pomaces was shown to enhance by 2.1-fold the recovery of polyphenols and by 2.8-folds the anti-tyrosinase activity (686.3 mg KA eq/L) compared to the wet pomace (243.3 mg KA eq/L) [44].

Leal et al. compared the antioxidant and anti-tyrosinase activities of red (Tinta Roriz, Touriga Nacional, Castelão, Syrah) and white grape stems (Arinto and Fernão Pires) by means of DPPH, ABTS and FRAP assays. Touriga Nacional variety had the highest antioxidant activities among the white and red grape stems with values of 0.64 Trolox per gram of dry weight (T/g dw), 0.84 T/g dw and 1.03 T/g dw respectively. As for the white varieties, Ferno Pires had the highest antioxidant activity for the three assays (0.55 T/g dw, 0.69 T/g dw and 0.99 T/g dw respectively). As for the anti-tyrosinase activity, the white and red grape stem extracts (1 mg/mL) inhibited the tyrosinase enzyme from 41.47% to 53.83%. The Syrah variety exhibited the highest activity making it more suitable as a raw material for recovering polyphenols with high anti-tyrosinase activity [46].

Michailidis et al. demonstrated that, on the one hand, ultrasound grape seed paste extracts (500 µg/mL), obtained using EtOH solvent or EtOH:H_2O (1:1 v/v) mixture, showed higher anti-tyrosinase activity (75% and 72.4%, respectively) than the kojic acid positive control (7.1 µg/mL, 52%). On the other hand, the extracts obtained by supercritical fluid extraction (using 10% and 20% EtOH w/w) showed lower anti-tyrosinase activity (≈15%) than the positive control (kojic acid 7.1 µg/mL, 52%). The difference in the anti-tyrosinase activity between both extraction techniques is attributed to the higher proanthocyanidin derivates content detected in the ultrasound extracts compared to the supercritical fluid extracts [40]. The anti-tyrosinase inhibitory properties of the grape pomace extracts made the latter a potential anti-hyperpigmentation agent.

3.3. Antiaging Activity

Elastase, collagenase and matrix metalloproteinase-1 (MMP-1) are enzymes associated with skin aging. The elastase and collagenase enzymes are involved in degrading collagen and elastin responsible to providing the skin with strength and elasticity, while MMP-1 causes the degradation of fibrillar collagen in the skin (Figure 4) [37,40].

White and red grape by-products extracts have been studied for their effectiveness as antiaging agents [37,40,46,58]. Matos et al. reported that the Tempranillo red pomace extracts can inhibit the activity of both enzymes in vitro: elastase (IC_{50} 0.87 mg/mL) and MMP-1 (IC_{50} 1.08 mg/mL) suggesting it as a bioactive with a key role for antiaging in cosmetics [37]. From that perspective, Leal et al. reported that white (Arinto and Fernão Pires) and red (Tinta Roriz, Touriga Nacional, Castelão, Syrah) grape stems (1 mg/mL) inhibited the elastase enzyme in a range from 67.98% to 98.02%. In concordance with the anti-tyrosinase activity, Syrah variety showed the highest inhibition activity against elastase enzyme (98.02%) [46].

Concerning the anti-elastase enzyme activity, Michailidis et al. reported that the ultrasound grape seeds paste extract (300 µg/mL) using EtOH solvent and EtOH: H_2O (1:1 v/v) mixture, have higher inhibitory effects (91.3% and 83.2%) than the positive control, Elastatinal (0.5 µg/mL, 51.3%). In concordance with the results showed for anti-tyrosinase activity, the supercritical extracts (using 10% and 20% EtOH w/w) had lower anti-elastase activity (≈35%) than the positive control (Elastatinal 0.5 µg/mL, 51.3%). As for the anti-collagenase enzyme activity, the ultrasound extracts (600 and 200 µg/mL) using EtOH solvent and EtOH: H_2O (1:1 v/v) mixture reached around 100% of inhibition. The supercritical extract (600 µg/mL) (using 10% and 20% EtOH w/w) was also higher (up to 80% and 90%) than the positive control, Phosphoramidon (16 µM, 46.4%) [40]. Moreover, Weisser Riesling grape pomace were also shown to have inhibitory effects for both enzymes: collagenase and elastase. The highest polyphenol value evaluated (35.3 µg/mL) lead to inhibit 80% and 73% respectively of collagenase and elastase [58].

The results suggested the use of grape pomace extract as antiaging agent due to its inhibitory effects of the elastase, collagenase and matrix metalloproteinase-1 enzymes.

Many other aspects were also evaluated on the grape extracts such as the photoprotection capacity [41,42] and the cytotoxicity effects [41,47].

4. Incorporation of the Grape By-Products Extracts in Cosmetic Products and Their In Vitro and/or In Vivo Testing

Following the favorable in vitro tests conducted on grape extracts, the latter was incorporated in different cosmetic products such as creams [41–43,45,51], lotions [50], toothpastes [39] and serums [52] to test their stability and their in vitro and/or in vivo effectiveness. Table 3 studies the stability [42,43,45,50–52], in vitro [39,41,42,45,49,50] and in vivo [39,43,45,51] evaluation of the incorporation of the grape pomace extracts in cosmetic products. The grape by-product (pomace, skin, seeds) extract was incorporated in the final products in a range varying from 1% to 10%, in freeze-dried form [45], or in liquid form [41–43].

4.1. Sunscreen Application

Grape by-products' extracts were studied for their potential use as bioactive ingredients for UV protection [41,42,45,49], whether deriving from pomaces [45] or seeds [41,42,49]. Cabernet Sauvignon pomace extract was obtained using percolation with a hydro-ethanolic mixture (70:30 v/v) [45], while grape seed extracts were whether commercially bought [50] or recovered by maceration (1 week, 95% ethanolic solvent) [41,42].

Extracts were incorporated in creams in different percentages ranging from 1% 1.46%, 3% or 5% [41,42,45,49] to 8.54% or 10% [45], being combined or not with UV filters ingredients.

For example, Hübner et al. developed, using the factorial design, several formulations by varying the UV filters concentration, the extract concentration, and the irradiation time. The most stable formulations exhibiting high antioxidant activities were selected for the clinical in vivo analyses. Therefore, the mixture of the Cabernet Sauvignon pomace extract (10%) and the UV filters (butylmethoxydibenzoyl methane 2.5%, ethylhexyl methoxycinnamate 5% and ethylhexyl dimethyl PABA 4%) were selected and studied in an oil-in-water emulsion and compared to a formula that contains only the same UV filters without the extract. The effectiveness of this product (extract + UV filters) was confirmed by the highest obtained antioxidant activity (519.92 $\mu mol \cdot g^{-1}$). The synergy of the extract and the UV filters provided higher in vitro and in vivo SPF values (16.33 and 12.30, respectively) compared to the other formulation when the chemical UV filters were alone (6.00 and 10.20, respectively). A synergism between natural grape pomace extracts and synthetic UV filters is suggested to provide photoprotection effects. Grape pomace extract has antioxidant activity and can be safely applied in sunscreens [45].

In concordance with these findings, Yarovaya et al. reported the effectiveness of combining grape seeds extracts (3%) with UV filter octyl methoxycinnamate (OMC, 7%) in a sunscreen formulation. The extract (25 µg/mL) was evaluated in vitro prior to its incorporation in the cosmetic product. It showed to significantly increase the fibroblasts viability up to 68% and protect the cells from the UVA damages by means of the MTT assay. The extract was capable of restoring the original morphology of the UVA irradiated cells up to 46% compared to the untreated cells. Subsequently, the sunscreen cream was formulated and the synergy between OMC (7%) and the extract was proven. The photodegradation of catechins was reduced to ≈4.6% and that of epicatechins to ≈7.0%, showing a photostability of the molecules [41].

Moreover, Khunkitti confirmed the in vitro photoprotective effect of grape seed extracts when added at 3% in base cream formula. The results showed that the extract enhanced the sunscreen protection effect by increasing the SPF value from 18.22 to 23 in the product [42].

Limsuwan and Amnuikit also confirmed the high photoprotection capacity of the lotion when combining grape seed extracts, even at a 1% concentration, with UV filters (8% anisotriazine and 12% titanium dioxide). Indeed, the SPF value increased from 45.17 to 53.58 after the incorporation of the extract (1%) in the sunscreen lotion [50].

Therefore, grape seed and pomace extracts are suggested to be added from 1% to 10% in sunscreen products to enhance the photoprotection effects.

4.2. Skin Penetration

Many efforts were made aiming to improve the penetration of the plant-derived phenolic compounds into and through the skin. Accordingly, many phytosome formulas containing grape seed extracts were prepared and characterized in terms of morphology, zeta potential, size distribution and entrapment efficiency. The selected phytosome contained a 1:1 mass ratio of grape seeds extracts and Phospholipon 90 G. It was spherical with a zeta potential of −25.2 mV, a D_{mean} volume of 398.23 nm, and an entrapment efficiency of 75.01 ± 0.25%. A gel-based serum was then formulated containing 10% of grape seed extract phytosomes and tested in an in vitro penetration study. The phytosomal serum promoted the penetration of the bioactive total phenolic into the skin by 27.25% compared to 11% for the non-phytosomal serum [52].

4.3. Antiaging and Skin Depigmenting Activities

It is important to validate the in vitro antiaging (anti-elastase, anti-collagenase and anti-matrix metalloproteinase-1 activities) and skin depigmenting effects (anti-tyrosinase activity), by studying the in vivo results to validate the claims of the grape by-products extracts.

Grape seeds extract was clinically evaluated over 12 weeks for its antiaging effects [43,49,51,53]. The extract was incorporated at 2% [53], 3% [51], 4% [43] and 5% [49] in a cosmetic product and its efficacy was evaluated by means of biophysical parameters.

Rafique and Hussain Shah studied the antiaging activity of the cream containing 3% of the dried grape seed extract in comparison with the control formulation. The stability of the product was confirmed in vitro. The clinical study (20 females, 12 weeks) was evaluated using biophysical measurements. It resulted in a remarkable reduction of pore size (56.8%) and roughness (18.98%), along with enhancement in skin elasticity (47.95%), sebum content (93.85%) and hydration (47.56%). The results were in accordance with the score of the questionnaire answered by the volunteers [51].

Grape seed extract was incorporated at 2% in a water-in-oil emulsion. The clinical effects of the stable product were evaluated in vivo and were compared to the control formulation. The study (110, 8 weeks) was realized by using non-invasive instruments. The application of the cream containing the extract showed to be safe. It showed to have skin depigmenting activity by reducing the melanin content (~18%), and skin moisturizer activity on the cheeks of the volunteers. Moreover, it showed promising antiaging effects by increasing the skin elasticity (~13%). The product containing the extract also showed to decrease the skin sebum content (~15%) [53].

In another study, the organic phase of the grape seeds extract was evaporated after the extraction in EtOH: H_2O (95:5 v/v) for 7 days. The extract was rich in phenolic compounds (catechin, epicatechin, gallic acid, epicatechin gallate, and procyanidin dimers (B-1, B-2 and B-3)) as determined by HPLC. The liquid extract was added in 5% to an emulsion and to an emulgel product. Then the formulations were physically characterized and their rheological parameters were studied. After confirming the stability and the safety of the products, clinical trials on 40 females for 12 weeks were conducted to test the antiaging claims. Results highlighted the reduction in roughness (14% and 55%), scaliness (13% and 26%), wrinkles (21% and 23.9%) and sebum content (26.13% and 30.3%), for the emulsion and the emulgel respectively. Furthermore, the increase of elasticity (45.3% and 50%) and hydration (29.85% and 32.2%) was highlighted. The emulgel presented overall better antiaging results than the emulsion due to its better-controlled release effect. The hydrating, anti-inflammatory and anti-wrinkle effects are associated with the presence of phenolic compounds in the grape seed extract [49].

Waqas et al. obtained concentrated grape seeds extract after the evaporation of the organic solvent from the MeOH: H_2O (70:30 v/v) blend used during maceration (72 h). The remaining aqueous extract was incorporated at a 4% concentration in a cosmetic emulsion. After confirming the stability of the cream (pH, color, electrical conductivity etc.), and its non-irritability, it was tested in clinical trials on 11 males for 12 weeks. The results underlined the regular increase of the elasticity and moisture of the skin and the

effective reduction of the wrinkles. Moreover, skin depigmenting effects were associated to the reduction of melanin content. The amelioration of the skin status is attributed to the presence of phenolic compounds and flavonoids in the extracts [43].

Therefore phenolic compounds contained in grape by-products are suggested to be beneficial ingredients for the production of cosmetics with antiaging and skin depigmenting properties [43,51].

4.4. Oral Care Application

Phenolic compounds extracts from grape by-products were suggested as oral care products and were especially studied in toothpastes [39].

Emmulo at al. evaluated the effect of several extraction parameters such as red or white grapes, skins or seeds; water or ethanol; ultrasounds, etc., on polyphenol recovery. The latter was then freeze-dried and added at different percentages (2–10%) to commercial toothpastes. The hydroethanolic (60:30 v/v) white Grechetto seeds extracts are almost 2 times richer in total polyphenol content than the skin. Moreover, HPLC results showed that ethanolic solvent recovered 2 times more quercetin (≈20.6 mg/L) than water extract (≈10.4 mg/L) and that ultrasounds did not intensify (≈19.7 mg/L) its extraction in ethanol.

The water or hydroethanolic extracts were then freeze-dried and added into commercial toothpaste at concentrations of 5% or 10%, and of 2.5% or 5%, respectively. The addition of white grape seeds and skins as well as red grape seed pomace extracts increased the polyphenol content in commercial toothpastes.

The stability and shelf-life study confirmed that the toothpaste enriched with aqueous extracts (5% and 10%) showed a persistent loss in polyphenol content (3.9 and 9.4%, respectively) after 4 months. On the other hand, toothpastes enriched with whereas ethanol extracts were stable. The in vitro studies showed that the toothpaste with 10% aqueous seeds extract showed the highest antiradical activity, after 4 months. However, the toothpaste with only 5% of seeds extract obtained by aqueous extraction was the most appreciated among the consumers. This was associated with the lower content in proanthocyanidins compared to the other samples, affecting the astringency of the toothpaste [39].

5. Conclusions

Grape pomace extracts have big potential to be used as key components for the formulation of innovative cosmetic products due to their high content in bioactive molecules and polyphenols. The latter have several health benefits at skin level, such as antiaging, skin depigmenting and photo protection. Grape seed and skin extracts were also reported as antioxidants for the formulation of oral care products.

The recovery of highly bioactive compounds is conducted using classical or innovative methods. However, the traditional hydroethanolic solid liquid extraction technique is still the most widely used. The main bioactive compounds detected in grape pomaces were gallic acid, catechin, epicatechin, epicatechin gallate, and quercetin. The activities of the extracts were studied by referring to enzymatic, in vitro cellular culture assay and DPPH methods.

Many studies were published on the use of grape by-products in cosmetics and others need to be further developed to better understand the beneficial effect connected to the incorporation and formulation of polyphenol extracts into the cosmetic products. Moreover, more clinical trials on cosmetic products containing grape pomace extracts are needed to better evaluated and confirm the beneficial properties of these molecules on the human skin.

Finally, it is extremely important to master the extraction process that will allow to control the quantity and quality of the recovered polyphenols. The link between the extraction parameters, the recovered components and their influence on the stability of the cosmetic formulations needs to be further investigated. Finally, more research is

needed to understand even more the link between the extraction techniques allowing the recovery of certain classes of polyphenols and the desirability of the cosmetic product by the end consumer.

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