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Review

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The cosmetic potential evaluation of the fungus resistant grapevine extracts using metabolomic approaches

Magdalena A. Malinowska [1]✉, Manon Ferrier[2], Marta Sharafan[1], Agnieszka Szopa[3], Marin-Pierre Gémin[2], Małgorzata Miastkowska[1], Katarzyna Bialik-Wąs[1], Anna Dziki [1], Elżbieta Sikora[1], Adam Kiszka[4], Christophe Hano[5], Nathalie Giglioli-Guivarc'h[2], Arnaud Lanoue [2]✉

[1] Department of Organic Chemistry and Technology, Faculty of Chemical Engineering and Technology, Cracow University of Technology, 24 Warszawska St., 31-155 Cracow, Poland,

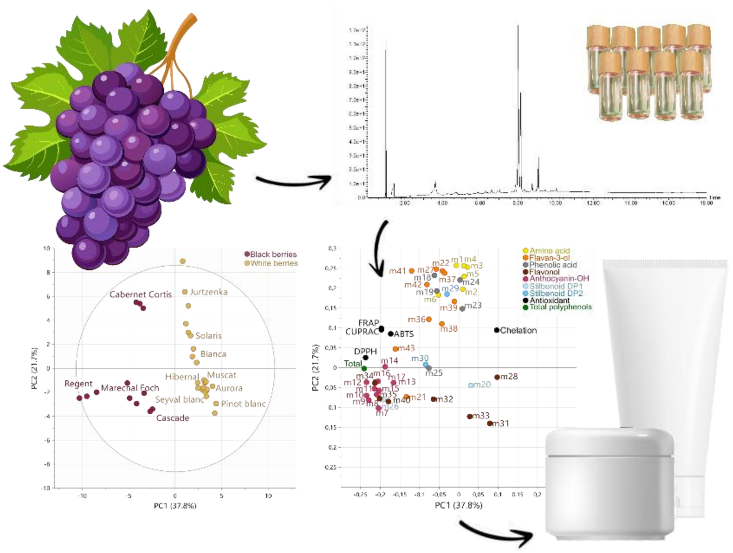
[2] EA 2106 «Biomolécules et Biotechnologie Végétales», UFR des Sciences Pharmaceutiques, Université de Tours, 31 av. Monge, F37200 Tours, France

[3] Department of Plant Biotechnology and Medicinal Fungi Faculty of Pharmacy, Jagiellonian University, Medical College, Medyczna 9, 30-688 Cracow, Poland,

[4] Rolniczy Zakład Doświadczalny Łazy, Jagiellonian University in Cracow, 24 Gołębia St., 31-007 Cracow, Poland,

[5] Institut de Chimie Organique et Analytique, Université d'Orléans-CNRS, UMR 7311 BP 6759, CEDEX 2, 45067 Orléans, France

✉ Correspondence to: magdalena.malinowska@pk.edu.pl; arnaud.lanoue@univ-tours.fr



Abstract: Natural product effectiveness is an important criterion to develop new active ingredients for cosmetic industry. Plant metabolites exhibit wide range of natural activities and in recent years, there has been a growing interest in the development of plant-based cosmetic products. The complex composition of plant extracts and their natural variability makes it difficult to select and produce plant-based natural ingredients with the most effective and constant biological capacity. Grapevine (Vitis vinifera L.) is known for its abundance in bioactive polyphenols, but the quality and the quantity in polyphenols vary depending on several parameters including the variety, the geographical origin, the year, and the extraction methods. In the temperate regions of Central Europe, there is currently significant growth in the cultivation of grape varieties that are well-suited to the humid and cool climate. Interestingly, these fungus-resistant varieties exhibit a specific metabolic composition associated to climatic adaptation, paving the way for the development of new active ingredients for skincare. Metabolomics aims to detect, identify and quantify small molecules in living system in response to environmental changes. In this literature review, we present the advantage of metabolomic approaches to evaluate the cosmetic potential of fungus-resistant varieties cultivated in Central and Eastern Europe.

Keywords: Fungus-resistant grapevine cultivars; PIWI, Metabolomics; Polyphenolic profile, Cosmetic activity

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Introduction

Grapevine is an important fruit crop worldwide, renowned for its numerous health benefits that contribute to its widespread consumption. In particular, the biological activity of grapes has garnered much attention due to its potential role in the prevention of chronic diseases such as cancer, cardiovascular diseases, and diabetes [1,2]. Grape extracts are widely used as food supplements rich in numerous polyphenols and stilbenoids, particularly trans-resveratrol, exhibiting beneficial effect on human health and well-being [3]. For instance, it has been shown to exhibit activity such as antioxidant, anti-inflammatory, anticancer, cardioprotective, and neuroprotective [3,4]. Meanwhile, the cosmetic activity of grape extracts, including berries, seeds, leaves, canes, has garnered significant attention in recent scientific research. Interest in the cosmetic effects of grapevine extracts is continuously growing, and studies increasingly confirm their beneficial impact on the skin. Grape extracts, from different organs, have demonstrated notable antioxidant, antibacterial, skin-brightening and rejuvenating properties [5–8]. Grape polyphenols play a crucial role in neutralizing free radicals, thereby mitigating oxidative stress and contributing to skin health

[9]. Studies have suggested that the application of cosmetic formulations containing grape extracts may contribute to the enhancement of repairing process. Moreover, the presence of bioactive compounds in grape extracts may exert protective effects against UV-induced damage, making them promising ingredients for sunscreen formulations [10]. The multifaceted cosmetic activities of grape extracts underscore their potential in skincare products, providing a scientific basis for their incorporation into formulations aimed at promoting skin health and well-being [11]. According to Eurostat, in the year 2020, the European Union (EU) encompassed a total vineyard area of 3.2 million hectares [12]. Notably, among the 16 Member States surpassing the threshold of 500 hectares of vineyards, Spain led with 0.9 million hectares, closely followed by France with 0.8 million hectares, and Italy with 0.7 million hectares. Together, these three countries contributed to approximately three-quarters (74.9%) of the EU's overall vineyard area. The remaining vineyard landscapes within the EU, are distributed across Romania, Portugal, Germany, and Greece, each cultivating between 0.1 million and 0.2 million hectares of vines [12]. Many countries in Central and Eastern Europe, traditionally less associated with vine cultivation, are gaining significance, especially in the cultivation of hybrid grapevines that are resilient the harsher climates. For instance, Poland was not included in the statistics for the year 2020 because the vineyard area remained under 500 hectares with only 475 hectares. Although recently, a sharp increase in surface aera has been observed reaching 563 hectares in 2021 and 835 hectares in 2023 [12]. This shows the rapid growth in significance of vine cultivation in countries that were previously not renowned for their wine production. Several factors contribute to this trend, including climate warming, as well as the introduction of new fungus-resistant grape varieties. These countries, now gaining significance for the wine production, are classified as the coldest wine-growing zones in Central and Eastern Europe [13]. Despite facing low winter temperatures and frosts in autumn and spring, wines produced in these regions are characterized by distinct aromas and high quality [14–16]. The intensified cultivation of grapevines in cold climates became possible with the use of fungus-resistant grape varieties, also called PIWI, from the German word "pilzwiderstandsfähige" [13,17]. These varieties were bred to acquire resistant traits to fungal diseases, such as downy mildew and powdery mildew, that are prevalent in humid and cool climate [18]. Considering the specific properties of these grapevine varieties, particularly their resistance to selected pathogens and challenging climatic conditions, Lisek et al., (2010, 2013) conducted research to compare their phenotypic characteristics [17,19].

These investigations focused on winter hardiness and susceptibility to fungal diseases including downy mildew, powdery mildew, gray mold and excoriose. Several interspecific hybrids, notably Vineland 64035, and cultivars Seyval Blanc and Cayuga White, exhibited the highest levels of productivity (3.08, 3.07 and 2.90 kg/bush respectively) Furthermore, these varieties demonstrated a lower susceptibility to frost damage and fungal diseases when compared to *Vitis vinifera* cultivars, like Chasselas Doré or Riesling. Noteworthy interspecific hybrids, including Bianca, Sibera, Marechal Foch, Regent, Rondo, and Seyval Blanc, emerged as high-quality grape varieties well-suited for winemaking. These varieties, are well-adapted to the climatic conditions of Poland, enabling optimal fruit quality. Their high disease resistance reduces the need for chemical treatments, enhancing the natural quality of the wines. These varieties produce grapes with high sugar content, acids, and tannins, which are essential for balanced and flavorful wines. The other cultivated hybrids consistently delivered reliable yields. It is important to note that none of the varieties showed specific resistance to grey mold or excoriose. This underscores the significance of interspecific hybrids in viticulture, particularly for regions susceptible to frost and fungal challenges like Poland. Differences in the phenotypic characteristics might be associated to specific composition in chemopreventive polyphenols. Indeed, previous studied showed the grape polyphenol composition is influenced by the genotype together with environmental factors [20,21]. *In fine*, the variations in polyphenol composition impacted the biological activities of the corresponding extracts [22,23]. In parallel, metabolomics, the comprehensive analysis of low molecular mass metabolites, provides a powerful tool to evaluate the complex phytochemical composition of the ingredients and to identify the key environmental factors influencing the composition in active compounds.

Despite the growing interest in natural ingredients derived from plants, PIWI grape varieties have yet to be utilized as active ingredients in the cosmetic industry. Currently, the cosmetic sector predominantly harnesses the potential of grape extracts from varieties grown in warmer climates, which are known for their high content of beneficial phytochemicals, such as polyphenols. These compounds have been extensively studied for their antioxidant, anti-inflammatory, and anti-aging properties. However, PIWI varieties, which are specifically bred for resistance to fungal diseases and are often cultivated in cooler climates, remain underexplored in this context. The unique phytochemical profiles of PIWI grapes could offer novel bioactive compounds for cosmetic formulations, but their application has not been fully investigated or adopted by the industry. This gap highlights an opportunity for future research to evaluate the potential benefits of PIWI grape extracts in cosmetic products and to diversify the sources of active ingredients used in skincare and other cosmetic applications.

This review highlights the potential of metabolomics to evaluate the cosmetic potential of natural ingredients based on fungus-resistant grape varieties.

The cosmetic industry largely relies on readily available, non-specific grape varieties when utilizing extracts from different parts of the grapevine, such as pomace, leaves, and seeds. This broad approach may overlook the unique properties that specific grape varieties could bring to cosmetic formulations. The commercially available cosmetics do not typically disclose the specific grape varieties used in the extraction process. This underscores the need to explore the application of metabolomics as a strategic tool for the selection of PIWI grape varieties that are particularly rich in key polyphenols and flavonoids, thereby optimizing the efficacy of cosmetic formulations.

Fungus-resistant grapevine varieties

The fungus-resistant grape varieties, also called PIWI varieties, have been specifically bred to resist fungal diseases such as downy mildew and powdery mildew, which can cause significant damage in the vineyards. PIWI varieties result from interspecific crossing between cultivars of the European *V. vinifera* species and American or Asian Vitis spp. resistant to fungal diseases but also from intraspecific crossing of *V. vinifera* varieties [24]. For red wine production, the dominant PIWI varieties include Regent, Rondo, Pinot Noir, Maréchal Foch, Cabernet Cortis, Tryumf Alzacji, Cascade, and Dornfelder [13]. Regent, for instance, one of the most common variety used in winemaking and was obtained from a cross between the varieties Diana and Chambourcin, stands out for its strong resistance to fungal diseases and ability to ripen properly in cooler climates. The resulting Regent wines are medium-bodied with flavors of blackberries, cherries, and spices. Another notable, not less popular, red grape variety is Rondo. The grape of Rondo is a cross of Zarya Severa (an hybrid which has *V. amurensis* in its pedigree) and St. Laurent [25]. Both cultivars, Rondo and Regent currently represent the most valued varieties for red wine production in Poland, for instance they stand out as the primary red grape varieties responsible for over 80% of the total red wine production. Their exceptional adaptability to cold climates and resistance to pathogens further contribute to their prominence in the winemaking industry in Central and Eastern Europe countries [26]. Also, a very common variety cultivated in these regions is Cabernet Cortis, resulting from a crossing between Cabernet Sauvignon and Solaris. Cabernet Cortis is renowned for its resistance to fungal diseases and cold temperatures. It produces full-bodied red wines characterized by flavors of dark fruits, black currants, and spices [17].

Considering the white wine production, the prominent grapevine PIWI cultivars in central Europe include Solaris, Riesling, Seyval Blanc, Pinot Gris, Johanniter, Jutrzenka, Hibernal, Aurora, Bianka, Traminer, and Sibera [13]. Solaris is highly valued for its resistance to fungal diseases and its ability to withstand cold temperatures, making it well-suited to European climate. Johanniter, Jutrzenka, and Seyval Blanc are additional white grape varieties known for their resistance to fungal diseases. These varieties are recognized for producing high-quality wines with a fruity aroma [27].

Compared to traditional grape varieties, fungus-resistant grape varieties are specifically bred for their resistance to diseases rather than focusing solely on flavor and yield. Consequently, they may exhibit different flavor profiles and potentially have different yields when compared to traditional *V. vinifera* varieties. Good examples are the cultivars such as Seyval, Siberia, Marechal Foch, Rondo and Regent [17]. Therefore, their cultivation may require different viticultural practices such as specific pruning techniques and irrigation needs, as they may have unique growing requirements (Table 1) [18].

Table 1. Winter hardiness and resistance of the selected grapevine varieties including PIWI (adapted from Lisek et al 2010). 1: Resistance; 2-4: intermediate resistance 5-6 : Susceptibility.[17,19]

Name of cultivar	Origins	Resistance to pathogens				Winter hardiness	Colour: W (white) R (red)
		gray mold (scale 1-6)	excoriose (scale 1-5)	powdery mildew (scale 1-5)	downy mildew (scale 1-5)	(scale 1-5)	
Aurore	Hybrid: Seibel788 x Seibel 29	1.7	1.2	1.2	1.1	1.0	W
Bianca	Hybrid: Villard blanc x Bouvier	1.3	2.5	2.5	1.5	2-3	W
Cascade	Hybrid: Seibel 7042 x Seibel 5409	1.1	1.8	1.8	1.5	2.0	R
Cayuga White	Hybrid: Seyval blanc x Schuyler	2.0	1.8	2.0	2.0	2.0	W
Chasselas Dore	*V. vinifera*	1.8	1.5	3.5	3.8	3-4	W
Delaware	Hybrid: (*V. labrusca* x *V. aestivalis*) x *V. vinifera*	1.5	1.2	2.5	2.0	1.0	R
Golubok	Hybrid: 40 Let Oktyabrya x Severnii	1.3	1.5	3.0	3.0	2.0	R
Marechal Foch	Hybrid: Millardet et Grasset 101 OP x Goldriesling	1.1	1.5	1.2	1.2	1.0	R
Ortega	*V. vinifera* (Mueller thurgau x Siegerrebe)	1.8	1.5	4.3	3.8	3.0	W
Regent	Hybrid: Diana x Chambourcin	1.1	2.0	1.5	1.3	3.0	R
Riesling	*V. vinifera*	2.5	1.6	3.9	4.0	4.1	W
Rondo	Hybrid: Severnyi x Saint Laurent	1.5	1.8	3.0	1.5	2-3	R
Seyval blanc	Hybrid: Seibel 5656 x Seibel 4986	2.0	1.8	1.5	1.1	1-2	W
Sibera	Hybrid: Saperavi Severnyi x (Foster's White Seedling x Prachttraube)	1.1	1.5	3.0	1.3	1-2	R
Silvaner	*V. vinifera* (Savagnin blanc x Oesterreichisch Weiss)	2.3	1.6	4.0	3.6	4.1	W
Traminer Rot	*V. vinifera* (mutation Savagnin blanc)	2.1	1.6	3.5	3.5	3.5	R
Vineland 64035	Hybrid: (Alden x Joannes Seyve 23-416)	1.6	2.5	2.5	3.0	2.0	W

In summary, fungus-resistant grapevine varieties play a crucial role in sustainable grape cultivation because of the reduced needs for pesticides, especially in temperate zones where grapevines are vulnerable to fungal diseases. The development and the cultivation of PIWI varieties have proven to be invaluable for grape growers, providing an effective tool to minimize fungicide use and promote sustainable agricultural practices [15].

Metabolomics

Metabolomics is a powerful analytical tool to identify and quantify small molecule metabolites in complex biological systems in response to environmental factors. It provides a comprehensive overview of the metabolic profile of an organism, and can be used to decipher metabolic changes under different conditions, such as stress or disease [28]. In the case of grapevines, metabolomics plays a crucial role in investigating the intricate metabolic pathway dynamics, offering insights into the regulation of metabolic processes involved in grape development, ripening, and response to environmental stressors [29,30]. It is also a technique of choice to select grapevine varieties with biomolecule profiles of interest [29,31]. Several complementary techniques are available in metabolomics, there are mainly based on Nuclear Magnetic Resonance (NMR) spectroscopy, Gas Chromatography coupled to Mass Spectrometry (GC-MS) and Liquid Chromatography coupled to Mass Spectrometry (LC-MS). NMR spectroscopy is a non-destructive technique capable of detecting a diverse array of metabolites that are present in abundance such as amino acids, organic acids, and sugars, without the need for prior separation [32]. GC-MS is a highly sensitive technique that can separate and identify volatile and semi-volatile compounds such as fatty acids and terpenoids [33]. LC-MS, on the other hand, is a highly sensitive technique that can detect a wide range of soluble metabolites [34]. Recently, molecular networking emerged as a powerful tool to facilitate the annotation and the identification of known metabolites. Molecular networking involves the construction of a network that connects related metabolites based on mass spectrometry fragmentation patterns. The application of molecular networking in grape metabolomics will facilitate the rapid exploration of bioactive compounds and their valorization for nutrition, healthcare, and well-being [29,35,36]. Metabolomics has the advantage over traditional analytical techniques that investigate a limited number of metabolites, to provide a comprehensive overview of the whole metabolic fingerprint of an organism'. It can also identify unknown metabolites, which can lead to the discovery of novel biomolecules with potential pharmaceutical or agricultural applications. Metabolomics can also be used to study the dynamics of metabolic pathways, providing insight into the regulation of metabolic processes [21]. Metabolomics analyses provide large datasets that contain high number of chemical features, and very often chemometrics analysis are coupled to extract the relevant information [37]. Principal Component Analysis (PCA) is an unsupervised technique that reduces the dimensionality of the data while preserving its essential features [38,39]. Cluster analysis (CA) groups samples based on similarities in their metabolite composition, allowing for the identification of distinct metabolic profiles. PCA and

CA are often used together as complementary tools for data classification [40,41]. Metabolomics approaches have been largely applied to harness the chemical diversity of grape berries but the knowledge on the berry composition in peculiar interspecific hybrid varieties remains unknown or incomplete. Grape polyphenols are usually classified according to their biosynthetic origin, and chemical structure including phenolic acids, flavonols, flavanols, anthocyanins and the non-flavonoids stilbenoids (Figure 1).

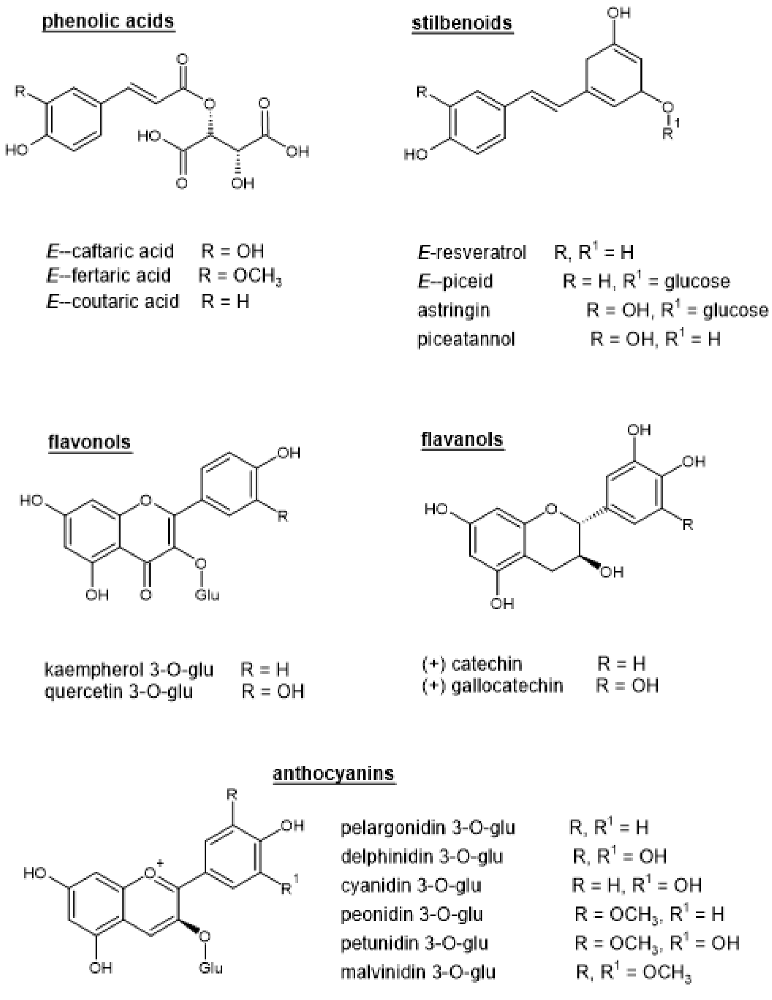

Figure 1. Examples of chemical structures of various phenolic compounds found in grape extracts [42].

The stilbenoids are derived from the common precursor *E*-resveratrol and constitute a typical type of grape phytoalexins. Indeed, they present antimicrobial activities and are locally *de novo* synthesized following a pathogen attack. In downy mildew infected leaves, at 6 days post infection, a large set of stilbenoids are strongly induced including *E*-resveratrol, *E*-piceatannol, *E*-piceid, pallidol, *Z*-ε-viniferin, *E*-ε-viniferin and *E*-δ-viniferin [43]. Although these compounds may take part in grapevine disease resistance through their antifungal properties [44,45], only little direct evidence of their role *in vivo* have been reported [46]. Incorporating targeted metabolomic analysis on polyphenols will shed light on the composition of polyphenols in PIWI grape varieties, which remained largely unknown [47].

Biological activity of grape extracts

Polyphenols from grapevines contribute to deliver cosmetic benefits of the corresponding extracts, and also contribute to overall health-promoting properties. Regarding cosmetic activity, it is essential to highlight the ability to reduce free radicals. The antioxidant ability is not only associated with the ability to maintain good skin condition but also has many positive health benefits for the entire body. Several studies have investigated the antioxidant activity of grapevine extracts, with promising results [36,48–50]. Antioxidative activity has been assessed in numerous scientific studies, mainly using *in vitro* assays, where the activity was correlated with the composition of the extracts or the extraction conditions. For instance, Llobera et al. in 2012, evaluated the total antioxidant activity of extracts obtained from red and white grape stems in 80% ethanol or 70% acetone. They examined the correlation between the total content of polyphenols and flavanols with the antioxidant activity of the extracts. They found that the extracts obtained from red grape stem presented EC50 values of 0.14 g DW/g DPPH (acetone extract) and 0.20 g DW/g DPPH (ethanol extract) while the extracts obtained from white grape stem present EC50 values of 0.26 g DW/g DPPH (acetone extract) and 0.37 g DW/g DPPH (ethanol extract). Red grape stem extract in 70% acetone had lower EC50 values, indicating higher antioxidant activity compared to other extracts. The study also identified significant correlations between the total content of polyphenols and flavanols in the grape stem extracts with their antioxidant activity. These findings suggest that the extracts from red grape stems, which had higher polyphenol and flavanol content, exhibited stronger antioxidant properties compared to extracts from white grape stems [51]. Another study by Oprică et al. (2016) found that grape berry methanolic extracts were characterized by the highest total polyphenols (118-124 mg GAE/g DW), using Folin-Ciocalteu's method. Seeds were the richest source of polyphenols in comparison to skin and pulp These findings indicate that grape seeds are a rich source of bioactive compounds, which contribute to the overall antioxidant capacity of grape berries [52]. Similarly, a study by Weidner et al. (2013)

reported the antioxidant activity and phenolic composition of Japanese and European grape species, with a focus on the content of phenolic compounds, tannins, and their radical scavenging and reducing power. The total content of phenolic compounds was measured by Folin-Ciocalteu's method, the content of tannins was determined by the vanillin and BSA precipitation methods. Phenolic compounds were identified using HPLC. The antioxidant capacity was determined using DPPH free radical and ABTS cation radical scavenging activities. Grape seed extracts had high concentrations of tannins and gallic acid, as well as lower quantities of catechins, *p*-coumaric acid, ferulic acid, and caffeic acid. The study also found that European grape seed extracts have higher total phenolic content, tannin content, and levels of catechins and phenolic acids (except for caffeic acid) compared to Japanese grape extracts. The extracts from European grape seeds exhibited higher radical scavenging properties and stronger reducing power. Additionally, acetone extracts showed higher total phenolic compound and tannin content compared to methanolic extracts, and they demonstrated stronger antiradical properties and reducing power. These results suggest that grape seeds, particularly those from European varieties , possess significant antioxidant activity and phenolic composition, contributing to their potential health benefits [53]. The results obtained enable the selection of the most potent cultivars, plant organs, cultivation conditions and extraction methods to obtain the most potent natural ingredient for further application in cosmetic and pharmaceutical industries.

In addition to *in vitro* assays, the antioxidant activity of grape extracts can also be measured *in vivo* through microorganisms, animal, or human studies. These studies involve the administration of grape extracts to animals or humans and measuring the antioxidant activity in their blood or tissues (more specifically in cells). For example, a study by Lingua et al. (2016) on three red grape varieties showed that polyphenols from berries, wine and pomace were capable of rescuing yeast cells from oxidative stress, probably by the induction of antioxidant enzymes, such as glutathione reductase and glutathione peroxidase [54]. Grapevine extracts thus exhibit an interesting and broad spectrum of effects on the skin. However, it should be noted that most studies focus on varieties cultivated in the warmer climates of countries known for global wine production. Grape varieties cultivated in Central and Eastern Europe are still not fully explored considering the cosmetic activities. Tarko et al. (2010) determined the antioxidant activity and the total polyphenolic content in ten wines from Poland (seven white ones and three red ones). Red wines were characterized by significantly higher antioxidant activity (from 670 to 745 mg of Trolox/100 mL) in comparison to white wines. The lowest antioxidant potential was noted for Seyval Blanc and Bianca wines (89 and 100 mg of Trolox/100 mL, respectively). The polyphenol content in the analyzed wines was closely correlated with their antioxidant activity (R2 = 0.96). Red wines were distinguished by high concentration of polyphenol compounds (from 97 to 135 mg of catechin/100 mL). Those values were about 4 times higher than for white wines, in which the total polyphenol content was at a moderate level (97 mg of Trolox/100 mL) [55]. Muzolf-Panek et al. (2022) investigated the association between the color of red grape skins, individual phenolic compounds, total polyphenol content (TPC), total anthocyanins (ACNs) as well as antioxidant activity (DPPH) for five various grape berries. Fruits were purchased from the local suppliers near Poznań in Central Poland. The range of TPC in grape skins ranged between 2.58–8.37 mg GAE/g FW (fresh weight), with the highest content found in the Black Magic variety and the lowest in the Red Globe pink variety. The antioxidant activity (DPPH) of table grapes ranged from 32 to 90 µmol/g DW. Among the varieties, Black Magic and Red Globe showed the highest antioxidant activity, whereas the lowest was determined for Red Globe pink [16].

In addition to the antioxidant action, the protection against ultraviolet radiation of cosmetic ingredients is also of great importance. UV radiation can accelerate the skin aging process, leading to the formation of wrinkles, discoloration, and loss of elasticity. Moreover, it can increase the risk of developing skin cancer. As grape extracts are shown to exert antioxidant properties, they are crucial because they help neutralize free radicals induced by UV radiation, thereby protecting the skin from cellular damage. However, it is crucial that, in addition to the ability to neutralize free radicals, active substances also demonstrate photoprotective properties. The combination of these two activities collectively helps maintain healthy, firm, and youthful-looking skin, making protection against UV radiation a key element in skincare routines [56]. The study conducted by Yarovaya et al. in 2021 aimed to assess the photoprotective effects of Grape Seed Extract (GSE) on human dermal fibroblasts exposed to UVA light and to investigate the photostability of catechins in cream formulations containing GSE, either alone or in combination with octyl methoxycinnamate (OMC). The researchers utilized the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay to evaluate the protective effects of GSE on fibroblasts exposed to UVA light. The study found that high doses of UVA light damaged fibroblast structures and inhibited their growth, but GSE increased cell viability and effectively protected them from UVA damage. Additionally, the combination of GSE and OMC improved the photostability of catechins and enhanced the overall efficacy of the formulation. The research suggests that GSE could serve as an effective and sustainable natural resource for preventing UV-induced skin damage, providing long-term protection against premature skin aging. The study also discussed the suitability of PMMA (polymethyl methacrylate) plates for *in vitro* photostability testing of sunscreen formulations, while acknowledging the economic viability of Transpore® tape as an alternative substrate despite its instability under UV exposure [10]. To confirm the protective activity of grape extracts. A study conducted by Limsuwam and Amnuikit (2017) aimed to formulate and assess sunscreen products incorporating an organic UV filter (Tinosorb®S) alongside an inorganic UV filter (microfined titanium dioxide, TiO2), supplemented by GSE. The primary objective was to determine the sun protection factor (SPF) value of the formulations. The inclusion of 1% w/w GSE in the chosen sunscreen lotion resulted in a notable increase in the SPF value (53.58±4.45), while also demonstrating remarkable antioxidant activity (84.04±3.92%). This underscores the significance of not only the ability to neutralize free radicals but also the photoprotective capabilities exhibited by active ingredients, as evidenced by the positive impact on SPF values in our formulations [57]. The photoprotective action of grape extracts is further supported by their ability to induce natural skin regeneration processes, reflected in strong protection against the damaging effects of temperature and demonstrated rejuvenating activity. In their study, Letsiou et al. (2020) investigated the impact of grape leaf extracts on UV-stressed human dermal fibroblasts, utilizing fresh leaves from variety Athiri extracted with a glycine-H2O solvent system (4:1). Primary normal human fibroblasts (NHDF) isolated from adult human skin were incubated with leaf extracts at a concentration of 0.1 μg/mL for 48 hours and subsequently exposed to UVA light. The analysis revealed a significant induction of sirtuin 1 (SIRT1) and heat shock protein 47 (HSP47) in the presence of leaf extract under both normal and UV conditions. Furthermore, the observation of changes in DNA methylation suggested an epigenetic influence exerted by the leaf extracts. The authors conclude that outcomes of the investigation unequivocally demonstrate the protective effects of grape leaf extracts, potentially associated with the transcriptional regulation of genes related to skin anti-aging. This highlights the potential of grape extracts as a promising natural ingredient for the development of skincare products with photoprotective and antiaging properties [58]. The broad-spectrum photoprotective, antioxidant, and formulation-stabilizing effects of grape skin extracts were confirmed by Cefali et al. (2019) [59]. In their study, their explored the efficacy of grape berry skin extracts from variety Benitaka concerning sun protection, antioxidative activity, and stability in skincare formulations. This comprehensive investigation provides valuable insights into the multifaceted properties of grape skin extracts, encompassing its potential as a sun protective agent, antioxidant, and formulation stabilizer in skincare applications [59].

An additional benefit of supporting natural rejuvenation processes is the skin brightening effect. Skin discoloration is a common occurrence during the aging process and can be attributed to various factors. A primary cause is the cumulative exposure to ultraviolet (UV) radiation, which leads to the overproduction of melanin, the pigment responsible for skin color. Grape polyphenols, particularly stilbenoids, offer a promising solution for addressing skin discoloration. These compounds help inhibit the activity of enzymes involved in melanin synthesis, thereby reducing the appearance of age-related pigmentation [3]. In our previous studies, we investigated the rejuvenating potential of grape cane extracts, rich in stilbenoids. The extracts exhibited skin-whitening effects, comparable to pure *E*-resveratrol and *E*-ε-viniferin. SIRT1 activation was observed across most extracts, where their activities were comparable with pure *E*-ε-viniferin and *E*-resveratrol standards. Tyrosinase inhibition assays demonstrated the extract efficiency, with *E*-ε-viniferin and *E*-resveratrol being the most effective inhibitors. Notably, Riesling and Villard Noir extracts exhibited significant inhibition activities. These findings highlight the promising skin health benefits of grape cane extracts [23]. Table 2 presents biological activities of grape extracts obtained from various organs and varieties using different extraction solvents.

Table 2. Biological activity of grape extracts according to different grape varieties, organs and extraction solvents

Activity	Variety	Organ	Extraction solvent	Results	Reference
Antioxidant activity	Manto negro (red), Prensal Blanc (white)	stems	acetone 70% ethanol 80%	The values of EC_{50}, antiradical activity, and antioxidant activity (DPPH method) were comparable to vitamin C and vitamin E. Acetone extracts were more effective than ethanolic extracts Extracts from red variety were more effective that those from white variety	Llobera et al. (2012) [51]
	Grasă de Cotnari, Fetească, Tămâioasă	berries (seed, skin, pult)	methanol anhydrous	The highest phenolic content was found in seeds across all three cultivars, with no significant differences in pulps and skins	Oprică et al. (2016) [60]
	V. coignetiae *V. vinifera* (Pinot noir)	seeds	methanol 80% acetone 80%	*V. vinifera* extracts had higher total phenolics, tannins, catechins, and phenolic acids (except caffeic acid), with stronger radical scavenging and reducing power. Acetone extracts surpassed methanolic extracts in phenolic content, tannins, and antioxidant activity.	Weidner et al. (2013) [53]

	Chardonnay, Chenin, Melon, Muscat, Sauvignon (white), pinot gris, pinot meunier, pinot noir (red)	seeds	methanol/chloroform/water (2:2:1, v/v/v) with 0.1% formic acid	Concentration of catechin, epicatechin, procyanidins B1-B4, C1 and C-type procyanidins was twice higher in red varieties Concentration of galloylated procyanidins was higher in white varieties (as their biomarkers)	Munsch et al., (2024) [61]
	Syrah, Merlot, Cabernet Sauvignon	pomace, wine	acidified methanol (0.1% hcl, v/v)	Protective effect on yeast cells against oxidative stress	Lingua et al. (2016) [54]
	Red globe, Autumn royal, Black magic, Palieri	skin	methanol anhydrous	Strong relation between the color parameters of grapevine fruits and the content of specific polyphenols, as well as the total antioxidant activity and total polyphenolic content.	Muzolf-Panek et al. (2022) [16]
	44 varieties	canes	ethanol 60%	Strong varietal effect for each antioxidant test (ORAC, ABTS, DPPH, FRAP, CUPRAC, chelation ability)	Ferrier et al. (2022) [36]
	Chardonnay, Hibernal, Riesling, Johanniter, Solaris, Cabernet Cortis, Regent, /*in vitro* shoots	*in vitro* shoots	ethanol 60%	Antioxidant activity up to 33.57% (DPPH method) and up to 50.93% (Fe^{2+} chelating activity assay)	Sharafan et al. (2023) [62]
UV protective and rejuvenating activity	not described	seeds	ethanol 95%	Photoprotective effect against UVA light and increased cell viability (MTT assay) Improvement of catechins photostability and enhancement of the formulation efficacy	Yarovaya et al.(2021) [10]
	not described	seeds	not described	Notable increase in the SPF value of sunscreen lotion (from 45.17 to 53.58)	Limsuwam and Amnuikit (2017) [57]

	Not described	leaves	Glycerine 25%	Induction of sirtuin 1 (SIRT1) and heat shock protein 47 (HSP47) in UV-stressed human dermal fibroblasts	Letsiou et al. (2020) [58]
	Benitaka	skin	ethanol, anhydrous	Broad UV spectrum photoprotective, antioxidant, and formulation-stabilizing effect, SPF 12,45	Cefali et al. (2019) [59]
Skin-brightening activity	Villard Noir, Sauvignon, Savagnin, Riesling and Magdeleine Noire des Charentes	canes	ethanol 60%	- Tyrosinase inhibition activity up to 62% comparable to pure trans-resveratrol (75%)	Malinowska et al. (2020) [5]
	Chardonnay, Hibernal, Riesling, Johanniter, Solaris, Cabernet Cortis, Regent	*In vitro* shoots	ethanol 70%	Brightening effect up to 17.50% (tyrosinase inhibition assay)	Sharafan et al. (2023) [62]

In conclusion, grape extracts have high antioxidant, rejuvenating activity, skin whitening properties, as well as photoprotective ability. This multifunctional action enables achieving a multidimensional nurturing and protective effect on the skin, making these natural cosmetic ingredients highly interesting for use in specialized cosmetic products. However, further researches are needed to understand what are the key compounds within polyphenol mixtures responsible for the cosmetic activity of grape extracts and their potential skincare benefits. Metabolomics can be an efficient approach for optimizing the selection of best grape cultivars, growing conditions, and extraction methods.

Metabolomics to evaluate the cosmetic potential of grape extracts

Metabolomics has emerged as a powerful tool for analyzing the chemical composition of grape varieties with a focus on bioactive compounds. It enables a holistic and comprehensive analysis, allowing for the identification and quantification of a wide range of compounds within grape extracts. Metabolomics combined to biological assays is particularly crucial in unraveling the complex interplay of amino acids, organic acids, phenolic compounds, flavonoids, and stilbenoids, and their respective roles in influencing antioxidant activities, tyrosinase inhibition, and other bioactive functionalities. Table 3 presents examples of relationship between metabolic profiling and biological activities of grape extracts.

Table 3. Combined metabolomics and biological tests of grape extracts

Grape varieties	Organs	Metabolomic tools	Biological tests	Statistics	Key results	Reference
5 varieties of *V. vinifera*	Berries	HPLC-UV, color measurements	DPPH	PCA and Spearman's and Pearson's correlations	Correlations between phenolic compounds, berry color and antioxidative properties.	[16]
3 varieties of *Muscadinia rotundifolia*	Berries	UPLC-TOF-MS	DPPH, FRAP, ABTS, CUPRAC, NORS	PCA, PLS-DA and Pearson's correlations	9 compounds identified from untargeted metabolomics were correlated with antioxidant properties	[63]
44 varieties of *V. vinifera*	Canes	UPLC-MS	ORAC, ABTS, DPPH, FRAP, CUPRAC and chelation	PCA and Spearman's correlations	6 stilbenoids were correlated with antioxidant capacities	[36]
7 fungus resistant varieties	*In vitro* shoots	UPLC-MS	DPPH, chelation, anti-tyrosinase	PCA	genotypes and culture media influenced polyphenol composition	[62]
30 fungus resistant varieties	Berries	UPLC-QTOF-MS, UPLC-PDA-FL	ABTS, FRAP and ORAC	PCA	Strong correlations between flavan-3-ols and reducing power.	[64]

Muzolf-Panek et al. (2022) explored the correlations between phenolic compounds, berry color, and antioxidative properties in several grape genotypes using HPLC-DAD and *in vitro* antioxidant tests ans the results were visualized by PCA. Key phenolics like *E*-resveratrol, hesperidin, myricetin, rutin, and quercetin were significant for antioxidant power. The darker grape varieties (i.e. Autumn Royal and Black Magic) had higher levels of *E*-resveratrol, myricetin, quercetin, hesperidin, and total anthocyanins, while brighter varieties like Red Globe contained more rutin. Red Globe and Black Magic varieties showed high antioxidant activity, unlike the pink Red Globe variety. The study found strong correlations between color and antioxidant activity, suggesting color measurements can effectively assess grape quality [16].

A study on three muscadine genotypes analyzed the metabolite profiles and the antioxidant activities at different berry developmental stages using UPLC-TOF-MS. AS a result, 329 compounds were identified, including amino acids, organic acids, sugars, and phenolics. PCA showed that developmental stages influenced metabolic profiles more than genotypes. Key metabolites varied according to the developmental stage. Catechin, epicatechin-3-gallate, and gallic acid were prominent in ripening seeds, while tartaric acid and malonic acid were abundant during fruit set. Malic acid was prevalent at véraison stage. PLS-DA identified 27 key biomarker compounds, and Pearson's correlation heatmap linked 9 of these compounds to antioxidant activities, including gallic acid, catechin and epicatechin-3-gallate [63].

The use of targeted UPLC-MS metabolomics has also enabled to investigate the relationship between polyphenols variations and antioxidant capacities in grape cane extracts from 44 European grape varieties. Pairwise Spearman's correlations between polyphenol variations and antioxidant capacities were performed to identify the key drivers of antioxidant capacities. Several compounds including *E*-resveratrol, *E*-piceatannol, *E*-ε-viniferin, hopeaphenol, isohopeaphenol and *Z*/*E*-vitisin B were highly correlated with ABTS and DPPH capacities [36].

Metabolomics was also used to evaluate the metabolic profiles of 7 grapevine cultivars in shoot cultures under four different growth conditions. The quantitative analyses using UPLC-MS allowed the identification of 45 compounds. PCA representation highlighted that grape cultivar had a higher influence on metabolic composition than the culture media. Antioxidant and anti-tyrosinase activities varied according to the cultivar and the culture medium. The cultivar Johanniter exhibited the highest DPPH inhibition, whereas Cabernet Cortis showed the greatest iron chelation, and Hibernal the strongest tyrosinase inhibition. These cultivars were particularly rich in phenolic acids, flavan-3-ols and stilbenoids [62].

Until now, very few articles studied the potential of PIWI grape varieties for a cosmetic purpose. A study on thirty PIWI genotypes investigated the metabolic profiles together with antioxidative power. As a result, UPLC-QTOF-MS and UPLC-PDA-FL analyses identified 49 compounds belonging to anthocyanins, flavonols, flavan-3-ols and phenolic acids. The antioxidant power was assessed using ABTS, FRAP and ORAC tests. Correlations between group of phenolic compounds and antioxidant activities were analyzed revealing strong correlations between antioxidant activities and the presence of flavan-3-ols [64]. These examples highlight the importance of comparing metabolomics data with biological activity results to accurately identify and select high-value extracts.

Conclusions

This article has highlighted the potential of metabolomics in the study of grape extracts, in the context of cosmetic activity and fungus-resistant grape varieties. Several studies have demonstrated the utility of metabolomics to evaluate the cosmetic potential of grape extracts. Indeed, metabolomics enables the selection cosmetic natural ingredients from grape origin according to the chosen organ (leaf, seed, cane), the variety and the extraction method. This information can be used to assist breeding programs aimed at developing new grape varieties with enhanced cosmetic activity. In addition, metabolomics can also be used to optimize grape cultivation practices, including the use of biofertilizers and biopesticides, to promote the production of grape extracts with high biological capacities. Despite the significant potential of metabolomics in grapevine research, there are still several challenges that need to be addressed. One of the main challenges is the standardization of metabolomics protocols, which can vary significantly between laboratories. Additionally, the interpretation of metabolomics data can be complex, requiring expertise in both analytical chemistry and chemometrics. The cosmetic use of grape-based natural ingredients containing a mixture of polyphenols, may reveal synergistic, additives or antagonist effects regarding their biological activities especially with antioxidant capacities. Future researches address these challenges. The integration of metabolomics with other omics approaches, such as genomics, epigenomics, transcriptomics and proteomics, can also improve the knowledge on molecular mechanisms underlying the biosynthesis of grape biomolecules, with the aim to guiding growing practices to produce grape extracts with high cosmetic properties. In conclusion, metabolomics is a valuable tool in grapevine research, enabling the comprehensive analysis of the chemical composition of extracts and facilitating the identification of compounds associated to cosmetic activities. The potential applications of metabolomics in grape breeding and cultivation are vast, providing opportunities for the development of new grape varieties with enhanced health benefits and the promotion of sustainable grape cultivation practices.

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