

Review

# Cosmetic and Pharmaceutical Products with Selected Natural and Synthetic Substances for Melasma Treatment and Methods of Their Analysis

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**Abstract:** Melasma is a fairly common condition that is the result of hyperpigmentation caused by increased melanin secretion. In the course of melasma, certain areas of the skin become darker than the rest of the epidermis. Although the pathogenesis remains incompletely clarified, several contributing factors have been identified, namely exposure to ultraviolet and visible light, family predisposition, pregnancy, and the use of exogenous hormones. Since current beauty standards associate healthy skin with its flawless and uniform color, people strive to eliminate any unaesthetic discoloration. Cosmetic and pharmaceutical products containing active substances with a whitening effect then become helpful. The most commonly used for this purpose are hydroquinone, arbutin, retinoids, organic acids (e.g., kojic, azelaic, and ellagic), and vitamins (B3, C, and E). However, the undesirable side effects they cause and the drive to replace synthetic chemicals with their natural counterparts have resulted in numerous reports on extracts of natural origin that exhibit skin-whitening effects. The purpose of this paper is to review the most recent scientific literature, which presents active substances of natural and synthetic origin with potential for the treatment of melasma. In addition, analytical techniques that can be used for qualitative and quantitative analysis of these substances present in cosmetic and pharmaceutical products will also be presented.

**Keywords:** hyperpigmentation; melasma; skin-whitening agents; plant extracts; mushroom/fungi extracts; analytical techniques; cosmetics; pharmaceutical products



**Citation:** Wawrzyńczak, A. Cosmetic and Pharmaceutical Products with Selected Natural and Synthetic Substances for Melasma Treatment and Methods of Their Analysis. *Cosmetics* **2023**, *10*, 86. <https://doi.org/10.3390/cosmetics10030086>

Academic Editor: Enzo Berardesca

Received: 30 April 2023

Revised: 29 May 2023

Accepted: 31 May 2023

Published: 2 June 2023



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## 1. Introduction

Current beauty canons in some cultures particularly value light skin color since it is associated with health, beauty, and prosperity, while darker skin tones may be correlated with a lower social class [1]. Sometimes the lightening of skin pigmentation has a medical justification—this is especially the case with dermatological conditions and dysfunctions based on excessive melanin synthesis. Skin afflictions such as melasma, freckles, birthmarks, senile/solar lentigo, pigmented acne scars, post-inflammatory hyperpigmentation, and lentiginosities are among the most commonly diagnosed skin conditions based on the process of hyperpigmentation. They are caused by a disruption of the melanogenesis process that occurs in human skin. During this process, melanin is produced, the light-absorbing pigment that determines the coloration of human skin and hair. Melanin is produced in melanocytes, which are specialized cells located mostly in the epidermal-dermal junction. From melanocytes, melanin is distributed by melanosomes (specialized lysosome-lineage organelles) and through the elongated dendrites to neighboring keratinocytes [2].

The precursor in melanogenesis is L-tyrosine, the amino acid that, through a series of enzymatic reactions, including the hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) and the oxidation of L-DOPA to dopachinone, is eventually converted to brown-black eumelanin or yellow-red pheomelanin. One of the enzymes involved in the conversion of L-tyrosine to melanin is tyrosinase. Inhibiting its activity is the main target of many topically applied whitening preparations. Important regulators of melanogenesis are also

melanotropin, adrenocorticotrophic hormone (ACTH), and some cytokines. The processes leading to the onset of pigmentary disorders are very complex and have still not been fully clarified. Three mechanisms are considered the main triggers for the lesions named hypermelanosis and include: (1) an increase in the number of melanocytes; (2) a disturbance in the melanin synthesis process; and (3) a disturbance in the growth, transport, and transfer of melanosomes to keratinocytes. Uncontrolled melanocyte proliferation is a feature of melanomas, pigmented nevi, and lentigines, among others. In the cases of melasma, post-inflammatory hyperpigmentation, and freckles, it is currently accepted that the predominant pathological process is excessive melanin production. Hypermelanosis can be caused by several genetic and environmental factors, the most important of which are inflammation, hormonal factors, drugs, exposure to UV radiation, visible light and heat, and mechanical trauma [3].

Currently, the scientific literature presents numerous possibilities for the use of active substances with whitening effects, including hydroquinone, kojic acid, azelaic acid, retinoids (isotretinoin, tretinoin), arbutin, and vitamins (B3, C and E) in the treatment of skin hyperpigmentation of various origins [4]. At the same time, the literature also reports adverse effects of this type of therapy, which most commonly include skin drying, irritation, peeling, or hypopigmentation [5]. This, in turn, stimulates the search for more natural substitutes and directs researchers' attention toward plant extracts [2,6,7], substances of marine origin [8,9], and even compounds extracted from mushrooms/fungi [10], which show the potential to lighten skin hyperpigmentation.

Surprisingly, whitening agents may also be helpful in the treatment of vitiligo, which is a chronic skin condition manifested by discoloration of large fragments of the skin and caused by a permanent dysfunction of skin pigment cells. In this case, whitening substances are applied to unaffected parts of the skin, allowing them to be matched to the fragments affected by vitiligo [11].

Nonetheless, it should not be forgotten that the etiology of skin hyperpigmentation is still not fully recognized, and it is difficult to select an effective therapy to permanently remove hyperpigmentation. Therefore, very often, in addition to topical treatments, other procedures are used, which can independently affect hyperpigmentation or support the action of products applied directly to the skin. These include peels (mainly chemical) as well as laser and light therapy. Frequently used chemical peels are based on glycolic, salicylic, and trichloroacetic acids, while laser- and light-based therapies involve, among others, intense pulsed light (IPL), Q-switched neodymium-doped yttrium aluminum garnet (QS-Nd:YAG) lasers, pulsed-dye lasers (PDL), and fractionated lasers [5].

An extremely important aspect of the study of the effectiveness of new cosmetic and pharmaceutical preparations containing skin-whitening agents is the quantification of the active substances in both the extracts prepared from natural sources and the final cosmetic or pharmaceutical product. For this purpose, methods based on chromatographic techniques (including TLC, GC, HPLC, and UHPLC) are used. Nevertheless, it frequently becomes a challenge to adequately separate the tested ingredients from the complex matrix of cosmetic and pharmaceutical products. In such cases, various extraction techniques assisted by ultrasound or microwave radiation are often used.

Taking into account all of the aforementioned aspects, this paper presents a compilation of scientific publications published over the past five years that describe the therapeutic effects of already well-known skin-whitening substances, as well as those that suggest potential for such use and which are derived from plant extracts and medicinal and edible mushrooms. This paper will also describe the analytical techniques currently available for the qualitative and quantitative analysis of skin-lightening substances, both those present in extracts of natural origin and those introduced as a component into a cosmetic or pharmaceutical product.

## 2. Melasma and Other Common Hyperpigmentation-Based Skin Disorders

Melasma, also referred to as chloasma or “the mask of pregnancy” because it is often associated with pregnant women, is one of the most common hyperpigmentation-based skin disorders. It manifests itself as light to dark brown, clearly delineated stains on the skin, usually located symmetrically on the face but sometimes taking unusual shapes. It usually occurs on the forehead, cheeks, nose, and area above the upper lip, sometimes also affecting the neck, neckline, and forearms. Melasma may be categorized by both location and depth of involvement. The most common types of melasma that describe the facial location are: (1) centrofacial, (2) malar, and (3) mandibular. On the other hand, considering the depth of involvement, melasma can be further divided into four categories: (1) epidermal, (2) dermal, (3) mixed, and (4) indeterminate. This is evaluated by illumination of the skin with long-wave ultraviolet light (Wood’s lamp) [12].

Melasma mainly affects women of childbearing age and less frequently affects men and postmenopausal women. It is most common in people with a high skin phototype (with Fitzpatrick skin types III-IV), corresponding to European and North African Mediterranean populations. Histologically, melasma is characterized by an elevated concentration of melanin in the epidermis and/or dermis. The pathophysiology of chloasma is still not fully elucidated, but the most significant factors influencing the onset of symptoms include exposure to sunlight, family predisposition, and hormonal factors (pregnancy, hormonal contraception, premenstrual period, and less commonly hormone-producing tumors such as ovarian cancer). In addition, it was also determined that melasma may originate from vascular disorders since some studies reported that melasma-affected skin had increased vascularity [13]. It is possible for melasma to resolve completely on its own (especially if it is caused by pregnancy). However, it is not uncommon for this condition to show resistance to treatment and a tendency to recur under the influence of various factors, such as even minor exposure to sunlight [5].

Sunlight, with its UV radiation component, is referred to as one of the main causes of melasma formation. One possible mechanism in this case is the induction of the synthesis of higher amounts of tyrosinase, an enzyme that promotes melanogenesis in the skin. It is widely accepted that the influence of genes is also of similar importance since tyrosinase-encoding genes and tyrosinase-related proteins are involved in pigmentation disorders caused by many exogenous and endogenous factors. However, there have been few reports that straightforwardly associate genetic polymorphisms with melasma—one showed that almost 279 genes are involved in the development of melasma [14]. It is more noticeable in the epidemiological studies that patients’ racial differences and positive family history may play a vital role in the occurrence of melasma [15]. Furthermore, several studies have revealed the influence of sex steroids on the development of melasma, suggesting a possible role of hormones in melasma pathogenesis as elevated expression of estrogen receptors in the dermis and progesterone receptors in the epidermis was observed. This may be related, for example, to pregnancy or the use of oral contraceptives. In contrast, male hormones seem not to play any role in hyperpigmentation; therefore, UV radiation is considered a main factor for elevated melanogenesis in the male skin [16].

The other most common skin pigmentation disorder is post-inflammatory hyperpigmentation. It usually arises as a consequence of acute and chronic inflammatory skin conditions, which may be caused by a number of inflammatory dermatological diseases, some procedures in cosmetic or aesthetic medicine, certain medications, and accidental mechanical, thermal, or chemical traumas to the skin. The location and severity of post-inflammatory hyperpigmentation depend on the nature of the triggering factor. It may occur at any age, regardless of gender, but people with phototypes IV–VI according to the Fitzpatrick classification are more susceptible to its occurrence. It may undergo gradual lightening (spontaneous or treatment-related), which usually lasts 6–12 months but may also persist for many years. Moreover, post-inflammatory hyperpigmentation sometimes shows a tendency to recur [17].

Another skin condition based on hyperpigmentation is lentigines, also known as actinic lentigines, liver spots, or age/sun spots. Lentigines take the form of brown, clearly demarcated spots that are sometimes clinically similar to freckles but can reach larger sizes. They do not lighten with limited exposure to sunlight and have a particular tendency to appear at an older age. They come in several clinical variants, the most common of which are (1) lentigo simplex, unrelated to sun exposure or systemic disease, and (2) lentigo solaris, which is considered a marker of photodamage to the skin and occurs mainly on the face, back of the hands, arms, and upper torso, that is, parts of the body particularly exposed to sunlight. The development of multiple lentigines spots can also be a symptom of rare and genetically determined conditions, such as Peutz–Jeghers, LEOPARD, or Laugier–Hunziker syndrome [18].

### 3. Current Methods of Melasma Treatment

In general, hyperpigmentation can noticeably affect the quality of life, although it cannot be considered a detrimental or lethal disorder. There are several options for hyperpigmentation treatment available nowadays. They include mainly topical routes in the form of creams, gels, or ointments. However, quite often they are accompanied by various side effects such as drying, irritation, peeling, or hypopigmentation of the skin. Additionally, even prolonged treatment, which can last up to several years, may produce poor results and low patient satisfaction [3].

To avoid this situation, there is a drive to develop methods based on so-called combination therapies, which use peels and light- and laser-based treatments in addition to topical therapy. This is particularly advisable for dermal melasma, which is less likely to respond to topical therapy. Triple combination cream (TCC) is one of the primary topical treatments for melasma. In general, it consists of hydroquinone, a retinoid, and a fluorinated corticosteroid and is widely regarded as a safe and effective treatment for melasma. There are several options for the composition of TCC, such as 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide, with the so-called Kligman–Willis formula (5% hydroquinone, 0.1% tretinoin, and 0.1% dexamethasone) that has been used for hyperpigmentation treatment for more than 30 years [19,20].

Chemical peels are commonly used for several skin disorders, even though they may cause skin irritation and post-inflammatory hyperpigmentation. Glycolic acid seems to be the most broadly used for chemical peeling, whereas salicylic acid represents a safer choice for patients with sensitive skin and dark phenotypes [21]. Additionally, Jessner's solution (an alcohol solution containing 14% resorcinol, salicylic acid, and lactic acid) could also be effective [22]. Looking for other options in the treatment of melasma, a study was conducted comparing the effectiveness of chemical peels based on 70% glycolic acid and 1% tretinoin, which showed that the efficiency of peels based on tretinoin was similar to those based on glycolic acid. Furthermore, the side effects in both groups of patients were rather negligible [23]. Quite frequently, attempts are also made to combine chemical peels with topical therapy. Chaudhary et al. described a study showing that the combination of topical application of 2% hydroquinone, 1% hydrocortisone, and 0.05% tretinoin with sequential use of glycolic acid-based peeling significantly improves the therapeutic efficiency in the treatment of melasma in Indian patients [24]. Hagag et al. conducted a similar study in which the efficiency of topically delivered nano-vitamin C enhanced with iontophoresis was compared with that of a chemical peel containing 20% trichloroacetic acid. The authors concluded that nanosomal vitamin C supported by iontophoresis may be an easy, safe, effective, painless, and non-invasive alternative in the treatment of melasma since its effectiveness was found to be as effective as trichloroacetic acid peelings [25].

In recent years, it has been well recognized that intense pulsed light, fractional and pigment lasers, or radiofrequency may be successfully used in melasma treatment [26–29]. However, it has also been documented that therapies based on laser and light sources can lead to adverse effects, namely paradoxical hyperpigmentation resulting from direct damage to the skin, especially for patients with high skin phototypes. Hence, it has also

been suggested to limit this therapeutic approach to patients with disorders resistant to topical treatment [5]. It should also be taken into consideration that non-ablative fractional lasers are the only laser-based systems approved by the FDA (since 2003), producing well-documented results in the treatment of melasma [30].

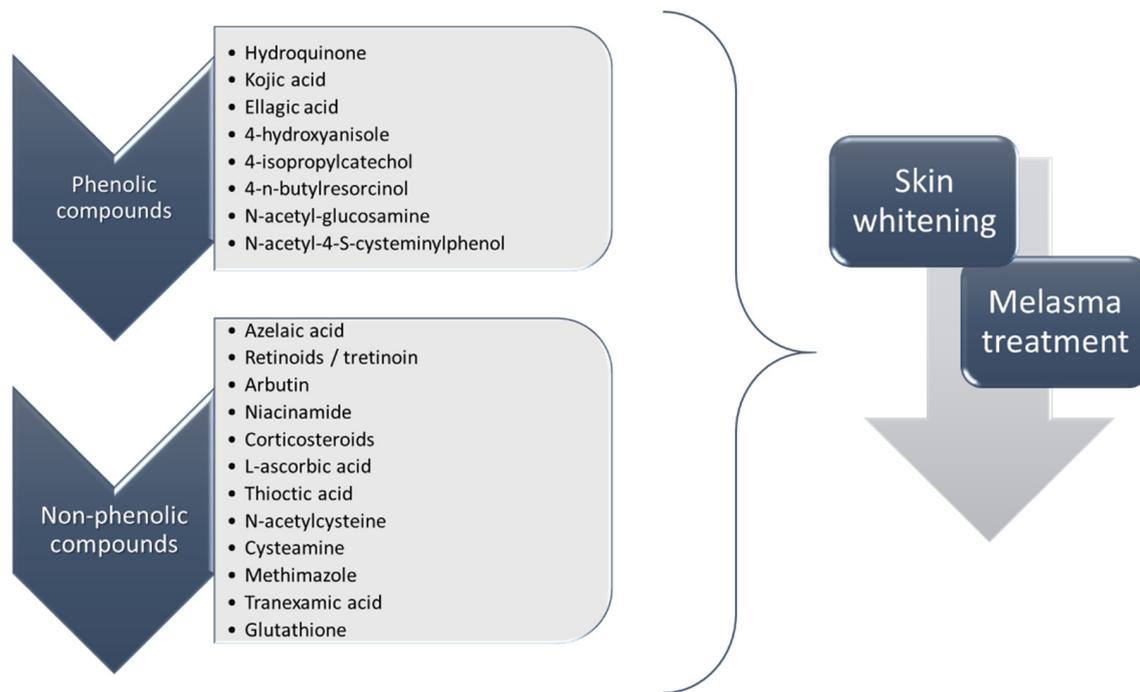
Intense pulsed light uses a flash lamp light source to emit noncoherent light with wavelengths between 515 nm and 1200 nm. The application of filters allows the targeting of a particular chromophore, namely melanin, in the case of melasma [31]. Q-switched lasers generate high-intensity laser beams with very short pulse intervals. These types of lasers target melanin and are available in multiple wavelengths, with the most commonly used being 532 nm or 1064 nm from a neodymium-doped yttrium aluminum garnet (QS-Nd:YAG) laser [32]. Recently, comparative studies were also performed on 1064 nm QS-Nd:YAG laser and Jessner's peeling, proving that these therapies are equally effective in the treatment of melasma [33]. Moreover, the skin-lightening effect achieved by laser therapy can be further sustained by using an appropriate combination therapy based on classical whitening substances, namely serums containing vitamin C, ferulic acid, and phloretin [34]. Pulsed-dye lasers target hemoglobin, which may be considered the vascular component of melasma [35]. In contrast, fractional lasers act by creating thousands of microthermal treatment zones with each pulse. These microthermal damages are able to penetrate into the deeper layers of the skin, influencing dermal melanin. The most important advantage of fractional laser therapy is that it does not create open wounds, allowing for faster recovery and reducing the risk of scarring or pigmentary alterations [36]. Elmorsy et al. showed that low-power fractional laser can serve as a safe and effective melasma treatment in patients with different skin types, especially Fitzpatrick skin type III. Additionally, its combination with Jessner's peel gives faster improvement and higher patient satisfaction compared to separate treatments with laser or Jessner's solution [37].

In addition to the laser-based equipment, devices using radiofrequency may also be used in the treatment of melasma. For example, a monopolar radiofrequency was successfully applied to facilitate the drug delivery of a phytocomplex of 1% kojic acid [38].

In the context of treating hyperpigmentation-based conditions, one of the most important aspects is preventive action, which in this case is mainly based on photoprotective measures. A natural factor that protects against the harmful effects of sunlight is eumelanin, one of the natural pigments of the skin, which is associated with dark skin pigmentation. The light phototype skin preferentially contains pheomelanin; the amount of eumelanin is not sufficient to provide full photoprotection, and therefore the application of complementary sunscreens is essential [2]. Today, many cosmetic UV filters with a wide range of photoprotection are available. In addition, much research is currently being conducted on new sunscreens and novel methods to incorporate them into cosmetic formulations and extend their durability after application to the skin [39]. It was found that the best solution for patients with hyperpigmentation-based skin conditions such as melasma is the use of broad spectrum sunscreens along with protection against visible light [40].

#### 4. Chemicals Commonly Used in the Treatment of Melasma

To date, a number of chemicals have been used in the treatment of melasma, primarily aimed at abolishing excessive tyrosinase production (so-called tyrosinase inhibitors). They can be administered through the skin or orally. An additional determining factor in the usefulness of a given substance is the duration of therapy [16]. The most common chemicals used in topical melasma treatment are shown in Figure 1, and examples of publications from the last five years describing this type of research are included in Table 1.



**Figure 1.** The most common chemical compounds in the treatment of melasma.

**Table 1.** The most common chemical compounds with skin-whitening properties published in the last five years.

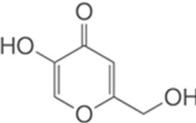
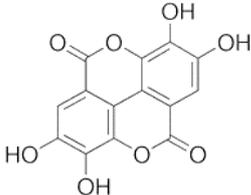
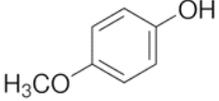
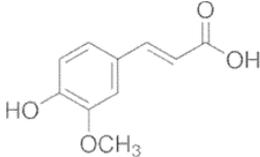
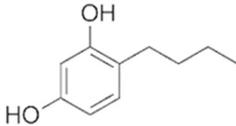
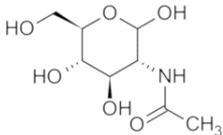
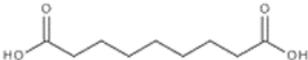
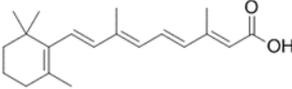
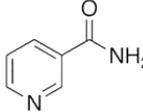
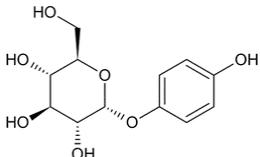
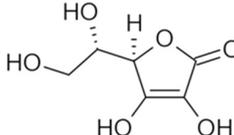
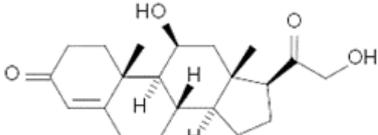
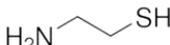
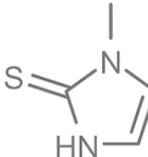
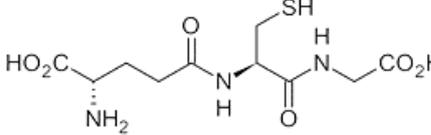
Chemical Substance	Chemical Structure	References
<b>Phenolic Compounds</b>		
Hydroquinone		[41,42]
Kojic acid		[43]
Ellagic acid		[44]
4-hydroxyanisole (mequinol)		[12]
Ferulic acid		[45]

Table 1. Cont.

Chemical Substance	Chemical Structure	References
<b>Phenolic Compounds</b>		
4-n-butylresorcinol		[46,47]
N-acetyl-glucosamine		[48]
<b>Non-phenolic compounds</b>		
Azelaic acid		[49,50]
Retinoids / tretinoin		[51]
Niacinamide		[52,53]
Arbutin		[54,55]
L-ascorbic acid		[56]
Corticosteroids		[57]
Cysteamine		[58,59]
Methimazole		
Glutathione		[60]
Tranexamic acid		[61]

Current research indicates that these substances can act as individual therapies or can be used in combination with other chemicals or other techniques, such as peels and/or laser therapy, as already outlined in Section 3 of this paper. Consequently, the literature reports from the last few years show that research on treatments based on combinations of several different ingredients administered topically is still ongoing [62–66]. An interesting approach was proposed by Martínez-Gutiérrez et al., who used artificial intelligence-based tools to determine the optimal combination of substances with depigmentation effects. The mathematical models they developed indicated that the optimal combination for skin whitening would be a mixture of retinol, diosmin, and ferulic acid, which would have synergistic effects in the treatment of melasma [67].

### 5. Substances of Natural Origin Prepared on the Basis of Plant and Mushroom/Fungi Extracts Showing Skin-Whitening Properties

Treatment of melasma is a challenging task due to the recurrent nature of this condition. Current trends in the treatment of melasma involve several procedures, namely the application of sunscreens, the use of topical whitening agents such as hydroquinone alone or in combination with tretinoin, and a corticosteroid. Superficial chemical peels and laser therapy are also recommended. However, the use of hydroquinone in cosmetic products is currently forbidden in many regions, as its application can be associated with many undesirable side effects, such as skin irritations, cytotoxicity, mutagenicity of melanocytes, contact dermatitis, or exogenous ochronosis [68]. Therefore, natural compounds with an anti-pigmentary action are currently in great demand, as they are expected to exhibit comparable efficiency with lower toxicity than existing skin-whitening agents [7,69–71]. The scientific literature of the past few years abounds with examples of studies on plant extracts that may have the potential to alleviate skin conditions based on hyperpigmentation (Table 2). Of course, it is important to keep in mind that these studies are in various stages of development and are often based only on *in silico* tests, requiring further testing before they can be introduced as an official therapy for the treatment of melasma.

**Table 2.** Selected substances of plant origin recently tested as topical whitening agents with potential in the melasma treatment.

Chemical Compounds	Origin	Suggested Mechanisms of Action	References
Ginsenosides (protopanaxadiol, protopanaxatriol, floralginsenoside A, ginsenoside Rd, ginsenoside Re, ginsenoside F1, ginsenoside Rg5 and Rk1)	Ginseng extracts	Suppression of tyrosinase activity	[72–76]
Aloesin	Aloe extracts	Suppression of tyrosinase activity	[77–79]
Liquiritin, isoliquiritin, isoliquiritigenin, glabridin	Licorice extract	Suppression of tyrosinase activity	[80–82]
Hydroxytyrosol	Olive extract	Suppression of tyrosinase activity	[83]
Gallic acid, catechin, caffeic acid, syringic acid, rutin, ferulic acid, naringin	Chestnut spike extract	Suppression of tyrosinase activity	[84]
Hesperidin; kaempferol; apigenin	<i>Stachys cretica</i> subsp. <i>Smyrnaea</i> extract	Suppression of tyrosinase activity	[85]
Vanillic acid, p-coumaric acid, protocatechuic acid, caffeic acid, ferulic acid, chlorogenic acid isomers	<i>Polypodium leucotomos</i> extract	Melanogenesis inhibition	[86,87]
Phenolic compounds (e.g., 2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]-1,3-propanediol)	<i>Juglans mandshurica</i> fruit extract	Melanogenesis inhibition	[88]
Cuparene, $\beta$ -funebrene, barbatene	<i>Dorema ammoniacum</i> gum extract	Suppression of secretory functions and biosynthesis of melanocytes	[89]
Flavones, flavanones, chalcones, stilbenes, arylobenzofurans	Mulberry ( <i>Morus alba</i> L.) extracts	Suppression of tyrosinase activity	[90–92]
Flavonoids, tannins, alkaloids, phenols, saponins, coumarins, glycosides, polysaccharides	Paper Mulberry ( <i>Broussonetia papyrifera</i> ) extracts	Suppression of tyrosinase activity	[93]
Flavonoids, lignins, benzenoids	Seed cake of <i>Camellia oleifera</i> extracts	Melanogenesis inhibition	[94]
Phenolics, flavonoids	<i>Cuminum cyminum</i> L. extract	Suppression of tyrosinase activity	[95]

Table 2. Cont.

Chemical Compounds	Origin	Suggested Mechanisms of Action	References
L-(+)-ascorbic acid 2,6-dihexadecanoate, 9-octadecenoic acid (Z) methyl ester, N-hexadecanoic acid methyl ester	Pitaya / dragon fruit ( <i>Hylocereus</i> spp.) peels extract	Suppression of tyrosinase activity	[96]
Anthocyanins, polyphenols, flavonoids	<i>Rosa gallica</i> petals extract	Suppression of matrix metalloproteinase (MMP)-1	[97,98]
Kaempferol 3-O- $\alpha$ -l-rhamnopyranosyl (1 $\rightarrow$ 6)-(2'',3''-O-digalloyl)- $\beta$ -d-glucopyranoside, multiflorin B, 2-phenylethyl	<i>Rosa chinensis</i> flower extracts	Suppression of tyrosinase activity	[99]
1-O- $\beta$ -d-(6'-O-galloyl)-glucopyranoside, ethyl gallate	Flower petal extracts from eight different varieties belonging to the <i>Liliaceae</i> family	Suppression of tyrosinase activity	[100]
N,O-di-boc-hydroxylamine, L-(+)-Valinol; 4-aminobenzoic acid, DL-glutamic acid	<i>Maackia amurensis</i> branch extract	Suppression of melanin synthesis by inhibiting the expression of MITF, tyrosinase, TRP-1, and TRP-2 in B16F10 melanoma cells	[101]
Formononetin, genistein, trans-resveratrol, piceatannol, tectoridin	<i>Litsea cubeba</i> (Lour.) Pers. fruit extracts	Suppression of tyrosinase activity	[102]
Oxygenated terpenes (e.g., neral, geranial), monoterpene hydrocarbons (e.g., D-limonene, 3-carene)	<i>Solanum khasianum</i> C.B. Clarke leaves and berries extracts	Suppression of tyrosinase activity	[103]
Alkaloids, flavonoids, saponins, steroids, terpenoids, phenols, oxalates, cardiac glycosides	<i>Garcinia atroviridis</i> Griff. ex. T. Anderson fruit pericarp extract	Suppression of tyrosinase activity; melanogenesis inhibition	[104]
Phenolics, flavonoids	Pomegranate ( <i>Punica granatum</i> L.) peel extract	Suppression of cellular melanogenesis through tyrosinase and TRP-2 inhibitions	[105]
Phenolics	<i>Artocarpus</i> species ( <i>A. altilis</i> , <i>A. heterophyllus</i> , <i>A. integer</i> , <i>A. elasticus</i> , <i>A. rigidus</i> ) leaf, peel, and stem bark extracts	Suppression of tyrosinase activity; melanogenesis inhibition	[106]
Flavonoids	Ceylon Olive ( <i>Elaeocarpus serratus</i> ) leaf extract	Antityrosinase activity, inhibition of melanin formation (in zebrafish embryos)	[107]
Phenolic acid, gallic acid, two flavonoids: myricetin and mearnssetin	<i>Alnus cordata</i> stem bark extract	Antityrosinase activity	[108]
Hydroxycinnamic acids, flavanones, diarylheptanoids (E)-3-(3,4-dimethoxyphenyl)-2-propenal, cis-3-(3,4-dimethoxyphenyl)-4-[(E)-2,4,5-trimethoxystyryl]cyclohex-1-ene, 1-feruloyloxy cinnamic acid, (1E,4E,6E)-1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one, bisdemethoxycurcumin, curcumin	<i>Zingiber cassumunar</i> Roxb. rhizome extracts	Antityrosinase activity	[109]
ent-kaur-16-en-19-ol, 18-oxokauran-17-yl acetate, $\beta$ -sitosterol	<i>Annona squamosa</i> L. leaves extracts	Suppression of the tyrosinase activity and expression of proteins associated with melanogenesis	[110]
Phenolics, flavonoids	Extracts from: (1) the pedicels and leaves of <i>Cotinus coggygria</i> , (2) the pericarpium of <i>Pistacia vera</i> and <i>Garcinia mangostana</i> , (3) the aerial parts of <i>Lamium purpureum</i> spp. <i>purpureum</i> , (4) the flowers of <i>Punica granatum</i> , (5) the seeds of <i>Vitis vinifera</i>	Tyrosinase inhibition	[111]
Phenolics	<i>Baptisia tinctoria</i> root extract	Tyrosinase inhibition	[112]
Vitamin E ( $\alpha$ -tocopherol), $\gamma$ -sitosterol, neophytadiene, $\beta$ -tocopherol, linolenic acid, methyl ester, phytol	<i>Stenocarpus sinuatus</i> leaves extract	Tyrosinase inhibition	[113]
Flavonoids, flavonol, phenolics, anthocyanin	<i>Ficus carica</i> L. peel extracts	Tyrosinase inhibition	[114]
$\epsilon$ -viniferin, vitisin B	<i>Vitis amurensis</i> root extract	Tyrosinase inhibition	[115]
Ferulic acid	<i>Tetragonia tetragonioides</i> extract	Inhibition of melanin synthesis and tyrosinase expression in B16F10 cells	[45]
p-coumaric acid, gallic acid, quinic acid, chlorogenic acid, malic acid, protocatechuic acid, rutin, quercitrin, isoquercitrin	<i>Hypericum perforatum</i> L., <i>Hypericum calycinum</i> L., <i>Hypericum confertum</i> Choisy extracts	Tyrosinase inhibition	[116]

Table 2. Cont.

Chemical Compounds	Origin	Suggested Mechanisms of Action	References
Isoflavonoids (puerarin, daidzin)	<i>Pueraria lobata</i> stem extracts	Inhibition of melanin production in the 3-isobutyl-1-methylxanthine-induced B16/F10 cells	[117]
Coumarine (umbelliprenin)	<i>Anethum graveolens</i> , <i>Pimpinella anisum</i> , <i>Ferulago campestris</i> extracts	Modulation of melanogenesis in cultured murine Melan A cells	[118]
Gallic acid, protocatechuic acid	<i>Euphorbia supina</i> Raf. extract	Reduction of tyrosinase activity and melanin content in B16F10 melanoma cells	[119]
Phenolics (apigenin 7-glucoside, rosmarinic acid, hyperoside, hesperidin, luteolin 7-glucosid)	<i>Onosma pulchra</i> extracts	Tyrosinase inhibition	[120]
Arbutin, syringin, chlorogenic acid, platycoside E, platycodin D3, baicalin, platycodin D, luteolin	<i>Platycodon grandiflorum</i> extract	Inhibition of tyrosinase activity and melanin production in B16F10 melanocytes	[121]
1,3-O-dicaffeoylglycerol; tricrin; 9-hydroxyoctadecadienoic acid	<i>Sorghum bicolor</i> extracts	Inhibition of melanin production in B16F10 melanoma cells	[122]
Phenolics and flavonoids (chlorogenic acid, caffeic acid, kaempferol, catechin hydrate)	<i>Hibiscus cannabinus</i> L. leaves extract	Inhibition of tyrosinase activity and melanin production in B16F10 melanocytes	[123]
Polyphenols, flavonoids	<i>Paeonia suffruticosa</i> Andrews	Tyrosinase inhibition	[124]
Kaempferol compounds (kaempferol 3-O-[ $\alpha$ -rhamnopyranosyl-(1 $\rightarrow$ 6)- $\beta$ -glucopyranoside] kaempferol-3,7-O- $\alpha$ -L-dirhamnoside)	<i>Camellia oleifera</i> Abel shell extracts	Tyrosinase inhibition	[125]
Ferulic acid	<i>Phoenix dactylifera</i> L. seed extract	Inhibition of melanin production in B16F10 melanoma cells	[126]
Phenolic glycoside (gastrodin)	<i>Grammatophyllum speciosum</i> pseudobulb extract	Inhibition of melanin synthesis	[127]
Flavonoids, polyphenols, glycans, reducing sugars, chlorogenic acids	<i>Chrysanthemum morifolium</i> Ramat extract	Tyrosinase inhibition	[128]
Flavanones ((-)-prunin, persiconin, (+)-dihydrokaempferol, (-)-naringenin)	<i>Prunus persica</i> twig extract	Tyrosinase inhibition	[129]
Vitamin C, vitamin E, phenolics, flavonoid components	<i>Musa sapientum</i> rejected unripe fruit extracts	Tyrosinase inhibition	[130]

Among substances of natural origin, a widely studied group of compounds with hypopigmentation potential are polyphenols and their derivatives, which additionally exhibit antioxidant activity, thus counteracting skin aging processes [131]. Within the range of antioxidants that show inhibitory activity against tyrosinase, resveratrol, a compound present in a wide variety of plants such as berries or grapes (*Vitis vinifera*), has gained great interest among researchers in recent years. Studies have shown that this compound and its derivatives exhibit not only anti-inflammatory, anti-cancer, and anti-oxidant properties but may also be used as a skin-whitening agent [132–135]. Resveratrol derivatives characterized by better bioavailability, namely resveratrol glucosides, which were obtained by transglycosylation by amylosucrase of *Deinococcus geothermalis*, showed activity similar to that of arbutin in suppression of melanin synthesis and tyrosinase activity [136]. Higher bioavailability of resveratrol in the control of skin pigmentation can also be achieved by incorporating this stilbene derivative into a suitable carrier that will allow better penetration through the epidermal layers and thus a better whitening effect. An example is the use of microemulsion gel, which was able to significantly enhance the capability of resveratrol to inhibit melanin formation when compared to resveratrol-containing suspension and microemulsion [137]. Furthermore, Sheweita et al., in preclinical studies conducted on melanogenesis proteins, showed that trans-resveratrol introduced into emulsion systems also had the ability to suppress the protein expressions of tyrosinase and microphthalmia-associated transcription factors [138]. Due to the low absorption and poor solubility of resveratrol, studies have also been conducted to increase the bioavailability of this compound through the use of dissolving microneedle patches. Both in vitro and in vivo studies revealed that the use of these patches effectively improved intradermal resveratrol delivery compared to a cream formulation; therefore, it can be concluded that this approach is a

promising way for the effective local delivery of whitening ingredients in the melasma treatment [139].

*Vitis vinifera* and other grape varieties are not only rich in stilbene derivatives but also in flavonoids, phenolic acids, anthocyanins, and vitamins [140]. Most of these compounds show the ability to inhibit tyrosinase production and may therefore be attractive in the cosmetics and medicinal industries as depigmentation agents [141]. Malinowska and co-workers tested extracts from canes of five selected varieties of *V. vinifera*, namely Villard Noir, Sauvignon, Savagnin, Riesling, and Magdeleine Noire des Charentes, for their ability to inhibit tyrosinase production. All extracts were found to be relatively efficient tyrosinase inhibitors, with the Riesling-based extract being the most potent [142].

Many plants contain carotenoids, which are well-known for their antioxidant activity [143]. Recent studies have shown that cosmetic formulations containing 0.05% *w/w* tomato lycopene and 3.45% *w/w* wheat bran extract can be successfully used in the treatment of skin hyperpigmentation without causing side effects [144]. In addition, a recent study on Z-isomer-rich lycopene and  $\beta$ -carotene showed that carotenoid Z-isomers exhibit powerful skin-whitening action, promising their future application in skin care supplements and cosmetic products. This skin-whitening action may result from the regulation of gene expressions of tyrosinase-related enzymes; nevertheless, the exact mechanism still needs to be clarified [145].

The current literature also offers many suggestions for combining plant extracts with classic anti-pigmentation agents. As an example, there are studies on a French maritime pine bark extract containing pycnogenol in combination with triple combination cream [146], on an oral nutritional supplement containing extracts from *Pinus pinaster* and grape seed extract, used along with a high SPF sunscreen [147], and on a tomato extract supplement applied together with a topical sunscreen and cream containing 4% hydroquinone [148]. Licorice extract was also used in the tests on combined therapy based on dissolving microneedle patches containing tranexamic acid. It has been found that dissolving microneedles based on polyvinyl alcohol and polyvinylpyrrolidone can be successfully applied as a delivery platform for the combination of tranexamic acid and licorice extract in synergistic melasma therapy [149].

Not only extracts may be applied as a potential source of skin-whitening agents, but fermented plant materials can also serve as such. For example, Liu et al. have shown that ethanol extracts from *Lactobacillus plantarum* TWK10 fermented-nongerminated black soy milk and fermented-germinated black soy milk could inhibit melanogenesis, indicating their potential as whitening agents in cosmetic products [150]. The extracts of *Aloe vera* leaf skin fermented with *Lactobacillus plantarum* BN41 were tested for their whitening properties. According to the studies of Jeon et al., the inhibition of tyrosinase activity and melanin secretion was much higher for the fermented extracts than those of commercial skin-lightening ingredients, namely arbutin and aloesin [151]. The fermented by-product from aloe processing also contains compounds that have the potential to be used as tyrosinase-suppressing agents [152]. Lin and co-workers positively verified the skin-whitening properties of *Chenopodium formosanum* leaf extract fermented with the filamentous fungus *Aspergillus oryzae* [153].

Botanical products are constantly gaining interest in topical therapies for melasma and could potentially reach comparable efficacy with active compounds of pharmaceutical origin. Undoubtedly, the biggest advantage is that they are well tolerated, with no serious adverse effects reported. Thus, the use of substances from botanical sources may be a promising option for patients seeking alternative therapeutic options for hyperpigmentation-based conditions [154].

Although a lot of tests evaluating the skin-whitening effect of plant extracts have been described in the literature, many still lack sufficient evidence on safety and effectiveness in the treatment of hyperpigmentation. Only selected plant extracts with skin-lightening potential are currently used in cosmetic products legally available in the European market. *Vitis vinifera* seed extracts are present, among others, in products designed for skin treatment

in the eye area, while ginseng extracts are used in nourishing formulations that retard the onset of aging. Licorice extracts, which are rich in glabridin, are also used in cosmetic and medicinal skin care products, such as creams, lotions, and body washes, which are designed for hyperpigmented skin. Olive extracts are used to help protect skin from UV damage and regenerate it afterward. Correspondingly, mulberry extracts are used as skin-lightening ingredients in products protecting against pigmentation disorders and skin damage caused by overexposure to the sun. Extracts from the *Rosacea* family are used, for example, in cleansing and toning products, body care, and after-sun care formulations with depigmenting properties. Pomegranate extracts are used in formulations with skin-whitening properties, such as radiant and glowing cleansers, eye contour lighteners, spot fading treatments, and skin tone eveners.

Not only botanical extracts but also mushroom components and their secondary metabolites contain many compounds with potential antimicrobial, antiviral, anti-cancer, anti-inflammatory, anti-aging, antioxidant, anti-wrinkle, moisturizing, or skin-whitening activity. Edible mushrooms are considered valuable sources of new bioactive compounds with potential applications in cosmetics, as they are expected to exhibit low toxicity. Biologically active compounds of mushroom origin have been studied for skincare applications [10,155,156].

In recent years, there have been reports on the potential use of extracts derived from naturally occurring edible and medicinal mushrooms as cosmetic ingredients with potential skin-lightening effects [157]. Recently, Angelini et al. conducted a study on extracts of the edible mushroom *Tricholosporum goniospermum* (Bres.) Guzmán ex T.J. Baroni. According to their results, ethyl acetate extract acts as an anti-tyrosinase agent, mainly due to the presence of catechin [158]. *Neolentinus lepideus* (Fr.) Redhead and Ginns, a wood-decaying mushroom and one of the most popular edible mushrooms in East Asian countries, was also tested by Ishihara et al. for its tyrosinase-inhibiting activity. The results showed that the extracts contain 1,3-dihydroisobenzofuran and 4,5,7-triol-5-methoxy-1,3-dihydroisobenzofuran-4,7-diol, with  $IC_{50}$  values significantly lower than those calculated for hydroquinone and arbutin, giving them the ability to be used as active ingredients in skin-whitening formulations [159]. The same authors reported that 6-hydroxy-L-tryptophan isolated with hot water from the lyophilized fruiting body of *Lyophyllum decastes* may also act as a tyrosinase inhibitor with low  $IC_{50}$  values [160]. In vivo tests (zebrafish embryo model as a preclinical animal platform) of ethanol extracts from five edible mushrooms (*Lethiporus sulphureus*, *Agaricus silvaticus*, *Agrocybe aegerita*, *Pleurotus ostreatus*, and *Polyporus squamosus*) have been performed by Pavic and co-workers. They comprehensively evaluated their potential for use as topical depigmenting agents and concluded that extracts of *A. silvaticus* and *L. sulphureus* have a potent depigmenting activity based on inhibition of tyrosinase activity and melanin synthesis in skin melanocytes of zebrafish [161]. Methanol and hot water extracts from the fruiting bodies of *Phellinus vaninii*, a mushroom that grows on wood, were also investigated for their potential for depigmentation. The results obtained by Hoan et al. suggest that methanol extract was significantly more active in inhibiting melanin synthesis in B16F10 melanoma cells than arbutin [162]. The anti-tyrosinase effect was also verified for different extracts of cultivated edible mushrooms: *Schizophyllum commune* [163], *Pleurotus ostreatus*, *Ganoderma lucidum*, *Auricularia polytricha*, and *Schizophyllum commune* [164], *Polyozellus multiplex* [165], *Lentinula edodes* (Berk.) Pegler [166], *Ganoderma lucidum* [167], *Agaricus bisporus* (brown) [168], and *Inonotus obliquus* [169]. Sangthong and co-workers studied polysaccharides from *Volvariella volvacea* obtained by different extraction techniques. According to their results, a gel cream containing 0.2% mushroom extract may be considered a multi-functional cosmetic with whitening properties [170]. An interesting approach to obtaining skin-whitening agents was demonstrated by Pintathong et al., who used for this purpose solid-based residues from harvesting the fruiting bodies of cultured *Cordyceps militaris*. These residue parts were used to prepare extracts by solid-state fermentation with solid media containing a mixture of defatted rice bran, barley, white

rice, riceberry rice, and wheat. The obtained extracts were characterized, among others, by excellent tyrosinase inhibitory activity [171].

In addition to mushroom-based materials (a fruiting body of certain fungi), research has also been conducted on a number of fermentative fungi species, which exhibit anti-tyrosinase activities and can serve as a source of substances to aid in the therapy of melasma [172–177].

## 6. Analytical Methods for Determining the Content of Active Substances Present in Skin-Whitening Formulations

The precise qualitative and quantitative determination of active substances in skin-whitening preparations is a very important issue, not only for the effectiveness of the product but also for the safety of its use. Products containing skin-whitening ingredients, depending on the manufacturer's declaration, are subject to different regulations. As far as the European market is concerned, these are the regulations EC 1223/2009 or EC 726/2004 for cosmetic or pharmaceutical products, respectively. Cosmetic products are used for aesthetic reasons on large skin areas and are freely available, while for pharmaceutical products, the application and availability are quite different: they are used to correct skin disorders in small areas and are available only by prescription. There is an official analytical procedure for the determination of skin-whitening ingredients, which was published in 1995 under the EU framework (Sixth Commission Directive 95/32/EC). It combines thin-layer chromatography (TLC), followed by quantitative determination using liquid chromatography (LC) with ultraviolet/visible (UV-Vis) detection, and it primarily concerns the determination of hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether, and hydroquinone monobenzyl ether. There is also an extension of this method in which a procedure is described for analyzing not only hydroquinone and its esters but also the most common corticosteroids used illegally in cosmetic products [178].

Until now, many different analytical techniques have been applied to determine the chemical composition of extracts used in studies on skin-lightening potential, namely HPLC, UHPLC, or UV-Vis. However, the most commonly used are combined systems, such as GC-MS, LC-MS, or LC-MS/MS, which allow the chemical composition of extracts with the potential to counteract skin hyperpigmentation to be determined with a high degree of precision (Table 3).

**Table 3.** Techniques for qualitative analysis of extracts with skin-lightening potential.

Analyzed Sample	Applied Technique	References
Ethanol extracts from <i>Ferula assa-foetida</i> L.	GC-MS	[179]
Methanol extracts from <i>Acer caesium</i> , <i>Centella asiatica</i> , <i>Matricaria chamomilla</i> , <i>Betula utilis</i> , <i>Dipterocarpus retusus</i> , <i>Rhododendron anthopogon</i> , <i>Didymocarpus albicaulis</i> , <i>Lygodium flexuosum</i> , <i>Eucalyptus citriodora</i> , <i>Melaleuca cajuputi</i> , <i>Phyllanthus reticulatus</i> , <i>Phyllanthus virgatus</i> , <i>Thalictrum foliolosum</i> , <i>Prismatomeris tetrandra</i> , <i>Aegle marmelos</i> , <i>Pedicularis hoffmeisteri</i> , <i>Solanum erianthum</i> , <i>Sonneratia ovata</i>	Stable Isotope Dilution GC-MS	[180]
Ethanol extracts from <i>Platycodon grandiflorum</i>	HPLC-MS	[121]
Water extracts from fruits of <i>Schisandra chinensis</i>	UHPLC-MS	[181]
Ethanol extracts from <i>Lepisorus thunbergianus</i>	HPLC + prep-HPLC + <sup>1</sup> H and <sup>13</sup> C NMR	[182]
Methanol extracts from flowering aerial parts of <i>Hypericum perforatum</i> L., <i>Hypericum calycinum</i> L., <i>Hypericum confertum</i> Choisy	LC-MS/MS	[116]
Ethyl acetate, methanol and water extracts from <i>Onosma pulchra</i> Riedl.	LC-ESI-MS/MS	[120,183]
Acetone-water extracts from leaves of <i>Photinia × fraseri</i>	HPLC-ESI-MS	[184]
Enriched powder extracts from stem of <i>Pueraria lobata</i>	MALDI-TOF-MS	[117]
	HPLC(DAD)-MS/MS	[185]

Table 3. Cont.

Analyzed Sample	Applied Technique	References
Methanol extracts from <i>Vitis amurensis</i> root	LC-Q-TOF-MS coupled with bioassay (tyrosinase inhibitory assay) and response surface methodology	[115]
Hydroglycolic extracts from <i>Achillea biebersteinii</i>	HPLC-ESI-Q-TOF-MS	[186]
Ethanol, water and ethyl acetate extracts from roots of <i>Paeonia lactiflora</i>	HPLC-ESI-Q-TOF-MS/MS + prep-HPLC + <sup>1</sup> H/ <sup>13</sup> C NMR	[187]
Ethanol extracts from <i>Sorghum bicolor</i>	UHPLC-IMS-Q-TOF MS/MS	[122]
1,3-butanediol extracts from shell of <i>Camellia oleifera</i> Abel	UHPLC-Q-TOF MS/MS	[125]

<sup>1</sup>H/<sup>13</sup>C NMR—<sup>1</sup>H/<sup>13</sup>C Nuclear Magnetic Resonance Spectroscopy; DAD—Diode Array Detector; ESI—Electrospray Ionization; GC—Gas Chromatography; HPLC—High performance Liquid Chromatography; LC—Liquid Chromatography; MALDI-TOF-MS—Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry; MS—Mass Spectrometry; MS/MS—Tandem Mass Spectrometry; PDA—Photodiode Array Detector; prep. HPLC—preparative HPLC; Q-TOF-MS—Quadrupole-Time-of-Flight Mass Spectrometry; UHPLC—Ultra High Performance Liquid Chromatography.

While in the case of extract samples, analyses can be carried out almost immediately, the analysis of cosmetic or pharmaceutical products containing whitening agents requires a much more complicated sample preparation procedure as well as the use of appropriate validation procedures. Often, the preparation of a cosmetic product sample requires appropriate procedures for extracting analytes from the matrix. These are often based on solvent extraction assisted by ultrasound or microwave radiation.

Cosmetic products usually consist of mixtures of whitening agents, so their direct analysis by, e.g., UV-Vis spectroscopy may be difficult without a previous separation step. Therefore, chromatographic techniques are usually employed to enable the determination of a high number of these types of cosmetic ingredients. Nevertheless, Li and co-workers put forward a proposal for the quantitative analysis of five skin-whitening agents, namely arbutin, nicotinamide, kojic acid, hydroquinone, and phenol, in various cosmetic products (lotion, emulsion, and cream), based on the conventional UV-Vis determination with a Tchebichef curve moment approach, reaching the leave-one-out correlation coefficients of the established models with values higher than 0.9948 within the linear ranges [188].

The literature of recent years has been dominated by studies on the simultaneous determination of several whitening ingredients present in a cosmetic or pharmaceutical product. They are mainly based on chromatographic techniques and concern the simultaneous detection of chemicals such as hydroquinone and retinoic acid [189], hydroquinone, hydrocortisone acetate, and tretinoin [190], hydroquinone, tretinoin, and betamethasone [191], arbutin, niacinamide, and 3-O-ethyl ascorbic acid [192], hydroquinone, resorcinol, catechol, and 3,3'-dichlorobenzidine [193], as well as two glucocorticoids, namely clobetasol 17-propionate and betamethasone 17-valerate [194], present in various forms of cosmetic and pharmaceutical products.

In addition to the chromatographic separation-based methods mentioned above, there are also reports on electrochemical sensors that would allow rapid and simultaneous analysis of skin-whitening substances. An example of such an approach is the research presented by Butwong et al., who developed a glassy carbon electrode modified with a composite of Ag@AgCl, Ag<sub>2</sub>S, carbon nanotubes, and chitosan for the simultaneous analysis of hydroquinone, arbutin, and ascorbyl glucoside [195]. Another highly effective and promising analytic option for skin-whitening agents in cosmetic products was suggested by Wang et al., who established a simple, reliable, sensitive, and selective method for the detection of ellagic acid used in whitening cosmetics. This method is based on the seed-mediated growth of Au@Ag bimetallic core-shell nanorods and the monitoring of blue shifts in surface plasmon resonance [196]. In turn, Li and co-workers developed an electrochemical sensor based on nitrogen and sulfur co-doped Fe-Ni alloy (N,S-FeNi<sub>3</sub>/C) nanoparticles obtained via hydrothermal synthesis and high-temperature carbonization, which turned out to be an efficient tool for simultaneous analysis of arbutin and hydroquinone content in cosmetic products [197].

Arbutin, which is commonly used in skin-whitening products, has limitations on its allowable content due to the fact that it can generate hydroquinone during the decomposition process. Therefore, appropriate analytical techniques based on chromatography [198], fluorescence spectroscopy [199], and cyclic voltammetry [200] have been developed to precisely control the content of arbutin in cosmetic products.

It is worth mentioning here that hydroquinone is a banned ingredient in the EU for use in cosmetic topical preparations [201], and its use as an anti-hyperpigmentation agent is limited to pharmaceutical products. Therefore, it is very common in the literature to find descriptions of various methods for determining this substance in cosmetic products from non-EU countries or from illegal trade, which are widely available in online stores. Among them, chromatographic methods predominate, such as reversed-phase high-performance thin-layer chromatography (RP-HPTLC) [202] and reversed-phase high-performance liquid chromatography (RP-HPLC) [203,204]. However, there are also reports of methods based on electrochemical sensors [205–208] and descriptions of comprehensive analytical procedures to quantitatively verify the amount of hydroquinone in dermatological products [209].

A detailed review of the analytical techniques developed between 2006 and 2016, including a description of the preparation of cosmetic product samples, was published by Chisvert et al. [178]. Among them, the method developed and validated by Desmedt et al., based on ultra-high pressure liquid chromatography (UHPLC), allowed qualitative and quantitative analysis of eight illegal (hydroquinone, tretinoin, and six active dermatologic corticosteroids) and four legal (kojic acid, arbutin, nicotinamide, and salicylic acid) skin-whitening agents applied in different types of cosmetic preparations, namely creams, lotions, and soaps [210]. UHPLC analysis was preceded by the ultrasound-assisted extraction procedure performed with acetonitrile at 50 °C for 30 min. Importantly, this method of detection can be used for a market survey of suspected illegal whitening cosmetics products, which may pose a threat to public health.

## 7. Summary

This paper presents the currently used options in the treatment of melasma, a skin condition that is quite complex in its genesis and whose main symptom is hyperpigmentation of the skin. All therapeutic options, i.e., skin-lightening chemicals, laser light-based therapies, as well as chemical peels, are briefly characterized. What are also presented are the literature reports from the past five years describing research on plant and edible mushroom extracts with potentially skin-whitening ingredients. Despite the abundance of information on potential replacements for therapies based on synthetically derived chemicals used to date, it should be kept in mind that most of the studies presented in the literature are at a very early stage, and it will be a long time before these extracts can be officially incorporated into therapeutic regimes for the treatment of skin hyperpigmentation, including melasma.

An important element in the search for natural substitutes in the treatment of melasma is the development of appropriate analytical techniques and procedures that will allow full qualitative and quantitative characterization of the extracts obtained, thus ensuring the therapeutic efficacy and safety of their use. With the continuous improvement of the technique of obtaining natural extracts, the possibility of accurate qualitative and quantitative determination of the active ingredients present in these extracts will probably be achieved in the near future. In addition, it will be possible to precisely determine the effect of the active ingredients present in the extracts and find the substances with the best whitening effect. The continuous improvement of analytical techniques will also allow for the control of the composition of cosmetic preparations for patients with conditions based on hyperpigmentation, which are already available on the market.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The author declare no conflict of interest.

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