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Review

Recent Green Technologies in Natural Stilbenoids Production and Extraction: The Next Chapter in the Cosmetic Industry

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Abstract: Stilbenoids are well-known phytoalexins in the group of polyphenolic compounds. Because of their potent bioactivities, including antioxidant, antityrosinase, photoprotective, and antibacterial activities, stilbenoids are utilized as pharmaceutical active ingredient in cosmetic products. Thus, the demand for stilbenoids in the cosmetic industry is increasing. The main sources of stilbenoids are plants. Although plants are green and sustainable source materials, some of them do not allow a regular and constant supply due to seasonal and geographic reasons. Stilbenoids typically have been extracted by conventional organic solvent extraction, and then purified by separation techniques. This method is unfriendly to the environment and may deteriorate human health. Hence, the procedures called "green technologies" are focused on novel extraction methods and sustainable stilbenoids production by using biotechnology. In this review, the chemical structures together with the biosynthesis and current plant sources of resveratrol, oxyresveratrol, and piceatannol are described. Furthermore, recent natural deep eutectic solvents (NADES) for green extraction as well as plant cell cultures for the production of those stilbene compounds are updated.

Keywords: bioactivity; callus; cell suspension; green extraction; NADES; natural deep eutectic solvent; oxyresveratrol; piceatannol; resveratrol; stilbenoids

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1. Introduction

Cosmetic ingredients are generally originated from both chemical synthesis and natural sources [1–4]. Synthetic and/or semi-synthetic polymers are clear examples of chemical substances employed in cosmetics to prolong the release, improve delivery systems of each specific molecule to the target site of action, and decrease the evaporation rate of volatilizable formulations [1]. In some cases, the interaction between polymers and other compounds in the formulation can lead to hazardous effects on human health [1]. Moreover, some chemicals can act as pollutants that harm the environment, for example, parabens, a well-known preservative, from the factory contaminate the air, dust, soil, and water [5]. Thus, the cosmetic agents from nature such as plants, seaweed (macroalgae), ferns, animals, and marine creatures are preferred, and also attract customers [4,6–9]. Plants are renowned as enormous sources of pharmaceutical active ingredients since they accumulate diverse metabolites and show numerous biological activities.

Stilbenoids are one of the famous classes of the phyto-polyphenols [10]. The use of phytochemicals in cosmetic products is widespread because of their several prominent bioactivities [11,12]. For cosmetic purposes, several outstanding bioactivities of stilbenoids have been reported and have attracted the interest of customers, including antioxidant and anti-inflammatory activities, antityrosinase activity (depigmentation), antimicrobial activity, and photoprotective effect, i.e., ultraviolet (UV) protection [10,13–15]. Remarkably, stilbenoids are conventionally extracted from many plant species by several types of organic solvents such as methanol, ethanol, and acetone [16,17]. Nevertheless, these are not appropriate for the cosmetic industry since the procedures of extraction and purification are multifaceted, requiring high technical skills, the contamination of residual solvent, and are

expensive [18]. Furthermore, the yield fluctuates greatly depending on the quality of raw material, geography, temperature, humidity, rainfall, soil type and season [19]. Although the solvent is intentionally removed from the extract, residual solvents may remain in the extract because of incomplete evaporation processes. Thus, the residual solvents should be identified since they may potentially deteriorate human health. In the United States Pharmacopeia, the classification by risk assessment, limitation, identification, quantification, analytical procedures, and control strategy of residual solvents are described under the topic no. 467. The harvest of plant materials, especially perennial trees, directly from the natural resources is an unsustainable approach and also affects the ecosystem. Furthermore, direct cultivation of plants is not appropriate for the cosmetic industry because of its high cost, and because it is time-consuming and laborious work. Hence, other alternative methods for the extraction and sustainable production of stilbenoids are necessary to be considered for utilization in the future of the cosmetic industry.

The focus of this review is three well-known stilbenoids, resveratrol, oxyresveratrol, and piceatannol, and their chemical structures, biosynthesis, and bioactivities. Moreover, we provide the first summary of plant sources and current green technologies for stilbenoids production, i.e., green solvent extraction and plant cell cultures. Finally, future challenges and research gaps are also proposed and suggested.

2. Stilbenoids

Plants naturally produce chemical compounds called "plant-specialized (secondary) metabolites" to survive and protect themselves from abiotic and biotic stresses [20,21]. The phytochemical compounds are generally classified into three main groups based on their chemical structures and biosynthesis, including alkaloids, terpenoids, and polyphenols [20]. Polyphenols are abundantly present in daily diets, in foods such as vegetables, fruits, and nuts, and have been associated with health-promoting benefits [20]. The typical chemical structure of polyphenols consists of more than one hydroxyl group which are bound to one or more aromatic ring systems [22]. The most commonly known polyphenols are phenolic acids, flavonoids, tannins, lignans, coumarins, and stilbenoids [20]. Here, three compounds in stilbenoids containing resveratrol, oxyresveratrol, and piceatannol are emphasized and reviewed because of their outstanding bioactivities and high possibilities for utilization in cosmeceuticals.

2.1. Chemical Structures and Biosynthesis

The core structure of stilbene compounds comprises two aromatic rings connected with an ethylene bridge (C6–C2–C6 backbone) and is commonly found as monomers and oligomers in both aglycone and glycoside forms [20]. Phenylalanine and tyrosine are the amino acid precursors for stilbenoids biosynthesis in the phenylpropanoid pathway, although the chemical reactions occur differently [23]. Phenylalanine ammonia lyase (PAL) converts phenylalanine into *trans*-cinnamic acid and ammonia as by-products, then, cinnamate-4-hydroxylase (C4H) catalyzed *trans*-cinnamic acid to produce *p*-coumaric acid [23]. In addition, *p*-coumaric acid is also synthesized from tyrosine by tyrosine ammonia lyase (TAL) [23]. Hence, *p*-coumaric acid synthesis from tyrosine requires one step less than phenylalanine. Next, *p*-coumaric acid is the substrate for 4-coumarate:coenzyme A (CoA) ligase (4CL) to generate *p*-coumaroyl-CoA [23]. The *p*-coumaroyl-CoA is the most important intermediate compound for flavonoids and stilbenoids biosynthesis. In the case of stilbenoids, stilbene synthase (STS) or resveratrol synthase, the key enzyme for stilbenoids synthesis, and three molecules of malonyl-CoA are coupled with *p*-coumaroyl-CoA to yield resveratrol by the aldol reaction [23].

Resveratrol (3,4′,5-trihydroxystilbene) is the parent compound for other derivatives such as hydroxylated, methylated, and prenylated derivatives. Here, we focused on two hydroxylated derivatives, i.e., oxyresveratrol (2,3′,4,5′-tetrahydroxystilbene) and piceatannol (3,5,3′,4′-tetrahydroxystilbene), since these compounds have several potential bioactivities,

and may be possibly used in the cosmetic industry. An overview of the biosynthesis and chemical structures of stilbenoids is shown in Figure 1.

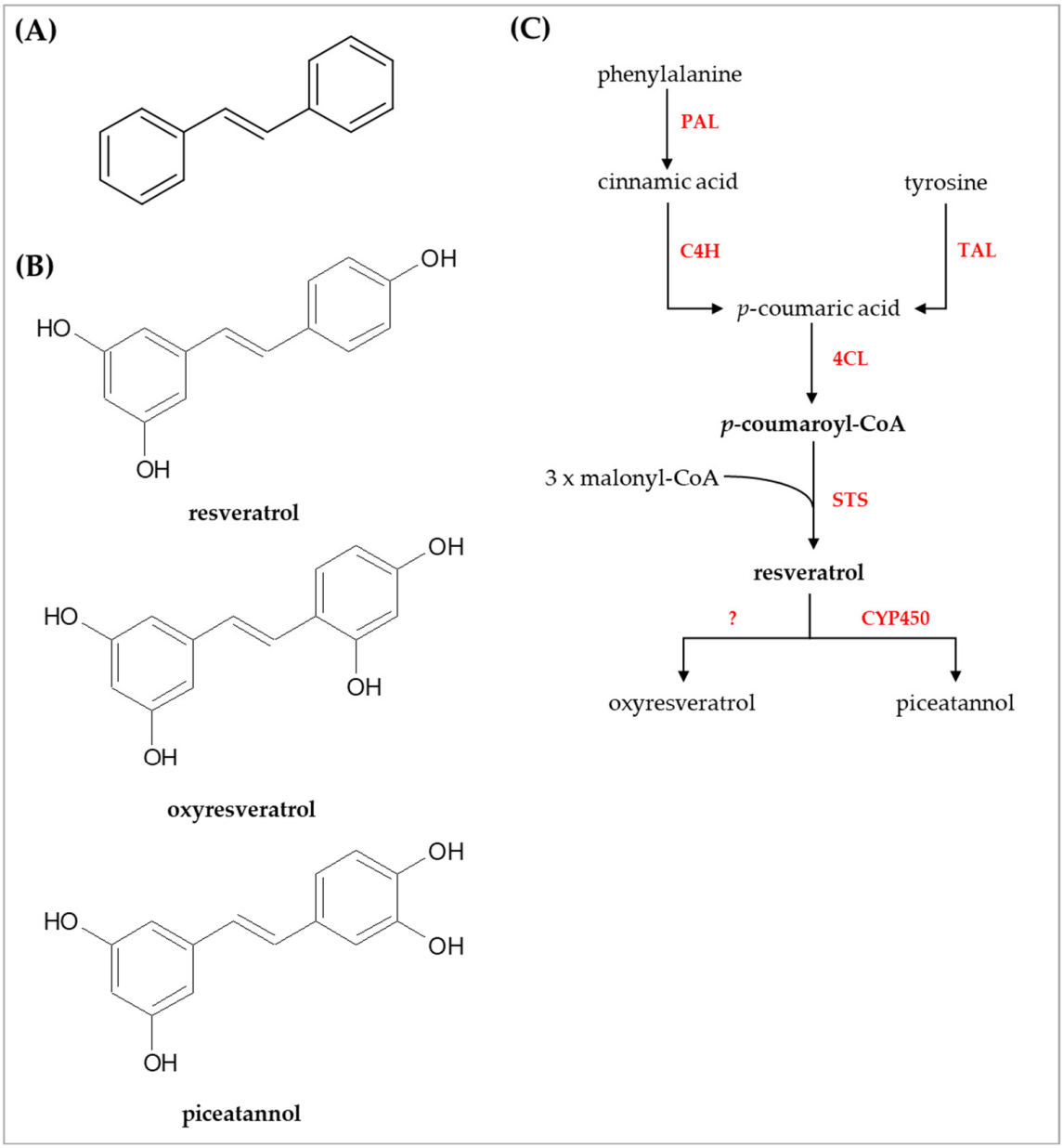

Figure 1. Chemical structures and biosynthesis of stilbenoids. (**A**) core structure of stilbenoids (**B**) chemical structures of resveratrol, oxyresveratrol, and piceatannol (**C**) overview of the biosynthetic pathway of stilbenoids. Abbreviations used: PAL, phenylalanine ammonia lyase; TAL, tyrosine ammonia lyase; C4H, cinnamate-4-hydroxylase; 4CL, 4-coumarate-CoA ligase; STS, stilbene synthase or resveratrol synthase; CYP450, cytochrome P450.

2.2. Plant Sources

To discover current plant sources of resveratrol, oxyresveratrol, and piceatannol, a search was conducted in the well-known phytochemical database "KNApSAcK: A Comprehensive Species-Metabolite Relationship Database", by chemical names (http://www.knapsackfamily.com/KNApSAcK/ accessed on 5 July 2022 [24]). The list of plant species is presented in Table 1.

Table 1. List of plant sources containing resveratrol, oxyresveratrol, and piceatannol retrieved from the KNApSAcK database.

Chemical Names	Family	Plant Species
Resveratrol	Acoraceae	*Acorus calamu* L.
	Agavaceae	*Yucca periculosa* Baker
	Cyperaceae	*Scirpus fluviatilis* (Torr.) A.Gray (synonym of *Bolboschoenus fluviatilis* (Torr.) Soják) *Scirpus maritimus* L.(synonym of *Bolboschoenus maritimus* (L.) Palla)
	Dipterocarpaceae	*Hopea utilis* (Bedd.) Bole *Vatica rassak* Blume
	Ericaceae	*Vaccinium alaskaense* Howell *Vaccinium angustifolium* Aiton
	Fabaceae	*Amorpha nana* C.Fraser *Arachis hypogaea* L. *Bauhinia racemosa* Lam. *Caesalpinia decapetala* (Roth) Alston *Caragana tibetica* Kom. *Cassia dentata* Vogel (synonym of *Chamaecrista dentata* (Vogel) H.S.Irwin & Barneby) *Haplormosia monophyla* (Harms) Harms *Intsia bijuga* (Colebr.) Kuntze *Maackia amurensis* Rupr. *Pterolobium hexapetallum* (Roth) Santapau & Wagh (synonym of *Pterolobium hexapetalum* (Roth) Santapau & Wagh) *Trifolium campestre* Schreb. *Trifolium dubium* Sibth. *Vicia faba* L.
	Gnetaceae	*Gnetum gnemon* L. *Gnetum latifolium* Blume *Gnetum parvifolium* (Warb.) W.C.Cheng *Gnetum pendulum* C.Y.Cheng *Gnetum venosum* Spruce ex Benth.
	Hyacinthaceae	*Scilla nervosa* (Burch.) J.P.Jessop (synonym of *Schizocarphus nervosus* (Burch.) van der Merwe)
	Iridaceae	*Belamcanda chinensis* (L.) DC. (synonym of *Iris domestica* (L.) Goldblatt & Mabb.)
	Melanthiaceae	*Veratrum album* L. *Veratrum grandiflorum* (Maxim. ex Miq.) O.Loes. *Veratrum nigrum* var.ussuriense O.Loes. (Synonym of *Veratrum nigrum* L.)
	Moraceae	*Artocarpus chaplasha* Roxb.(synonym of *Artocarpus chama* Buch.-Ham.) *Artocarpus dadah* Miq. *Artocarpus lakoocha* Roxb. (synonym of *Artocarpus lacucha* Buch.-Ham.) *Broussonetia papyrifera* (L.) L'Hér. ex Vent. *Cudrania javanensis* Trécul (synonym of *Maclura cochinchinensis* (Lour.) Corner)
	Myrtaceae	*Corymbia haematoxylon* (Maiden) K.D.Hill & L.A.S.Johnson *Corymbia papuana* (F.Muell.) K.D.Hill & L.A.S.Johnson *Eucalyptus abergiana* F.Muell. (synonym of *Corymbia abergiana* (F.Muell.) K.D.Hill & L.A.S.Johnson) *Eucalyptus astringens* (Maiden) Maiden *Eucalyptus caesia* Benth. *Eucalyptus calophylla* R.Br. ex Lindl. (synonym of *Corymbia calophylla* (R.Br. ex Lindl.) K.D.Hill & L.A.S.Johnson) *Eucalyptus campaspe* S.Moore *Eucalyptus citriodora* Hook. (synonym of *Corymbia citriodora* (Hook.) K.D.Hill & L.A.S.Johnson) *Eucalyptus crebra* F.Muell. *Eucalyptus decorticans* (F.M.Bailey) Maiden *Eucalyptus dichromophloia* F.Muell. (synonym of *Corymbia dichromophloia* (F.Muell.) K.D.Hill & L.A.S.Johnson) *Eucalyptus eremophila* (Diels) Maiden *Eucalyptus erythrophloia* Blakely (synonym of *Corymbia erythrophloia* (Blakely) K.D.Hill & L.A.S.Johnson) *Eucalyptus ficifolia* F.Muell. (synonym of *Corymbia ficifolia* (F.Muell.) K.D.Hill & L.A.S.Johnson)

Table 1. *Cont.*

Chemical Names	Family	Plant Species
		Eucalyptus gardneri Maiden
		Eucalyptus griffithsii Maiden
		Eucalyptus grossa F.Muell. ex Benth.
		Eucalyptus gummifera (Gaertn.) Hochr.
		(synonym of *Corymbia gummifera* (Gaertn.) K.D.Hill & L.A.S.Johnson)
		Eucalyptus intermedia F.Muell. ex R.T.Baker
		(synonym of *Corymbia intermedia* (F.Muell. ex R.T.Baker) K.D.Hill & L.A.S.Johnson)
		Eucalyptus maculata Hook.
		(synonym of *Corymbia maculata* (Hook.) K.D.Hill & L.A.S.Johnson)
		Eucalyptus x *nowraensis* Maiden
		Eucalyptus nutans F.Muell.
		Eucalyptus platypus Hook.f.
		Eucalyptus polycarpa F.Muell.
		(synonym of *Corymbia polycarpa* (F.Muell.) K.D.Hill & L.A.S.Johnson)
		Eucalyptus pruinose Turcz.
		(synonym of *Eucalyptus pyriformis* Turcz.)
		Eucalyptus sargentii Maiden
		Eucalyptus sideroxylon A.Cunn. ex Woolls
		Eucalyptus stricklandii Maiden
		Eucalyptus trachyphloia F.Muell.
		(synonym of *Corymbia trachyphloia* (F.Muell.) K.D.Hill & L.A.S.Johnson)
		Eucalyptus wandoo Blakely
		Eucalyptus woodwardia Maiden
	Palmae	*Phoenix dactylifera* L.
	Pinaceae	*Picea abies* (L.) H.Karst.
		Picea bicolor (Maxim.) Mayr
		(synonym of *Picea alcoquiana* (H.J.Veitch ex Lindl.) Carrière)
		Picea excelsa Wender.
		(synonym of *Abies alba* Mill.)
		Picea glehnii (F.Schmidt) Mast.
		Picea jezoensis (Siebold & Zucc.) Carrière
		Picea koraiensis Nakai
		Picea koyamae Shiras.
		Picea obovate Ledeb.
		Picea torano (Siebold ex K.Koch) Koehne
		Pinus sibirica (Ledeb.) Turcz.
		(synonym of *Abies sibirica* Ledeb.)
	Poaceae	*Festuca argentina* (Speg.) Parodi
		Festuca arundinacea Lilj
		(synonym of *Scolochloa festucacea* (Willd.) Link)
		Festuca versuta Beal
		Hordeum bogdanii Wilensky
		Hordeum brachyantherum Nevski
		Poa alsodes A.Gray
		Stipa robusta (Vasey) Scribn.
		Pleuropterus ciliinervis Nakai
		(synonym of *Reynoutria ciliinervis* (Nakai) Moldenke)
		Polygonum cuspidatum Siebold & Zucc.
		(synonym of *Reynoutria japonica* Houtt.)
		Polygonum multiflorum Thunb.
		(synonym of *Reynoutria multiflora* (Thunb.) Moldenke)
		Rheum rhaponticum L.
	Rosaceae	*Rubus idaeus* Vell.
		Rubus occidentalis L.
		Spiraea formosana Hayata
	Smilacaceae	*Smilax aspera* subsp. *mauritanica* (Poir.) Arcang.
		(synonym of *Smilax aspera* L.)
		Smilax bracteate C.Presl
		Smilax menispermoidea A.DC.

Table 1. *Cont.*

Chemical Names	Family	Plant Species
Oxyresveratrol	Vitaceae	*Ampelopsis brevipedunculata* (Maxim.) Trautv.
		Ampelopsis japonica (Thunb.) Makino
		Cissus Antarctica Vent.
		Cissus quadrangularis L.
		Parthenocissus quinquefolia (L.) Planch.
		Parthenocissus tricuspidata (Siebold & Zucc.) Planch.
		Rhoicissus rhomboidea (E. Mey. ex Harv.) Planch.
		Vitis coignetiae Pulliat ex Planch.
		Vitis riparia Michx.
		(synonym of *Vitis vulpina* L.)
		Vitis rupestris Scheele
		Vitis vinifera L.
	Fabaceae	*Erythrina variegata* L.
		Schoenocaulon officinale (Schltdl. & Cham.) A.Gray
	Melanthiaceae	*Veratrum album* L.
		Veratrum grandiflorum (Maxim. ex Miq.) O.Loes.
	Moraceae	*Artocarpus chaplasha* Roxb.(synonym of *Artocarpus chama* Buch.-Ham.)
		Artocarpus dadah Miq.
		Artocarpus gomezianus Wall. ex Trécul
		Artocarpus lakoocha Roxb.
		(synonym of *Artocarpus lacucha* Buch.-Ham.)
		Artocarpus reticulatus Miq.
		Chlorophora excelsa (Welw.) Benth.
		(synonym of *Milicia excelsa* (Welw.) C.C.Berg)
		Chlorophora regia A.Chev.
		(synonym of *Milicia regia* (A.Chev.) C.C.Berg)
		Cudrania javanensis Trécul
		(synonym of *Maclura cochinchinensis* (Lour.) Corner)
		Maclura pomifera (Raf.) C.K.Schneid.
		Morus alba L.
		Morus bombycis Koidz.
		(synonym of *Morus australis* Poir.)
		Morus indica L.
		Morus laevigata Wall. ex Brandis
		(synonym of Morus macroura Miq.)
		Morus rubra L.
		Morus serrata Roxb.
	Cyperaceae	*Scirpus fluviatilis* (Torr.) A.Gray
		(synonym of *Bolboschoenus fluviatilis* (Torr.) Soják)
		Scirpus maritimus L.
		(synonym of *Bolboschoenus maritimus* (L.) Palla)
	Fabaceae	*Caragana tibetica* Kom.
		Cassia dentata Vogel
		(synonym of *Chamaecrista dentata* (Vogel) H.S.Irwin & Barneby)
		Cassia garrettiana Craib
		(synonym of *Senna garrettiana* (Craib) H.S.Irwin & Barneby)
		Cassia marginata Roxb.
		(synonym of *Cassia roxburghii* DC.)
		Centrolobium robustum (Vell.) Benth.
		Intsia bijuga (Colebr.) Kuntze
		Laburnum alpinum (Mill.) Bercht. & J.Presl
		Laburnum anagyroides Medik.
Piceatannol		*Maackia amurensis* Rupr.
		Pericopsis angolensis (Baker) Meeuwen
		Pericopsis elata (Harms) Meeuwen
		Schotia brachypetala Sond.
		Vouacapoua americana Aubl.
		Vouacapoua macropetala Sandwith

Table 1. *Cont.*

Chemical Names	Family	Plant Species
	Pinaceae	*Picea abies* (L.) H.Karst. *Picea engelmannii* Parry ex Engelm. *Picea excelsa* Wender. (synonym of *Abies alba* Mill.) *Picea glauca* (Moench) Voss *Picea glehnii* (F.Schmidt) Mast. *Picea jezoensis* (Siebold & Zucc.) Carrière *Picea mariana* (Mill.) Britton, Sterns & Poggenb. *Picea obovate* Ledeb. *Picea rubens* Sarg. *Picea sitchensis* (Bong.) Carrière
	Poaceae	*Saccharum officinarum* L.
	Polygonaceae	*Eskemukerjea megacarpum* (H.Hara) H.Hara (synonym of *Fagopyrum megacarpum* H.Hara) *Rheum rhaponticum* L.
	Vitaceae	*Cissus quadrangularis* L.

It is known that stilbenoids are found ubiquitously in several plant species; however, only some of them are mentioned and discussed in this review based on quantity in the plant extract, known plant species, and potential application as a raw material for stilbenoids production.

Resveratrol was first discovered in the root of *V. grandiflorum* O. Loes. (white hellebore) and then detected in more than seventy plant species [25,26]. Grapes, mulberries, and peanuts are well-recognized as rich sources of resveratrol. Fruits of grapes (*V. vinifera* L.), especially a part of the skin and seeds contain 3.66×10^{-2} g/kg of resveratrol [27]. Numerous parts of mulberries (*M. alba* L.), i.e., root, fruit, aerial part, and leaves, are comprised of resveratrol in the range from 1.6×10^{-3} to 7.95×10^{-3} g/kg [27]. Resveratrol is found in peanut (*A. hypogaea* L.) stem and fruit from 1.1×10^{-2} to 1.5×10^{-2} g/kg. In addition, resveratrol is also detected in peanut skin and other nut species, such as whole almond seeds and pistachio kernel [20]. Apart from the KNApSAcK database, a list of plant sources containing resveratrol was also compiled by Tian and Liu in 2020 [27].

Oxyresveratrol is believed to be generated by hydroxylation at the C-2 position of resveratrol, although there is no reliable evidence to support this hypothesis [13]. Additionally, the enzyme involved in hydroxylation is still unknown (Figure 1). Mostly, oxyresveratrol is the major compound of plant species in the Moraceae family (Table 1). The dried aqueous extract (so-called "Puag-Haad") of heartwood extract of a well-known Thai medicinal plant named "Mahat" (*A. lacucha* Buch.-Ham.) is comprised of approximately 80% *w*/*w* oxyresveratrol [28–30]. Another source of oxyresveratrol is mulberries (*M. alba* L.). Oxyresveratrol is detected in the root, stem, and twig of mulberries [31–33]. In 2021, Likhitwitayawuid also well-summarized both gymnosperms and angiosperms which consist of oxyresveratrol [13].

Piceatannol is another hydroxylated derivative of resveratrol. It is formed by cytochrome P450 (CYP450) metabolism by adding a hydroxyl group to the C-3′ position [34]. Apart from the data in Table 1, piceatannol is also found in grapes, passion fruits, and blueberries. Both red and white grapes contain piceatannol but in different quantities [34]. Piceatannol is approximately nine times more accumulated in red than white grapes (red grapes: 374 ng/g; white grapes 43 ng/g) [34,35]. Passion fruit seeds are very rich in piceatannol, containing 4.8 mg/g [34,36]. The amount of piceatannol in blueberries is reported as 138–422 ng/g at dry concentration [34,37].

2.3. Bioactivities

As mentioned above, stilbenoids show various bioactivities that are beneficial to human health. In cosmeceuticals, five bioactivities, i.e., antioxidant, anti-aging—either as photoprotective or in terms of autophagy—MMP inhibitory, antityrosinase, and antibacte-

rial activities are mainly recognized to produce high-quality cosmetic products. Here, we summarized the bioactivities of resveratrol, oxyresveratrol, and piceatannol as follows.

Recently, stilbenoids have been promoted not only as a potential antioxidant, but also for skin aging protection. Skin aging is a complex physiological and pathological process, including a series of continuous changes, which leads to wrinkles, loss of elasticity, laxity, and rough-textured appearance [38]. It is caused by both intrinsic and extrinsic factors. Exposure to UV radiation is the primary factor of extrinsic skin aging by stimulating the generation and accumulation of reactive oxygen species (ROS), impairing the skin's antioxidant status, which causes damage to deoxyribonucleic acid (DNA), and proteins that lead to photocarcinogenesis and photoaging [39].

Resveratrol has been described as a potent antioxidant [40]. The capacity of antioxidant activity, including free radical scavenging and metal ion chelation, of resveratrol depends on the position and number of hydroxyl groups in the chemical structure [10]. Based on this activity, resveratrol is reported to protect cells from UV irradiation-induced cell death, and contains photoprotective effects [10,25]. Besides, resveratrol promotes the activity of antioxidant enzymes in the skin, i.e., glutathione S-transferase (GST), and superoxide dismutase (SOD). This activity leads to the reduction of superoxide ion production from UV-A and UV-B irradiation as well as lipid peroxidation activity [14]. Oxyresveratrol is also claimed as a potent antioxidant based on several reported models of antioxidant testing, such as DPPH (1,1-diphenyl-2-picrylhydrazyl radical), superoxide anion, hydroxyl radical, 2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) radical, etc. [13,41]. Combinations of resveratrol and oxyresveratrol result in the synergism of antioxidant activities [42]. Free radical scavenging of piceatannol has been described as it obviously reduces intracellular reactive oxygen species (ROS) levels in human keratinocytes (HaCat) cells irradiated by UV-B. Moreover, oxyresveratrol and piceatannol mostly contain antioxidant activity stronger than that of resveratrol due to an additional hydroxyl group [10,13,43,44]. However, resveratrol exhibits stronger inhibition of peroxy oxygen radical absorbance capacity (ORAC), lipopolysaccharide (LPS)-induced production of nitric oxide (NO) in murine BV-2 microglial cells, and cyclooxygenase 1 and 2 (COX-1, COX-2) than oxyresveratrol [13].

To date, the matrix metalloproteinase (MMP) inhibitory effect of stilbenoids is interesting to investigate for its known anti-aging effects. The MMPs are induced by extrinsic factors such as UV irradiation, inflammation, or toxins. Members of the MMP group show an important role in the degradation of corneocyte desmosomes (collagen and elastin) in the extracellular matrix of skin, such as MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, and MMP-13 [45]. This degradation results in the induction of wrinkle formation [46,47]. Among them, MMP-1 (collagenase) plays a major role in the specific degradation of collagen types I and III during the aging process of the human dermis, suggesting that inhibition of MMP-1 induction reduces UV-induced photoaging [48,49]. Meanwhile some MMPs are known to be involved in the degradation of elastin resulting in skin aging [50]. Resveratrol, oxyresveratrol, and its acetylated derivatives show markedly strong inhibition of UV-B-induced MMP-1 activity and expression in human dermal fibroblast cells, indicating that stilbenoids can prevent the degradation of collagens [51]. Moreover, it has been found that a reduction of UV-B-induced MMP-1 expression was inhibited via mitogen-activated protein kinases (MAPKs) and Akt/mammalian targeting of rapamycin (mTOR) signaling pathways. Chuang et al. demonstrated that autophagy is normally induced by the inhibition of the mTOR signaling pathway, which contributes to preventing the aging process [52]. There are fewer studies on anti-aging in terms of autophagy, although it has been found that resveratrol can enhance autophagy, which may be able to suppress oxidative stress and thus greatly to improve the aging process [53,54].

Resveratrol is able to inhibit melanogenesis causing skin-whitening effects or depigmentation via several mechanisms [14]. Melanogenesis is the process of melanin synthesis that utilizes *L*-tyrosine as a precursor [13]. Tyrosinase is the crucial enzyme for the conversion of *L*-tyrosine to *L*-DOPA (L-3,4-dihydroxyphenylalanine), dopaquinone, followed by cyclization, oxidation, and polymerization, until finally melanin is produced [13]. The

metabolite from the biotransformation of resveratrol by tyrosinase inhibits dopa oxidase activity and competes with tyrosine and *L*-DOPA as a substrate for melanogenesis [10,14,25]. In addition, resveratrol diminishes gene expression of melanogenesis-related proteins such as tyrosinase-related protein (TRYP) 1, TRYP2, and microphthalmia-associated transcription factor (MITF) in melanoma cells [10,14,25]. Oxyresveratrol shows potent tyrosinase inhibitory effects after testing with several methods, as concluded by Likhitwitayawuid [13]. Oxyresveratrol is a prominent compound for skin-whitening since its activity in this respect is obviously higher than that of resveratrol [13]. The anti-tyrosinase activity of piceatannol has also been studied, and its activity has been shown as stronger than that of resveratrol [43,55]. The mechanisms of action of piceatannol are the reduction of ROS and increasing the glutathione/oxidized glutathione ratio [55]. In addition, molecular targets of stilbenoids in skin cell lines are presented in Table 2.

Table 2. Studies of molecular targets of stilbenoids in skin cells.

Compounds	Biological Activities	Molecular Mechanism	Type of Cell Cultures	References
Resveratrol	antioxidative stress	↑ GST and SOD activities	HaCat	[56]
	MMP inhibition	↓phosphorylation of MAPKs and Akt/mTOR signaling pathways	HDF	[51]
	antioxidant	↑ SOD, and GSH-Px activities; ↓ lipid peroxidation	HaCat	[57]
	anti-tyrosinase	↓ melanin pigmentation	B16 F10 melanoma cells	[58]
Oxyresveratrol	suppression of UV-B-induced MMP-1	↓phosphorylation of MAPKs and Akt/mTOR signaling pathways	HDF	[51]
Piceatannol	antioxidant	↑ GSH activity; ↓ intracellular ROS level	HaCat	[59]

Abbreviation: ROS, Reactive Oxygen Species; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; GSH, Glutathione; GST, Glutathione S-transferase; Akt/mTOR, protein kinase B/mammalian target of rapamycin; MAPKs, mitogen-activated protein kinases; HaCat, human keratinocyte cell; HDF, human dermal fibroblast cells; B16 F10 melanoma cells, murine melanoma cell; ↑, increase; ↓: decrease.

Resveratrol has antimicrobial activity against numerous types of microorganisms [15,26]. One of the most concerning dermatological diseases is acne vulgaris. This disease is caused not only by sebum overproduction, hyperkeratosis of the hair follicles (epidermal hyperproliferation), but also the growth of *Cutibacterium acnes* (formerly *Propionibacterium acnes*) [25,60]. Resveratrol contains antibacterial activity against *C. acnes* and also decreases sebum production. The potency of resveratrol is comparable to conventional anti-*C. acnes* drug i.e., benzyl peroxide, as well as having none of its cytotoxicity [25,60]. In addition, resveratrol is reported to have a higher inhibitory effect on quorum-sensing of *Chromobacterium violaceum*, which is the motile gram-negative bacillus, than oxyresveratrol [61,62]. Piceatannol relieves *C. acnes*-induced HaCaT cell proliferation and migration via its antioxidant and anti-inflammatory activities [63]. Until now, there has been no study on the anti-*C. acnes* of oxyresveratrol. However, oxyresveratrol plays other roles in antibacterial activity, such as the inhibition of the periodontal pathogenic bacteria, *Staphylococcus aureus*, and *Bacillus subtilis* [13]. Oxyresveratrol has been associated with antifungal activity against human pathogenic fungi such as *Microsporum gypseum*, *Microsporum canis*, *Trichophyton mentagrophytes*, and its antistaphylococcal effects (inhibition of *S. aureus*) are more potent than those of resveratrol [13,64].

At present, resveratrol is extensively utilized as an ingredient in numerous cosmetic formulations, particularly moisturizing cream and serum. In Thailand, the heartwood extract of *A. lacucha* containing oxyresveratrol as the major active compound is used as an ingredient in moisturizing cream, serum, toner, and soap [29].

2.4. Safety

At present, there are few data on the safety of stilbenoids for use in humans. Resveratrol is non-toxic, safe, and well tolerated for oral and dermal administration since the 50% lethal dose (LD_{50}) is high (reported as 2 g/day), and irritation of the skin and eyes have not been recorded [25]. In a study with mice, resveratrol did not induce carcinogenesis,

and reproductive and developmental toxicity [25]. However, a high dose of resveratrol consumption may inhibit systemic P450 and can interact with numerous drugs [65]. Thus, additional studies of simultaneous medication with resveratrol must be investigated. Furthermore, adverse effects from the long-term application of resveratrol in both oral and dermal routes also have to be studied in order to limit usage or provide precautions to consumers. The safety information on oxyresveratrol for human use is still not reported, but has not been found to generate irritation, edema, or erythema when tested in a white guinea pig model [66]. Toxicological studies of piceatannol are very few and lacking in vivo studies. Based on current data, piceatannol does not cause any severe adverse effects; however, further in-depth studies to discover the safety of piceatannol are necessary [67].

3. Current Green Technologies for Stilbenoids Production

Green technologies are defined as the type of methods that are recognized as environment-friendly and sustainable in their procedures [68]. Stilbenoids are commonly produced by conventional extraction methods containing two major phases, i.e., solvent extraction, and separation by chromatographic methods [13]. There are several types of general extracting methods such as maceration, percolation, and soxhlet extraction. Based on the previous literature, the best solvent for stilbenoids extraction is alcohol (methanol or ethanol) in order to obtain optimum yields [16]. Nevertheless, the residual solvent after extraction may be harmful to our health, as mentioned, and the volatilized solvent may generate air pollution [69]. Thus, other methods are investigated for solving this problem. Here, we summarize recent green technologies for stilbenoids production, including green solvent extraction as well as plant cell cultures.

3.1. Green Solvent Extraction

The keyword "green" is defined as being non-toxic to the environment and less hazardous to human health. Natural deep eutectic solvents (NADES), the derivative of deep eutectic solvents (DES), are the efficient green methods for phytochemical extraction [69]. The DES solvent comprises at least two components that are grouped as hydrogen bond donors and acceptors [69]. The most common solvents for hydrogen bond acceptors are choline chloride and betaine [69]. On the other hand, NADES solvents are primary metabolites which are typically utilized by plants for development and survival, such as sugars, amino acids, and acids/bases [69]. There are numerous greater advantages of NADES compared to conventional methods, such as the components being easy to obtain, the low toxicity to the environment, being safely recyclable, safe products, greater selectivity, high quality of the extract, several choices of solvents, lower energy consumption, reduced solvents and waste, stability at high temperature, being nonflammable, highly soluble, and its time reduction and bioavailability [69–71]. Moreover, this method has been verified to obtain higher yields of active ingredients as well as bioactivities than using classical organic solvents, which also are appropriate for raw material preparation in the cosmetic industry [69,72]. Nevertheless, cost-effectiveness analysis and up-scalability of the extraction procedures should be further examined to confirm the effectiveness of production and safety in humans prior to real-world large-scale production in the industry [73,74]. At present, only a limited amount of stilbenoids extraction by NADES and DES has been reported, as presented in Table 3.

Table 3. Recent information of green solvent extraction for stilbenoids production.

Compound	Plant Species (Part)	Method Extract Condition (Temperature, Time, Soli-Liquid Ratio)	Solvent (Molar Ratio)	Yield (Mean)	References
Resveratrol	*P. cuspidatum*(root)	One-pot method based on DES 85 °C 80 min 1:50 g/mL	70% of tetrabutylammonium chloride: ethylene glycol (1:3) mixed with 30% of water	12.26 mg/g	[75]
	P. cuspidatum (root)	NADES with ultrasound-assisted extraction (UAE) 75 °C 80 min 1:50 g/mL ultrasonic power 250 W	70% of choline chloride: oxalic acid (1:1) mixed with 30% of water	12.31 mg/g	[76]
	A. hypogaea (skin)	NADES with UAE room temperature 15 min 1:20 g/mL	choline chloride: oxalic acid (1:1)	0.049 mg/g dry weight	[77]
	A. hypogaea (root)	DES with UAE 55 °C 40 min 1:30 g/mL	60% of choline chloride: 1,4-butanediol (1:1) mixed with 40% of water	38.91 mg/kg	[78]
	G. gnemon (seed)	NADES with UAE 10 min 1:10 g/mL	40% of betaine: lactic acid (1:1) mixed with 60% of water	0.227 mg/g	[79]
Oxyresveratrol	*M. alba* (callus)	NADES with UAE (40 kHz) 30 min 0.6:9 g/mL	70% of choline chloride: glycerol (1:2) mixed with 30% of water	0.13 mg/g dry weight	[80]
	M. alba (root)	NADES with UAE 15 min 1:20 g/mL	urea-glycerin (1:3)	2.42 mg/g dry powder	[81]

3.2. Plant Cell Cultures

Bioproduction of stilbenoids by plant cell cultures, including cell suspension, callus, and hairy root cultures, under controlled conditions are alternative methods for sustainable and large-scale production [82]. Several types of elicitors, such as methyl jasmonate (MeJA), cyclodextrin (CD), and UV irradiation, are supplemented for enhancing stilbenoids production [82,83]. Here, we summarized current data on plant cell cultures producing resveratrol, oxyresveratrol, and piceatannol as described in Table 4.

Table 4. List of plant cell cultures for stilbenoids production.

Compound	Plant Species	Types of Culture	Elicitors/Inducers	Quantity	References
Resveratrol	*A. hypogaea*	hairy root	-	<0.002 mg/g of extract (dry medium)	[84]
		hairy root	sodium acetate	0.05–0.098 mg/g of extract (dry medium)	[84]
		hairy root	-	0.8–1.5 mg/g dry weight of hairy root	[85]
		hairy root	MeJA, CD	16,716 nmol/g(dry medium)	[86]
		hairy root	sodium acetate	12 µg/mg of extract (dry medium)	[87]
		cell suspension	UV-C irradiation	3.14–6.93 µg/g of callus	[88]
		callus	UV-C irradiation	0.25–11.97 µg/g of callus	[88]
	A. lacucha	callus	-	0.66–0.79 mg/g of dry weight of callus	[89]
	Gossypium hirsutum L. (Coker 312)	cell suspension	-	2.44 ± 0.15 to 7.2 ± 0.19 µg/g of dry weight of cell suspension	[90]
	M. alba	root	-	41.6 ± 5.84 µg/g of dry weight of root	[32]
		root	MeJA, yeast extract	10.2 ± 0.53 µg/g of dry weight of root	[32]
		cell suspension	UV-C irradiation	0.044 ± 0.002 mg/g dry weight of cell suspension	[91]
		cell suspension	UV-C irradiation, 0.05 mM *L*-phenylalanine and/or 0.03 mM *L*-tyrosine	0.007 ± 0.003 to 0.025 ± 0.001 mg/g dry weight of cell suspension	[91]
		callus	2-hydroxypropyl-β-cyclodextrin	Non-immobilization: 3.95 ± 1.03 to 15.29 ± 0.53 mg/L of media Immobilization: 3.31 ± 0.16 to 5.81 ± 0.31 mg/L of media	[92]
	V. amurensis Rupr.	callus	-	0.004 ± 0.002 to 0.026 ± 0.010 %dry weight of callus	[93]
		callus	MeJA, salicylic acid, sodium orthovanadate, sodium nitroprusside, phenylalanine	0.017–0.15 %dry weight of callus	[93]
	Vitis labrusca L.	cell suspension	*L*-alanine	60 nmol/50 mL of media 20 nmol/g of fresh weight	[94]
	V. vinifera	cell suspension	MeJA	52 nmol/g of fresh weight	[95]
		cell suspension	sucrose	52 nmol/g of fresh weight	[95]
		cell suspension	MeJA, sucrose	120 nmol/g of fresh weight	[95]
		cell suspension	jasmonic acid	15 nmol/g of dry weight (intracellular) 15 nmol/g of dry weight (extracellular)	[96]
		cell suspension	MeJA	100 nmol/g of dry weight (intracellular) 37 nmol/g of dry weight (extracellular)	[96]
		cell suspension	0.1 nM sodium orthovanadate	115 nmol/g of dry weight (intracellular) 98 nmol/g of dry weight (extracellular)	[96]
		cell suspension	1 nM sodium orthovanadate	90 nmol/g of dry weight (intracellular) 80 nmol/g of dry weight (extracellular)	[96]
		cell suspension	MeJA	150 mg/L resveratrol (flasks) 209 mg/L resveratrol (bioreactor)	[97]
		cell suspension	MeJA, CD	1447.8 ± 60.4 µmol/g dry weight	[98]
		cell suspension	jasmonic acid, salicylic acid and HP2 MGL (adsorbent)	2666.7 mg/L	[99]
		cell suspension	MeJA, stevioside	12.2 mg/L	[100]
		cell suspension	MeJA, Methyl-*β*-cyclodextrin (Me*β*CD)	371.9 mg/L	[100]

Table 4. *Cont.*

Compound	Plant Species	Types of Culture	Elicitors/Inducers	Quantity	References
Oxyresveratrol	*M. alba*	root	-	136 ± 5.05 μg/g of dry weight of root	[32]
		root	MeJA, yeast extract incubation at 50 °C for 1 h	68.6 ± 3.53 μg/g of dry weight of root	[32]
		cell suspension		8.06 ± 0.14 μmol/g of dry weight	[101]
		callus	2-hydroxypropyl-β-cyclodextrin	Non-immobilization: 12.3 ± 2.71 to 190.41 ± 48.24 mg/L of media Immobilization: 2.9 ± 0.09 to 43.86 ± 6.25 mg/L of media	[92]
Oxyresveratrol (prenylated)	*A. lacucha*	callus	-	-	[102]
Piceatannol	*A. hypogaea*	hairy root	MeJA, CD	1909.92 nmol/g (dry medium)	[86]
		callus	UV irradiation	2.17 to 5.31 μg/g of callus	[88]

Based on the foregoing review, the plant species applied for plant cell cultures in order to produce stilbenoids are still limited. The addition of elicitors or inducers stimulates the synthesis of stilbenoids more than the normal culture. Resveratrol mostly accumulates in the medium of hairy root culture of *A. hypogaea*, callus of *A. lacucha*, and cell suspension culture of *G. hirsutum*. Root, cell suspension, and callus culture of *M. alba* are also potential sources for resveratrol production. However, numerous cultivars of grapevine (*V. vinifera*) have been claimed as the most well-known source of resveratrol in terms of plant cell cultures. Apart from the data in Table 3, Jeandet et al. have also presented information on several grapevine cell cultures for resveratrol production [103,104]. Cell cultures of *M. alba* are seen as potential sources for the synthesis of oxyresveratrol. In addition, only hairy root and callus cultures of *A. hypogaea* are reported for piceatannol production.

4. Future Research Challenges and Conclusions

Based on the several striking bioactivities of stilbenoids discussed above, resveratrol, oxyresveratrol, and piceatannol are presently utilized as pharmaceutical active ingredients in many cosmeceuticals. Hence, there is a demand for those compounds to be used as raw materials. Based on current data on plants containing stilbenoids in Table 1, it seems that several plant species have still not been investigated for stilbenoids composition and potential for large-scale production. Given the disadvantages of conventional extraction by using organic solvents, this method could not be employed in the cosmetic industry because of high costs, the need for highly skillful staff, environmental unfriendliness, and the contamination of undesired substances. Thus, NADES should be substituted for stilbenoids extraction in the cosmetic industry. The components and molar ratio of NADES should be studied to provide the highest yields of stilbenoids. Although there are several advantages of NADES extraction, the suitable viscosity of the solvent should be focused in order to receive the intended yield of stilbenoids. Plant cell cultures for stilbenoids production should also be explored, especially for oxyresveratrol and piceatannol, which are still not widely studied. Metabolic engineering of genes involved in stilbenoids biosynthesis into microorganisms, including bacteria and yeast, as well as plant cells, is very challenging. In addition, metabolic engineering can diversify and synthesize several stilbene derivatives which may provide better bioactivities than their parent compounds. Particularly, catalyzing enzymes as well as the responsible genes for oxyresveratrol synthesis is still unexplored and needs further study. However, the safety of stilbenoids from this process for humans and the environment should be extensively recognized.

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