

Plants and Natural Products for the Treatment of Skin Hyperpigmentation – A Review

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ABSTRACT

Skin hyperpigmentation is caused by several factors that up-regulate melanogenesis. Plants and natural products with skin-whitening effects are gaining interest among consumers and researchers because they are perceived to be milder, safer, and healthier than synthetic alternatives. This review extensively summarizes the status of plants and natural products currently used in skin-whitening cosmetics as well as potential candidates for future use, because the scope of natural choices for efficient treatment of skin hyperpigmentation is rapidly widening. Biological activities of plants and natural extracts are therefore available for cosmetic formulators and dermatologists interested in naturally derived ingredients for skin hyperpigmentation treatment and in accordance with the consumers' preferences and expectations upon natural cosmetic products.

Introduction

Skin hyperpigmentation is caused by several factors (i.e., UV radiation, radicals, inflammatory mediators, and hormones) as depicted in ► **Fig. 1**. Briefly, UV radiation causes skin hyperpigmentation by stimulating keratinocytes to secrete α -MSH, a small peptide hormone derived from proopiomelanocortin. Consequently, α -MSH binds to MC1R expressed on melanocyte surfaces and thereafter induces melanogenesis via multiple signaling pathways resulting from cAMP, PKA, CREB, and MITF activity. MITF is a key transcription factor regulating the transcription of melanogenic enzymes (i.e., TYR, TRP-1, and TRP-2). In addition, UV radiation modulates Nrf2 and further activates MAPKs. MAPKs consist of three subtypes: stress-activated protein kinases/JNK, p38, and ERKs. JNK and p38 kinases are stimulated by pro-inflammatory cytokines and environmentally induced stresses such as exposure to UV irradiation, heat, and hydrogen peroxide, resulting in DNA

damage. Melanogenesis is controlled by MAPKs, with MITF being activated by p38 phosphorylation. By contrast, ERK activation inhibits melanin synthesis by downregulating MITF expression [1].

Preliminary evaluation of skin-whitening agents is best achieved through *in vitro* assays including cell culture assessments. In this context, plant-based and naturally derived skin-whitening agents have been examined for their biological activities and safety. Scientific literature provided by the American Chemical Society, J-STAGE, Karger, ScienceDirect, Taylor and Francis, Thieme Medical, and Wiley-Blackwell publishers included those that are searchable using Google Scholar published from 1997 to 2017 and cosmetic suppliers' databases. The literatures were searched on active, activity, bio-based, cosmeceuticals, hyperpigmentation, herb, melanin, melanogenesis, melanoma, plant, natural product, skin-lightening, and skin-whitening. Only articles in the English language have been selected. Unclear botanical identification, inadequate or insufficient data in terms of

ABBREVIATIONS

ABTS	2,2'-azino-bis(3-ethylbenzothiazoline)-6-sulfonic acid
CREB	cAMP response element-binding protein
DPPH	1,1-diphenyl-2-picrylhydrazyl
EC ₅₀	half maximum effective concentration
ERKs	extracellular signal-regulated kinases
FRAP	ferric reducing ability of plasma
IC ₅₀	inhibitory concentration at 50%
IL-1 α	interleukin-1 α
JNK	c-Jun NH ₂ -terminal kinases
LD ₅₀	median lethal dose
MAPKs	mitogen-activated protein kinases
MC1R	melanocortin 1 receptor
MITF	microphthalmia-associated transcription factor
α -MSH	α -melanocyte-stimulating hormone Nrf2 nuclear factor E2-related factor 2
PDA	potato dextrose agar
PKA	protein kinase A
TNF- α	tumor necrosis factor- α
TRP	tyrosinase-related protein
TYR	tyrosinase
VEGFR-2	vascular endothelial growth factor receptor-2

examination assays with controls, and details on the preparation of natural products are excluded as described in ► Fig. 2. The above-mentioned criteria allowed selecting 77 eligible articles. The excluded literature does not satisfy the selection methodology. Natural products (plants, fungi, and marine organisms) that are potentially available for further *in vivo* assessments were therefore summarized based on their scientific names including their isolated pure compounds.

Active Ingredients for Skin Hyperpigmentation Treatment

Phenolics are the most widely used skin-whitening agents, and they are used as a single compound or in combination to achieve synergistic effects [2–4]. Of these, hydroquinone (1), vitamin C or ascorbic acid (2), arbutin (3), and kojic acid (4) as well as their derivatives are most commonly used. In addition, herbal extracts, for instance mulberry, artocarpus, and orchid extracts, are also widely known skin-whitening agents [5, 6].

Retinoids (or vitamin A) (5) stimulate cell turnover and promote rapid loss of melanin through epidermopoiesis. Tocotrienols are derivatives of vitamin E that are composed of four homologues: α -, β -, γ -, and δ -tocotrienols. Of these, δ -tocotrienol (6) was demonstrated to inhibit melanin production in B16 melanomas by downregulating TYR, TRP-1, and TRP-2 [7, 8]. At a maximum concentration of 20 μ M, δ -tocotrienol reduced melanin content and inhibited reactive oxygen species production by 20% and 15%, respectively. Moreover, its downregulating effects on TYR, MC1R, MITF, TRP-1, and TRP-2 expression were concentration-de-

pendent. Mechanistically, the enhancement of ERK phosphorylation levels occurs via MAPK signaling [9].

Other compounds downregulate melanogenesis via different mechanisms. For example, the phenolics caffeic acid (7), ferulic acid (8), quercetin (9), and rutin (10) modulate Nrf2 activity. UVA-induced melanogenesis in B16F10 cells is suppressed by TYR inhibition; in particular, quercetin (9), rutin (10), caffeic acid (7), and ferulic acid (8) reduce melanin content and inhibit TYR at IC₃₀ values of 7.8 ± 1.4 and 10.1 ± 3.1 μ M, respectively, 15.31 ± 4.7 and 18.56 ± 4.2 μ M, respectively, 17.54 ± 4.8 and 24.1 ± 6.2 μ M, respectively, and > 30 and > 30 μ M, respectively. Furthermore, caffeic acid (7) and quercetin (9) markedly suppress 8-hydroxy-2'-deoxyguanosine formation following UV irradiation, resulting in decreased DNA damage and glutathione depletion. Additionally, exposure to caffeic acid and quercetin prior to UVA irradiation induces cellular defenses against oxidative stress [10].

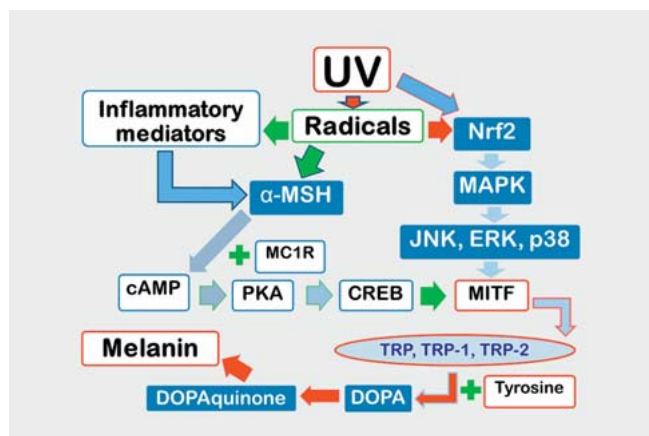
Caffeic acid phenethyl ester (11) occurs naturally in plants and propolis, and it is bioactivated by TYR, generating derivatives that are cytotoxic to melanoma cells. In B16F10 melanoma cells, it potentially suppresses tumor growth and neovascularization by preventing VEGFR-2 activation [11]. Caffeic acid phenethyl ester also effectively slows α -MSH-stimulated melanin synthesis by suppressing TYR, TRP-1, TRP-2, and MITF expression [12].

Genkwanin (12) was observed to significantly decrease melanin production in B16F10 melanoma cells in a concentration-dependent manner. Conversely, treatment with apigenin-7-glucoside (13) and naringenin (14) significantly stimulated intracellular melanin production (42.12 and 43.03 μ g/ 10^6 cells, respectively) compared with the control (23.93 μ g/ 10^6 cells) [13].

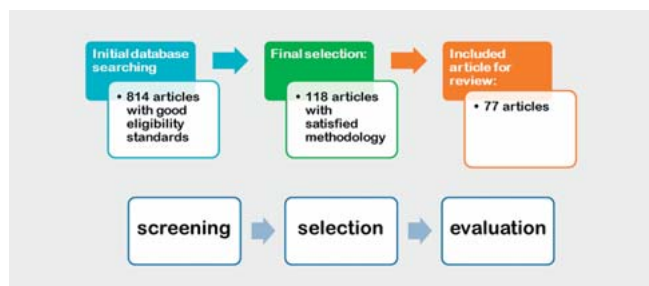
Hinokitiol (15) was found to be more potent in inhibitory activity against mushroom TYR than hydroquinone (1), resorcinol (16), hydroxyhydroquinone (17), kojic acid (4), ascorbic acid (2), and arbutin (3), which exhibit IC₅₀ values of 8.22×10^{-6} , 5.15×10^{-5} , 1.45×10^{-5} , 2.37×10^{-4} , 2.85×10^{-4} , 6.40×10^{-4} , and 7.48×10^{-3} M, respectively [14]. It was noncytotoxic toward Mel-Ab cells at a concentration of 10 μ M. Furthermore, treatment with 0.1 μ M hinokitiol significantly reduced cellular melanin content, with the effect increasing in a concentration-dependent manner. MITF is also effectively suppressed by hinokitiol [15].

Rhododendrol (18), or 4-(4-hydroxyphenyl)-2-butanol, inhibits TYR activity in cultured human melanocytes in a concentration-dependent manner (IC₅₀ = 5.3 μ M). This result was in accordance with radiolabeling experiments in B16 melanoma cells, which revealed that TYR utilizes rhododendrol as a substrate in place of L-tyrosine. Furthermore, the presence of rhododendrol resulted in no detectable reactive oxygen species in the melanocytes [16].

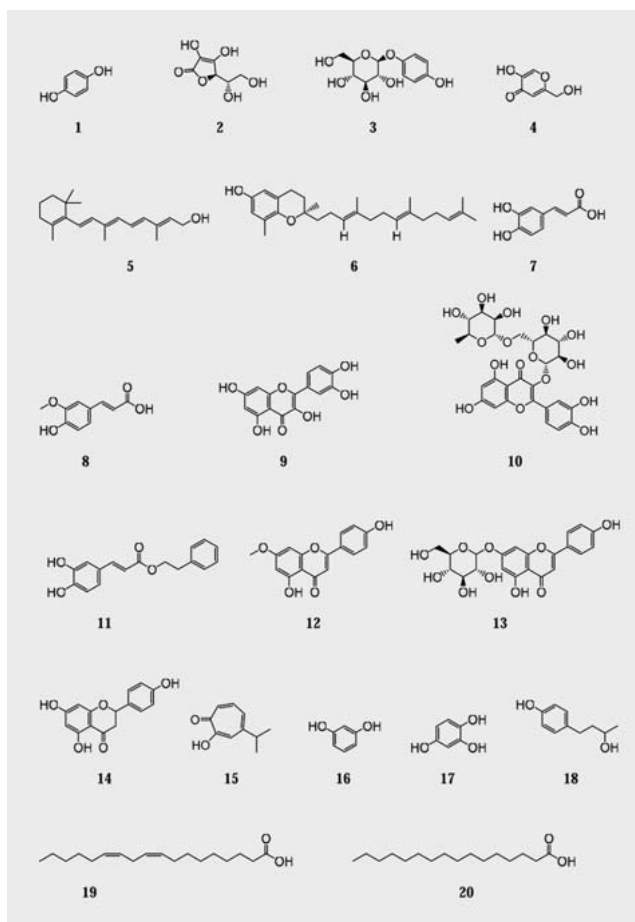
Linoleic acid (19) and palmitic acid (20) have divergent effects on melanogenesis in B16F10 melanoma cells relative to the control. Linoleic acid (19) decreases cellular melanin levels (30%), whereas palmitic acid (20) enhances melanogenesis (150%) in a time-dependent manner. These activities are regulated by TYR activity. Specifically, linoleic acid (19) suppresses its enzymatic activity by 50%, whereas palmitic acid (20) promotes its overexpression to 190%. However, neither acid affected the activity of TRP-1 and TRP-2, suggesting that they affect melanogenic enzymatic activity in a posttranscriptional manner. Further examination of the cellular mechanism revealed that the presence of linoleic acid



► Fig. 1 Mechanism of melanogenesis [1].



► Fig. 2 Criteria used to select the articles for the data presented in this review.



► Fig. 3 Chemical structures of the active ingredients for skin hyperpigmentation treatment.

(19) decreases TYR levels to 30% of the initial level, whereas palmitic acid (20) markedly increased its content (130% of the initial level). Radiolabeling assays indicated that linoleic acid (19) dramatically accelerates the proteolytic degradation of TYR compared with palmitic acid [17]. Linoleic acid (19) effectively modulates the proteasomal degradation of TYR via the selective degradation of a melanogenic enzyme through the ubiquitin-proteasome pathway [18].

A summary of the aforementioned compounds (► Fig. 3), their activities, and other characteristics and properties is provided in ► Table 1.

Plants for Treating Skin Hyperpigmentation

Treating aesthetically displeasing skin disorders using naturally derived agents including herbal extracts is gaining interest among consumers due to their perceived safety [2–4]. In this context, currently used herbs and those with potential skin-whitening effects are discussed.

Ten traditional Chinese herbs known to combat skin darkening were screened to identify their active components. Each herb was subjected to sequential soxhlet extraction using a range of solvents (i.e., hexane, CH₂Cl₂, MeOH) featuring an increasing polar-

ity gradient. Extraction was also conducted in parallel with boiling water. Following concentrating and drying, the extracts were tested in Melan-a cells, and hexane and dichloromethane extracts of *Angelica sinensis* (Oliv.) Diels Apiaceae exhibited the highest potency (IC₅₀ = 5.1 and 2.9 μg/mL, respectively), in addition to being noncytotoxic. Other *A. sinensis* constituents, namely 4-ethylresorcinol (21), 4-ethylphenol (22), and 1-tetradecanol (23), were also active in the same assay, with IC₅₀ values of 9.6, 3.6, and 19.37 μM, respectively [19].

Maceration of *Arnica montana* L. (Asteraceae) flowers in 80% EtOH followed by partitioning with EtOAc and chromatography afforded pure active 3β,16β-dihydroxy-21 α-hydroperoxy-20 (30)-taraxastene (24). This compound is a potent melanogenesis inhibitor in B16 melanoma cells with an IC₅₀ of 0.02 μg/mL (0.04 μM), compared with 0.25 μg/mL (2.01 μM) for the positive control 4-methoxyphenol (25). Its inhibitory function is related to TRP-1 and MITF suppression [20].

Tarragon (*Artemisia dracunculus* L., Asteraceae), a commonly used flavoring herb, has been highlighted as a source of melanin biosynthesis inhibitors. Two isolated compounds, undeca-2E,4E-dien,8,10-dynoic acid isobutylamide (26) and undeca-2E,4E-dien,8,10-dynoic acid piperidylamide (27), were found to be noncytotoxic toward B16 melanoma cells (IC₅₀ = 34.5 and 36.5 μg/mL,

► **Table 1** Biological activities of active ingredients for skin hyperpigmentation treatment.

Name	Study		Reference
	Enzyme inhibition	Cell culture	
Vitamin E (6)		TYR, TRP-1, and TRP-2 downrelations in B16F10 MC1R, MITF downregulation ERK phosphorylation enhancement	[7, 8]
Kojic acid (4)	mushroom TYR	TYR inhibitor	[9]
Caffeic acid (7)		TYR inhibition, DNA damage and glutathione depletion in B16F10	[10]
Caffeic acid phenyl ester (11)		VEGFR-2, α -MSH, TYR, TRP-1, TRP-2, and MITF suppression in B16F10	[11, 12]
Ferulic acid (8)		TYR inhibition, DNA damage and glutathione depletion in B16F10	[10]
Quercetin (9)		TYR inhibition, DNA damage and glutathione depletion in B16F10	[10]
Rutin (10)		TYR inhibition, DNA damage and glutathione depletion in B16F10	[10]
Genkwanin (12)		antimelanogenesis in B16F10	[13]
Hinokitol (15)	mushroom TYR	cellular melanin production and MITF suppression in Mel-Ab	[14, 15]

respectively) and to more potently suppress cellular melanin production (EC_{50} = 1.8 and 2.3 μ g/mL, respectively) than arbutin (EC_{50} = 24.0 μ g/mL). Their safety as skin-lightening agents was also confirmed, possessing safety coefficients (EC_{50}/IC_{50}) of 19.2 and 12.9, respectively [21].

Material from several Thai medicinal plants was macerated in EtOH, affording 77 crude extracts that were comparatively assessed for their inhibitory effects on mushroom TYR compared with standards kojic acid and *Artocarpus lakoocha* Roxb. (Moraceae) (20 μ g/mL). *A. lakoocha* extract was the most potent inhibitor followed by kojic acid (90.14% \pm 1.46% and 89.57% \pm 2.15%, respectively), with root, root bark, and wood extracts of *Artocarpus integer* (Thunb.) Merr. (Moraceae) (90.57% \pm 2.93%, 82.60% \pm 0.76%, and 80.02% \pm 3.22%, respectively), wood extract of *Cudrania javanensis* Trec. (Moraceae) (77.86% \pm 2.41%), and juice of *Averrhoa bilimbi* L. (Oxalidaceae) (61.23% \pm 1.55%) also exerting potent inhibitory effects. *A. integer* root extract was further chromatographed, affording pure artocarpin (28), cudraflavone C (29), and artocarpanone (30), among which artocarpanone (30) was the most potent inhibitor, albeit with less potency than kojic acid (4) (IC_{50} = 44.56 and 31.43 μ g/mL, respectively) [22]. In addition, *Artocarpus xanthocarpus* Merr. (Moraceae) root extracts provided artoxanthocarpane A (31) and chlorophorin (32), which proved to be more potent mushroom TYR inhibitors (IC_{50} = 59.3 \pm 3.7 and 2.5 \pm 0.4, respectively) than arbutin (3) and kojic acid (4) (IC_{50} = 81.8 \pm 2.3 and 63.7 \pm 4.5 μ M, respectively). Assessments using B16F10 melanoma cells highlighted their safety (cell viability = 110.1% \pm 3.7% and 95.2% \pm 3.4%) and abilities to suppress melanin production to 63.2% \pm 9.4% and 64.6% \pm 8.9% of the initial levels (at 40 μ M), respectively. These results corresponded to more potent cellular TYR activities (78.7% \pm 12.3% and 72.2% \pm 7.5%, respectively) than those observed for 300 μ M arbutin (3) and kojic acid (4) (76.4% \pm 6.3% and 85.8% \pm 6.8%, respectively; 73.8% \pm 5.4% and 81.1% \pm 13.7%, respectively) [23]. The skin-whitening effects of *A. integer* and *Artocarpus heterophyllus* Lam. (Moraceae) extracts were further confirmed with sapwood and heart wood extracts, which inhibited TYR activity (IC_{50} = 7 and 125 μ g/mL, respectively). Later isolation studies indi-

cated that their activity results from the presence of artocarpanone (30), as indicated by the mushroom TYR and melanin production activities in B16 melanoma cells (IC_{50} = 80.8 and 89.1 μ M, respectively) compared with those of arbutin- and kojic acid-treated cells (104 mM and 111 μ M, respectively; 15.5 and > 3521 μ M, respectively) [24].

Extraction of *Betula pendula* Roth (Betulaceae) leaves via homogenization in 80% EtOH afforded an extract containing substantial amounts of polymeric proanthocyanidins and phenolics. The crude extract inhibited mushroom TYR, albeit less potently than kojic acid (4) (IC_{50} = 119.08 \pm 2.04 and 2.24 \pm 0.18 μ g/mL, respectively) [25].

Methanol extract of sappanwood (*Caesalpinia sappan* L., Fabaceae) proved mildly effective in inhibiting melanin synthesis in B16F1 melanoma cells (84.5% \pm 13.5% at 10 μ g/mL). The crude extract was further partitioned with hexane, EtOAc and BuOH, giving different fractions that were subjected to the melanogenesis assay at the same concentration as the crude extract. The EtOAc fraction proved most potent, followed by the BuOH and hexane fractions (79.4% \pm 9.0%, 78.3% \pm 20.1%, and 0.3% \pm 1.2%, respectively). The EtOAc fraction was chromatographed, giving pure brazilin (33), 4-O-methylsappanol (34), brazilin (35), sappanchalcone (36), and 3'-deoxy-4-O-methylsappanol (37), all of which were more active (IC_{50} = 3.0 \pm 0.5, 4.6 \pm 0.7, 18.6 \pm 0.5, 42.6 \pm 1.8, and 50.4 \pm 2.0 μ M, respectively) than kojic acid (4) (IC_{50} = 70.6 \pm 3.0 μ M). Additionally, the compounds had more favorable cytotoxicity profiles (IC_{50} = 18.4 \pm 0.8, 20.2 \pm 0.8, 33.8 \pm 1.1, 83.1 \pm 4.0, and 72.0 \pm 2.4 μ M, respectively) than kojic acid (4) (IC_{50} = 99.7 \pm 2.1 μ M) [26].

Callicarpa longissima (Hemsl.) Merr., Verbenaceae leaf was extracted, affording a carnosol (38)-rich extract. This extract significantly suppressed melanin production in B16F10 melanoma cells, and its activity was associated with the downregulation of MITF gene transcription, diminishing TYR levels [27].

Safflower (*Carthamus tinctorius* L., Asteraceae) is the herbal source of the pigment carthamus yellow, which can suppress mushroom TYR in a concentration-dependent manner (IC_{50} = 1.01 \pm 0.03 mg/mL), although it is less potent than vitamin C (2)

($IC_{50} = 0.12 \pm 0.03$ mg/mL). Kinetic analysis of the herbal extract revealed it to be a competitive TYR inhibitor, similar to arbutin (3), azelaic acid (39), deoxyarbutin (40), hydroquinone (1), and kojic acid (4). The phenolic compounds safflomin A (41) and safflomin B (42) are responsible for the activity of the herbal extract, both of which are noncytotoxic toward B16F10 melanoma cells at concentrations of 1–4 mg/mL. At the highest concentration of 4 mg/mL, melanin production was decreased to $82.3\% \pm 0.4\%$ of the initial level, whereas the effects of the extract were less pronounced in cells treated with 0.1 mg/mL vitamin C (2) or arbutin (3) ($87.9\% \pm 1.6\%$ and $56.8\% \pm 1.7\%$, respectively) [28]. *N*-feruloylserotonin (43), *N*-(*p*-coumaroyl) serotonin (44), and acacetin (45) extracted from safflower seeds inhibited mushroom TYR with IC_{50} values of 0.023, 0.074, and 0.779 mM, respectively, compared with 0.223 mM for arbutin (3). Their effects on melanin production and cytotoxicity in B16 melanoma cells were further examined, with the reduction in melanin content in accordance with the *in vitro* results. *N*-feruloylserotonin (43), *N*-(*p*-coumaroyl) serotonin (44), and acacetin (45) suppressed melanin production ($IC_{50} = 0.191$, 0.245 and > 20 mM, respectively) with IC_{50} values of > 20 , > 20 , and 0.423 mM, respectively [29].

The inner skin of chestnut (*Castanea crenata* Siebold & Zucc., Fagaceae) kernels boiled in aqueous MeOH solvent and then further partitioned with EtOAc afforded an extract for skin-whitening assessments. The EtOAc fraction inhibited mushroom TYR ($IC_{50} = 160$ μ g/mL), and it was noncytotoxic toward B16F10 melanoma cells over the concentration range of 15–125 μ g/mL. The extract suppressed melanin production to 61.7%, 43.7%, and 25.5% of the initial levels at concentrations of 10, 50, and 100 μ g/mL, respectively [30].

The phenolic-rich ($17.4\% \pm 0.67\%$) extract of *Chenopodium quinoa* Willd., Chenopodiaceae or quinoa inhibited mushroom TYR activity at concentrations of 0.5 and 1.0 mg/mL (56.7% and 77.0%, respectively; $p < 0.001$ and $p < 0.0001$, respectively), although it was less potent than kojic acid (4) (45.7% at 0.01 mg/mL) [31].

Cocoloba uvifera L. (Polygonaceae) or Jamaican Kino or sea grape extract is an effective inhibitor of mushroom TYR, albeit to a lesser extent than kojic acid (4) ($IC_{50} = 90.4$ and 20.2 μ g/mL, respectively). This extract also had anti-inflammatory properties, suppressing IL-1 α and TNF- α in UVB-stimulated melanocytes in a similar manner as kojic acid. Furthermore, it slowed the release of α -MSH in melanocytes [32].

Colocasia antiquorum var. *esculenta* L. (Araceae), commonly known as Imperial Taro, is a source of biologically active fatty acids, sterols, and flavonoids. Its dried tuber bark was sonicated with MeOH, partitioned with EtOAc, and chromatographed to isolate the active constituents in five fractions. Biologically active fractions were further purified to afford refined *cis*-grossamide K (46) and (–)-pinoresinol (47), exhibiting IC_{50} values of 54.24 and 163.60 μ M, respectively, and LD_{50} values of 556.26 and > 500 μ M, respectively, as examined in Melan-a cells [33].

The aerial material of *Crataegus azarolus* L. (Rosaceae) macerated in MeOH for 10 d followed by further partitioning gave an EtOAc fraction containing ursolic acid (48), hyperoside (49), and virtexin-2"-*O*-rhamnoside (50) as major constituents. This fraction proved cytotoxic to B16F10 melanoma cells ($IC_{50} = 50$ μ g/

mL), and its application resulted in significant decreases in cellular melanin production at 50 μ g/mL ($p < 0.01$) [34].

Extraction of saffron (*Crocus sativus* L., Iridaceae) petals with MeOH, followed by partitioning and chromatography, afforded several pure compounds exhibiting mushroom TYR inhibitory activity. Crocusatin-K (51) displayed similar potency as kojic acid (4) ($IC_{50} = 260$ and 250 μ M, respectively), whereas crocusatin-L (52) and 4-hydroxy-3,5,5-trimethylcyclohex-2-enone (53) were less potent ($IC_{50} = 1.0$ and 1.1 mM, respectively) [35].

Cudrania tricuspidata (Carrière) Bur. ex Lavallée (Moraceae) extract containing oxyresveratrol (54) and *trans*-dihydromorin (55) exhibited inhibitory effects against cellular melanin production in Melan-a cells. The safety margin of *trans*-dihydromorin was wider (10–100 μ M) than that of oxyresveratrol (54) (10–20 μ M). Its anti-melanogenic effects resulted from MITF, TRP-1, and TRP-2 suppression, with oxyresveratrol (54) being less potent than *trans*-dihydromorin (55) [36].

The rhizome of nut grass, or purple nutsedge (*Cyperus rotundus* L., Cyperaceae), has been used in Oriental medicine due to its broad spectrum of activity against inflammation and cellular oxidation and proliferation. Extraction of the material afforded pure valencene (56), camphene (57), caryophyllene oxide (58), α -cyperone (59), and nootkatone (60), with valencene (56) proving the strongest inhibitor of photoaging-related ion channels, as examined in HEK293T cells. Investigation of its antimelanogenic effects in UV-induced B16F10 cells confirmed that the mechanism of action involved ion channels and not the suppression of TYR activity [37].

Euterpe oleracea Mart. (Arecaceae), commonly called açai palm, oil contains oleic (61), palmitic (20), linoleic (19), palmitoleic (62), stearic (63), and linolenic (64) acids (60.7%, 22.8%, 9.6%, 4.2%, 1.9%, and 0.3%, respectively), and it has been revealed to inhibit mushroom TYR ($IC_{50} = 66.08$ μ g/mL), albeit less effectively than kojic acid (4) ($IC_{50} = 5.86$ μ g/mL) [38].

Soxhlet extraction of *Garcinia livingstonei* T. Anderson (Clusiaceae) stem bark gave a crude extract that was further purified by chromatography. One isolated compound, morelloflavone-7"-sulphate (65), was assayed in MeWo melanoma cells and identified as the most promising active compound in the bark fraction concerning cytotoxicity and suppression of melanin production ($IC_{50} = 41.8 \pm 2.5$ μ M and $EC_{50} = 8.6 \pm 1.3$ μ M) [39].

The aerial foliage of ground ivy (*Glechoma hederacea* L., Lamiaceae) was centrifuged in water, giving a clear supernatant that was subsequently lyophilized to afford a dry extract. The extract inhibited melanin production in B16F10 melanoma cells without inducing cytotoxicity at concentrations of 0.1–1 mg/mL, with TYR inhibition occurring through MITF protein expression opposed to TRP-1 and TRP-2 [40].

Methanol extraction of *Juniperus chinensis* L. (Cupressaceae) yielded an extract exhibiting antioxidative scavenging (DPPH, $IC_{50} = 9.45 \pm 0.07$ μ g/mL) and anti-TYR activities ($IC_{50} = 55.18 \pm 0.55$ μ g/mL). α -MSH inhibition ($IC_{50} = 13.67$ μ g/mL) in B16F10 melanoma cells was also evident, with further examination of the extract resulting in the isolation of two antimelanogenic compounds, namely cedrol (66) and widdrol (67). In pure form (10 μ g/mL), each agent more significantly ($p < 0.05$) inhibited cel-

lular TYR activity and protein expression than arbutin (3) (100 µg/mL) [41].

Extraction of the rhizome material of *Kaempferia pandurata* Roxb., Zingiberaceae, a traditional Thai herb, using EtOH followed by partitioning with EtOAc afforded a crude mother liquor that yielded panduratin A (68) on chromatography. Panduratin A (68) more potently inhibited melanin production in Melan-a cells than kojic acid (4) or arbutin (3) (IC_{50} = 9.6, 152 and 990 µM, respectively) in conjunction with anti-TYR effects (IC_{50} = 8.2, 126 and 660 µM, respectively). This noncytotoxic agent (IC_{50} = 31.6 µM) effectively suppressed TYR, TRP-1, and TRP-2 expression [42].

Litchi (*Litchi chinensis* Sonn., Sapindaceae) pericarp macerated in 70% EtOH and partitioned gave rise to an EtOAc fraction, exhibiting significantly greater antioxidant activity than ascorbic acid ($p < 0.01$), as assessed by ABTS (IC_{50} = 7.137 ± 0.021 µg/mL), DPPH (IC_{50} = 2.288 ± 0.063 µg/mL), $O_2^{\cdot-}$ scavenging (IC_{50} = 29.57 ± 0.30 µg/mL), and FRAP ($EC_{1\text{ mM FeSO}_4}$ = $8,013.183 \pm 58.804$ µg/mL) assays. The extract exerted an *in vitro* TYR-suppressing effect (IC_{50} = 197.860 ± 1.230 µg/mL). Litchi extract, being more potent than kojic acid (4), suppressed melanin production in B16F10 melanoma cells by inhibiting TYR and TRP-2. Quercetin (9), rosmarinic acid (69), and gallic acid (70) were the main active phenolics in the extract [43, 44].

Mulberry (*Morus alba* L., Moraceae) is widely used to treat skin hyperpigmentation due to its high phenolic content, particularly the active compound oxyresveratrol (54). Mulberrosides are other active compounds isolated from mulberry, with mulberroside F (71) exhibiting more potent activity against mushroom TYR than kojic acid (4) (IC_{50} = 0.29 at 1.30 µg/mL), although its activity against mammalian TYR is weaker (IC_{50} = 68.3 at 58.5 µg/mL) [45]. Accordingly, mulberry extract is widely used in topical products for treating skin hyperpigmentation. Extracts of the closely related black or wild mulberry (*Morus nigra* L., Moraceae) leaf also inhibit mushroom TYR. The compounds responsible for the activity are isoquercitrin (72), rutin (10), and chlorogenic acid (73). The extract proved noncytotoxic toward B16F10 melanoma cells and human keratinocytes at 7.81 µg/mL, its IC_{50} against mushroom TYR [46].

Nutmeg (*Myristica fragrans* Houtt., Myristicaceae) oil has long been used as a traditional medicine with well-known therapeutic effects. Partitioning of its ethanolic extract with EtOAc and chromatography afforded the melanogenesis inhibitor macelignan (74), which inhibits melanin production and exerts anti-TYR effects in Melan-a cells with IC_{50} values of 13 and 30 µM, respectively. This noncytotoxic compound functions by downregulating TYR, TRP-1, and TRP-2 (10–50 µM), with TRP-2 being the most responsive to the compound [47]. In addition, another nutmeg-derived active safrole (75) inhibits the monophenolase and diphenolase activities of mushroom TYR (IC_{50} = 32.11 and 27.32 µM, respectively) [48].

Naringi crenulata (Roxb.) D.H. Nicolson (Rutaceae), synonyms *Hesperethusa crenulata* M. Roem. (Rutaceae) or *Limonia crenulata* Roxb. (Rutaceae), is commonly called Kra-jae in Thai or Thanaka in Burmese. This herb has been continuously documented as a traditional cosmetic for its skin-whitening effects. Its extract inhibits mushroom TYR (IC_{50} = 0.546 mg/mL) [49] due to its active components arbutin (3) and kojic acid (4) [50, 51].

Rambutan (*Nephelium lappaceum* L., Sapindaceae) peel extract exhibited antioxidant activities as assessed by ABTS, DPPH, and $O_2^{\cdot-}$ scavenging assays and inhibitory effects on mushroom TYR with IC_{50} values of 2.92 ± 0.02 , 1.86 ± 0.06 , 39.49 ± 0.52 , and 430.84 ± 0.57 µg/mL, respectively. This noncytotoxic herbal extract suppressed melanin production in B16F10 melanoma cells was by inhibiting TYR and TRP-2. Ferulic acid (8) was reported to be the most prevalent phenolic in the extract followed by gallic acid (70), rosmarinic acid (69), caffeic acid (7), kojic acid (4), quercetin (9), and chlorogenic acid (73) [44, 52].

The panicle or flower of Jamine rice (*Oryza sativa* cv. *indica*, Oryzaceae) has been shown to have a high content of *p*-coumaric (76), ferulic (8), and caffeic (7) acids. The extract did not show any cytotoxicity. It suppressed melanogenesis through TYR and TRP-2 inhibitions in B16F10 melanoma cells at a concentration of 0.1 mg/mL. To determine the safety profile and antioxidant activity of the extract in human skin fibroblast cells, the extract was tested in a concentration range that was similar to the concentrations used in B16F10 cells (0.0001–0.1 mg/mL). The cellular antioxidant activity was dose-dependent due to its protecting effect from oxidative stress [53].

The skin depigmentation effects of *Paeonia lactiflora* Pall. (Paeoniaceae) root extract were assessed in comparison with its pure active compound paeoniflorin (77). HPLC analysis of *P. lactiflora* extract indicated the presence of 53.25% paeoniflorin (77). Reconstructed human pigmented epidermis was topically treated with *P. lactiflora* extracts (300 and 500 µg/mL), paeoniflorin (77) (120 and 200 µg/mL), and the positive control 4-*n*-butylresorcinol (50 and 83 µg/mL). The cellular melanin content was significantly lower following treatment with the extract (28 and 30%) or paeoniflorin (77) (30 and 10%) than that obtained with the control (7% and 26%), as indicated by the melanin density determined via multiphoton microscopic analysis. *P. lactiflora* extract, paeoniflorin (77) (120 and 200 µg/mL), and 4-*n*-butylresorcinol reduced melanin content by 23% and 39%, respectively, 23% and 27%, respectively, and 24% and 40%, respectively [54].

Extraction of passion fruit (*Passiflora edulis* Sims, Passifloraceae) seeds using 80% EtOH afforded an extract rich in phenolics (total phenolic content = 33%) that significantly ($p < 0.01$) inhibited melanogenesis in MNT-1 human melanoma cells at a concentration of 20 µg/mL. LC/MS studies identified the major active constituent (4.8 mg/g) as piceatannol (78), with resveratrol (79) being a minor constituent (0.22 mg/g) [55]. Fractionation of the methanolic extract into the EtOAc fraction revealed that chlorogenic acid (73), rosmarinic acid (69), and quercetin (9) were the major phenolic constituents. The fraction with potent antioxidant activities ($IC_{50\text{ DPPH}}$ = 2.7 ± 0.2 µg/mL, $IC_{50\text{ ABTS}}$ = 9.0 ± 0.0 µg/mL, and $EC_{1\text{ mM FeSO}_4}$ = 2813.9 ± 11.6) also inhibited TYR activity ($39.9\% \pm 0.0\%$ at 1 mg/mL), and it was safe in Vero cells. The passion fruit seed extract was similarly protective against sun exposure as benzophenone-3, octylmethoxycinnamate and ferulic acid [56]. The extract was thereafter formulated into stable protective products (i.e., liquid foundation and concealer mousse covering UVA and UVB ranges) [57].

Phylla nodiflora (L.) Greene, Verbenaceae (frog fruit) is a common ingredient of herbal tea found in Taiwan. Dried aerial components of this herb macerated in MeOH followed by partitioning

and chromatography afforded pure eupafolin (**80**), a flavonoid that is noncytotoxic towards B16F10 melanoma cells (20–80 μM , 70–90% cell viability). At 5–10 μM , cell viability exceeded 90%; in this range, eupafolin (**80**) significantly ($p < 0.05$) decreased cellular melanin production as well as TYR and MITF activities. TRP-1 was also significantly suppressed at 10 μM , with TRP-2 and p-CREB protein expression being significantly reduced at 0.1, 1 and 10 μM . Furthermore, at 10 μM , this herbal active regulates MAPK signaling to inhibit melanogenesis [58].

The ethanolic extract of *Pinus tabulaeformis* Carr. (Pinaceae), commonly called Pini Nodi Lignum, exhibited similar inhibitory effects on mushroom TYR ($51.7\% \pm 9.1\%$ at 10 $\mu\text{g}/\text{mL}$) as arbutin (**3**) ($43.4\% \pm 7.3\%$ at 1 mM). The extract at 10 $\mu\text{g}/\text{mL}$ suppressed melanin production by 52% ($p < 0.05$) in HM3KO melanoma cells compared with untreated cells. The molecular mechanism was found to involve the suppression of TYR and TRP-1 [59].

An extract of *Punica granatum* L. (Punicaceae) or pomegranate peel enriched with 20% punicalgin (**81**) significantly suppressed cellular melanin content by 40% and 60% at 50 and 100 $\mu\text{g}/\text{mL}$, respectively, with no cytotoxic effects observed in Melan-a cells. Its antimelanogenic activity results from the potent suppression of TRP-1, TYR, and MC1R expression [60].

Acid hydrolysis of the aqueous ethanolic extract of *Rhodiola rosea* L. (Crassulaceae) root yielded several active principles, namely salidroside (**82**) and tyrosol (**83**), at levels of 0.28 ± 0.03 and 14.25 ± 0.27 mg/g, respectively. These agents inhibited TYR ($77.1\% \pm 0.5\%$ at 4 mg/mL) more efficiently than arbutin (**3**) ($63.1\% \pm 3.2\%$ at 2 mM). B16F0 cell viability was maintained ($73.4\% \pm 0.8\%$) following treatment with the most concentrated hydrolysate (70 $\mu\text{g}/\text{mL}$). Hydrolysate (50 $\mu\text{g}/\text{mL}$) suppressed melanin production similarly as arbutin (**3**). In addition, isolated tyrosol (**83**) significantly ($p < 0.001$) inhibited melanin synthesis at 0.4 and 4 mM, with the inhibitory effect arising from activity against MITF and TRP-2 [61].

Material from *Rhus verniciflua* Stokes (Anacardiaceae), synonym *Toxicodendron vernicifluum* (Stokes) F.A. Barkley (Anacardiaceae), also known as the Chinese lacquer tree, produced a crude extract (1 mg/mL) on sonication with 80% EtOH that completely inhibited TYR ($100\% \pm 10.95\%$). Cytotoxicity testing in B16F1 melanoma cells indicated that the extract was safe at ≤ 100 $\mu\text{g}/\text{mL}$. Cellular melanin levels following treatment with 10, 50, and 100 $\mu\text{g}/\text{mL}$ extract were $175.08\% \pm 7.42\%$, $79.96\% \pm 3.51\%$, and $46.30\% \pm 8.81\%$, respectively, of the control level, with the inhibitory action due to TYR and MITF suppression [62].

Chia (*Salvia hispanica* L., Lamiaceae) seed extract containing 0.5% linoleic acid (**19**) and 1.2% linolenic acid (**64**) inhibited melanin production to 55% and 65% of the initial levels in Melan-a cells at 100 and 400 $\mu\text{g}/\text{mL}$, respectively, with no effects on cell viability. This inhibitory effect was regulated by the suppression of TRP-1 and TYR, with MC1R expression being less affected at extract concentrations of 25 and 50 $\mu\text{g}/\text{mL}$ [60].

Sage (*Salvia officinalis* L., Lamiaceae), similar as oregano, is a common source of therapeutic essential oil. Extraction with MeOH followed by partitioning and chromatography enabled isolation of 7a-methoxyrosmanol (**84**) and isorosmanol (**85**), which proved noncytotoxic toward B16 melanoma cells and suppressed melanin production ($93.5\% \pm 13.6\%$ and $65.3\% \pm 9.5\%$ at 20 $\mu\text{g}/$

mL, and $105.3\% \pm 3.0\%$ and $50.4\% \pm 4.5\%$ at 10 $\mu\text{g}/\text{mL}$, respectively) [63].

Maceration of *Saururus chinensis* (Lour.) Baill. (Saururaceae) foliage in MeOH yielded a crude extract exerting no cytotoxic effects in B16F10 cells (1–500 mg/mL). The inhibitory effect of the extract (100–500 ng/mL) against cellular melanin production was comparable to that of arbutin (200 μM), and significant inhibition of cellular TYR (50–500 ng/mL) was observed. The mechanism of these effects was related to MITF and TYR downregulation via ERK activation [64].

Sesamol (**86**) isolated from sesame (*Sesamun indicum* L., Pedaliaceae) oil exhibits antioxidant and anti-TYR activities. The DPPH-scavenging activity of sesamol (**86**) ($\text{IC}_{50} = 5.44$ $\mu\text{g}/\text{mL}$) was comparable to that of butylated hydroxyl toluene ($\text{IC}_{50} = 5.81$ $\mu\text{g}/\text{mL}$). Sesamol (**86**) is a powerful inhibitor of mushroom TYR, acting against the monophenolase activity of the enzyme ($K_i = 1.4$ μM , $\text{IC}_{50} = 3.2$ μM) through complex formation. This activity proved more potent than that of kojic acid (**4**) ($\text{IC}_{50} = 59.72$ μM), and it was consistent with its inhibitory effects against melanin production in B16F10 melanoma cells (63% at 100 $\mu\text{g}/\text{mL}$) [65]. The compound was also more potent than kojic acid (**4**) in SK-MEL2 cells ($23.55\% \pm 8.25\%$ at 217 μM and $33.88\% \pm 1.43\%$ at 4222 μM) and arbutin (**3**) ($8.26\% \pm 8.78\%$ at 3673 μM) [66].

The inner bark of *Tabebuia avellanedae* Lorentz ex Griseb. (Bignoniaceae), synonym *Handroanthus impetiginosus* (Mart. ex DC.) (Mattos), or pink lapacho, contains β -lapachone (**87**), which proved noncytotoxic toward Melan-a cells (concentration range, 0.2–0.8 μM) and displayed significant reducing effects on melanin content at 0.8 μM . Cellular TYR activity was depressed by 60% at this concentration, and this effect was regulated by MITF inhibition. Moreover, reductions in the mRNA levels of TYR, TRP-1, and TRP-2 (but not MITF and mRNA) were detected, in addition to delayed phosphorylation of ERK in Melan-a cells. Examinations in a human skin model (MelanoDerm) indicated the highest efficacy at a concentration of 40 μM [67].

Sweet tamarind (*Tamarindus indica* L., Fabaceae) seed coat, with antioxidant activities according to ABTS, DPPH, and $\text{O}_2^{\cdot-}$ scavenging assays and mushroom TYR activity ($\text{IC}_{50} = 3.41 \pm 0.03$, 1.44 ± 0.01 , 27.44 ± 0.09 , and 96.15 ± 0.62 $\mu\text{g}/\text{mL}$, respectively), is a potential candidate herbal extract for skin hyperpigmentation treatment. In addition, the extract inhibited melanogenesis via inhibitory effects on TYR and TRP-2, as examined in B16F10 melanoma cells, due to its active compounds (–)epicatechin (**88**), epigallocatechin (**89**), chlorogenic acid (**73**), quercetin (**9**), gallic acid (**70**), rosmarinic acid (**69**), caffeic acid (**7**), and ferulic acid (**8**) [44, 68].

Cocoa (*Theobroma cacao* L., Sterculiaceae) powder was extracted with 80% EtOH, giving a crude extract that was assayed for mushroom TYR inhibition, affording an IC_{50} of 357.95 $\mu\text{g}/\text{mL}$, which was superior to those of kojic acid (**4**) and arbutin (**3**) ($\text{IC}_{50} = 572.28$ and 670.82 $\mu\text{g}/\text{mL}$, respectively). This activity is related to the presence of phenolics and fatty acids, as characterized by LC/MS/MS [69].

The traditional Asian herbal cocktail Ssanghwa-tang, which contains the medicinal herbs *P. lactiflora* (28%), *Angelica gigas* Nakai (Apiaceae) (11.2%), *Astragalus membranaceus* (Fisch.) Bunge (Fabaceae) (11.2%), *Cnidium officinale* Makino (Apiaceae)

► **Table 2** Biological activities of plants for skin hyperpigmentation treatment.

Name	Active		Study	Cell culture	Reference
	Scientific	Common			
<i>A. sinensis</i>	dong quai or female ginseng	4-ethylresorcinol (21), 4-ethylphenol (22), 1-tetradecanol (23)		Melan-a	[19]
<i>A. montana</i>	mountain tobacco or Leopard's bane	3β,16β-dihydroxy-21α-hydroperoxy-20(30)-taraxastene (24)		antimelanogenesis in B16 by TRP-1 and MITF suppressions	[20]
<i>A. dracuncul</i>	tarragon	undeca-2E,4E-dien, 8,10-cynoic acid isobutylamide (26), undeca-2E,4E-dien-8,10-dynoic acid piperidylamide (27)		antimelanogenesis in B16	[21]
<i>Artocarpus</i> spp.	Lakoocha, cempedak	artocarpin (28), cudraflavone C (29), artocarpinone (30), artocanthocarphone A (31), clorophorin (32)	mushroom TYR	antimelanogenesis in B16F10 by anti-TYR	[22–24]
<i>B. pendula</i>	silver birch or warty birch	proanthocyanins, phenolics	mushroom TYR		
<i>C. sappan</i>	sappanwood	brazilin (33), 4-O-methylsappanol (34), brazilin (35), sappanchalcone (36), 3'-deoxy-4-O-methylsappanol (37)		B16F1	[26]
<i>C. longissima</i>	beautyberry	carosol (38)		antimelanogenesis in B16F10 by MITF and TYR suppression	[27]
<i>C. tinctorius</i>	safflower	safflomin A and B (42,43), N-feruloylserotonin (44), N-(p-coumaroyl) serotonin, acacetin (45)	mushroom TYR	antimelanogenesis in B16F10 and B16	[28,29]
<i>C. crenata</i>	chestnut		mushroom TYR	antimelanogenesis in B16F10	[30]
<i>C. quinoa</i>	quinoa	phenolics	mushroom TYR		[31]
<i>C. uvifera</i>	Jamaican Kino or sea grape		mushroom TYR	anti-inflammatory and anti-α-MSH in melanocytes	[32]
<i>C. antiquorum</i> var <i>esculenta</i>	Imperial Taro	cis-grossamide K (46), (-)-pinoresinol (47)		antimelanogenesis in Melan-a	[33]
<i>C. azarolus</i>	azarole, azerole, or Mediterranean medlar	ursolic acid (48), hyperoside (49), virtexin-2''-O-rhamnoside (50)		antimelanogenesis in B16F10	[34]
<i>C. sativus</i>	saffron	crocusatin-K (51), crocusatin-L (52), 4-hydroxy-3,5,5-trimethylcyclohex-2-enone (53)	mushroom TYR		[35]
<i>C. tricuspidata</i>	silkworm thorn or storehouse-bush	oxyresveratrol (54) and trans-dihydromorin (55)		antimelanogenesis in Melan-a by MITF, TRP-1, and TRP-2 suppression	[36]
<i>C. rotundus</i>	nut grass or purple nutsedge	valencene (56), camphene (57), carryophyllene oxide (58), α-cyperone (59), nootkatone (60)		antimelanogenesis mechanism via the ion-channels in B16F10	[37]
<i>E. oleraceae</i>	açaí palm	oleic (61), palmitic (20), linoleic (19), palmitoleic (62), stearic (63) and linolenic acids (64)	mushroom TYR		[38]
<i>G. livingstonei</i>	African mangosteen or lowland mangosteen or Livingstone's garcinia	morelloflavone-7''-sulphate (65)		antimelanogenesis in MeWo	[39]
<i>G. hederacea</i>	ground ivy			antimelanogenesis in B16F10 by MITF suppression	[40]

continued

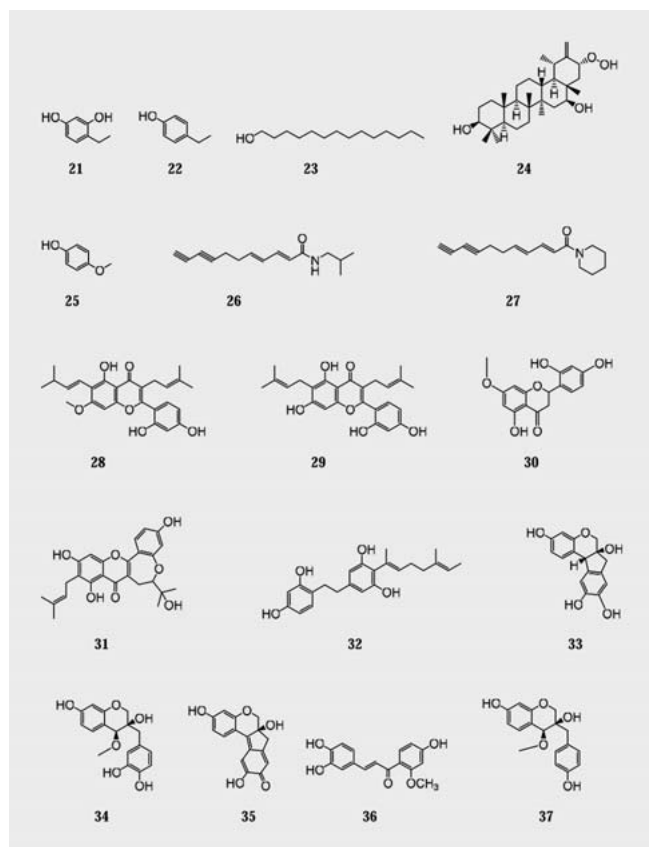
► **Table 2** Continued

Name Scientific	Common	Active	Study		Reference
			Enzyme inhibition	Cell culture	
<i>J. chinensis</i>		cedrol (66), widdrol (67)	mushroom TYR	α -MSH inhibition in B16F10 and TYR and TRP expressions	[41]
<i>K. pandurata</i>		panduratin A (68)		antimelanogenesis in Melan-a by TYR, TRP-1, and TRP-2 suppressions	[42]
<i>L. cinensis</i>	litchi	quercetin (9), rosmarinic acid (69), gallic acid (70)	mushroom TYR	antimelanogenesis in B16F10 melanoma by TYR and TRP-2 suppressions	[43, 44]
<i>M. alba</i>	mulberry	oxyresveratrol (54), mulberrosides (71)	mushroom and mammalian TYR		[45]
<i>M. nigra</i>	black mulberry	isoquercitrin (72), rutin (10), chlorogenic acid (73)	mushroom TYR	B16F10 melanoma and human keratinocyte	[46]
<i>M. fragrans</i>	nutmeg	macelignan (74), safrole (75)	mushroom TYR	antimelanogenesis in Melan-a by TYR, TRP-1, and TRP-2 suppression	[47, 48]
<i>N. crenulata</i>	Kra-jae or Thanaka	arbutin (3), kojic acid (4)	mushroom TYR		[49–51]
<i>N. lappaceum</i>	rambutan	ferulic (8), gallic (70), rosmarinic (69), caffeic (7), kojic (4) and chlorogenic (73) acids, quercetin (9)	mushroom TYR	antimelanogenesis in B16F10 melanoma by TYR and TRP-2 suppression	[44, 52]
<i>O. sativa</i> cv. <i>indica</i>	rice	<i>p</i> -coumaric (76), ferulic (8) and caffeic (7) acids	mushroom TYR	antimelanogenesis in B16F10 melanoma by TYR and TRP-2 suppression	[53]
<i>P. lactiflora</i>		paeoniflorin (77)		antimelanogenesis in reconstructed human pigmented epidermis	[54]
<i>P. edulis</i>	passion fruit	piceatannol (78), resveratrol (79), chlorogenic acid (73), rosmarinic acid (69), quercetin (9)	mushroom TYR	antimelanogenesis in MNT-1 human melanoma	[55, 56]
<i>P. nodiflora</i>	frog fruit	eupafolin (80)		antimelanogenesis in B16F10 by TYR, MITF, TRP-1, TRP-2, and CREB suppression	[58]
<i>P. tabulaeformis</i>	Chinese red pine		mushroom TYR	antimelanogenesis in HM3KO by TYR and TRP-1 suppression	[59]
<i>P. granatum</i>	pomegranate	punicalgin (81)		antimelanogenesis in Melan-a by TRP-1, TYR, and MCT1R suppression	[60]
<i>R. rosea</i>	golden root, roseroot	salidroside (82), tyrosol (83)		antimelanogenesis in B16F0 by TYR, MITF, and TRP-2 inhibitions	[61]

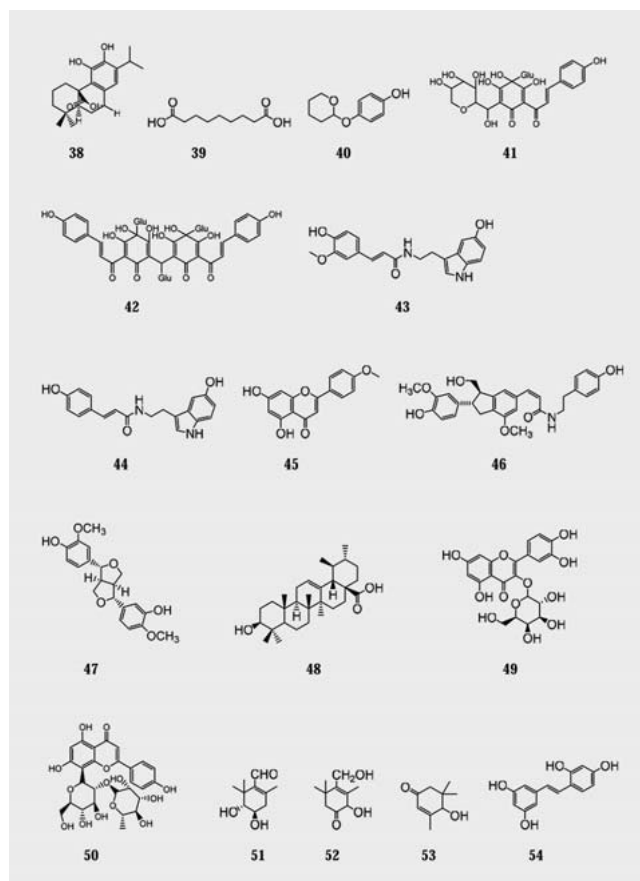
continued

► **Table 2** Continued

Name	Active		Study	Reference
	Common	Cell culture		
<i>R. verniciflua</i>	Chinese lacquer tree		Enzyme inhibition	antimelanogenesis in B16F1 by TYR and MITF inhibitions [62]
<i>S. hispanica</i>	chia	linoleic acid (19), linolenic acid (64)		antimelanogenesis in Melan-a by TYR, TRP-1, and MC1R inhibitions [60]
<i>S. officinalis</i>	sage	7 α -methoxyrosmanol (84), isorosmanol (85)		antimelanogenesis in B16 [63]
<i>S. chinensis</i>				antimelanogenesis in B16F10 by TYR and MITF inhibitions and ERK activation [64]
<i>S. indicum</i>	sesamin	sesamol (86)	mushroom TYR	antimelanogenesis in B16F10 and SK-MEL2 [65, 66]
<i>T. avellanedae</i>	pink lapacho	lapachone (87)		antimelanogenesis in Melan-a by TYR, TRP-1, TRP-2, and ERK and MelanoDerm [67]
<i>T. indica</i>	tamarind	epicatechin (88), epigallocatechin (89), clorogenic (73), gallic (70), rosmarinic (69), caffeic (7) and ferulic (8) acids, quercetin (9)	mushroom TYR	antimelanogenesis in B16F10 melanoma by TYR and TRP-2 suppression [44, 68]
<i>T. cacao</i>	cocoa	phenolics, fatty acids	mushroom TYR	antimelanogenesis in B16F10 by CREM, MITF, and TRP-1 suppressions [69]
<i>P. lactiflora</i> , <i>A. gigas</i> , <i>A. membranaceus</i> , <i>C. officinale</i> , <i>R. glutinosa</i> , <i>G. glabra</i> , <i>Z. officinale</i> , <i>C. cassia</i> , <i>Z. jujube</i>	Ssanghaiwa-tang	paeoniflorin (77), benzoic acid (90), nodakenin (91), liquiritin (92)		antimelanogenesis in B16F10 by CREM, MITF, and TRP-1 suppressions [70]



► **Fig. 4** Chemical structures of the active ingredients isolated from *A. sinensis*, *A. montana*, *A. dracunculus*, *Arthrocarpus* spp., and *C. sapan*.



► **Fig. 5** Chemical structures of the active ingredients isolated from *C. longissima*, *C. tinctorius*, *C. crenata*, *C. antiquorum* var. *esculenta*, *C. azarolus*, and *C. sativus*.

(11.2%), *Rehmannia glutinosa* (Gaertn.) Steud. (Orobanchaceae) (11.2%), *Glycyrrhiza glabra* L. (Fabaceae) (8.4%), *Zingiber officinale* Roscoe (Zingiberaceae) (4.4%), *Cinnamomum cassia* Presl (Lauraceae) (8.4%), and *Zizyphus jujube* Mill. (Rhamnaceae) (6.0%), was refluxed in water for 3 h and then lyophilized to give a dried extract. The extract proved noncytotoxic toward B16F10 melanoma cells over a wide concentration range (up to 2 mg/mL), and it suppressed cellular melanin production (to 70% and 45% of the initial level at 250 and 500 $\mu\text{g/mL}$, respectively). At these concentrations, TYR activity was decreased by 17% and 36%, respectively, with the mode of action involving CREB and MITF activities (including TRP-1). HPLC analysis revealed paeoniflorin (**77**) as the key active agent (1.136 μM), followed by benzoic acid (**90**), nodakenin (**91**), and liquiritin (**92**) (0.415, 0.130, and 0.122 μM , respectively) [70].

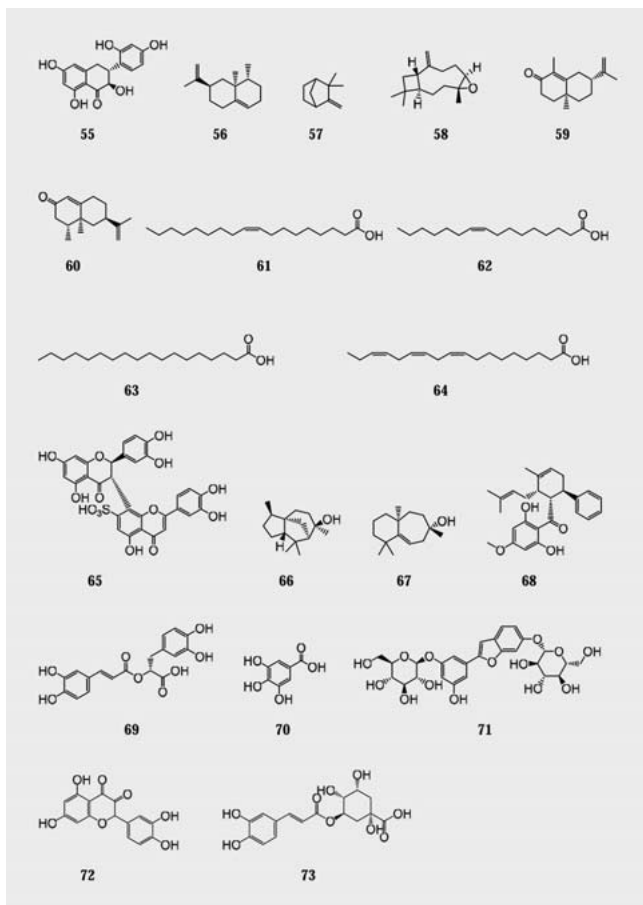
► **Table 2** summarizes the key properties and activities in relation to the botanical extracts and compounds described in this section. In addition, the isolated compounds are summarized as shown in ► **Figs. 4–8**.

Fungal Agents for Treating Skin Hyperpigmentation

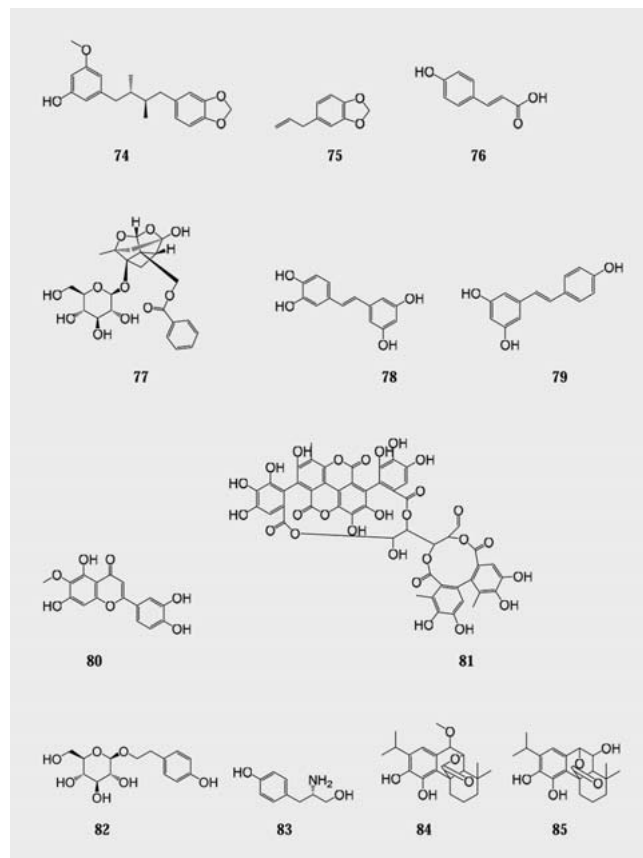
Fermentation of *Alternaria alternata* var. *monosporus* (Fr.) Keissl. (Pleosporaceae), a microorganism from the bark of the yew tree, provided alteronol (**93**). Alteronol (**93**) at concentrations $< 2 \mu\text{g/mL}$ is noncytotoxic toward B16F1 and B16F10 cells, although the compound suppressed cellular migration by 79.9%, 58.9%, and 42.9% (B16F1) and 63.3%, 45.5%, and 23.1% (B16F10) at concentrations of 0.5, 1, and 1.5 $\mu\text{g/mL}$, respectively [71].

Crude laccase isolated from *Lentinus polychrous* Lév. (Polyporaceae), having an enzymatic activity of 6.99 U/mg protein, was demonstrated to decolorize synthetic melanin on examination using PDA plates. High levels of melanin decolorization were observed at pH 4.5–6.5, with optimum bleaching (87%) occurring within 5 h at pH 6.5. Enzymatic activity was enhanced in the presence of the synthetic radical ABTS and was the highest at 35 °C (77.5%), with higher temperatures (60 °C) resulting in suppression [72].

Monascus spp. Tiegh. (Elaphomycetaceae) produces an orange pigment that was further derivatized via exposure to an amino acid and amine in separate experiments to afford glutamic acid (**94**)



► **Fig. 6** Chemical structures of the active ingredients isolated from *C. rotundus*, *E. oleraceae*, *G. livingstonei*, *G. hederacea*, *J. chinensis*, *K. pandurata*, *L. chinensis*, and *M. alba*.



► **Fig. 7** Chemical structures of the active ingredients isolated from *M. fragrans*, *O. sativa* cv. *indica*, *P. lactiflora*, *P. edulis*, *P. nodiflora*, *P. granatum*, *R. rosea*, and *S. officinalis*.

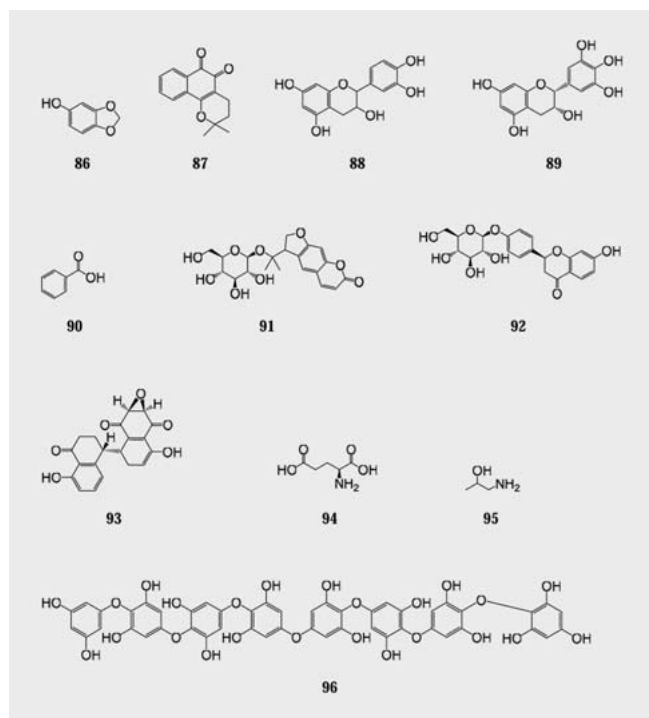
and 1-amino-2-propanol (95), respectively, as characterized by HPLC and LC/MS. These modified compounds were highly active in B16F10 melanoma cells, exhibiting anti-TYR activity and suppressing TRP-1 and TRP-2 expression over concentration ranges of 2.5–10 μM (glutamic acid, 94) and 1.25–5 μM (1-amino-2-propanol, 95) [72, 73]. The fungus *Monascus purpureus* Went (Elaphomycetaceae) in the form of red rice yeast (angkak), or red koji, is traditionally used in eastern Asia as a food colorant and medicine. The extract obtained from sonicating angkak powder in water was subjected to chromatography to separate active principles. The extract inhibited mushroom TYR, albeit less potently than kojic (4) and ascorbic (2) acids ($\text{IC}_{50} = 5.57, 5.00 \times 10^{-3}$ and 5.00×10^{-2} mg/mL, respectively) [74].

Fungi with extracts exhibiting potential as skin-whitening agents and their activities are summarized in ► **Table 3** as well as the isolated pure compounds as shown in ► **Fig. 8**.

Marine Algae for Skin Hyperpigmentation Treatment

The 80% methanolic extract of *Ishige foliacea* Okamura (Ishigeaceae) on partitioning with EtOAc and chromatography afforded pure octaphloretol A (96), which proved noncytotoxic toward B16F10 melanoma cells over a concentration range of 12.5–50 μM . TYR activity was significantly ($p < 0.05$) suppressed in concert with reduced melanin content. The active compound also suppressed MITF expression and reduced p38 phosphorylation, while significantly enhancing ERK and JNK phosphorylation [75].

Sargassum polycystum C. Agardh (Sargassaceae), an edible brown seaweed, was extracted with EtOH, and the extract was further fractionated with hexane and EtOAc. Mushroom TYR inhibitory assays of these fractions (100 $\mu\text{g}/\text{mL}$) indicated that the hexane fraction was the most potent, followed by the crude extract and EtOAc fraction (activity = $97.10\% \pm 0.55\%$, $97.78\% \pm 1.34\%$, and $100.58\% \pm 1.81\%$, respectively). All of these agents were less potent than kojic acid at the same concentration ($11.73\% \pm 1.51\%$). Cytotoxicity and cellular TYR activity studies using B16F10 melanoma cells illustrated that the hexane fraction



► **Fig. 8** Chemical structures of the active ingredients isolated from *S. indicum*, *T. avellanadae*, *T. indica*, the herbal cocktail Sanghwatang, *A. alternata* var. *monosporus*, *Monascus* spp., and *I. foliace*.

possesses superior effects regarding noncytotoxicity and enzyme suppression (96.38% ± 4.77% and 79.25% ± 2.99%, respectively) over the crude extract (86.99% ± 3.48% and 86.86% ± 2.35%, respectively) and EtOAc fraction (77.32% ± 0.98% and 89.08% ± 3.07%, respectively). Notably, the cell viability and enzymatic activity of kojic acid-treated cells were 92.70% ± 1.63% and

84.56% ± 1.62%, respectively. On further screening, the chemical constituents of the extract were identified as saponins, flavonoids, tannins, terpenoids, phenols, sugars, amino acids, and amines [76].

The EtOAc fraction obtained from partitioning ethanolic wakame (*Undaria pinnatifida* [Harvey] Suringar, Alariaceae) extract proved noncytotoxic toward B16F10 melanoma cells at concentrations of 25–31.25 µg/mL. At these concentrations, cellular melanin content was decreased in a concentration-dependent manner, with the suppression of TYR and MITF expression being responsible for this effect [77].

A summary of marine algae and their potential utility in skin hyperpigmentation treatment, including the active compounds, is shown in ► **Table 3** (► **Fig. 8**).

Conclusion

The biological activities of natural products, including plants, fungi, and marine organisms, potentially useful for treating skin hyperpigmentation were summarized in this text. Those with confirmed safety and biological activities in cell cultures including the precise mechanism of actions as well as the characterized actives responsible for the activities are therefore firstly encouraged to be applied. According to the sufficient data for safety profile and quality control practice, which are mandatory for manufacturing of the natural products and topical products comprised with the plant extracts; plants and natural products that are therefore first priority recommended for use as the key ingredients for skin-whitening products are *A. montana*, *A. dracunculus*, *Artocarpus* spp., *C. sappan*, *C. tinctorius*, *J. chinensis*, *K. pandurate*, *M. fragrans*, *P. nodiflora*, *R. rosea*, *R. verniciflua*, *S. indicum*, and *T. avellanadae*. Furthermore, *A. alternata* var. *monosporus* and *Monascus* spp., and marine-sourced algae (i.e., *I. foliacea*) are highlighted as the potential candidates for skin hyperpigmentation treatment. Some of the plants and algae summarized in this

► **Table 3** Biological activities and potential of fungus and marine algae extracts for skin hyperpigmentation treatment.

Name		Active	Study		Reference
Scientific	Common		Enzyme inhibition	Cell culture	
<i>A. alternata</i> var. <i>monosporus</i>		alteronol (93)		antimelanogenesis in B16F1 and B16F10	[71]
<i>L. polychorus</i>		laccase	melanin decolorization		[72]
<i>M. spp.</i>	angkak	glutamic acid (94), 1-amino-2-propanol (95)	mushroom TYR	antimelanogenesis in B16F10 by TYR, TRP-1, and TRP-2 suppressions	[73, 74]
<i>I. foliacea</i>		octaphloretol A (96)		antimelanogenesis in B16F10 by TYR, MITF, and p38 suppressions, enhance ERK and JNK	[75]
<i>S. polycystum</i>	sargassum weed	saponins, flavonoids, tannins, terpenoids, phenolics, sugars, amino acids, amines	mushroom TYR	antimelanogenesis in B16F10 by anti-TYR	[76]
<i>U. pinnatifida</i>	wakame			antimelanogenesis in B16F10 by TYR and MITF suppressions	[77]

► **Table 4** Commercializing herbal extracts for skin hyperpigmentation treatment.

Herbs/INCI name	Trade name	Supplier	Use level (%)
<i>A. millefolium</i>	Alpaflor Gigawhite	DSM	
	Vegewhite	Sensient Cosmetic	
<i>A. chinensis</i> fruit	Botanykem Kiwifruit	Berkem	
	Synerlight 2	Gattefossé	0.5–3
	Gatuline Spot-Light		3
	Morechem Kiwi Extract	Morechem	
<i>A. polygama</i> fruit	Nikkol Silver Vine Extract BG30	Nikkol	
<i>A. vulgaris</i>	Alpaflor Gigawhite	DSM	
<i>A. speciosa</i> leaf	Nikkol Alpina Leaf Extract BG	Nikkol	
<i>A. paniculata</i> leaf	Actives International ViaPure Andrographis	Actives International	0.1–0.2
<i>A. polymorpha</i> root	QS anti-inflammatory formula	Fenchem	
<i>A. uva-ursi</i>	Herbalia Bearberry	BASF	
	Vegewhite	Sensient Cosmetic	
<i>A. uva ursi</i> leaf	Bearberry Extract	Carrubba	
	Melfade J	DSM	1–8
	Bearberry Dry Extract Uva Ursi 20%	GfN-Selco	0.3–1
	Depigmentation Factor 2 U	Lipoid Kosmetik	
	Etioline	Sederma (Croda International Group)	
<i>A. catechu</i> seed	Areca Catechu Extract	Bioland	1–3
<i>A. capillaris</i>	Nikkol Botanical Extract Complex B	Nikkol	
<i>A. heterophyllus</i> seed	Whitessence	Lucas Meyer Cosmetics	0.5–2
<i>B. roxburghii</i> seed	Lighttime Be	Ephyla	1
<i>B. vulgaris</i>	Morechem Bamboo Extract	Morechem	
<i>B. perennis</i> flower	Belides NP	CLR Berlin	2–5
<i>B. pilosa</i>	Revinage	Chemunion Quimica	1–2
<i>B. napus</i> seedcake	Achromaxyl ISR biofunctional	Ashland Specialty Chemical	
<i>B. pekinensis</i> root	VITA GENESIS WHITE	Vitalab	0.5
<i>B. papyrifera</i> bark	Paper Mulberry Extract	Carruba	
<i>C. vulgaris</i>	Vegewhite	Sensient Cosmetic	
<i>C. sinensis</i>	Herbalia Green Tea	BASF	
<i>C. sinensis</i> leaf	Green OL	Morechem	
<i>C. tinctorius</i> bud	Natural TSC	Natural Solution	
<i>C. papaya</i>	Actipone Green Papaya GW	Symrise	
<i>C. aurantium</i> flower	ORGANIC ORANGE BLOSSOM DISTILLATE	Biocosmethic	
<i>C. aurantium</i> fruit	Orange Extract	Morechem	
<i>C. limon</i> fruit	Flashwhite Unispheres	Induchem	0.5–2
<i>C. paradisi</i> fruit/seed	FULL BRIGHT EX.	Morlab	2–3
<i>C. unshiu</i> fruit	Mandarin Extract	Morechem	
<i>C. armoracia</i> root	Actiphyte Horseradish	Active Organics	5–10
<i>C. arabica</i> seed	GREEN COFFEA VITA	Vitalab	0.5
<i>C. sativus</i>	Extrapone Saffron	Symrise	
<i>C. sativus</i>	Flashwhite Unispheres	Induchem	0.5–2
<i>C. longa</i>	BioNatural Tumeric Root	BioOrganic Concepts	
<i>C. rotundus</i>	Actipone Nutgrass (Motha) Root GW	Symrise	
<i>D. villosa</i> root	Herbex Wild Yam Extract	Biospectrum	
<i>D. carota</i> root	FULLBRIGHT EX.	Morlab	2–3

continued

► Table 4 Continued

Herbs/INCI name	Trade name	Supplier	Use level (%)
<i>E. euineensis</i>	Revinage	Chemunion Quimica	1–2
<i>E. canadensis</i> flower	Jeju Cana	Biospectrum	
<i>E. elatior</i> flower	Ginger Torch	Naturex	
<i>F. foetida</i> root	NAB Asafetida Extract	Lonza	
<i>G. hederacea</i>	ActivGH	ActivON	
<i>G. glabra</i> root	BIO-OSLP	Bioland	0.05–0.2
	Bio-SWF	Bioland	0.5–1
	Herbex Licorice Extract	Biospectrum	
	PHYTODERMINA WHITENING	I. R. A. Istituto Ricerche	5–10
	Nikkol Botanical Extract Complex B	Nikkol	
	Nikkol Polyol Soluble Licorice Extract	Nikkol	
	Nikkol Aqua Licorice	Nikkol	
	Vegewhite	Sensient Cosmetic	
	SMACTIV	SMA Collaboratives	
Whitesphere Premium XP	Soliance		
<i>G. herbaceum</i> seed	Revinage	Chemunion Quimica	1–2
<i>H. sabdariffa</i> flower	Hibiscus Exfoliator	Lessonia	
<i>H. rhamnoides</i>	Actipone Sea Buckthorn GW	Symrise	
<i>H. lupulus</i>	Wonderlight	Sederma (Croda International Group)	3
<i>I. britannica</i> flower	Morechem Elecampane Extract	Morechem	
<i>L. sibirica</i> wood	SIBWHITE	Biocosmethic	
<i>L. sativum</i> sprout	SulforaWhite	Mibelle Biochemistry	2–5
	Delentigo	Mibelle Biochemistry	2–6
<i>L. usitatissimum</i> seed	Revinage	Chemunion Quimica	1–2
<i>L. citriodora</i>	Allplant Essence Organic Verbena	Symrise	
<i>L. chinense</i> fruit	Morechem Goji Berry Extract	Morechem	
<i>M. officinalis</i>	Extrapone Magnolia GW	Symrise	
<i>M. officinalis</i> bark	QS anti-inflammatory formula	Fenchem	
<i>M. sylvestris</i>	Alpaflor Gigawhite	DSM	
<i>M. indica</i> fruit	Melan' oWhite	ID bio	
<i>M. officinalis</i> leaf	Alpaflor Gigawhite	DSM	
<i>M. aquatica</i>	Extrapone Watermint P	Symrise	
<i>M. piperita</i> leaf	Alpaflor Gigawhite	DSM	
<i>M. scaber</i>	Etioline	Sederma (Croda International Group)	
<i>M. alba</i> root	Cosme-Phytami Mulberry (white) tree	Alban Muller International	
	Bio-SWF	Bioland	0.5–1
	Nikkol Botanical Extract Complex B	Nikkol	
	Perperse Incorporated-Mulberry Root Extract	Persperse	0.5–1
<i>M. alba</i> leaf	Herbex Mullberry Extract	Biospectrum	
<i>M. alba</i> fruit	FULL BRIGHT EX.	Morlab	2–3
<i>M. dubia</i> fruit	CAMU-CAMU VITANEY C	Neyber	
<i>N. alba</i> flower	Sepicalm VG	Seppic	
<i>O. europaea</i> leaf	ILLUMISCIN	Rahn	3–7
<i>O. vulgare</i>	Allplant Essence Organic Oregano	Symrise	
<i>P. erosus</i>	Actipone Bengkoang	Symrise	
<i>P. suffruticosa</i> bark	Peony Root Extract	Morechem	

continued

► **Table 4** Continued

Herbs/INCI name	Trade name	Supplier	Use level (%)
<i>P. maritimum</i>	Neurolight.61 G	Codif	1.5
<i>P. tectorius</i> fruit	Pandanas (wild pinneapple)	Lucas Meyer Cosmetics	
<i>P. densiflora</i> pollen	Pine Pollen Extract	Morechem	
<i>P. sativum</i>	Actiwhite LS 9808	Laboratoires Serobiologiques	2–3
<i>P. tenax</i> flower	Jeju Lily	Biospectrum	
<i>P. emblica</i> fruit	Premier Amla Super	Premier Specialties	
<i>P. lanceolata</i> leaf	Senestem	Sederma (Croda International Group)	
<i>P. cuspidatum</i>	Herbex Resverol 0.5 Extract	Biospectrum	
<i>P. veris</i>	Alpaflor Gigawhite	DSM	
<i>P. persica</i> leaf	Bio-SWF	Bioland	0.5–1
<i>P. granatum</i>	Herbex Pomegranate Extract	Biospectrum	
<i>P. granatum</i> flower	Pomegranate flower	Naturex	
<i>R. rhaponticum</i> root	Unilucent PA-13	Induchem	0.5–1
<i>R. officinalis</i> leaf	Herbex Rosemary Extract	Biospectrum	
<i>R. occidentalis</i>	Tyrostat	Lucas Meyer Cosmetics	1–3
<i>S. chinensis</i>	Saururus Chinensis Extract	Morechem	
<i>S. baicalensis</i> root	Nikkol Botanical Extract Complex B	Nikkol	
	Vegewhite	Sensient Cosmetic	
<i>S. angustifolia</i> root	Synerlight 2	Gattefossé	0.5–3
<i>S. flavescens</i> root	Gatuline Spot-Light	Gattefossé	3
<i>S. japonica</i>	Vegewhite	Sensient Cosmetic	
<i>T. officinale</i>	Extrapone Dandelion	Symrise	
<i>T. chebula</i>	Ellagic Acid	Sabinsa	
<i>T. aestivum</i>	Axolight	Soliance	
<i>T. pratense</i>	NioSkin RCL40	Linnea	
<i>V. officinalis</i>	Alpaflor Gigawhite	DSM	
<i>Z. jujuba</i> fruit	Nikkol Botanical Extract Complex B	Nikkol	

► **Table 5** Commercializing microorganism extracts for skin hyperpigmentation treatment.

Microorganism/INCI name	Trade name	Supplier	Use level (%)
<i>Aspergillus</i> sp.	PHYTODERMINA WHITENING	I. R. A. Istituto Ricerche	5–10
<i>D. membranacea</i>	3M3.WHITERIS G	Codif	3
<i>H. fusiforme</i>	Hijiki Extract	Morechem	
<i>L. digitata</i>	Seanergilium BG	BASF	
<i>L. edodes</i>	Herbex Shiidake Extract	Biospectrum	
<i>P. sajor-caju</i>	ViaFerm White	Actives International	2
<i>U. pinnatifida</i>	KIMARINE	Gelyma	
	OROSEA		
	PHYACTYL		
	Wakamine 1 %	Naturactiva	
	Wakamine XP		
	Wakamine		
	Whitesphere Premium XP	Soliance	

group are of economic importance; thus, there is therefore less risk of availability lacking, and some of them are commercialized offerings are detailed in ► **Tables 4** and **5**. This information would meet the interests of cosmetic and formulation chemists in natural product applications. However, precise mechanisms of action remain unclear in some commercializing ones. Furthermore, screening with *in vitro* assays is still recommended for inclusion of the natural products assessment in cell culture prior to evaluation in human skin models and human skin, respectively, although the *in vitro* results are in contrast with the cell culture and skin model in some cases as per se there are some differences in *in vitro* mediums and *ex vivo* that is more similar to the *in vivo* study [3]. Medicinal plant researchers will have an interest in the presented data. They are therefore encouraged to fill in the gap of some unclear issues in an order to strengthen and widen application of plants and natural extracts for pharmaceutical and cosmetic industries. In addition to the priority plants and marine algae listed above, the rest are potentially challenging to examine due to their precise safety and the mechanism and characterization of their biological activities.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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