Review

Plants as Modulators of Melanogenesis: Role of Extracts, Pure Compounds and Patented Compositions in Therapy of Pigmentation Disorders

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Abstract: The kingdom of plants as a “green biofabric” of valuable bioactive molecules has long been used in many ailments. Currently, extracts and pure compounds of plant origin are used to aid in pigmentation skin problems by influencing the process of melanogenesis. Melanin is a very important pigment that protects human skin against ultraviolet radiation and oxidative stress. It is produced by a complex process called melanogenesis. However, disturbances in the melanogenesis mechanism may increase or decrease the level of melanin and generate essential skin problems, such as hyperpigmentation and hypopigmentation. Accordingly, inhibitors or activators of pigment formation are desirable for medical and cosmetic industry. Such properties may be exhibited by molecules of plant origin. Therefore, that literature review presents reports on plant extracts, pure compounds and compositions that may modulate melanin production in living organisms. The potential of plants in the therapy of pigmentation disorders has been highlighted.

Keywords: plant; phytochemicals; melanogenesis; signaling pathways; in vivo studies

1. Introduction

The human skin is an important organ in the body and a source of various cells, including melanocytes that reside on the basal layer of epidermis [1]. The main feature of melanocytes is the production of melanin in special organs-melanosomes during a physiological process, called melanogenesis. The quality, quantity and distribution pattern of melanin determines the color of mammalian skin, eyes and hairs. Constitutive pigmentation level of melanin is genetically determined. However, pigment cells have the ability to adopt their melanogenic potential via different internal or external stimuli. The internal stimuli are factors generated inside the organism, whereas the external stimuli are environmental agents including the most potent one, i.e., ultraviolet (UV) radiation [2].

Melanogenesis consists of different stages and involves action of various enzymes. Tyrosinase (TYR) is the key enzyme, which takes part in melanin synthesis by catalyzing hydroxylation of L-tyrosine to 3,4-dihydroxy-phenylalanine (DOPA) and oxidation of DOPA to DOPAquinone. The produced pigment is transferred from melanocytes into keratinocytes. This compound constitutes the first line of defense against UV radiation and provides scavenging of reactive oxygen species (ROS) [3]. However, the disturbance of melanogenesis process may lead to overproduction, deficiency, abnormal transport or transfer of melanin, which in turn may result in pigmentation disorders [4].

Numerous studies showed a beneficial effect of plant extracts or pure compounds in various skin ailments. According to literature, plants provide, e.g., antioxidant, antiaging and anti-inflammatory properties [5,6]. Such an effect is due to the presence of
plant secondary metabolites. These molecules, characterized with high structural diversity, belong to different chemical classes, including phenolics, terpenes, alkaloids, saponins, lipids and carbohydrates [7]. Many of them are able to modulate different signaling pathways, including those which regulate the expression and activity of melanogenesis-related proteins. The most crucial signaling pathway is mediated by the melanocortin-1 receptor (MC1R). Other pathways include those mediated by the tyrosine kinase receptor (c-KIT), Frizzled receptor and endothelin B receptor (ETBR). Microphthalmia transcription factor (MITF) is a downstream target, being the main regulator of melanogenesis. MITF propagates melanogenesis by induction of the expression of TYR and other pigmentation genes, including tyrosinase-related proteins, i.e., TYRP1 and TYRP2. Therefore, up-regulation or down-regulation of such signal transduction is one of the most desirable ways in the therapy of skin hyperpigmentation or hypopigmentation [8,9].

Studies focused on the modulatory role of molecules of plant origin on melanogenesis mechanisms, are performed on various model systems, including in vitro and in vivo. The in vitro model comprises studies that examine the influence of phytochemicals on melanocytes in monolayers whereas the in vivo model comprises studies investigating the influence of phytochemicals on living organisms. Numerous approaches are currently available, but each has its own advantages and limitations. Moreover, growing data on possibility of modification of melanogenesis-related pathways by plants is followed by an increasing number of patented compositions.

The aim of the study is to present the role of plants, including extracts, pure compounds and patented compositions as modulators of melanogenesis process in living organisms. Their beneficial effects on skin and applicability in the therapy of pigmentation disorders have been also highlighted.

2. Study Design

This literature review includes data published in the years 2012–2022 obtained from NCBI-PubMed, Google Scholar, Scopus, and ScienceDirect databases. The following keywords were selected: plant extract, plant pure compound, melanogenesis, signaling pathways, in vivo study. Studies on plant extracts and pure compounds as well as their impact on the melanogenesis process in in vivo model were explored. Only compounds isolated directly from plants were included. In addition, patented compositions were added. An analysis of cell lines in monocultures was rejected. Items published in languages other than English or containing only an abstract were also excluded. In order to standardize scientific names of plants, the “Medicinal Plant Names Services” (https://mpns.science.kew.org/mpns-portal/searchName?) (accessed on 12 September 2022) was used. PubChem (https://pubchem.ncbi.nlm.nih.gov) (accessed on 12 September 2022) enabled to obtain IUPAC names of pure compounds.

3. Melanocyte Characteristics

Melanocytes are a heterogeneous group of cells found in different locations in a human body. They consist of the central body and dendrites. Melanocytes originate from melanoblasts, neural pluripotent cells of neural crest. Dermal melanocytes derive from several populations of neural crest cells, including cranial, dorsal and ventral trunks. Melanoblasts successively undergo migration, proliferation and differentiation into melanocytes. Mature cells acquire the ability to produce melanin in special organelles, called melanosomes. There are two types of dermal melanocytes. One is present in the basal layer of the epidermis, while the other is found within hair follicles. Melanocytes located in the epidermis account for 5–10% of all cells. They form epidermal melanin units, which are a dendritic junction of one melanocyte with about 30–40 neighboring keratinocytes. Dermal melanocytes transport mature melanosomes into keratinocytes, which is followed by cell death [2,10,11].

Cross-talk between melanocytes and keratinocytes and fibroblasts is demonstrated. Melanocyte biology is controlled through various signaling molecules. Keratinocytes-
derived factors, such as basic fibroblast growth factor (bFGF), stem cell factor (SCF), or endothelin 1 (ET-1), initiate melanocyte division. Moreover, keratinocytes upon UV radiation produce the following factors: bFGF, ET-1, interleukin (IL) IL-1α/1β, adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (α-MSH), prostaglandin E2 (PGE2), PGF2α, granulocyte-macrophage colony-stimulating factor (GM-CSF), nitric oxide (NO), tumor necrosis factor α (TNF-α), nerve growth factor (NGF), bone morphogenetic protein 4 (BMP-4). They affect proliferation, dendriticity, melanogenesis efficiency and survival of melanocytes. Fibroblast-derived factors, such as bFGF, hepatocyte growth factor (HGF), or endothelin 3 (ET-3), initiate melanocyte division. Fibroblasts also produce stem cell factor (SCF) and neuregulin 1 (NRG1) which determine melanocyte growth, shape and motility. These paracrine regulations play a very important role in maintaining skin homeostasis.

The melanocyte itself also secretes a number of signaling molecules such as pro-inflammatory cytokines IL-1α, IL-2, IL-3, IL-6, IL-10 and TNF-α. Some of these, including L-1, IL-6 and TNF-α inhibit melanogenesis. In contrast, factors secreted by melanocytes that stimulate melanin production are eicosanoids and melanocyte stimulating factor (α-MSH). Other factors produced by melanocytes include transforming growth factor (TGF-β), chemokines, catecholamines, serotonin and NO [2,12,13].

The primary function of melanocyte is melanin production. Melanins are responsible for pigmentation of the skin, as well as hair or eyes. There are two main groups of melanins: eumelanins and foemelanins. Eumelanins give a brownish to dark black color while foemelanins give a yellowish or reddish color. Pigment amount varies depending on the activity of melanosomes, differences in the production and deposition. A higher content of pheomelanin relative to eumelanin is observed for fair skin, while the opposite ratio is observed for dark skin. There are no significant differences in melanocyte density in different racial groups. However, the density is different in a different body region. It is estimated that there are between 900 and 1500 melanocytes per mm² on the back and genital area on average about 1000 melanocytes per mm² [14].

Biochemical pathway leading to synthesis of melanin is called melanogenesis. It is estimated that pigment production is regulated by more than 250 genes that determine melanocyte development, migration, proliferation, differentiation, and survival [15,16]. Pigment cells express among others TYR, TYRP1, TYRP2 and MITF proteins which are closely related to melanogenesis. TYR, being an oxidase located in the membrane of melanosomes, is responsible for converting L-tyrosine, a precursor of melanosins to DOPAquinone [17]. Apart from TYR, TYRP-1 and TYRP-2 are other enzymes which are also involved in melanogenesis. These proteins are structurally similar to TYR. TYRP1 is an oxidase involved in the final stage of melanogenesis; it can increase the ratio of eumelanin to pheomelanin and it is also involved in activation and stabilization of TYR by forming a complex with it. TYRP2 is a tautomerase responsible for the conversion of DOPAchrome to carboxylic acid derivatives. In the melanosome, it forms complexes with TYR and TYRP1 [18]. MITF is a transcription factor which recognizes the sequences of TYR, TYRP1 and TYRP2 genes and modulate their transcription. The signaling cascade involving MITF is one of the most important for melanogenesis regulation [19].

Protection against UV radiation is the primary function of melanins. Melanins have both UV absorbing and scaterring properties. Black epidermis transmits only 7.4% of UVB and 17.5% of UVA, whereas 24% of UVB and 55% of UVA pass through white skin. This role is very important due to the fact that UVB radiation induces DNA bases damage, whereas UVA radiation leads to production of ROS as well as single strand breaks or crosslinks between DNA and proteins. Photodamage can cause mutations in critical genes. Therefore, UV radiation is a primary harmful environmental factor, inducing occurrence of skin cancers such as malignant melanoma, squamous cell carcinoma and basal cell carcinoma. In turn, melanosomes transferred from melanocytes to keratinocytes form characteristic perinuclear caps that create a DNA protection shield. In addition to its UV radiation protective role, melanin also exhibits antioxidant activity as well as anti-inflammatory and immunomodulatory properties [20–22].
4. Plant Extract and Pure Compounds–Biological Properties and Modulatory Effect on Melanocyte

Plants are a rich source of phytocompounds. It is estimated that any single species may contain as many as 5000 metabolites [23]. These are chemically diverse substances that can play many different roles, including determination of plant growth and development, protection against pathogens, and response to environmental stress. The metabolites produced by plants are classified as primary and secondary. The second group includes mainly intermediates or by-products of primary metabolism. Terpenoids, alkaloids, phenylpropanoids, polyketides, quinones and cyanogenic glycosides are formed in the process of carbon and nitrogen metabolism; glucosinolates are formed by sulfur metabolism, while alkylamides are formed by fatty acid metabolism. [24]. Plant secondary metabolites may also positively affect the human body [25]. Some of these substances demonstrate therapeutic effects on cells or tissues and may be useful in alleviating numerous ailments [26]. In addition, their contribution to disease prevention is being considered [27]. A lot of efforts are put to isolate highly desirable molecules and to determine their chemical structure, as well as activity, functions and toxicity [28,29].

Annual production of plants, characterized with medicinal properties, is worth more than $100 billion [27]. Molecules of natural origin may have several properties, including photoprotective [30] as well as anti-inflammatory [9], antioxidant [25] or anticancer [26] via modulation of cellular signaling pathways [31–38].

Plant-derived compounds may counteract the harmful effects of UV exposure on human skin. Phenolic compounds are the most important class of phytochemicals that may be used as sunscreen agents. These molecules equipped with aromatic rings are able to absorb UVA and UVB radiation at wavelengths of 200–400 nm. Two flavonoids, quercitin and rutin at 10% (w/w) concentrations provide SPF values of about 12 [39]. Moreover, combining 0.1% (w/w) rutin with 6% benzophenone, a synthetic organic filter, increased the SPF value from about 24 to 33 [40]. Similarly, synergistic effects were observed between 0.1% rutin (w/w), 1% benzophenone (w/w) and 3.5% (w/w) ethylhexyl methoxycinnamate, another synthetic organic filter [41]. Choquenet tested twelve phenolic compounds at various concentrations, including myricetin, apigenin, luteolin, pueraarin, baicalin, baicalein, naringenin, hesperidin, hesperetin, diosmin, caffeic acid and chlorogenic acid. Of these, apigenin and chlorogenic acid were found to be the most effective UVB and UVA filters, with SPF values at about 7 and 10, respectively [42]. Similarly, among fifteen tested phenolic compounds at 7% (w/v) concentrations (resveratrol, quercetin, catechin, kaempferol, piceid, galangin, apigenin, naringenin, chrysins, pinocembrin, ferulic acid, coumaric acid, caffeic acid, caffeic acid phenylethyl ester and dimethyl caffeic acid), the highest SPF value was observed for apigenin, i.e., about 28.8 [43]. In addition, studies show that plant extracts from different plant species have also a photoprotective action, especially plants of the species which stand out large amounts of phenolic compounds [30].

Bioactive compounds are known to improve the anti-inflammatory response via downregulation of different inflammatory pathways, including mitogen-activated protein kinases (MAPKs), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activators of transcription (JAK/STAT) pathways. This stimulation contributes to production of various pro-inflammatory mediators, while their inhibition bestows an anti-cancer effect.

Oxidative stress is implicated in the pathogenesis of many chronic diseases, including diabetes, cardiovascular diseases, atherosclerosis, rheumatoid arthritis, chronic inflammation, cancer, aging, and various other neurodegenerative disorders. ROS activates signaling pathways, such as MAPK, NF-κB, nuclear factor erythroid 2-related factor 2 (Nrf2) and various transcription factors, including activator protein 1 (AP-1), tumor protein p53, hypoxia-inducible factor 1-alpha (HIF-1α), peroxisome proliferator-activated receptor gamma (PPARγ), and signal transducer and activator of transcription (STAT-3). Nrf2 pathway upregulates cell defense mechanisms and antioxidant gene expression. This pathway
is known to be stimulated by plant-derived chemicals with antioxidant properties, thus providing beneficial effects against ROS-related disease, including cancer.

Phytochemicals also exert a direct detrimental effect on cancer cells by cell cycle arrest via downregulation of (MAPKs) and phosphoinositide 3-kinases (PI3K)/protein kinase B (AKT) pathways [44]. Data indicate that suppression of PI3K/AKT signaling pathway leads to inhibition of proliferation, apoptosis, induction of autophagy of cancer cells [45]. In addition, molecules of natural origin can block cancer cell differentiation and angiogenesis by downregulation of the HIF-1α pathway and vascular endothelial growth factor (VEGF), and influence cancer cell survival by altering p53, death receptor expression and pro-apoptotic:anti-apoptotic protein balance [44].

Secondary metabolites obtained from plants can also modulate signaling pathways involved in the melanogenesis process in melanocyte cells. A lot of studies have been focused on the ability to regulate MC1R, c-KIT, WNT and ETBR pathways.

Induction of G-protein-coupled receptor MC1R is a canonical regulatory mechanism of melanin production by melanocytes. This occurs through its agonist, α-melanocyte-stimulating hormone (α-MSH) binding. Activation of adenylyl cyclase is followed by an increase in the cyclic adenosine monophosphate (cAMP) level. cAMP is a second messenger produced from ATP by adenylyl cyclase that regulates numerous cellular functions, including growth, proliferation, differentiation, migration, as well as genes expression. Protein kinase A (PKA) is one of effector proteins, which gets activated by high cAMP levels. Consequently, PKA activates target proteins including cAMP response element-binding protein (CREB) [46]. PKA is responsible for Ser133 phosphorylation of CREB, which is then followed by CREB-mediated MITF expression. It was also observed that the binding of α-MSH to MC1R contributes to triggering PI3K/AKT signaling pathway. PI3K activity results in recruitment of AKT to the cell membrane, where phosphorylation and activation of AKT occur. A direct target for AKT is, among others, glycogen synthase kinase 3β (GSK3β), which then phosphorylates on Ser298 and activates MITF [47–49]. Data also indicate that AKT can directly phosphorylate MITF on Ser510 [42]. In turn, cAMP levels in the cell can modulate the MAPKs pathway. Increased cAMP amounts induce ERKs and inhibit p38 activation [50]. Active ERK phosphorylates MITF on Ser73 and triggers proteasomal degradation mediated by ubiquitin [51]. In contrast, active p38 causes CREB phosphorylation and MITF activation [52]. Similarly, PI3K/AKT and MAPKs signals also regulate numerous cellular functions, including proliferation, differentiation and migration [53,54].

MITF can be also regulated via c-KIT receptor and its ligand stem cell factor (SCF) junction, which is dependent on PI3K/AKT and p38 signaling [55]. Data indicate that induction of c-KIT constitutively stimulates PI3K by its phosphorylation, as well as activate Src-homology 2 domain-containing proteins, of which the Src family kinases promote p38 action [56].

WNT signaling is initiated by binding of Wnt ligands to Frizzled receptor-related protein receptor complexes. In the absence of Wnt ligands, β-catenin phosphorylation by GSK3β results in its degradation by a protein complex consisting of Dishevelled, GSK3β, axin or conductin, and the adenomatous polyposis coli tumor suppressor protein. In the presence of Wnt ligand, β-catenin phosphorylation is blocked. This provides β-catenin stabilization followed by nuclear translocation, where it can interact with TCF/LEF transcription factor and regulate the expression of downstream genes. MITF is one of positively regulated genes targeted by WNT signaling [57,58].

ETBR is also a G-protein coupled receptor. Its activation by ligand–endothelin 3 (ET-3) results in elevated phosphorylation of ERK, CREB and MITF. ETBR acts synergistically with MC1R. The action is followed by MITF activation and increased expression of its target genes, including TYR, TYRP1 and TYRP2. In addition, increased phosphorylation of AKT was also observed [59].

Modulating of MITF activity can affect the efficiency of melanogenesis. In some cases, inhibition of MITF activity leads to reduced melanin production, while in some others,
stimulation of MITF activity results in increased melanin production. Both the effects may be achieved through implementation of plant-derived compounds [60]. Therefore, these molecules may exert a beneficial therapeutic effect on skin of patients with hyperpigmentation or hypopigmentation, including postinflammatory hyperpigmentation, solar lentigines, melasma, café au lait macules, ephelides (freckles) as well as postinflammatory hypopigmentation, vitiligo, pityriasis alba, tinea versicolor [61–65].

5. The Effect of Plant Extracts or Pure Compounds on Melanin Content in the Danio rerio Model

*Danio rerio* (zebrafish) is a popular model for biomedical research. It is characterized with fully sequenced genome, being approximately in 70% orthologues to the human genome, easy genetic manipulation, rapid development, high fecundity, external fertilization, transparent embryo and presence of main organs necessary for metabolism. Moreover, that small freshwater fish is also easy to breed and maintain [66].

The zebrafish is also highly desirable in dermatological studies due to the fact that components of the epidermis and dermis get formed just 1 day post-fertilization (dpf), whereas skin structure is fully developed 6 dpf. As a consequence, after 6 dpf zebrafish skin is composed of multilayer epidermis and collagenous stroma with well-demarcated keratinocytes and numerous fibroblastic cells. Besides, presence of a pigment cell system is a crucial feature of zebrafish skin [67,68]. Interestingly, zebrafish skin is similar to human skin and consists of the epidermis, dermis and hypodermis. Unlike human skin, it does not have a keratinized outer layer and mammalian appendages, including sebaceous glands and hair follicles. However, studies on that non-mammalian vertebrate model constitute a fundamental part of skin-related research [69].

The zebrafish model is getting more and more applicable in exploration of pigment disorders due to having a conserved melanogenesis pathway and visible melanin development in melanophores from 1 dpf. The zebrafish pigment cells are derived from neural crest stem cells. They generate melanophores. Melanocytes and melanophores look alike similar. Melanophores are located in the epidermis and hypodermis and they do not transfer melanin, while melanocytes reside in the epidermis and transfer melanin to keratinocytes. However, the biology of melanophores is similar to that of melanocytes. In that model organism, numerous genes which control pigment production and function of melanocytes, such as MITF, TYR and TYRP1, are conserved and similar to those observed in a human body. In addition, regulation of MITF activity by signaling pathways, including MC1R, WNT, c-KIT and ETBR, has been found in both human and zebrafish pigment cells [70]. Studies on melanogenic potential of plant extracts and pure compounds of the zebrafish embryos are presented in Tables 1 and 2. According to that studies, analyzed extracts and pure compounds were mostly noncytotoxic towards zebrafish embryos in the range of tested concentration.
Table 1. Melanogenic potential of plant extracts evaluated on the zebrafish model.

| Name of the Species/Family | Part of the Plant | Type of Solvent | Compounds Identified in Extract | Concentration | Incubation Time | Effect | Ref. |
|---------------------------|-------------------|-----------------|---------------------------------|---------------|-----------------|--------|------|
| *Acalypha indica* L./Euphorbiaceae | whole plant | methanol–ethyl acetate fraction | dioctyl phthalate, (-)-erythromycin, rhamnetin, berberine, keracyanin, spectinomycin, andrographolide, methyl caffeate | 10–100 µg/mL | 48 hpf | antimelanogenic activity | [71] |
| *Artocarpus chama Buch.-Ham./Moraceae* | stem | methanol, water | - | 200 µg/mL | 9–72 hpf | antimelanogenic activity | [72] |
| *Bletilla striata* (Thunb.) Rchb.f./Orchidaceae | roots, tuber | ethanol | 39 chemical compositions, including 24 stilbenoids | 10 and 30 mg/mL | 6–72 hpf | antimelanogenic activity | [73] |
| *Blumea balsamifera* (L.) DC./Asteraceae | leaves | ethanol–ethyl acetate fraction | - | 10–300 µg/mL | 9–57 hpf | antimelanogenic activity | [74] |
| *Dioscorea nipponica* Makino/Dioscoreaceae | bark | ethanol–methanol fraction | - | 6.25–25 µg/mL | 9–72 hpf | antimelanogenic activity | [75] |
| *Elaeocarpus serratus* L./Elaeocarpaceae | leaf | ethanol | gallic acid, myricetin, mearnsetin | 50 µg/mL | 9–57 hpf | antimelanogenic activity | [76] |
| *Hosta longipes* (Franch. and Sav.) Matsum./Asparagaceae | whole plant | ethanol–hexane fraction | linolenic acid and linoleic acid | 1 µg/mL | 9–81 hpf | antimelanogenic activity | [77] |
| *Morus alba* L./Moraceae | wood | methanol | oxyresveratrol, kuwannon C, mulberroside A, resorcinol, dihydrooxyresveratol, 2,4,3′-trihydroxydihydrostilbene, kuwannon H, 2,4-dihydroxybenzaldehyde, morusin, moracin M and kuwanon G | 70 µg/mL | 24–48 hpf | antimelanogenic activity | [78] |
| *Panax ginseng* C.A.Mey./Araliaceae | whole plant | methanol–water fraction | - | 12.5–50 µg/mL | 7–72 hpf | antimelanogenic activity | [79] |
| *Pistacia vera* L./Anacardiaceae | hulls | methanol:water:acetic acid | cyanidin-3-O-galactoside, cyanidin-3-O-glucoside | 2.5–10 µg/mL | 24–72 hpf | antimelanogenic activity | [80] |
| *Reynoutria multiflora* (Thunb.) Molderken/Polygonaceae | root | water | - | 87.5 mg/L | 3–4 hpf–4 dpf | antimelanogenic activity | [81] |
| *Rhanterium suecoclens* Desf./Asteraceae | flowers | methanol | flavonoids and hydroxycinnamic acids | 0.5 and 1 mg/mL | 24–47 hpf | antimelanogenic activity | [82] |
| *Senecio alata* (L.) Roxb./Fabaceae | leaf | methanol | - | 50 µg/mL and 100 µg/mL | 9–55 hpf | antimelanogenic activity | [83] |
| *Sonneratia alba* Sm./Lythraceae | bark | methanol | - | 50 µg/mL and 100 µg/ml | 9–55 hpf | antimelanogenic activity | [84] |
| *Streblus taxoides* (B.Heyne ex Roth) Kurz/Moraceae | wood | ethyl acetate, methanol | - | 50 µg/mL | 9–72 hpf | antimelanogenic activity | [72] |
Table 2. Melanogenic potential of plant pure compounds evaluated on the zebrafish model.

| Name of the Species/Family | Part of the Plant | Identified Compounds | Chemical Class of the Compounds | Concentration | Incubation Time | Effect | Ref. |
|----------------------------|-------------------|----------------------|---------------------------------|---------------|-----------------|--------|------|
| *Agastache rugosa* (Fisch. and C.A.Mey.) Kuntze/Lamiaceae | leaves | demethyleugenol β-D-glucopyranoside | glucopyranoside | 5–30 µM | 9–72 hpf | antimelanogenic activity | [85] |
| *Arctium lappa* L./Asteraceae | seed | arctigenin | lignan | 10 µM | 15–40 hpf | antimelanogenic activity | [86] |
| *Artemisia capillaris* Thurb./Asteraceae | leaves and stems | 4,5-O-dicaffeoylquinic acid | polyphenol | 25 µg/mL | 9–72 hpf | antimelanogenic activity | [87] |
| *Artemisia capillaris* Thurb./Asteraceae | - | isofraxidin 7-O-(6′-O-p-coumaroyl)-β-glucopyranoside | glucopyranoside | 12.5 and 25 µg/mL | 9–72 hpf | melanogenic enhancer | [88] |
| *Conioselinum anthriscoides* (H.Boissieu) Pimenov and Kljuykov/Apiaceae | rhizoma | neocnidilide | gamma-lactone | 10–20 µM | 7–72 hpf | antimelanogenic activity | [89] |
| *Elaeocarpus serratus* L./Elaeocarpaceae | leaves | gallic acid, myricetin, mearnsetin | phenolic acid, flavone, O-methylated flavonol | 50 µM | 9–57 hpf | antimelanogenic activity | [76] |
| *Eurya emarginata* (Thub.) Makino/Pentaphylacaceae | root | rengyolone | cyclohexylethanoid | 16.2 and 32.5 µM | 9–48 hpf | antimelanogenic activity | [90] |
| *Hosta longipes* (Franch. and Sav.) Matsum./Asparagaceae | whole plant | linolenic acid and linoleic acid | fatty acids | 1 µg/mL | 9–81 hpf | antimelanogenic activity | [77] |
| *Inula japonica* Thub./Asteraceae | flowers | inularin | sesquiterpene | 10–100 µM | 10–48 hpf | antimelanogenic activity | [91] |
| *Inula japonica* Thub./Asteraceae | flowers | 6-O-Isobutyrylbritannilactone | lactone | 10–100 µM | 10–48 hpf | antimelanogenic activity | [92] |
| *Juniperus communis* L./Cupressaceae | fruits | hypolaetin-7-O-D-xyloside | flavonoid | 1–400 µg/mL | 9–72 hpf | antimelanogenic activity | [93] |
| *Lonicera japonica* Thub./Caprifoliaceae | whole plant | sweroside | iridoid glycoside | 150 and 300 µM | 9–72 hpf | antimelanogenic activity | [94] |
| *Morus alba* L./Moraceae | wood | oxyresveratrol | stilbenoid | 50 µg/mL | 24–48 hpf | antimelanogenic activity | [78] |
| *Panax ginseng* C.A.Mey./Araliaceae | berry | floragalinsenoside A | ginsenoside | 40–160 µg/mL | 9–72 hpf | antimelanogenic activity | [95] |
| *Panax ginseng* C.A.Mey./Araliaceae | leaves | picronioside A | glucoside | 40 and 80 µg/mL | 9–72 hpf | antimelanogenic activity | [96] |
| *Panax ginseng* C.A.Mey./Araliaceae | roots | isomaltool glycoside | glycoside | 50 and 100 µg/mL | 9–72 hpf | antimelanogenic activity | [97] |
| *Panax ginseng* C.A.Mey./Araliaceae | leaves | Rh23 | ginsenoside | 40 and 80 µM | 9–72 hpf | antimelanogenic activity | [98] |
| *Panax ginseng* C.A.Mey./Araliaceae | aerial parts | Rh6, R4, R13 | ginsenosides | 80 µM | 9–72 hpf | antimelanogenic activity | [99] |
| *Persicaria amphibia* (L.) Delarbre/Polygonaceae | aerial parts | epicatechin-3-gallate | catechin | 50–200 µM | 24–48 hpf | antimelanogenic activity | [100] |
| *Viscum album* L./Santalaceae | whole plant | velutin | flavonoid | 30 and 300 µg/mL | 5–30 hpf | antimelanogenic activity | [101] |
| *Ziziphus jujuba* Mill./Rhamnaceae | seeds | jujuboside B, epicanothoic acid, 6′′′-feruloylspinosin | flavonoid glycosides | 20 µM | 48–72 hpf | antimelanogenic activity | [102] |
The rodent model allows both to evaluate the impact of molecules on the whole organ, i.e., the skin, and to observe interactions of this organ with other body organs, which makes this model advantageous. On the other hand, results of the rodent model obtained in preclinical studies are sometimes impossible to translate into clinical practice. Of all rodent models, the mouse model is most commonly used. Mice are easy to breed and maintain. They are genetically modifiable, have a short lifespan, and their skin properties are similar to those observed in human skin. However, there are some structural and molecular differences. The most obvious difference is the fact that rodent skin is more permeable than human skin, which is contributed by fur which covers most of its body. Besides, it is also thinner than human skin. Body areas not covered by fur, i.e., the ears and tail, have thicker epidermis, like in humans. In addition, the skin of rodents contains muscle tissue, which is not found in human skin and epidermal regeneration takes 8–10 days, whereas this process in humans takes 26–28 days. Moreover, a different distribution of melanocytes is observed in mice. They are found mainly in hair follicles, while in humans, they are present in both hair follicles and the basal layer of the epidermis [103].

Studies conducted on the rodent model and investigating melanogenic potential of plant extracts and single compounds which are administered topically are available in the literature. The experiment lasts on average from a few days to several months. The shortest-lasting research was conducted on UVB-irradiated HRM-2 hairless mice exhibited to *Pueraria thunbergiana* in the form of cream containing 1 or 3% of the extract on the dorsal skin. Findings show great efficacy of the extract on pigmentation and melanogenesis induction after 3 days of exposition [104]. Jegal et al. tested *Juniperus communis* extracts at concentration of 5 to 50 µg/mL for 11 days as well as their main constituent, i.e., hypolaetin-7-O-β-D-xylopyranoside at a concentration of 50 µM on UVB-irradiated HRM-2 hairless mice. Solution at 200 µL volume was applied to a dorsal skin site 3 × 3 cm. Histological findings of skin samples indicate a reduction in melanin deposition after extract treatment and a reduced number of melanocytes after exposition to pure compounds [105]. *Nelumbo nucifera* extract, used at 1% or 2% concentration and administered to UVB-irradiated guinea pigs on the back region for 2 weeks demonstrates similar activity. The main identified constituent was gallic acid [106]. Data show that 200 µL of *Nymphaea noouchali* extract, applied on UVB-irradiated HRM-2 hairless mice at a concentration 100 µg/mL to a 3 cm × 3 cm designated area on the dorsal skin for 4 weeks exhibit antimelanogenic effects [107]. *Medicago sativa* extract used at 10% or 20% concentrations and administered to dorsal region of C57/BL6 mice for 4 weeks exhibit a remarkable skin and hair pigmentation [108]. A study conducted by Choi et al. on UVB-irradiated brown guinea pig skin models revealed that *Cyrtomium fortunei* used at 3% concentration on back area and administered for 6 weeks exhibited depigmenting properties [109]. In addition, UVB-irradiated C57BL/6 mice treated with *Nelumbo nucifera* extract at concentrations of 1.25 mg/cm² and 2.5 mg/cm² for 8 weeks inhibited melanin production in the ear skin sample. The main component of this extract was identified as epigallocatechin [110]. *Pyrostegia venusta* extract used at 10% and administered to dorsal region of Swiss mice mice for 65 days show a increased epidermal melanin level and diminished dermal depigmentation [111]. The longest studies, covering a period of 5 months, were conducted on C57BL/6 Ler-vit/vit mice. *Lespedeza bicolor* extract applied at an amount of 0.2 mL/cm² to those animals significantly increase the level of melanocytes in the skin. The main constituent of extract was identified as quercetin [112]. Application of 0.2 mL/cm² *Rhododendron schlippenbachii* extract for 5 months leads to melanin production [113].

Other research involves oral administration of plant extracts or pure compounds. The experiments lasted from few days to several weeks. The shortest-lasting study was provided by Niu et al. on SD rat serum exposed to *Caesalpinia sappan* extract, applied at a dose of 1.15 g/kg, significantly reduced the content of TYR. Isolated compounds were
identified as sappanone B, brazilin, protosappanin A, protosappanin B, caesalpin J [114]. C57BL/6J mice exposed to *Adenostemma laevia* extract administered at a concentration of 100 mg/kg for 2 weeks show inhibited hair pigmentation. The main constituent was identified as ent-11-hydroxy-15-oxo-kaur-16-en-19-oic acid [115]. Improved depigmentation was observed after UVB-irradiated HRM-2 hairless mice treatment with *Panax ginseng* extract at doses of 150 and 300 mg/kg for 5 weeks [116] as well as 100 and 200 mg/kg of *Zingiber mioga* extract for 6 weeks [117]. Moreover, C57BL/6 mice and brown guinea pigs undergoing hydroquinone and H2O2 induced hypopigmentation, respectively. Both were then treated with *Vernonia anthelmintica*, administered at concentrations of 61.5–246 mg/kg to the mice and 22–88 mg/kg to the guinea pigs for 30 days. In consequence, the extract darkened the dorsal skin samples and hair both in the mice and the guinea pigs [118].

7. The Effect of Plant Extracts or Pure Compounds on Melanin Content in the Human Model

In the human model, analyzing plant extracts were administered primarily topically. The research was mainly focused on an analysis of extracts with whitening properties. The experiments lasted an average several weeks. The shortest-lasting studies, i.e., covering the period of 4 weeks, involved application of *Perilla frutescens* extract at a concentration of 0.1% in 30 patients to the forearms [119] and *Salacca edulis*, rich in flavonoids, extract administered at 3% concentration to the forearm of 17 participants [120]. Other studies included exposure of 24 volunteers to 1% *Eblingera elatior* extract [121] and 30 subjects to *Piper betle* extract applied at a dose of 5 mg/cm² [122] to the forearm. Another studies involved 30 volunteers that tested 0.2 or 0.3 g of *Perilla frutescens* [123] and phenolic-rich *Punica granatum* extracts [124], applied to the face. *Panax ginseng* extract was applied as 3% cream by 10 volunteers onto foreheads and cheeks [116]. *Gnetum gnemon* extract at 3.5% concentration was applied to upper arms of 38 patients [125]. A study lasting 6 weeks evaluated the effect of *Rosa gallica* 0.05%, extract on facial skin of 10 participants [126] and *Chrysanthemum indicum* 0.5% extract on facial skin of 30 patients. It was revealed, that luteolin and acacetin-7-O-rutinoside are major flavonoid compounds in that extract [127]. For 7 weeks, 0.05 or 0.1% *Litchi chinensis* extracts were tested on 29 volunteers on the forearm [128]. Some other studies covered a period of 8 weeks. The 3% *Crocus sativus* extract was applied to cheeks and forearms by 10 volunteers [129] and 68.6% *Aster yomena* extract was applied to the face by 22 participants [130]. The effect on humans facial skin of a single compound isolated from *Pterocarpus marsupium*, called pterostilbene and administered at 0.4% concentration was evaluated in 38 participants for 8 weeks [131]. Another study took 12 weeks. A study conducted by Ali et al. evaluated phenolic-rich *Acacia nilotica* 3% extract [132], while that carried out by Khan et al. evaluated both *Hippophae rhamnoides* and *Cassia fistula* extracts applied at a concentration of 500 mg to cheeks of 11 and 25 volunteers, respectively [133].

On the other hand, ointment with *Piper nigrum* extract as well as its constituent—a alkaloid piperine at concentration of 5 mg/mL and 2 mg/mL, respectively promote melanocyte activity. Pigmentation was achieved in all the treated areas of 3 vitiligo patients during 12 weeks [134]. Similar effects were observed for 20 patients treated for 12 weeks with ointment containing *Psoralea corylifolia* seed powder (10% w/w). Ointment could be an effective monotherapy for small circular white lesions of vitiligo [135].

Three studies involved oral administration of plant formulations in forms of syrup, tablets or infusion. Aafi et al. show that extracts of *Ziziphus jujuba* and other herbal plants rich in phenolics and flavonoids, used for 8 weeks by 46 healthy volunteers have a positive effect on patients with facial skin hyperpigmentation and can be used to treat this skin disorder. One daily dose of 7.5 mL of syrup containing *Ziziphus jujuba* was applied: 30% wt/wt, *Berberis vulgaris*: 10% wt/wt, *Rhus coriaria* 10% wt/wt, *Prunus domestica* 7% wt/wt, and *Rosa damascene* 3% wt/wt [136]. In addition, Cloucci et al. indicate that combination of *Phyllanthus emblica* extract and vitamin E and caroteinoids showed a valuable instrument to increase the effectiveness of vitiligo treatments. Sixty-five subjects treated with one tablet of an oral supplement containing *Phyllanthus emblica* (100 mg), vitamin E (10 mg),
and carotenoids (4.7 mg) three times/day for 6 months had a mild repigmentation on the head/neck regions and on the trunk [137]. Resende et al. revealed that combination of Solanum paniculatum, Jacaranda brasiliensis and Sonchus oleraceus extracts showed beneficial properties in the therapy of patients with vitiligo. Consumption of a 800 mL infusion per day (concentration of 15 g of each plant, in total 45 g/2 L) for one year resulted in depigmentation, manifesting with 80% or more of depigmented patches [138].

8. In Vitro Studies

Detailed analyses of the modulation of melanogenesis upon treatment with plant extracts and isolated plant compounds in in vitro model were presented in our previous study [60]. However, selected investigations of plant extracts and pure plant compounds on in vivo models, given above, were also conducted on melanocyte monocultures. They included an analysis of gene expression and signaling pathways modulation after treatment.

It was revealed that Cyrtomium fortunei [109], Panax ginseng [116], Artocarpus chama [72] and Punica granatum [124] extracts suppress cellular melanogenesis. Lespedeza bicolor [112] and Rhododendron schlippenbachii [113] extracts show the opposite effect. Rosa gallica and Aster yomena extracts evoke skin whitening by modulation of MAPKs [126] and ERK and AKT [130] signaling. An opposite response via modulation of p38 signaling was observed after application of Baccharoides anthelmintica [118] and Nelumbo nucifera [110] extracts. The first one exerts an anti-melanogenic effect, whereas the other one-melanogenic effect. Regulation of cAMP/CREB/MITF and PKA/CREB/MITF axis and suppression of melanogenesis takes place by Nymphaea nouchali [107] and Nelumbo nucifera [106] extracts. Pueraria montana var. lobata exhibits a similar effect by modulation the AKT/GSK3β axis [104].

It was revealed that demethyleugenol β-D-glucopyranoside [85] and epicatechin-3-gallate [100] modulate the expression of MITF, TYR, TYRP-1 or TYRP-2. In addition, linolenic acid and linoleic acid significantly inhibit melanin production by blocking MRC1 signaling [77]. Arctigenin reduce the cellular cAMP level followed by suppression of melanin production [86]. The cAMP-CERB-MITF axis is inhibited by jujuboside B, epiceanothic acid and 6′′′-feruloylspinosin [102] and melanogenesis is limited. Sweroside [94] and isomaltol glycoside [97] influenced AKT and ERK activation and decrease melanin synthesis.

The detailed information about the impact of given above plant extracts and pure compounds on melanocytes biology are presented in Tables 3 and 4. According to that studies, analyzed extracts and pure compounds were noncytotoxic towards melanocytes in the range of tested concentration.

Table 3. The effects of selected plant extracts on melanocytes biology.

| Name of the Species                      | Type of Cell            | Tested Concentration | Biological Properties                                         | Ref.         |
|------------------------------------------|-------------------------|----------------------|----------------------------------------------------------------|--------------|
| Artocarpus chama Buch.-Ham./Moraceae     | B16 melanoma cells      | 100 µg/mL            | TYR and melanin biosynthesis inhibitory effect                | [72]         |
| Aster yomena (Kitam.) Honda/Asteraceae    | B16 melanoma cells      | 15–120 µg/mL         | Melanin biosynthesis inhibitory effect, modulation of CREB, MITF, TYR1, and TYR2 expression | [130]        |
| Cyrtomium fortunei J.Sm./Polypodiaceae   | Melan-a cells           | 100 µg/mL            | TYR and melanin biosynthesis inhibitory effect                | [109]        |
| Lespedeza bicolor Turcz./Fabaceae        | B16 melanoma cells      | 5–20 µg/mL           | TYR and melanin biosynthesis activatory effect                | [112]        |
| Nelumbo nucifera Gaertn./Nelumbonaceae   | B16 melanoma cells      | 10–20 µg/mL          | TYR and melanin biosynthesis inhibitory effect, modulation of TYR1 expression | [110]        |
| Nelumbo nucifera Gaertn./Nelumbonaceae   | B16 melanoma cells      | 0.3–0.5 mg/mL        | TYR and melanin biosynthesis inhibitory effect, modulation of TYR1 and MITF expression | [106]        |
Table 3. Cont.

| Name of the Species                                      | Type of Cell                  | Tested Concentration | Biological Properties                                                                 | Ref. |
|----------------------------------------------------------|------------------------------|----------------------|---------------------------------------------------------------------------------------|------|
| Nymphaea nouchali Burm.f./Nymphaeaceae                  | Melan-a cells                | 3–30 µg/mL           | TYR and melanin biosynthesis inhibitory effect, modulation of TYRP1, TYRP-2 and MITF expression | [107]|
| Panax ginseng C.A.Mey./Araliaceae                       | B16 melanoma cells           | 500 µg/mL and 1 mg/mL | TYR and melanin biosynthesis inhibitory effect                                        | [116]|
| Pueraria montana var. lohata (Willd.) Maesen and S.M.Almeida ex Sanjappa and Predeep/Fabaceae | B16 melanoma cells           | 10–100 µg/mL         | modulation of TYR and TYRP1 expression                                                  | [104]|
| Punica granatum L./Lythraceae                           | B16 melanoma cells           | 0.02 mg/mL           | TYR and melanin biosynthesis inhibitory effect                                          | [124]|
| Rhododendron schlippenbachii Maxim./Ericaceae            | B16 melanoma cells           | 5–20 µg/mL           | TYR and melanin biosynthesis activatory effect                                          | [113]|
| Rosa gallica L./Rosaceae                                | B16 melanoma cells           | 50–200 µg/mL         | TYR and melanin biosynthesis inhibitory effect, modulation of ERK, JNK, p38 and MITF expression | [126]|
| Baccharoides anthelmintica (L.) Moench/Asteraceae        | B16 melanoma cells           | 1–5 µg/mL            | TYR and melanin biosynthesis activatory effect, modulation of MITF expression           | [118]|

Table 4. The effects of selected plant pure compounds on melanocytes biology.

| Name of the Pure Compounds | Type of Cell                  | Tested Concentration | Biological Properties                                                                 | Ref. |
|----------------------------|------------------------------|----------------------|---------------------------------------------------------------------------------------|------|
| arctigenin                 | B16 melanoma cells           | TYR and melanin biosynthesis inhibitory effect                      | [86]|
| demethyleugenol β-D-glucopyranoside | Melan-a cells                  | 5–10 µg/mL           | TYR and melanin biosynthesis inhibitory effect, modulation of TYRP1 and MITF expression | [85]|
| epicatechin-3-gallate      | B16 melanoma cells           | 25–200 µM            | TYR and melanin biosynthesis inhibitory effect, modulation of TYRP1, TYRP2 and MITF expression | [100]|
| isomaltol glycoside        | B16 melanoma cells           | 25–100 µg/mL         | TYR and melanin biosynthesis inhibitory effect, modulation of TYRP1 and MITF expression | [97]|
| jujuboside B, epicatecholic acid and 6′′′-feruloylspinosin | B16 melanoma cells                  | 20 µM                | TYR and melanin biosynthesis inhibitory effect, modulation of MITF expression           | [102]|
| linolenic acid and linoleic acid | B16 melanoma cells             | 10–100 nM            | TYR and mela-nin biosynthe-sis inhibitory effect                                      | [77]|
| sweroside                  | Melan-a cells                | 300 µM               | TYR and mela-nin biosynthe-sis inhibitory effect, modulation of TYRP1 and TYRP2 expres-sion | [94]|

9. The Patented Plant-Based Compositions and Their Role in the Therapy of Hyperpigmentation and Hypopigmentation

Inventions in the field of cosmetics, including plant-based compositions of topically applied skin care products, effective in reducing and enhancing pigmentation are presented in Tables 5 and 6. Some patented formulations contain also pure compounds isolated from plants. For example, the effect of skin lightening was exhibited for rebaudioside A, a diterpene glycoside obtained from Stevia genus (WO2014132217A1), B salvianolic acid, a phenolic acid from Salviae miltiorrhize, (CN102895308A) and madecassoside, a triterpenoid saponin from Centella asiatica (WO2014003224A1). In contrast, silybin, a flavonoid from Silybum marianum shows stimulating properties for skin pigmentation (US8569358B2).
| Name of the Species/Part of the Plants                                                                 | Number of Patents                                                                                           |
|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| *Alpinia officinarum*–rhizome, *Physalis angulate*–leaves, stems and roots, *Bidens pilosa*–leaves,     | US20170100326A1                                                                                             |
| *Achyrocline satureioides*–flowers *Amorphophallus konjac*–tuber                                        | US20160184218A1                                                                                             |
| *Aspalathus Linearis*, *Matricaria*, *Saxifraga*, *Astragalus*, *Taraxacum officinale/mongolicum*,       | US9801809B2                                                                                                 |
| *Carthamus tinctorius*, *Sophora flavescentis*, or *Chrysanthemum morifolium*                          |                                                                                                             |
| *Atractylodis macrocephalae rhizoma*, *Glycyrrhiza radix et rhizoma*, *Angelicae sinensis radix*,       | US9511013B2                                                                                                 |
| *Carpocephalum alatum*–flowers, *Butea monosperma* (Identified compound: butrin)                        |                                                                                                             |
| *Fabiana imbricata*–whole plant, or its portion, including stems, leaves, nectar and/or flower petals   | US20150342853A1                                                                                             |
| *Ficus serum fraction derived from fresh Ficus cell juice of fresh Ficus leaves*                         | US20120201768A1                                                                                             |
| *Glycyrrhiza glabra*, *Rubia cordifolia*, *Symlocos racemosa*, *Terminalia arjuna*, *Myristica fragrans* |                                                                                                             |
| *Phyllanthus emblica*–fruits, *Bellis perennis*–flowers, *Glycyrrhiza glabra*–roots                   | US20160074316A1                                                                                             |
| *Piper longum*–roots                                                                                 | US2014014515A2                                                                                             |
| *Quassia undulata*–leaves                                                                            | US20160074314A1                                                                                             |
| *Rhododendron moupinense*–whole plant                                                                  | US9333167B2                                                                                                 |
| *Salvia hispanica*–seeds                                                                              | US8916212B2                                                                                                 |
Table 6. Patented topical anti-hypopigmentation plant-based compositions.

| Name of the Species/Part of the Plants | Number of Patents |
|----------------------------------------|-------------------|
| **Coreopsis tinctoria**                | CN104523796A      |
| Cortex Dictami, Rhizoma Gastrodiae, Flos Carthami, Fructus Psoraleae, Radix Salviae Militorrhizae, Radix Angelicae Dahuricae, Flos Lonicerae, Fructus Mume, Radix Astragali, Borneolum Syntheticum, Scorpio, Fructus Lycii, Radix Saposhnikoviae | CN104474298A      |
| Folium Fici, Herba Spirodelae and Pericarpium Citri junoris                     | CN102274359B      |
| Folium Ginkgo, Herba Spirodelae, Pericarpium Citri junoris                      | CN102846500A      |
| Fructus Mume, Fructus Psoraleae, Rhizoma Zingiberis Recens,                      | CN104338104A      |
| Fructus Mume, Fructus Psoraleae, Rhizoma Zingiberis Recens,                      | CN104338104A      |
| Fructus Tribuli, Herba speranskiae tuberculatae, hair Rhizoma Zingiberis Recens, Cortex Cinnamomi, Fructus Psoraleae, Radix Polygoni Multiflori Preparata, Radix Salviae Militorrhizae, Radix Arnebiae (Radix Lithospermi) | CN105535128A      |
| **Gynostemma pentaphyllum** (Isolated compounds: saponins)                       | US20150209376A1   |
| Herba Schizonepetae, Radix Saposhnikoviae, Herba Menthae, Scorpio, Periostracum Cicadae, Radix Ginseng, Radix Astragali, Semen Persicae, Radix Angelicae Sinensis, Rhizoma Chuanxiong, Radix Paoniae Alba, Radix Rehmanniae Preparata, Radix Notoginseng, Fructus Ligustri Lucidi, Herba Ecliptae, Fructus Psoraleae, Radix Angelicae Dahuricae, Stigma Croci, Fructus Fici, Radix Arnebiae (Radix Lithospermi), Semen Astragali Complanati, Fructus Cnidii, Radix Polygoni Multiflori, Fructus Mume, Borneolum Syntheticum, Flos Caryophylli | CN103385986A      |
| Herba Taraxaci, Radix Rehmanniae, Flos Primulae Vittatae, Radix Salviae Militorrhizae, Stigma Croci | CN104274628A      |
| **Pueraria genus**–roots (Identified ingredient: puerarin)                       | US20120329739A1   |
| Radix Rehmanniae, Radix Angelicae Sinensis, Ramulus Cinnamomi, Rhizoma Chuanxiong, Flos Carthami, Cortex Moutan, Cortex Dictami, Radix Polygoni Multiflori, Fructus Tribuli, Herba Ephedrae, Radix Euphorbiae Fischerianae (Radix Euphorbiae Ebracteolatae), Radix Cyathulae, Fructus Cnidii, Periostracum Cicadae, Flos Lonicerae, Spina Gleditsiae, Radix Saposhnikoviae, Radix Sophorae Flavescentis, Rhizoma Atractylodis, Semen Astragali Complanati, Fructus Ligustri Lucidi, sub-lotus grass, Radix Notoginseng | CN104257857A      |
| **Sophora japonica**                                                            | US8673371B2       |

In addition, an invention entitled “Methods useful in studying or modulating skin or hair pigmentation, plant extracts used in compositions and cosmetic care method” (US8409633B2) presents methods useful in modulation of skin pigmentation. According to its inventors, myosin-X (Myo X) is a crucial protein that controls melanin transfer from melanocytes to keratinocytes. Therefore, compounds that have the ability to impact the expression and activation of Myo X can modulate the skin tone. Accordingly, the molecules that decrease expression of Myo X may reduce skin pigmentation, whereas molecules that increase expression of Myo X may enhance skin pigmentation. The first groups include extracts of the following genus plants: Artocarpus, Cyathea, Secale, Thalassiosira and Buddleja. The second group includes: a soybean extract, preferably a soy seed extract, more preferably a soy seed pericarp extract.

10. Conclusions

This literature review presents the impact of plant extracts or pure compounds on melanogenesis potential in in vivo models. Most of the reviewed studies focus on the
whitening potential of plants. A relatively large number of studies were performed on the zebrafish model. This organism was used to evaluate the melanogenic potential of both plant extracts and pure compounds. Fewer studies were performed on rodent and human models and were mainly focused on the analysis of plant extracts. In rodent models, plant extracts were administered orally or topically to the skin, and with regard to the human model, they were administered mainly topically. In addition, the majority of patented plant-based compositions were formulations containing plant extracts, applied topically to the skin. The authors evaluated extracts isolated from plants belonging to different species and families as well as pure compounds belonging to different chemical classes. Panax ginseng plant, which exhibits significant whitening activity, was the most often studied in various model systems. In contrast, Salvia miltiorrhiza extract repeatedly added to patented plant-based formulations, demonstrated hypopigmentation properties. Selected investigations of plant extracts and pure plant compounds on the vivo models were also conducted on melanocyte monocultures. It was revealed that many phytochemicals are able to modulate different cellular signaling pathways, including those which regulate the expression and activity of melanogenesis-related proteins. In conclusion, molecules of natural origin may play an important role in the therapy of dermatological disorders, including hyperpigmentation and hypopigmentation.

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