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# Phytochemicals; Targeted-Based Therapeutic Approaches for Pigmentation Disorders

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**A B S T R A C T**

Skin pigmentation disorders refer to conditions that affect the color of the skin due to alterations in the production or distribution of melanin, the pigment responsible for skin color. The development of skin pigmentation is a complex process involving various signaling pathways, including the melanin synthesis pathway, the cyclic AMP pathway, and the Wnt signaling pathway. Dysregulation of these pathways can lead to the development of skin pigmentation disorders. Phytotherapeutic approaches have been increasingly studied as a potential treatment for skin pigmentation disorders. This literature review aimed to describe the basic mechanism of melanogenesis, various pathways involved in melanin formation, and certain diseases and their treatment through plant extracts. Plant extracts containing bioactive compounds such as flavonoids, phenolic acids, and tannins have been shown to have anti-pigmentary effects through various mechanisms, including inhibition of tyrosinase activity, reduction of melanin synthesis, and modulation of melanogenesis-related signaling pathways. Skin pigmentation disorders are complex and multifactorial conditions that can significantly impact a person's quality of life. Targeting the signaling pathways involved in pigmentation regulation, particularly through phytotherapeutic approaches, represents a promising avenue for the development of new therapies for these disorders.

## 1. Introduction

Pigmentation is a response to sun exposure and is characterized by irregularly pigmented skin leading to dark areas known as lentigines and light areas known as idiopathic guttate hypomelanosis. This irregular skin hypopigmentation is also accompanied by skin injury where melanocytes are damaged, and traumatic tissue damage heals with unattractive white scars. Post-inflammatory hyperpigmentation is considered an immune response to skin injuries like acne, sunburn, skin disease, irritant contact dermatitis, allergic contact dermatitis, or a traumatic scratch which is in the form of darkening of the skin, and the reason for this reaction is still unknown. Pustule formation due to the burrowing of ingrown hairs beneath the skin surface also causes post-inflammatory hyperpigmentation. Pigmentation problems are commonly seen in Asian Skin because Asian and black skin have more melanin as compared to White ethnicity, and thus, more photoprotection slows down aging. Melanin is an unstable radical that can absorb an electron from highly energetic unstable oxygen species, preventing the activation of collagenase and the resulting dermal damage. Therefore, dark skin typically does not demonstrate photoaging to the same degree as lighter skin.[1-4] This

literature review aimed to describe the basic mechanism of melanogenesis, various pathways involved in melanin formation, and certain diseases and their treatment through plant extracts.

**Melanogenesis plays a role in various skin pigmentation disorders**

Extra melanin produces must be phagocytized or consumed by white blood cells and then removed from the skin to reduce pigmentation irregularities. Low doses of retinol and retinyl propionate in placebo-controlled facial testing (12 weeks duration) proved significantly effective in reducing facial hyperpigmentation. The study of skin and colors of skin is on some serious note and recently developed a lot.[4] The human skin is the largest organ and outer covering of the body. It covers 12 to 15% of the total weight of body. The skin consists of two basic layers, the outer and the inner layer, named epidermis and dermis, respectively. Skin plays a vital role in the body, and there are about five basic functions known. These are photoprotection, Thermoregulation, Immune, barrier function, and cutaneous circulations. Different human skin colors like red, yellow, brown, and blue are known. These layers have some pigments for each color in capillaries, and oxygenated hemoglobin produces a red color. In the epidermis, melanin produces blue and brown colors, and in keratinocytes produces a yellow color. Among these individuals, melanin is the major component that is known for skin color.[5-8]

The skin consists of three different types of cells: keratinocytes, fibroblasts, and melanocytes.[9] Among these melanocytes are the color-producing cells arising from the follicular and interfollicular epidermis, which produces a specific type of lysosomal-related organelle known as the melanosomes. Melanin is the major determining factor for skin color and provides a defense against harmful radiation. It is present in almost all types of organisms. Melanin is the heterogeneous biopolymers of phenolic compounds which are produced, synthesized, and stored in special organelles (melanosomes) via enzymatic complex reactions called melanogenesis.[10,11] As shown in Figure 1, majorly it is divided into two groups: Eumelanin and pheomelanin. Eumelanin (black/brown) in color is different in plants and animals. Earlier in 1895, it was considered that in plants, it is catechol melanin, while in mammalian, it is indole melanin. The key compounds are catechol and indole-5,6-quinone. It is produced by the oxidation of tyrosine to o-dihydroxyphenylalanine (DOPA) and from DOPA to DOPA quinone and DOPA chrome which undergoes further to 5,6-dihydroxyindole (DHI) or 5,6-dihydroxyindole-2-carboxylic acid (DHICA).[8-10]

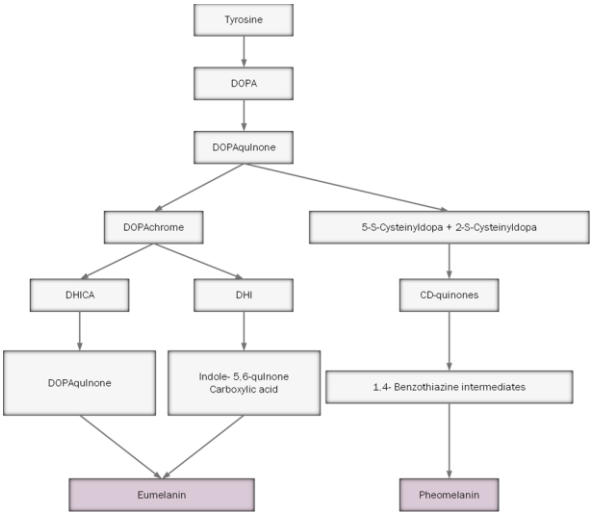


Figure 1. Melanogenesis is the basic pathway for the synthesis of eumelanin and pheomelanin. Tyrosinase and their related proteins TRP-1 and TRP-2 play a key role in the degradation and hydroxylation and lead to the formation of melanin.

Human skin has a variety of colors, from the darkest brown to the lightest hues. Melanin, a heterogeneous biopolymer is responsible for skin coloration as well as the protection of the internal body from external assaults. The production of melanin comes from molecular and cellular interactions of melanocytes, keratinocytes, and fibroblasts. A slight change in melanin production leads to pigmentation disorder, whether in a positive or negative manner. Thus, the required amount of melanin must be available for the skin. When the required amount of melanin is not available for the skin, it results in hyperpigmentation (excess of melanin) or hypopigmentation (lesser amount of melanin). Hypopigmentation results from the limiting number of melanocytes. It may be congenital or acquired, diffused or localized, or linked with a distinct distribution manner. Hyperpigmentation is the increase in the production of melanin or the activity of melanocytes, together with the late breakdown and elimination of melanin. There are about 4000 known skin diseases linked with changes in skin color.[10,11]

**Phytotherapeutic approach**

Phytotherapy, or the use of plant-derived substances for medicinal purposes, has been employed in the treatment of skin pigmentation disorders. Some plant extracts have been found to have depigmenting effects, while others may function as melanogenic stimulators.

***Angelica dahurica***

*A. dahurica* belongs to the family Apiaceae. Studies reveal that certain coumarins and flavonoids present in its roots are responsible for anti-inflammatory action and tyrosinase-inhibitory properties, and it has been used in Chinese medicines for treating various diseases throughout history. The structure of newly found compounds that showed DPPH radical scavenging activities with IC50 values close to that of L-ascorbic acid (83.32±0.26) were angelicoside A i.e., C20H24O8 exhibited a good radical scavenging activity with 69.80±0.36% inhibition, angelicol B C18H20O6 with 74.40±0.35 and (1S)-2-O-E-feruloyl-1-(4-hydroxyphenyl) ethane-1,2-diol with 72.74±0.30 inhibition. However weaker anti-tyrosinase activity was observed in all isolated compounds as compared to kojic acid inhibition (26.00±0.67%, IC50=44.29±0.06 µM).[12]

***Artocarpus sp.***

Several isolated compounds from the Moraceae family, including *Artocarpus chama, A. hirsutus* Lam., *A. gomezianus*, *A.heterophyllus* were studied for suppressing pigmentation. The strong anti-tyrosinase activity of *A. chama* was reported in an intracellular and enzymatic assay. However, its petroleum ether extract could stimulate melanogenesis. Moreover, its ethyl acetate stem extract showed significant toxicity to Zebrafish. The ethyl acetate extract of *A. chama* showed 64.41% ±1.27% inhibition at 5 µg/mL, and tyrosinase enzyme inhibition reduces melanogenesis. Oxyresveratrol has been isolated from several species of Artocarpus, including *A.hirsutus* Lam., *A.lakoocha* which exhibits strong melanogenesis inhibition i.e., 83 times greater than kojic acid and anti-tyrosinase activity i.e., 142 times potent than kojic acid. Hydroglycolic extracts of *A.lakoocha* heartwood show melanin inhibition in both in vitro and vivo analysis.[13,14]

***Acacia nilotica***

*A. nilotica* is a commonly used medicinal plant in Sudan. Anti-melanin vitro activity of *A. nilotica* is observed because of catechin derivative compounds, which show an inhibitory effect for tyrosinase protein and thus can treat hyperpigmentation. More clinical trials and investigations in pigment cell assays are needed for further applications in cosmetics formulation.[15]

***Arthrophytum scoparium***

The medicinal importance of this plant is because of several bioactivities such as antioxidant, anti-

plasmodial, hepatoprotective, and anti-cancer activities. *A. scoparium* ethanol extract showed a significant melanogenesis inhibitory effect in B16 melanoma cells. *A.scoparium* prevents the TRP1 gene expression and increases the Dct gene regulation according to PCR results. Phenomena of inducing cell differentiation along with morphological changes in B16 cells may be due to Dct gene expression. Some extracted identified phenolic compounds in Ascoparium are coumaric acid, cinnamic acid, chrysoeriol, cyanidin, catechol and caffeoylquinic acid, which are responsible for melanogenesis inhibitory effects and thus, making *A. scoparium* a potential whitening agent. Geographically, this halophytic shrub is widely present in North Africa, Turkey, Iran, Syria, Iraq and have been traditionally used for eye disorders and as a snuff powder.[16]

**Asparagus**

Hydrothermal treatment of asparagus extract ASEH leads to the increased concentration of gallic acid, coumaric acid and hydroxybenzoic acid, which significantly enhance the anti-tyrosinase and antioxidant activity in B16F10 melanoma cells. Recent studies reveal 39.78% intracellular tyrosinase inhibition in B16F10 melanoma cells at 200 µg/mL ASEH concentration.[17]

***Cassipourea flanaganii***

*C. flanaganni* is about 12 m tall with slender stems and dark grey bark, distributed in South Africa. It is considered a potentially safer skin-lightening agent alternative to hydroquinone. The human primary epidermal melanocyte cells are used for checking anti-tyrosinase activity and melanin inhibition of stem bark extract of *C. flanaganii.* Its higher concentration with a longer period (48 hours) is required to evaluate its efficiency. Extract compounds ent-manoyl oxide and ent-kaur-16-en-19-al show strong tyrosinase inhibition at one hundred µM. Some other compounds from *C. flanaganni* i.e., ent-kaur-16-en-19-al, ent-manoyl oxide, guinesine A, guinesine B, guinesine C, lichenxanthone, 2,4-dihydroxy-3,6-dimethyl benzoic acid methyl ester, lynoside, lupeol and β-amyrin show effect on melanogenesis respective to time-concentration with low cytotoxicity and with no dependency on tyrosinase activity.[11]

***Cassipourea congoensis***

This shrub is like 3-5 m high small tree geographically grows in Africa, Senegal to Nigeria, Uganda, Tanzania, Malawi and across Uganda to Congo. Among a few newly found compounds, a cycloartane triterpenoids 26-hydroxy-3-keto-24-methylene cycloartan-30-oic acid and, a known mahuannin, 7-methoxygeranin A were observed showing a strong anti-tyrosinase activity by inhibiting the TRP1 and TRP2 mechanism by lowering the rate at 10 µM of melanin production. *C.congoensis* basically stops the conversion of tyrosine to the precursor of melanin, dihydroxyphenylalanine and thus preventing further hyperpigmentation.[18]

***Camellia sinesis***

Green tea extracted from the leaves of *C.sinesis* contains catechins, polysaccharides, amino acids and lipids. Among all, catechin categories, including epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin-3-gallat (EGCG) show strong antioxidant activity, increasing glucose metabolism in adipocytes and blocking inflammatory response. EGCG has been studied more because of its cancer chemo-preventive properties and anti-inflammatory activities. *C. sinesis* shows anti-melanin properties despite removing its catechins. However, its metabolic pathway or action mechanism is still needed to be studied.[19]

***Combretum micranthum***

*C. micranthum* extract is potentially active for browning inhibition because of various phenolic and triterpenoid compounds with anti-tyrosinase activities. Not only its ethanol extract but water extract shows strong dose-dependent inhibitory activities against tyrosinase enzyme. The most dominant compounds in CM leaves included dihydrodaidzein-7-

O-glucuronide (isoflavonoid), micromeric acid (triterpenoid) and syringic acid (phenolic acid) with relative percentages of 33.38, 16.59, and 11.38%, respectively.[20]

***Dendrobium tosaens***

*D. tosaens* grow in topical and sub-tropical regions and is used in Chinese folk medicines for various disorders such as nourishing Yin. *D. tosaens* are rich in polysaccharides, alkaloids, fluorenones, sesquiterpenoids, amino acids, bibenzyls, phenanthrenes, and trace elements. The RT + 50E extract of *D. tosaens* exhibits the strongest mushroom tyrosinase inhibition ability at IC50 6.40 ± 0.30 mg/mL. Therefore, *D. tosaens* can be potential lightening material in skincare. Cell-based assays should also be further studied to investigate melanogenesis inhibition in vivo.[21]

***Euphorbia hirta***

A significant amount of quercetin compounds was detected in *Euphorbia hirta* extract that could be responsible for strong anti-tyrosinase activity especially a high percentage of quercetin-3-O-(6″-malonyl-glucoside) (flavanol), and 4-hydroxycoumarin (phenolic acid) with relative proportions of 11.25 and 11.14%, respectively. Quercetin and its derivatives are known to be anti-tyrosinase. However, this compound must go through more studies for further evaluation. Enzymatic kinetic studies revealed that morin (29.38%) present in *E.hirta* extract inhibited tyrosinase by binding at the tyrosinase active site by hydrogen bonds and van der Waals interaction, which resulted in conformational and arrangement changes in the enzyme. Chlorogenic acid and kaempferol were also reported (80). Old studies showed that kaempferol-3-O-(6-O-malonyl)-β-d-glucopyranoside and quercetin-3-O-(6-O-malonyl)-β-d-glucopyranoside from mulberry leaves were tyrosinase inhibitors.[22]

***Garcinia atroviridis***

*G. atroviridis* belongs to the family Clusiaceae and is native to Indonesia, Malaysia and Thailand. Aqueous extracts of its fruits show antihyperlipidemic and antifungal activity along with inhibiting acetylcholinesterase. *G. atroviridis* fruit pericarp extract treatment significantly reduced melanin content in α-MSH-stimulated B16F10 cells (IC50 of 40.72 ± 1.83 μg/mL) which shows its tyrosinase inhibitory action. This extract has whitening potential for treating hyperpigmentation. Further studies aim to identify the signaling pathway that leads to anti-tyrosinase action and major active constituents of *G.atroviridis* related to this activity.[23]

***Gracilaria fisheri***

Sulfated galactans derived from *Gracilaria fisheri* showed an inhibitory effect on the activity of cellular tyrosinase and melanin production in B16F10 melanoma cells by downregulating the MITF, TRP-1, TRP-2, tyrosinase mRNA and protein. Hence, it was concluded that SG could be a desirable alternative to skin-whitening ingredients for treating hyperpigmentation disorder. However, sulfated galactan evaluation in vitro studies of mushroom tyrosinase activity showed no inhibition on cellular tyrosinase activity.[24]

***Glycyrrhiza glabra***

*G. glabra* belongs to the family Fabaceae and is commonly grown in Turkey, Italy, China, Syria, Uzbekistan, and Pakistan. This perennial herb has been widely utilized as a flavoring agent and in folk medicines for skin eruptions, diabetes, respiratory disorders, and gastrointestinal diseases. Glabridin is considered an active compound for anti-tyrosinase activity in melanocytes. However, glabridin shows a poor ability for skin penetration and instability in formulations. This can be resolved by using a combination of *A. lakoocha* heartwood and *G. glabra* root extract in skin care formulations for treating hyperpigmentation disorders. Further investigation should be done for its long-term application.[25]

***Hizikia fusiforme***

*H. fusiforme* is an edible brown algae and has been used in Asian cuisine. Celluclast-assisted extract of *Hizikia fusiforme* consists of sulphated polysaccharides (SP), which are responsible for anti-wrinkle and antioxidant properties. Moreover, *H. fusiforme* SP inhibits the melanin-related protein expressions such as TRP-1, TRP-2 via downregulating MITF expression in α-MSH stimulated B16F10 melanoma cells in vitro studies. *H.fusiforme* SP is quite toxic to B16F10 cells. Hence, 50 µg/mL is the determined highest concentration in further studies of HFPS on B16F10 cells. Further biological vivo evaluation should be done for cosmeceutical application.[26]

***Hypericum calycinum***

Hypericaceae family species is found in all continents except Antarctica. Methanol extract of *H.calycinum* is rich in chlorogenic acid, isoquercitrin, quercitrin, gallic acid and quinic acid. Some studies claim gallic acid and quinic acid to be strong anti-tyrosinase, and that makes *H.calycinum* a potential source of treating hyperpigmentation. Its chemical behavior should be studied further.[27]

***Juglans mandshurica***

*J. mandshurica* has been used in folk medicines for cancer, diarrhea, dermatosis, gastritis, leucorrhoea, and dermatologically in allergic-dermatitis-like skin lesions in China and Korea. Studies show the inhibitory effect of stem bark & flower extract on tyrosinase activity and melanogenesis. 2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]-1,3-propanediol is involved in increasing the ERK pathway, that results in the degradation of MITF. Anti-melanogenesis activity is observed in both B16F10 melanoma cells and PHEMs. More clinical investigation will provide the lead of using it in the medical field.[28]

***Kummerowia striata***

*K. striata* is an annual plant native to China, Japan and Korea. Vitro and cell-culture model systems of *K. striata* extract show a significant effect on melanin biosynthesis process. It exhibits decreased melanin production in melanoma cells by downregulating the melanogenic genes and proteins such as tyrosinase, TRP-1, TRP-2 and MITF. Identified compounds in *K. striata* extract are luteolin, rosmarinic acid, genistein, p-coumaric acid, quercetin and (+)-catechin. Its compounds, specifically p-coumaric acid and quercetin, can be promising whitening and anti-aging agents in cosmetic formulations. Further studies should be done to find more of its active constituents, including in vivo evaluations.[29]

***Litchi chinensis***

*L. chinensis* belongs to family Sapindaceae family native to Southeast Asia and Philippines, Malay, China, Indonesia, Peninsula, and Guinea. *L.chinensis* crude extracts obtained with methanol and dichloromethane are used for vitro testing. Litchi chinensis exhibits high anti-tyrosinase activity (95.1 ± 0.06%). Through a bio-guided purification followed by molecular characterization of extracts from the roots of *Litchi chinensis* Sonn., the structure of cinnamtannin D2 responsible for the biological activity was obtained. Further trials can prove the potential use of this class of compounds.[30]

***Morus alba* L.**

Mulberry is from Moraceae family and is widely present in tropical to temperate regions. Pulsed Electric Field PEF Extraction is used to extract bioactive compounds such as phenolic compounds from *M. alba* leaves with 95% v/v ethanol as cosmeceutical ingredients for topical application. PEF extraction from *M. alba* leaves enhances the phenolic extraction that results in obtaining more anti-tyrosinase actives with IC50 values against tyrosinase activity on l-tyrosine and l-DOPA of 54.1 ± 5.4 and 32.2 ± 3.4 µg/mL. Promising natural ingredients for anti-aging and whitening are observed. However, the mechanism of action needs further studies.[31]

***Nelumbo nucifera***

*N. nucifera* is an Asian aquatic plant used in cooking as folk medicine. NLE is effective against hepatic injuries, atherosclerosis, obesity, breast cancer, diabetes, and hepatocarcinogenesis. *N. nucifera* leaves extracts NLE shows an inhibitory effect on melanogenesis and epidermal hyperplasia on guinea pigs by downregulating the ERK and CREB pathways that lead to a decrease in mRNA expression of MITF, tyrosinase and TRP-1. Both vitro and vivo studies prove tyrosinase inhibition through the MITF pathway. Among six identified phenolic compounds in *N. nucifera*, catechin(7.42 ± 0.69 μg/mg NLE) and gallic acid (6.11 ± 0.15 μg/mg NLE) are reported as the reason for anti-tyrosinase behavior. However, the synergistic effect of these natural plant extracts leads to desired benefits that cannot be as beneficial if using a single compound of NLE. The mechanism of these synergistic interactions of polyphenolic compounds of NLE deserves comprehensive investigation.[32]

***Nigella sativa***

*N. sativa* is native to the Middle East, the Indian subcontinent, Eastern Europe, Northern Africa, west and middle of Asia. Several studies reported its antimicrobial, anti-inflammatory, antioxidant, anticarcinogenic and immunological effects. Thymocid is a seed extract of *N. sativa*. Thymocid (2.5 and 20 μg/mL) suppressed the production of melanin (57.5%, and 38.4%) by inhibiting the mRNA expressions related to MITF, TRP-1, TRP-2. In murine melanoma B16F10 cell. Thymocid inhibits the synthesis of melanin by decreasing the activity of cellular tyrosinase by 20.9% at the highest tested concentration (20 μg/mL) in vitro enzymatic and cell-based assays. Further investigations are required for utilizing *N.sativa* seed extract in cosmeceutical applications.[33]

***Nymphaea nouchali***

*N. nouchali* flower extract reduces melanin synthesis in both vitro and vivo by suppressing the expression of MITF via cAMP with a decrease in CREB phosphorylation and inducing phosphorylation of JNK, p38, and ERK1/2. This decreases levels of TYR, TRP-1 and TRP-2 as well. Cellular tyrosinase activity is suppressed with an IC50 value of 9.85 ± 0.11 μg/mL by its flower extract. This inhibition of melanin and strong anti-tyrosinase activity may be because of the synergistic effect of polyphenolic compounds present in *N. nouchali* extract. Moreover, almost no cytotoxicity makes this extract a strong depigmentation agent for future cosmeceutical applications.[34]

***Oenothera laciniata***

*O. laciniata* belongs to the genus Oenothera which is a herbeceous flowering plant native to America. Various biological activities observed in this genus are anti-inflammatory, anti-viral, anti-aging, anti-microbial, anti-melanogenic, and anti-tumor. The antioxidant activity of the methanol extract of *O. laciniata* was studied in vitro assays with a correlation to radical scavenging activity and total phenolic content. However, the biological activity of phytoconstituents of this plant still needs to be investigated more.[35]

***Orostachys japonicas***

*O. japonicus* has been widely used in Asian folk medicines for hepatitis, fever, arthritis, cancers, and rhinorrhagia. Some studies reveal the potential use of its extract for skin treatments such as connective tissue maintenance and melanin inhibition. Quercetin, astragalin, kaempferol, afzelin, quercitrin and isoquercetin have been isolated from *O .japanicus*. In human fibroblast cells, *O. japonicus* extract exhibits approx. 70% suppression of tyrosinase activity at 500 μg/ml concentration. Its extract inhibits the melanogenesis in murine B16F10 melanoma cells with a drastic change due to the induced phosphorylation of Erk and Akt. The phosphorylation of MITF is increased by the extract. No change in the JNK pathway is observed.[36]

***Oroxylum indicum***

*O. indicum* is a tropical tree commonly found in Japan, China, India, Malaysia and Sri Lanka. Recent research shows that this plant is rich in polyphenols and exhibits properties like immunostimulant, antiulcer, anti-inflammatory, anticancer and antioxidant. *O.indicum* underlying molecular mechanism in melan-a cells suggests its promising use for treating a variety of skin troubles like aging, hyperpigmentation and cancer because ethyl acetate fraction of its seeds shows anti-tyrosinase activity at its monophenolase phase by steric hindrance i.e., causing hindrance to the binding site of the substrate to tyrosinase enzyme, that changes protein conformation and take enzymatic activity. This suppressed the mRNA level of MITF. The mechanisms through which *O.indicum* seed extract extenuated melanin production by downregulating MITF expression through the interference with the phosphorylation of p38, extracellular signal-regulated kinase 1/2 (ERK1/2), and c-Jun N-terminal kinase (JNK), with the reversal of OISEA-induced melanogenesis inhibition after treatment with the specific inhibitors SB239063, U0126, and SP600125 ERK1/2, JNK, and p38 phosphorylation, besides decreasing tyrosinase, TYRP-1, and TYRP-2 levels. Chrysin and baichalein found in OISEA inhibited melanin formation 60% and 20%, at 100 μM and 50 μM, respectively. *O. indicum* seed ethyl acetate extract suppressed melanin production by 58% at 30 μg/mL. Further studies can be done to evaluate its therapeutic use in folk medicines for fever, jaundice, ulcer, diarrhea and cancer. Moreover, its whitening property may lead to *O. indicum*-based cosmetics in the future and a potential whitening agent in the food industry as well.[37]

***Paederia foetida***

*Paederia foetida* L. belongs to Rubiaceae family and is widely distributed in Asia. *P. foetida* has been traditionally used to treat gastrointestinal disorders. Besides its other pharmaceutical activities, its anti-tyrosinase or anti melanin activity is not sufficiently investigated. However, a study confirms the inhibitory effect of *P.foetida* L. extract on melanin synthesis in B16F10 cells treated with alpha-Melanocyte-stimulating hormone i.e., melanin contents of *P.foetida* (50, 100, and 200 μg/mL) was reduced by 13.7%, 22.3%, and 26%, respectively, compared to the α-MSH treated alone group. *P.foetida* reduced the expression level of melanogenic enzyme and MITF via the MAPK signaling pathway, thus exerting anti-melanogenic effects in B16F10 cells. Extensive research for analyzing its individual components responsible for whitening property is still not done so far.[38]

***Polygonum tinctorium***

Anti-tyrosinase and anti-melanin effect of *P. tinctorium* fermented flower extract in 200 nM α-MSH-treated group was observed with a positive control by 32% and 43% in 250 μg/mL, respectively. Western blots analysis showed significant inhibition of TRP-1, TRP-2, tyrosinase and MITF expression through the AKT signaling pathway and by increasing ERK phosphorylation. Human skin irritation test proves it is a safe raw material for cosmetic formulation.[39]

***Phragmites communis***

*P. communis* is a hydrophytic specie found in Korea, China and Japan. This medicinal herb is commonly used to remove heat, ease the mind, promote the production of body fluid, and relieve omitting. Effective for lipid-lowering antioxidant activity and tyrosinase inhibition. Young leaves water extract of *P. communis* decreased the intracellular melanin content in B16F10 murine melanoma cells by suppressing mRNA expression of TRP-1, TRP-2 and of MITF, by upregulating the ERK and AKT and down-regulated the p38 and cAMP response element-binding protein (CREB) in a dose-dependent manner. Anti-melanogenesis activity induced by *P. communis* young leaves extract is associated with phosphorylation of ERK and AKT, which promotes MITF degradation. Certain compounds present in *P. communis* like methyl gallate, p-hydroxy cinnamic acid, (+)-lyoniresionol, (+)-lyoniresinol-90 -O-b-D-

glucopyranoside, b-sitosterol, vanillic acid, and ferulic acid inhibit tyrosinase activity and melanin production in a-MSH stimulated B16F10 melanoma cells. Further experiments are required for stable skin care product formulation with its anti-melanogenesis constituents to treat hyperpigmentation.[40]

***Phyllostachys nigra* henosis**

A bamboo specie with attractive bioactive compounds belongs to the family Poaceae. Noticeable active compounds include e8-C-glucosyl apigenin, luteolin derivatives, chlorogenic acid, caffeic acid, p-coumaric acid, and ferulic acid. The IC50 values of *P.nigra* 80% ethanol extract, ascorbic acid, and p-coumaric acid for tyrosinase inhibition were 243.7, 38.5, and 87.0 µg/mL, respectively in a cell-free system. No cytotoxicity was observed by *P.nigra* EtOH with potent inhibition in mRNA expression of all genes; tyrosinase, TRP-1, TRP-2 and MITF (89.36% at 25 µg/mL) in B16F10 cells. PKA/CREB signaling mechanism was suppressed.[41]

***Photinia x fraseri***

Proanthocyanidins isolated from *Photinia x fraseri* leaves exhibit strong anti-tyrosinase activity via chelation of copper ions and by disturbing o-quinone production. It decreases melanin synthesis by downregulating the MITF expression and inhibits other tyrosinase activities related to TRP-1 which results in the apoptosis of melanoma cells. The main components found in Proanthocyanidins are oligomer, catechin and epicatechin. Current studies support its further use in drug development for treating melanogenesis.[42]

***Scabiosa columbaria***

*S. columbaria* is an evergreen perennial herb widely distributed in South Africa. Roots and leaves have been used for medical purposes since old times. Its constituents are anti-fungal, anti-bacterial and anti-protozoan. The anti-tyrosinase characteristic of *S. columbaria* could be due to extracting competing against the melanin substrate such as L-Dopa for the same active site of the enzyme or affects the chelating activity of Cu at the active site of the enzyme as a competitive inhibitor, which ultimately prevents binding of Cu ion to oxygen leading to deactivation of tyrosinase enzyme. Another FRAP assay shows the reducing power of *S.columbaria* due to polyphenol compounds in its extract which break the free radical chain by donating oxygen as free radical scavengers and also prevent hyperpigmentation. Hence, hyperpigmentation due to oxidative damage caused by free radicals can be suppressed by *S.columbaria* methanol extract. However, in Vivo studies should be done for biological activity.[43]

***S. toxoids***

Ethyl acetate and methanol wood extracts of *S. toxoids* reduced the size of black spots on Zebrafish but showed toxicity to Zebrafish, resulting in coagulation of embryo and lack of heartbeat. About 54.37% ±1.55% inhibition at 50 µg/mL was reported by its ethyl acetate extract resulting in reduced melanin content in both enzymatic and intracellular assays. Investigation into human melanocytes should be done for biological analysis. Further isolation and study of its constituents will lead to the cosmetic formulation of new whitening agents.[13]

***Sorghum bicolor***

Ethanol extract of *S.bicolor* effectively decreased IBMX-induced MITF expression by downregulating the related proteins in B16F10 melanoma cells. This prevented the first step of melanogenesis by inhibiting α-glucosidase and tyrosinase using L-tyrosine and L-DOPA as substrates. The major compounds were analyzed as 9-HODE, tricin and 1,3-O-dicaffeoylglycerol. *S.bicolor* extract showed in vitro antioxidant activity and an anti-melanogenic effect in B16/F10 cells which could be a lead for treating melanin as a potential whitening agent. Research is required for its further use in cosmetic applications.[44]

***Schinus terebinthifolius***

*S.terebinthifolius* is a medium-sized tree that belongs to the family Anacardiaceae. The Methanol and acetone extract of its leaves showed high anti-tyrosinase activity. Its leaves contain secondary metabolites such as phenols, xanthones, flavonoids, flavanones and leucoanthocyanidins. Tyrosinase inhibitory effect with IC50 of 105.03 μg mL−1 was observed by the essential oil of its leaves.[45]

***Sageretia thea***

*S.thea* belongs to Rhamnaceae family, used in folk medicines for various skin issues in Korea and China. The n-hexane fraction of *S. thea* fruit showed anti-melanogenesis by suppressing the expression of TYP, TRP-1 and MITF. The Akt/ GSK3β signaling pathway promotes the reduction of β-catenin which reduces the MITF expression. Methyl linoleate and methyl linolenate, major constituents of this fraction, participate in this mechanism and thus, reduces melanin content. Its fruit consists of active metabolites for anti-aging.[46]

***Semecarpus caudata***

The dried stem of *S.caudata* MeOH extract contains emedienone, semetrienone (diarylalkanoids), 2,6-dimethoxybenzoquinone, p-coumaric acid, methyl p-coumarate, trans-4-(3,4-dihydroxyphenyl)but-3-en-2-one, and ferulic acid. Emedienone and semetrienone exhibited remarkable inhibitory effects with IC50 values of 0.033 and 0.11 μM, respectively, more potent than that of kojic acid (IC50, 44.6 μM.[47]

***Vigna angularis***

*V.angularis* is widely found in East Asia. Its seed extract is rich in condensed tannins. Structural analysis shows homo- and heteropolymers of procyanidins, prodelphinidins, and their derivatives in it. At 400 μg mL−1 condensed tannins concentration, the cell-survival rate is decreased by to 45.7 ± 1.8%. With the concentration of tannin polymers at 400 μg mL 1, the relative cellular tyrosinase activity of B16 mouse melanoma cells declined to 41.7 ± 1.2%. By increasing the concentration of condensed tannins up to 400 μg mL 1, melanogenesis is gradually inhibited with the rate of 40.7 ± 1.3%. It shows strong anti-tyrosinase and melanin inhibition in B16 mouse melanoma cells. The maximum fluorescence intensity decreased from 101.1 ± 2.5 to 28.3 ± 1.6 when the condensed tannins concentration reached 100 μg mL−1. The concentration leading to a 50% loss of maximum fluorescence intensity of tyrosinase was 52.5 ± 3.2 μg mL−1. This strong potent can be used as anti-tyrosinase and melanin inhibitor in the food, pharmaceutical, and cosmetics industries.[48]

***Zingiber mioga***

*Z. mioga* is a perennial plant that belongs to the ginger family and is present widely across East Asia. *Z.officinale* contains coumaric acid. However, *Z. mioga* and its content specifically the role of p-coumaric acid have not been studied extensively. Rutin is a flavonoid found in *Z. mioga*, shows effectiveness in preserving phospholipid membranes in skin fibroblasts destroyed after UV irradiation. Protein expressions of CREB, MITF, tyrosinase, and TRP-1 are reduced by its extract as compared to UVB-irradiated control group in vivo studies. It can be utilized for depigmentation products. However, the safety and efficiency of *Z. mioga* in human models have not been studied yet.[49]

## 2. Conclusion

Phytotherapeutic is one of the potential therapeutic modalities to be developed in the management of various skin pigmentation disorders.

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