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A REVIEW ON SKIN WHITENING PROPERTY OF PLANT EXTRACTS

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ABSTRACT

One of the serious aesthetic problems in human beings is skin darkening which is more prevalent in middle aged and elderly individuals. Skin whitening is the practice of using chemical substances or traditional herbal formulations, in an attempt to lighten skin tone or provide an even skin complexion by the reduction of concentration of the pigment melanin. Tyrosinase is the key enzyme in melanin synthesis. Tyrosine inhibitors are the substances which reduce or block melanin synthesis leading to skin whitening. A number of potent tyrosinase inhibitors are from synthetic, semi-synthetic and natural origins. Natural cosmetics is a growing industry manufacturing skin whitening products which replaces harsh chemicals with natural plant extracts. The diverse medicinal plants extract with potent skin whitening property are discussed.

KEYWORDS: Skin whitening, plant extracts, tyrosinase, melanin

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INTRODUCTION

The pigment melanin in human skin is a major defense mechanism against ultra violet light of the sun. The production of abnormal pigmentation, such as melasma, spots and other forms of melanin hyper pigmentation can be a serious aesthetic problem[1]. Melanin formation is also the main cause of enzymatic browning in human beings[2]. The most common skin lightening and depigmentation agents available commercially are kojic acid, arbutin, catechins, hydroquinone (HQ) and azelaic acid[3]. Some adverse effects of these synthetic compounds are irreversible. They cause cutaneous damage, ochronosis etc. Most skin-lightening treatments which reduce or block melanin production are aimed at inhibiting tyrosinase. The main causes of skin darkening (skin hyper pigmentation) are as follows auto immune conditions, sun damage (UV radiation and ionizing radiation), drug reactions (chemicals), hormonal changes, genetic factors, medications, hormonal therapy or birth control pills resulting in the hyper secretion of melanin from melanocytes[3,4]. It can be caused by skin damage, such as remnants of blemishes, wounds or rashes. This is especially true for those with darker skin tones.

In recent years the practice of skin lightening has come under fire because of its potential negative health effects. The skin of the face can become thinned and the area around the eyes can have increased pigmentation causing a 'bleach panda effect'. There is a growing market in skin lightening products that are non-toxic. However they are more costly due to their expensive ingredients. Many people now are thus attracted to the traditional herbal formulations which are largely free of any side-effects. Commonly used house hold skin bleachers are honey, cow's milk, turmeric, gram flour, milk of tender coconut, liquorice, mint, asafoetida, orange & other citrus fruits, cucumber, almond, papaya, tomato, potato, strawberry, blueberry, blackberry, milk thistle, carrot and others.

Tyrosinase is a copper-containing, multifunctional, glycosylated, monooxygenase widely distributed in nature. It catalysis the first two steps of mammalian melanogenesis, (process leading to formation of dark macromolecular pigments melanin). This determines the color of mammalian skin and hair[5, 6, 7, 8]. Over-activity of this enzyme leads to overproduction of melanin in-turn leading to hyper-pigmentation of the skin[9]. Inhibition of tyrosinase can also lead to reduced melanin production. The two step process are hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine, L-DOPA, and the oxidation of L-DOPA to dopaquinone[1]. This O-quinone is a highly reactive compound and can polymerize spontaneously to form melanin[10]. The anti-tyrosinase activity (skin whitening) was analyzed through inhibition ability of dopachrome formation. Tyrosinase inhibitors have become increasingly important in medication and in cosmetics to prevent hyperpigmentation by inhibiting enzymatic oxidation. Thus the natural products containing the tyrosinase inhibiting activity are the potential sources for skin whitening.

CHEMICAL SKIN WHITENERS

A number of potent tyrosinase inhibitors are of synthetic, semi-synthetic and natural origins. The commonly used chemical skin whiteners contain dangerous toxic chemicals like mercury as mercury
chloride or ammoniated mercury as the active ingredient. Even small amount may lead to mercury poisoning while long-term use can cause systemic absorption that leads to tissue accumulation of the substance, increase in pigmentation in joints of the fingers, toes, buttocks and ears. Other chemical skin whiteners includes hydroquinone, arbutin, tretinoin (also known as all-trans retinoic acid), alpha hydroxy acids (AHAs) — primarily in the form of lactic acid and glycolic acid, kojic acid, azelaic acid, the various forms of vitamin C namely magnesium ascorbyl phosphate, L-ascorbic acid, ascorbyl glucosamine, ascorbic acid and monobenzone. Lasers can also have a profound effect on melasma. However, the

results are not always consistent and problems have been reported (such as hypo- or hyperpigmentation). Another alternative is cryosurgery using liquid nitrogen. The use of these hazardous chemicals can cause many skin and health problems, from mild cases such as irritation, patching and rashes to serious illnesses. Many of the creams will cause skin to be increasingly sensitive to the sun, actually contributing to the premature aging of skin. These adverse effects have lead to the search for safer alternative plant based natural skin lightening ingredients (Tyrosinase inhibitors) which are safe, non-toxic and cost effective.

HERBAL SKIN WHITENERS

As medicinal plants are a rich source of bioactive chemicals, free from harmful side-effects, potentially safe and effective Skin Lightening Agents (SLAs), there is an increased interest to identify natural tyrosinase inhibitors from plants which finds its application in skin care products[11]. For the past few years, medicine, food and cosmetics containing natural plant extracts have significantly increased due to their therapeutic properties, charming fragrance, and the general opinion that they are safer than synthetic compounds[12, 13]. In addition, a lot of active components from botanical origin have been shown to exhibit the therapeutic effects for numerous physiological and skin diseases[14, 15].

Naturally occurring tyrosinase inhibitors are from several chemical classes like phenolics, flavanols, flavonols, flavonones, isoflavanoids, terpenes, steroids, chalcones, flavonoids, alkaloids, long-chain fatty acids, coumarins, stilbenes, , bipiperidines, biscoumarins, oxadiazole, tetraketones, etc. have been described[7, 16, 17, 18, 19]. Many are polyphenol derivatives of flavonoids or of trans-stilbene (t-stilbene) have been investigated intensively. They are usually constructed from one of two distinct substructures, which dictate their mechanism of tyrosinase inhibition: containing either a 4-substituted resorcinol moiety or catechol. The 4-substituted resorcinol group has been reported to be a potent tyrosinase inhibitor[20]. Another group of compounds, with a similar structure to t-stilbene, is the chalcones, which are widely distributed in higher plants[6, 21]. Other potentially active agents, such as kojic acid (5-hydoxy-4-pyran-4-one-2-methyl), a fungal metabolic product, and arbutin (hydroquinonebeta-D-glucopyranoside), a glycosylated hydroquinone found at high concentrations in certain plants[22]. Hydroquinone, a widely used skin-lightening agent, is a compound considered to be cytotoxic to melanocytes and, hence, potentially mitogenic[23, 24, 25]. Azelaic acid is a naturally occurring, saturated dicarboxylic-acid originally isolated from *Pityrosporum ovale* and is a rather weak competitive inhibitor of tyrosinase *in vitro*. In addition, azelaic acid has a cytotoxic effect on melanocytes[26]. Several other natural compounds such as quercetin, myricetin, and glycoside of myricetin, have been reported to have various degrees of inhibitory activity toward tyrosinase[17, 27, 28], flavonoids and stilbenes obtained from *Artocarpus incisus* and other plants also suggest that compounds having the 4-substituted resorcinol skeleton have potent tyrosinase inhibitory ability[20]. Among the licorice constituents, glabridin exhibited superior activity compared to that of glabren, isoflavene, and chalcone[6]. The crystal structure of mushroom tyrosinase complexes with a highly potent inhibitor tropolone has been reported. Computational tools like QSAR-based and ligand-based virtual screening are used to identify novel and potent inhibitors of the enzyme[29].

Seven secondary metabolites, p-hydroxybenzoic acid (1), 3,4-dihydroxybenzoic acid (2), ferulic acid (3), 2,6-dimethoxy-4-hydroxy acetophenone (4), lupeol (5), 2'-O-ethylmurrangatin (6) and hibiscetin heptamethyl ether (7) were isolated naturally from various medicinal plants. The compounds 1-7 were screened for their tyrosinase-inhibitory activity and p-hydroxybenzoic acid (1) was found to have potent activity against tyrosinase enzyme, lupeol (5) also showed significant activity[30]. Search for new agents with strong tyrosinase activity led to the synthesis of the tyrosinase inhibitor (E)-3-(2,4-dihydroxybenzylidene)pyrrolidine-2,5-dione

(3-DBP) which can be an effective skin-whitening agent[31]. Of 47 synthesized curcumin-like diarylpentanoid analogues those compounds assayed, (2E,6E)-2,6-bis(2,5-dimethoxybenzylidene) cyclohexanone showed the most potent anti-melanogenesis effect, the mechanism of which is considered to be the degradation of the melanin pigment in B16 melanoma cells, affecting neither the tyrosinase activity nor tyrosinase expression[32]. Clinical and biophysical test methods have shown that prolonged treatment with L (+) lactic acid resulted in no significant effects on skin pigmentation. However treatment with L (+) lactic acid supplemented with ascorbic acid did produce a whitening effect which becomes apparent after three months. A general skin lightening did see a modest preferential lightening of age spots with the combination of acids[33]. Curcumin is a plant-derived polyphenol, which has been reported to suppress melanogenesis in B16 melanoma cells[34].

Tyrosinase inhibitors are present in both lower and as well higher forms. Tyrosinase inhibitor was purified from *Trichoderma viride* strain H1-7 (marine bacteria) which showed inhibition toward monophenolase activity of mushroom tyrosinase by binding to a copper active site of the enzyme[35]. The ethanolic extract of *Sargassum polycystum* (an alga) and its fractions had little or no inhibitory effect on mushroom tyrosinase activity. However, when tested on cellular tyrosinase, the ethanolic extract and hexane fraction showed significant inhibition of cellular tyrosinase activity. Thus, hexane fraction may be useful for treating hyperpigmentation and as a skin-whitening agent in cosmetics[36]. Dieckol isolated from *Ecklonia stolonifera* (marine brown alga) showed three times more activity than that of kojic acid (standard) [37]. The acetone, methanol and hot water extracts of *Lentinus lepideus* (edible mushroom) of Korea and the fruiting bodies of *Pleurotus nebrodensis* were assayed for their antityrosinase inhibitory activity. There was an increase in tyrosinase activity with increase in concentration[38, 39]. The fruiting body of *Phellinus linteus* yielded a potent natural inhibitor of benzaldehyde type – protocatechualdehyde which exhibited 7.8 fold more tyrosinase inhibitory activity than that of kojic acid [40]. 6-*n*-pentyl-pyrone isolated from *Myrothecium sp*. (marine–derived fungus) was found to be 9.6-fold more inhibitory activity than kojic acid[41]. The methanolic extracts of one year old symbiotic cultures of lichen species *Arthothelium awasthii, Heterodermia podocarpa* and *Parmotrema tinctorum* were evaluated for their potential to inhibit tyrosinase enzyme activity. The extracts of all cultured lichen symbionts showed a concentration-time dependent inhibition of tyrosinase activity suggesting their possible application as natural tyrosinase inhibitors[42].

Among the gymnosperm, *Gnetum gnemon* contain gnetol (2,6,3',5'-tetrahydroxy-*trans*-stilbene) in the roots which exhibited 30-fold more diphenolase inhibitory activity of tyrosinase than that of kojic acid[43]. The cosmeceutical activity *Pinus rigida* and its possible use as a cosmetic ingredient for application in cosmetic industries were assessed. The tyrosinase inhibition effect related to skin-whitening was higher in water extract of *P. rigida* when compared with ethyl acetate soluble fraction[44].

Tyrosinase inhibition activity was also assayed using different solvent extracts. Among the different solvent extracts of *Elaeagnus multiflora* (Elaeagnaceae), the ethyl-acetate extract exhibited the greatest tyrosinase inhibition activity[45]. Five medicinal plants extract prepared using different solvent systems by decoction method were assessed for antityrosinase activity. The results of the study showed that among the five medicinal plants the aqueous extract of *Asparagus racemosus* (Liliaceae) exhibited the maximum tyrosinase inhibiting potential[46]. In yet another study crude ethanolic extract of roots of *Asparagus racemosus* showed potent tyrosinase inhibition activity. Thin Layer Chromatography (TLC) and High Performance Liquid Chromatography (HPLC) finger printing showed the presence of steroids-terpenes, alkaloids and flavonoids[47].

Freeze-dried juice and methanolic extract from the root of *Raphanus sativus* L. (Thai radish) were evaluated for

antityrosinase activity. The freeze-dried juice showed higher potency of tyrosinase inhibition than the methanolic extract. The higher contents of phenolic compounds in the freeze-dried juice appeared to be responsible. However, the activities of both extracts were much less than that of the reference antityrosinase agent (purified licorice extract) and the pure antioxidants (L-ascorbic acid and Trolox©) used as positive controls[48]. Indonesian plant *Intsia palembanica* (merbau) methanolic and 50% ethanolic extracts are the most potent tyrosinase inhibitor (for monophenolase and diphenolase). Merbau methanolic extract was the most potent extract as whitening agent based on scoring data from its tyrosinase inhibitory activities[49].

Several plants extracts were tested for their inhibitory action on melanogenesis in mouse melanoma cells. Studies on 14 medicinal plants from central Kalimantan province were tested for tyrosinase inhibiting action and their ability to inhibit melanin formation in B16 mouse melanoma cells. The aerial root of the *Dendrophthoe petandra* showed the highest anti-tyrosinase activity. The bark of the aerial root of *Willughbeia coricea* and aerial root of the *Dentdrophthoe petandra* inhibited melanin formation and tyrosinase activity[50]. Extract of *Citrus unshiu* Marc. (Mandarin peel) showed a significant inhibition on melanogenesis[51]. Ten fatty acid alkyl esters isolated from *Oxalis triangularis* also showed anti-melanogenic effect mediated by the inhibition of cAMP production. Methyl/ethyl linoleate and linolenate isolated from *Oxalis triangularis* have pigment inhibition activity. These compounds may be useful as the cosmetic agent to stimulate skin whitening[52]. Four new megastigmane glycosides, named gusanlungionosides A-D, together with 10 known other compounds were isolated from the stems of *Arcangelisia gusanlung*. The four new compounds exhibited strong inhibitory effects not only on the tyrosinase activity *in vitro* but also on melanogenesis in cells[53]. Cinnamic acid in *Cinnamomum cassia* and *Panax ginseng* was reported to exert a tyrosinase inhibitory effect. There was a significant reduction of melanin production in the melanoma cells[54]. *Garcinia mangostana* (mangosteen) leaf extract showed tyrosinase inhibitory activity in a dose-dependent manner without any significant effects on cell proliferation. It suggests that mangosteen leaf extract may be a promising candidate for the treatment of hypopigmentation disorder and useful for self-tanning cosmetic products[55]. The effect of lignans – sesamin, sesamolin and sesamol from *Sesamum indicum* seeds on melanin synthesis using mouse melanoma B16F10 cells was studied. Sesamol inhibited the synthesis of melanin by 63% while sesamin and sesamolin had negligible effects[56]. Investigated was made on the *in vitro* inhibitory effects of macelignan isolated from *Myristica fragrans* on melanogenesis and its related enzymes such as tyrosinase, tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (TRP-2) in melan-a murine melanocytes. The results indicate that macelignan effectively inhibits melanin biosynthesis and thus could be employed as a new skin-whitening agent[57]. *Punica granatum* rind extract (PE) containing ellagic acid was tested for its skin-whitening effect. PE showed inhibitory activity against mushroom tyrosinase *in vitro* with arbutin as standard. This effect was probably due to inhibition of the proliferation of melanocytes and melanin synthesis by tyrosinase in melanocytes[58].

Pyrostegia venusta leaves and flowers extract increased the melanin content in a concentration dependent manner after 4 days of incubation on melanoma cells[59].

Effect of *Magnolia officinalis* extract (MOE) on anti-melanogenesis in both mouse B16 melanoma cells and zebrafish was investigated. The results showed that MOE inhibited melanogenesis in a dose-dependent manner. MOE inhibited cellular tyrosinase activity while no inhibitory activity was found by MOE against cell-free tyrosinase activity. Studies using zebrafish as a depigmenting assay system showed that MOE could inhibit both melanogenesis and tyrosinase activity in the *in vivo* model[60]. Similar studies were done with *Rheum officinale* (raspberry). Raspberry ketone (RK)) inhibited melanogenesis through a post-transcriptional regulation of tyrosinase gene expression

which resulted in down regulation of both cellular tyrosinase activity and the amount of tyrosinase protein[61].

Several plants were studied for skin whitening property using mushroom tyrosinase. Studies on 67 tropical plants belonging to 38 families showed that extracts of 5 plants, *Stryphnodendron barbatimao, Portulaca pilosa, Cariniana brasiliensis, Entada africana* and *Prosopis africana* showed *in vitro* mushroom tyrosinase inhibition[62]. Ten kinds of Korean traditional teas were screened for their skin whitening activity using mushroom tyrosinase. Green tea was the strongest inhibitor[63]. Inulae Flos, Horsetail, Chinese Leucas, Broomweed and Indian Wikstroemia are five herbal teas commonly consumed by Asians. The hot water extracts of these five herbal teas were assayed for their hyper-pigmentation. Inulae Flos water extract served as a potential natural food additive to prevent browning [64]. 100 plant extracts were screened to elucidate their whitening effects using *in vitro* inhibition of tyrosinase and DOPA auto-oxidation activity. Plant extracts of *Chaenomeles speciosa, Dryopteris crassirhizoma, Gastrodia ellata, Glycyrrhiza glabra, Morus alba, Myristica fragrans, Rheum palmatum* and *Sophora japonica* showed inhibition of mushroom tyrosinase activity *in vitro*. *Bupleurum falcatum, Caragana sinica, Morus alba* and *Tussilago farfara* showed inhibition of DOPA auto-oxidation activity[65]. Tiliroside from raspberry was found to inhibit 34.5% of intracellular mushroom tyrosinase activity and 54.1% inhibition of melanin production suggesting its potential use as a skin-whitening agent and pigmentation medicine[66]. Dihydromorin (5,7,2',4'-tetrahydroxyflavanol) and artocarpetin (5,2',4'-trihydroxy-7-methoxyflavone), isolated from the wood of *Artocarpus heterophyllus* were two potent inhibitors against mushroom tyrosinase[67,68]. Heartwood of *Chlorophora excelsa* contain chloroporin (4-geranyl-3,5,2',4'-tetrahydroxy-*trans*-stilbene) with 14.8 fold inhibitory activity of kojic acid against diphenolase of mushroom tyrosinase[69]. Haginin A (2',3'-dimethoxy-7,4'-dihdroxyisoflav-3-ene) and Dalbergioidin (5,7,2',4'-tetrahyroxyisoflavan) isolated from the branch of *Lespedeza cyrtobotrya* was shown to be active than kojic acid against monophenolase activity of mushroom tyrosinase. Haginin inhibited body pigmentation in the zebrafish model system[70, 71]. Stems of *Morus nigra* contain 2,4,2',4'-tetrahydroxy-3-(3-methyl-2-butenyl)-chalcone with 26-fold more potent than kojic acid in diphenolase inhibitory activity of mushroom tyrosinase[72]. Another flavanol, taxifolin (5,7,3',4'-tetrahydroxyflavanol) isolated from the sprout of *Polygonum hydropiper*, showed equal inhibitory activity of kojic acid toward monophenolase activity of mushroom tyrosinase[73]. Coumarin derivative - 8'-epi-cleomiscosin A isolated from the aerial parts of *Rhododendron collettianum* showed 12.8-fold diphenolase inhibitory activity of kojic acid toward mushroom tyrosinase[74]. Piceatannol (3,5,3',4'-tetrahydroxy-*trans*-stilbene) isolated from *Vitis vinifera* (grapes) and red wine showed 32.7-fold antimonophenolase activity of kojic acid toward mushroom tyrosinase[75]. The *Piper betle* essential oil exhibited concentration-dependent inhibition of mushroom tyrosinase. The presence of 4-allylphenolic components in the essential oil may play an important role in the inhibition of tyrosinase[76].

Out of 299 parts of 263 plant species collected from Jeju Island of the Korean Peninsula, *Maackia fauriei*, *Toxicodendron succedaneum* and *Sophora flavescen* showed significantly greater tyrosinase inhibition activity than the positive controls *Distylium racemosum* and arbutin. However, they showed lower activity compared to the positive controls *Morus alba* and *Morus bombycis* [77]. Leaves of *Etlingera* were rich in Total Phenolic Content (TPC). Of the five species of *Etlingera,* leaves of *E. elatior* displayed the strongest tyrosinase inhibition activity, followed by leaves of *E. fulgens* and *E. maingayi*. Values of their inhibition activity were significantly higher than or comparable to the positive control[78]. 9-hydroxy-4-methoxypsoralen, a coumarin isolated from *Angelica dahurica* exhibited six times more tyrosinase inhibitory activity than that of kojic acid[79]. Compounds from the *Artocarpus* plants namely artocarpanone, norartocarpetin, artocarpesin,

artogomezianol, andalasin, artocarbene and chlorophorin showed tyrosinase inhibitory activity. The prenylated polyphenols isolated from *Artocarpus* plants, such as artocarpin, cudraflavone C, 6-prenylapigenin, kuwanon C, norartocarpin, albanin A, cudraflavone B and brosimone I showed potent inhibitory activity on melanin formation. *In vivo* experiments using human volunteers have shown that water extract of *Artocarpus lakoocha* reduced the melanin formation in the skin of volunteers. These indicate that the extracts of *Artocarpus* plants are potential sources for skin whitening agents[80]. Bioguided fractionation of *Dalea elegans* led to the isolation of 5,2',4'-trihydroxy-2″,2″-dimethylchromene-(6,7:5″,6″)-flavanone (1) as the active compound. The novel flavanone, dalenin, showed notable activity at inhibiting tyrosinase using l-tyrosine or l-DOPA as substrates. The flavanone was 52 and 495 times more effective as a monophenolase inhibitor than hydroquinone and kojic acid, respectively. With l-DOPA as a substrate, compound 1 showed is 59 times more effective at inhibiting the enzyme than hydroquinone and showed the same level of effectiveness as that of kojic acid[81]. The polyphenols were isolated from the leaves of six selected *Diospyros persimmon* kaki Persimmon cultivars. Out of seven compounds obtained by reverse-phase HPLC, chrysontemin showed tyrosinase inhibitory activity[82]. Esculetin, a coumarin analog from seeds of *Euphorbia lathyris* showed one-quarter of the anti-tyrosinase activity of kojic acid[83]. Glabridine and glabrene (two isoflavans) isolated from roots and seeds of *Glycyrrhiza* species (Leguminoseae) had15 times higher activity than kojic acid and 100-fold less active than glabridine respectively as potent tyrosinase inhibitors[84, 85]. *Morus* species has many polyphenols with potent tyrosinase inhibitors in different parts of the plant. Mulberroside F (moracin M-6,3'-di-*O*-glucopyranoside) from the leaves was 4.5-fold higher than that of kojic acid[86], Norartocarpetin (5,7,2',4'-tetrahydroxyflavone) isolated from the stem bark was found to be 10.4-fold more active than kojic acid[87] and oxyresveratrol, norartocarpetin, and streppogenin (5,7,2',4'-tetrahydroxy-flavavone) isolated from roots were found to be potent tyrosinase inhibitors[88, 89]. Four anthraquinones and two stilbenes isolated from the root of *Polygonum cuspidatum* were examined for their antityrosinase potency. No antityrosinase activity was detected with treatment using stilbenes, while the anthraquinones showed moderate to strong inhibition of tyrosinase. Anthroquinone physcion showed a higher permeation compared with emodin, suggesting it as a potent candidate for dermal use[90]. *Salicornia herbacea* (SH), a halophyte from South Korea was investigated for the skin-whitening effects. The incubation of SH in tyrosinase inhibited the oxidation of l-dopa to o-dopaquinone, which implies that SH is a potent tyrosinase inhibitor[91]. Among the many lignans isolated from roots of *Vitex negundo* with higher tyrosinase inhibitory activity than kojic acid, (+)-lyoniresinol exhibited 5.2-fold higher activity than that of kojic acid[92].

The leaf extract of *Duabanga grandiflora* showed a profound effect on skin whitening. The active compound eugeniin has strong dose dependent activity for type III collagen production. It was the first example of stimulation activity for type III collagen production[93].

The anti-melanogenic effects *Alpinia galanga* (AG) and *Curcuma aromatica* (CA) extracts were assessed for tyrosinase activity, tyrosinase mRNA levels, and melanin content in human melanoma cells exposed to UVA. The study demonstrated that UVA induced both tyrosinase activity and mRNA levels and UVA -mediated melanin production was suppressed by the AG or CA extracts at non-cytotoxic concentrations. Both extracts were able to protect against UVA-induced cellular oxidant formation. This was the first report representing promising findings on AG and CA extract-derived anti-tyrosinase properties correlated with their antioxidant potential. Inhibiting cellular oxidative stress and improving antioxidant defenses might be the mechanisms by which the extracts yield the protective effects on UVA-dependent melanogenesis[94].

The wound healing effect of *Salvia* species was comparatively evaluated with the

standard skin ointment Madecassol(®). Inhibition of tyrosinase, a key enzyme in skin aging, was achieved using ELISA microplate reader[95].

The methanolic extract of dried skin of *Allium cepa* shows potent melanin biosynthesis inhibitory activity in B16 melanoma cells. The active compound responsible was quercetin-3'-O-beta-D-glucoside[96]. The methanol extract of the leaves of *Eupatorium triplinerve* a plant used for skin treatment by native people of East Kalimantan showed anti-melanogenesis activity in a melanin biosynthesis assay and 7-methoxycoumarin was the active compound[97]. The active 20% methanol chromatographic fraction from the ethyl acetate layer of *Nardostachys chinensis* suppresses melanin synthesis[98].

Methanolic extract of 14 medicinal plants from Central Kalimantan province, Indonesia was screened for a tyrosinase inhibition assay. The bark of the aerial root of *Willughbeia coriacea*, root of *Phyllanthus urinaria* and aerial root of the *Dendrophthoe petandra* showed potent tyrosinase inhibitory activity of more than 40% using L-tyrosine as a substrate[99]. Thirteen phenolic compounds namely curcumin (1), desmethoxycurcumin (2), retrodihydrochalcone (3), apigenin (4), tangeretin (5), nobiletin (6), O-methyldehydrodieugenol (7), dehydrodieugenol (8), beta-hydroxypropiovanillone (9), p-coumaric acid (10), p-hydroxybenzaldehyde (11), vanillin (12), and vanillic acid (13) were isolated from methanolic extract of heartwood of *Artocapus altilis*. Compounds 1, 2, and 10 showed more potent tyrosinase inhibitory activities when compared with positive control kojic acid. The most active compound p-coumaric acid (10) was 22 times more active in tyrosinase inhibitory activity than kojic acid[100]. Out of the three new monoterpenoids namely crocusatin-J , crocusatin--K , and crocusatin--L and a new naturally occurring acid, (3S), 4-dihydroxybutyric acid (4), together with 31 known compounds isolated from the methanol extract of the petals of *Crocus sativus* (saffron), crocusatin-K, crocusatin-L, and 4-hydroxy-3,5,5-trimethylcyclohex-2-enone showed significant antityrosinase activity[101]. An active skin depigmenting agent namely (2Z,8z)-matricaria acid methyl ester isolated from the methanol extract of *Erigeron breviscapus* showed strong whitening activity and thus can be a promising compound as skin-whitening agents[102]. The tyrosinase inhibition activity of methanolic leaf extracts of *Macaranga gigantea, Macaranga pruinosa, Macaranga tanarius* and *Macaranga triloba* was assessed. *M. pruinosa* showed the best tyrosinase inhibition activity[103]. Study of methanolic extract of *Psidium guajava* leaves showed *in vitro* tyrosinase inhibition activity and thus can be used as skin whitening agent[104]. Eight lignans namely negundin A , negundin B, 6-hydroxy-4-(4-hydroxy-3-methoxy)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaledehyde, vitrofolal E, (+)-lyoniresinol, (+)-lyoniresinol-3[alpha]-O-[beta]-D-glucoside, (+)-(-)-pinoresinol and (+)-diasyringaresinol were isolated from methanolic extract of *Vitex negundo*. The compound (+)-lyoniresinol was found to be the most potent tyrosinase inhibitor when compared to others. It was found that the substitution of functional group at C-2 and C-3 positions and the presence of the -COH group plays a vital role in the potency of the compounds. Thus the compound (+)-lyoniresinol can act as a potential leading molecule to develop drugs for hyperpigmentation[105].

Ethanolic extract of *Areca catechu* L. was found to be a potent whitening agent[106]. The ethanolic extracts of *Angelica dahurica* showed the suppression of tyrosinase synthesis in B16 melanoma cell but no inhibition of tyrosinase activity. Two coumarin compounds isolated namely isoimperatorin (10-[(3-methyl-2-butenyl)oxy]-7H-furo[3,2-g][l] benzopyran-7-one) and imperatorin (9-[(3-methyl-2-butenyl)oxy]-7H-furo[3,2-g][l] benzopyran-7-one) were responsible for the activity. The *in-vitro* findings must be verified in *in-vivo* skin-lightening studies[79].

50% ethanolic extract obtained from *Balanophora fungosa* indicated an inhibitory effect on mushroom tyrosinase activity. The compounds 1-O-(E)-caffeoyl-3-O-galloyl-4,6-(S)-HHDP-β-d-glucopyranose and 1-O-(E)-caffeoyl-3,4,6-tri-O-galloyl-β-d-glucopyranose prevented pigmentation of melanin in a three-

dimensional cultured human skin model. Furthermore, they have even indicated inhibitory activities against trypsin and tryptase[107]. Ethanolic extract of *Betula pendula* leaves was evaluated on mushroom tyrosinase activity. Results showed that extract was capable to inhibit dose-dependently l-DOPA oxidation catalyzed by tyrosinase. These results suggest the usefulness of birch leaves extracts in cosmetic and pharmaceutical industries for their skin-whitening and antioxidant effects[108]. Two novel 2-arylbenzofuran dimers, morusyunnansins A and B (1 and 2), two new biflavonoids, morusyunnansins C and D (3 and 4), two new flavans, morusyunnansins E and F (5 and 6), and four known flavans (7-10) were isolated from the leaves of *Morus yunnanensis*. Compounds 5-8 showed potent inhibitory effects on mushroom tyrosinase[109].

The tyrosinase inhibitory activity of ethanolic extract of *Morus alba* twigs increased with increase in sample concentration and was superior to that of the ethanolic extract of mulberry root bark. High-performance liquid chromatography (HPLC) analysis showed its phenolic components maclurin, rutin, isoquercitrin, resveratrol, and morin acted as an antioxidant and a tyrosinase inhibitor[110]. Ethanolic extract of *Greyia flanaganii* leaves showed significant anti-tyrosinase activity. The data indicates that isolated phenolic constituents could be possible skin lightening agents[111].

Phytochemical investigations on the ethyl acetate-soluble fraction of the whole plant of *Isatis costata* led to the isolation of the 6 oxindole alkaloids costinones A, costinones B, isatinones A, isatinones B, indirubin and trisindoline. All the compounds exhibited pronounced tyrosinase inhibitory activity when compared with the standard tyrosinase inhibitor L-mimosine[112]. Ethyl acetate extract of the leaves of *Tibouchina semidecandra* yielded four flavonoid compounds, identified as quercetin, quercetin 3-O-a-l-(2''-O-acetyl) arabinofuranoside, avicularin and quercitrin, while the stem bark gave one ellagitannin, identified as 3,3'-O-dimethyl ellagic acid 4-O-a-l-rhamnopyranoside. Quercetin exhibited strong anti-tyrosinase activity with a percent inhibition of 95.0% inhibition equivalent to the positive control kojic acid in the tyrosinase inhibition assay[113].

The most commonly used is mushroom tyrosinase but has some limitations related to the applications of the mushroom tyrosinase inhibitors for human use due to the differences between the fungal tyrosinase and the human one. The mushroom tyrosinase is a cytosol enzyme while the human tyrosinase is membrane bonded[114]. In addition, mushroom tyrosinase is a tetramer in contrast to the monomer type of the human enzyme, which is highly glycosylated during its complex maturation process[115]. Assay of human tyrosinase inhibition activities of 50 plant extracts using the lysates of transformed human embryonic kidney (HEK293)-TYR cells were undertaken. The strongest inhibition of human tyrosinase was shown by the extract of *Vaccinium bracteatum* followed by the extract of *Morus bombycis*. The former extract did not inhibit mushroom tyrosinase activity whereas significant inhibition was observed with the latter extract, demonstrating the importance of using human tyrosinase in the screening for human tyrosinase inhibitors[116].

CONCLUSION

It can be concluded that the natural skin whiteners from plant extracts are more effective, more safe, non-toxic and cost effective when compared with the chemical skin whiteners with diverse side effects. Human tyrosinase may be preferred to mushroom tyrosinase for human use.

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