Review on Antityrosinase Activity of Some Indian Medicinal Plants and their Phytoconstituents

Gupta Ruchi *, Saxena Rajiv, Patidar Archana, Chourasiya Yashu, Malviya Neelesh
Smriti College of Pharmaceutical Education, Indore (M.P.), India

ABSTRACT
Tyrosinase (polyphenolic oxidase) is a multifunctional and copper containing enzyme. Tyrosinase is an enzyme which is responsible for melanin biosynthesis which is responsible for color of the skin. Melanin is synthesized in melanocyte cells by melanogenesis process. Melanogenesis protects skin surface from harmful ultraviolet radiations. Melanin is mainly synthesized in plants, microorganisms and mammalian cells. Melanin pigment is responsible for hyperpigmentation and hypopigmentation. When melanin is present in very less amount it causes local vitiligo and posttraumatic hypopigmentation. When melanin is present in very less amount it causes local vitiligo and posttraumatic hypopigmentation. Abnormal amounts of melanin deposit in the specific sites of skin causes abnormal skin colored patches like solar lentigos, chloasma, freckles, post inflammatory hyperpigmentation etc. Tyrosinase is also responsible for color changes in fruits due to enzymatic reactions. Tyrosinase inhibitor compounds are used in cosmetics, food, agriculture science and also used in remedy for imbalance in pigmentation. Some Indian herbal plants and agents like Aloe barbedensis, Crocus sativus, Curcuma longa, Camellia sinensis, Glycyrrhiza glabra, Glycine max, Nelumbo nucifer, Hericium erinaceus, Broussonetia papyrifera, resorcinol, arbutin, kojic acid, hydroquinone and ascorbic acid have antityrosinase enzymatic activity. So these plants and inhibitory agents are used in cosmetic industries due to their tyrosinase inhibitory effects or antityrosinase activity or antihyperpigmentation effects.

Keywords: Anti-hyperpigmentation, Tyrosinase Inhibitor, Melanin, Herbal drugs.

Introduction
Tyrosinase (polyphenolic oxidase) is a multifunctional and copper containing enzyme. Tyrosinase is an enzyme which is responsible for melanin biosynthesis which is responsible for the color of the skin. Melanin is synthesized in melanocyte cells by melanogenesis process. Melanogenesis protects the skin surface from harmful ultraviolet radiations. Melanogenesis is also inhibited by tyrosinase inhibition, avoiding of UV radiation, inhibition of proliferation and metabolism of melanin in melanocyte cells. Melanin enzyme is responsible for hyperpigmentation and hypopigmentation. When melanin is present in very less amount it causes local vitiligo and posttraumatic hypopigmentation. Abnormal amounts of melanin deposit in the specific sites of skin causes abnormal skin colored patches like solar lentigos, chloasma, freckles, post inflammatory hyperpigmentation, freckles etc.

Melanogenesis process by Involvement of Tyrosinase Enzyme.
Melanin is a pigment which is responsible for the color of the skin and pigmentation. Melanin composed of pheomelanin (yellow or red brown color), DHC (enriched eumelanin, light brown), DH (eumelanin, blue, black color).
Hypopigmentation Disorders and its Causes

- **Solar Lentigos**

Solar lentigos is also known as *Actinic lentigos* or age spot which is caused by chronic exposure of skin to UV radiations causing inflammation. Solar lentigos mainly affects the skin of hands, arms and faces which are generally exposed to sun. It results in darkness of exposed areas of the skin. It is identified by histological analysis of darken area and normal area of the skin. These observations indicate changes in melanocytes within the darken area as compared to melanocytes in normal skin. The Actinic lentigos site has increased level of Tyrosinase enzyme, Tyrosinase related protein-1 (TyrP1), Dopachrome tautomerase (DCT), Microphthalmia-associated transcription factor (MITF) etc. Epidermal endothelin cascade factor and stem cell factor both are responsible for the hypopigmentation in case of solar lentigos\(^3,4\). Even when UV light is avoided some spots persist permanently due to alteration of epidermal-melanin axis and factor XIII melanophages \(^5\).

- **Chloasma**

Chloasma is also known as melasma. This is also caused when body parts are exposed to sunlight or UV light which causes hyperpigmentation. This condition has become worse in summer season. Chloasma is also caused by hormonal disturbance (progesterone, during pregnancy), hormonal birth control pills (depends upon extravascular macrophages), stimulation of α-melanocyte-stimulating hormone (keratinocyte cells) and stem cells factors (fibroblast cells) these all factors are responsible for melasma\(^3,6\).

- **Freckles**

Exposure of particular parts of the body to sunlight is responsible for Freckles, which causes small brown patches on the skin. It is mostly dependent upon the epidermal melanin. It also depends upon climate (darken in the summer and lighten in winter).

- **Post Inflammatory Hyperpigmentation**

Post inflammatory Hyperpigmentation is also caused in sites of skin exposed to UV radiation after the inflammation caused in sunburn sites. This is identified by histopathological analysis of the inflammatory site of the skin. This sunburn inflammation mainly depends upon the stimulation of melanocyte cells by some mediators like IL-1, endothelin-1 and stem cell factor\(^7,8,9\). Some time reactive oxygen species like nitric oxide and superoxide (secreted by the inflammatory cells in damaged skin) may stimulate melanocyte cells. Additionally, some damaged epidermal cells can secrete the endocrine inducer pigments like melanocyte stimulating hormones which is responsible for the hyperpigmentation in UV exposed area of the skin. Post inflammatory hyperpigmentation is a lifelong skin problem in which melanin is produced in the inflammatory damaged skin cells which enters in the dermis where it is engulf by macrophages resulting in production of melanophages\(^10\).

Some Depigmenting Agents and their action

Many processes are involved in the formation of pigment in the skin. This is called melanogenesis (synthesis of melanin pigments). This synthesis involves the action of tyrosinase enzyme. Depigmenting agents have different types of mechanism of action for an antihyperpigmentation activity so there is a wide array of target against which to screen for pigmentation control agents\(^11,12\). Among various depigmenting agents which work by different mechanisms of action like by inhibition of melanin enzyme synthesis (tyrosinase, tyrosinase protein 1 and 2) by inhibition of melanocyte stimulating (by anti inflammatory agents, antioxidant), by inhibition of melanosomes transport...
within the melanocyte. But this review mainly focuses on tyrosinase Inhibition agent (some agents like hydroquinone, kojic acid, resorcinol, ascorbic acid, arbutin, ellagic acid and sulfhydryl) which is involved in inhibition of conversion of tyrosine to melanin synthesis\textsuperscript{12,14}. Several depigmenting agents work through different mechanisms of action which is mentioned in Figure 2 and Table no. 1.

![Figure 2: The cycle of mechanisms of action of various Depigmenting Agents](image-url)

**Table 1: Some Depigmenting Agents and their mechanisms of action**

| S.no. | Mechanism of Depigmenting Agents | Example of Depigmenting Agents |
|-------|---------------------------------|--------------------------------|
| A.    | Inhibition of Tyrosinase enzyme  | Hydroquinone, resorcinols, kojic acid, arbutin, ascorbic acid (vitamin C) |
| B.    | Copper chelation of Tyrosinase enzyme | Ellagic acid |
| C.    | Inhibition of glycosylation of enzyme tyrosinase | Glucosamine, N-acetyl glucosamine, tunicamycin |
| D.    | Transfer of Melanosome          | Niacinamide, protease inhibitors |
| E.    | Tyrosinase Down regulation      | Retinoid |
| F.    | Antioxidant                     | Vitamin C compounds, vitamin E, sulphydryl compounds |
| G.    | Anti-inflammatory agent         | Hydrocortisone, phytosterol, glycyrrhetinic acid |
Table 2: Few examples of botanical extracts with De-pigmenting Activity\textsuperscript{38}

| Component                          | Plant source                  | Depigmenting Mechanism                      |
|------------------------------------|-------------------------------|--------------------------------------------|
| Arbutins, α- Arbutin, Deoxyarbutin | Pear, cranberry, blueberry, bearberry shrub | ↓Tyr. ↓DHICA polymerase                     |
| Aloesin                            | Aloe                          | ↓Tyr. Competitively ↓DOPA oxidase           |
| Flavonoids                         |                               |                                            |
| Flavones                           | Most plants                   | ↓Tyr. Uncompetitively                      |
| Flavonols                          | Most plants                   | Copper chelation                           |
| Hesperidin                         | Citrus fruits                 | ↓Tyr. Antioxidant of collagen               |
| p-Coumaric acid                    | Panax ginseng                 | ↓L-tyrosine oxidation                      |
| Niacinamide                        | Root vegetables, yeast        | ↓Melanin transfer, antioxidant of collagen  |
| Licorice extracts                  |                               |                                            |
| Glabridin                          | Licorice                      | ↓Tyr. ROS scavenger                        |
| Liquiritin                         | Licorice                      | Melanin dispersibility Epidermal remove    |
| Mulberry                           | Morus alba                    | ↓Tyr. ROS scavenger                        |
| Polyphenols                        |                               |                                            |
| Procyanidins                       | Grape seeds, cranberry        | ↓Tyr. ROS scavenger                        |
| Ellagic acid                       | Strawberry, geranium          | Copper chelation MC proliferation          |
| Traditional Chinese medicine       |                               |                                            |
| Sophorcarpidine                    | Kuhseng                       | ↓Tyr.                                      |

↓ Inhibit, DHICA; 5,6-dihydroxyindole-2-carboxylic acid, DOPA; 3,4-dihydroxyphenylalanine, HQ: hydroquinone; KC: keratinocyte, MC: melanocyte, Tyr: Tyrosinase

Some plants and their constituents have Tyrosinase Inhibitory activity.

Numerous plants have tyrosinase inhibitory activity and they have been used in the treatment of Skin Pigmentation Disorder. So these drugs are used as a de-pigmenting agents. Some of potential drugs are mentioned, discussed here as:

Aloe

It belongs to Liliaceae family and this drug is mainly used in cosmetic industries as skin whitening agents. It contains aloesin and 2-ferulonylaloesin isolated from aloe arborescens mill. These constituents show mushroom tyrosinase inhibition activity\textsuperscript{15,16}. They have synergistic action with arbutin for inhibition of melanin production\textsuperscript{16,39,40}. Combination therapy of aloesin and arbutin is useful in UV mediated hyperpigmentation\textsuperscript{17}.

*Crocus sativus*

It is also known as spice saffron and it has belonged to Iridaceae family. It is mainly used as skin whitening agents. Kaempferol, its 3-o glycoside derivative and flavonols (quercetin 3-o-glycoside) are isolated from the fresh flowers of crocus sativus and tyrosinase inhibitory activity is investigated in mushroom\textsuperscript{18}. Inhibition of Diphenolase is due to crocin obtained from stigmas of Crocus sativus, but studies showed that the affinity specifically to mushroom tyrosinase was less\textsuperscript{19}.

*Curcuma longa*

It belongs to Zingiberaceae family. It is also known as turmeric. Rhizome powder of Curcuma longa is present in Ayurvedic semisolid preparations which are called “Uptan” that enhances the color of the skin\textsuperscript{22,20}. Curcumin and curcuminoids phytoconstituents are isolated from Curcuma longa which shows tyrosinase inhibitory activity in mushroom. Curcumin as compared to curcumin-bis- β-D-glycoside shows less tyrosinase inhibition potential\textsuperscript{21,23}.\textsuperscript{39,40}
**Camellia sinensis**

It comes under theaceae family, which is also called as Green tea. Tea extract content Polyphenols, (-) epicatechin, (+) catechin, (-) epicatechin-3-o-gallate (ECG) and (-) -epigallocatechin 3-o-gallate (EGCG) were investigated on mushroom tyrosinase inhibitory activity (monophenol inhibition). Gallic acid along with epigallocatechin 3-o-gallate, (-) epicatechin-3-o-gallate and Catechin polyphenolic compound tested in B16 melanoma cells so all these inhibited melonogenesis by inhibition of tyrosinase protein except catechin. The study on the depigmentation potential study on inhibition of enzyme and murine cell-line analysis showed that the depigmentation activity is due to flavones that contains a 3-position gallic acid moiety.

**Glycyrrhiza glabra**

It comes under fabaceae family and it is also called as liquorice. It is also used in cosmetic preparation in skin whitening agents. It contains glabridin which shows anti melanogenesis activity (on B16 murine melanoma cells), tyrosinase inhibitory activity (due to the presence of hydroxyl groups at 2 and 4 position) and also inhibition of UVB induced pigmentation and inflammation in guinea pig skin.

**Glycine max**

It comes under fabaceae family and it is called as Soybean. It is mainly used as nutraceutical in dietary supplements. It is a good source of antioxidant such as α-tocopherol, isoflavones, flavonols, flavan-3-ols, proanthocyanidins and anthocyanins. It has tyrosinase inhibitory potential. Soybean seed extracts contain two protease inhibitors i.e. Kunitz-type trypsin inhibitor (soybean trypsin inhibitor) and Bowman-Birk protease inhibitor. These inhibitors have been explored as depigmenting agents. The inhibition mechanism mainly responsible is phagocytosis of keratinocyte and melanin distribution (in dark-skinned Yucatan swine) which shown to reduced pigmentation.

**Nelumbo nucifera**

It comes under nelumbonaceae and it is also called as lotus. According to Ayurveda it has a lot of medicinal properties. Phytochemical and pharmacological studies show the diverse role of this medicinal herb. Aqueous extract of leaf, seed and flower from Nelumbo nucifera shown to possess DOPA-oxidase inhibition effect or in other words whitening effect. This shows that Nelumbo nucifera has whitening effect and anti-wrinkle effect on the skin.

**Vitis vinifera**

Vitis vinifera is also called as “wine grape” and grapevine. Phenolic compounds are mostly present in grape’s skin, pulp and seeds. Compared to other plant parts, a higher number of phenols are present in seeds. Polyphenols (proanthocyanidins) of grape seed shows free radical scavenging activity and reduced hyper pigmentation in female melasma patients.

**Hemidesmus indicus**

It comes under Asclepiadaceae family and it is also called as Anantmul.It has a strong and persistent fragrance. Phenolic compound 2-hydroxy-4- methoxybenzaldehyde is the main component of H. indicus. It shows inhibitory action against tyrosinase’s bifenolase activity. Monophenolase activity can be inhibited more effectively by 2-hydroxy-4-methoxybenzaldehyde as compared to vanillin.

**Broussonetia papyrifera**

It comes under Moraceae family and it is also called as “Mulberries”. Its leaf and root extracts shows antimalanogenic properties. Chloroform extracts of B. papyrifera (flavones, uraleno, quercetin and broussonetion) have better mushroom tyrosinase inhibitory activity when compared to arbutin. Isoquiritigenin isolated from plant Broussonetia papyrifera demonstrated weak tyrosinase inhibitor potential as compared to arbutin and lactic acid.

**Conflict of Interest**

The authors declare there is no conflict of interest.

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