

# Multifunctional Skin Tone Lighteners from Nature: An Overview

By Lakshmi Prakash, Ph.D.\* and Muhammed Majeed, Ph.D.\*

## Introduction



Skin lightening products form a major segment of cosmetic products worldwide and carry with them the promise of flawless skin free from age spots, blemishes and scars. Whatever the color of the skin, it is susceptible to damage due to environmental agents, physiological changes and psychological factors. The demand for “skin fairness products” is rooted in the need to eliminate localized hyperpigmentation as well as to lighten the general skin tone. Motives behind the use of skin lightening products vary considerably between cultures. In Western countries, people wish to eliminate or inhibit the development of irregular pigmentation including melasma (chloasma or localized discoloration), age spots (*Lentigo senilis*) or liver spots (associated with sun damage or aging sometimes appearing as raised spots or *Seborrheic keratoses*) and freckles (*Lentigo aestiva*). In Asia, a lighter skin color is associated with beauty and aristocracy. Therefore, in Asian countries, skin lightening products are used with the intent to lighten and brighten the skin tone.

Skin pigmentation is influenced by several factors, including hemoglobin in the blood vessels, carotenoids in the dermis and, particularly, the dark pigment, melanin in the epidermis. Two forms of melanin are produced in the epidermis: pheomelanin, which is red brown to yellow in color, and eumelanin which is dark brown to black. The relative proportions of these also influence skin color. In addition, individuals differ in the number and size of melanin particles. Melanin biosynthesis (melanogenesis) is influenced by genetics, environmental factors, diet and medication. The production of melanin by specialized cells called melanocytes (in the basal layer of the epidermis in light skinned people and in the basal as well as horny layer in dark skinned people) occurs through the action of the enzyme tyrosinase.

The rate-limiting step in melanogenesis is the conversion of L-tyrosin to melanin (Figure 1), through the action of tyrosinase. Copper and oxygen act as catalysts. Other enzymes also control melanin

\*Sabinsa

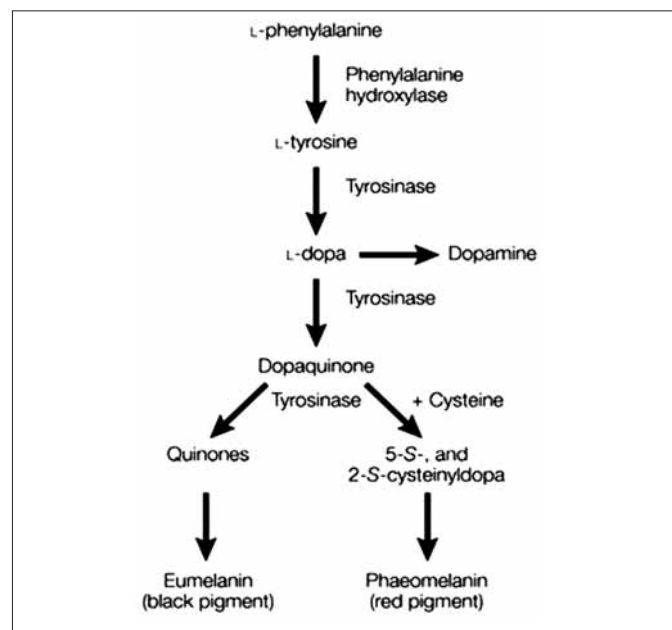


Figure 1: Formation of Melanin

production, particularly in the presence of sulfur. These include dopachrome oxidoreductase which controls melanogenesis in the absence of tyrosinase. It helps to convert dopachrome into 5,6-dihydroxyindole, and alpha-glutamyl transpeptidase which helps to maintain the balance in the biosynthesis of eumelanin and pheomelanin<sup>1-3</sup>).

Variation in skin pigmentation is attributed to the levels of melanin produced and the number of melanocytes present. Although light skinned and dark skinned people may have the same number of melanocytes present, the rate of melanin production is greater in darker skin tones. Additionally, the melanin present in the epidermal layers of darker skins is resistant to enzymatic degradation. Increased production of melanin on one side of the skin and dramatically reduced decomposition of melanin on the other side results in darker

skin tones, in light skinned people. Melanin granules synthesized in the melanocytes are then transferred from the cytoplasm of the melanocytes to the basal cytoplasm of the keratinocytes. Thus they form a protective covering in the inner layers of the epidermis, absorbing UV rays and inhibiting their penetration. Various types of inflammatory mediators such as leukotrienes and prostaglandins, cytokines and growth factors may influence melanin synthesis by affecting the proliferation and functioning of melanocytes. This explains why inflammatory diseases often induce hypopigmentation or hyperpigmentation. The enzyme, protein kinase C that phosphorylates proteins may also influence the growth and differentiation of melanocytes. Cytokines such as endothelins (also known as vasoconstrictive peptides) are also reported to accelerate melanogenesis.



health benefits. Placental proteins and estrogen were used earlier as depigmenting agents, but are rarely used nowadays. Ascorbic acid derivatives such as ascorbyl acetate and ascorbyl palmitate have been used for over 25 years as depigmenting agents in concentrations of 2-3%. These are now replaced by the more stable derivative magnesium ascorbyl phosphate in several formulations<sup>1</sup>.

Tyrosinase inhibitors such as arbutin (from the leaves of the common bearberry, (*Arctophylos urva ursi* and other plants), glabridin from licorice (*Glycyrrhiza glabra* roots), ascorbic acid and its derivatives, kojic acid (a bacterial carbohydrate metabolite) are better tolerated than hydroquinone. Aloesin from Aloe is reported to be a non-competitive inhibitor of tyrosinase, affecting the action of tyrosinase complex in the substratum and reducing the conversion of DOPA into melanin. Arbutin and kojic acid inhibit tyrosinase directly, while L-ascorbic acid and its derivatives are believed to act as reducing agents on intermediates in melanin biosynthesis at various points in the oxidation chain reaction from tyrosine/DOPA to melanin<sup>1-3</sup>).

## Skin Lightening Products: A Historical Perspective

Ancient cultures used botanicals and mineral compositions of various kinds to facilitate skin lightening. Several of these materials, researched in recent years, have been found to contain natural enzyme/hormone inhibitors, antioxidants and sunscreens. Commercial skin bleaching products in the earlier part of the last century were based on phenolic derivatives such as hydroquinone/resorcinol and peroxygenated mercury derivatives. The efficacy of hydroquinone as a skin bleaching agent was discovered accidentally during World War II, when African-American workers in rubber manufacturing factories (where hydroquinone (monobenzene) was a process chemical) complained of discolored areas on their hands and forearms.

The inherent toxicity of hydroquinone and mercury triggered research into safer botanicals and natural/nature identical isolates that would achieve similar functional effects. Hydroquinone is known to produce serious side effects if used over a long period of time. This has led to regulations or ban on its use in several countries. For instance, in France, hydroquinone usage was first restricted to 5% and then to 2% and current European legislation prohibits its use completely, in cosmetics. The USFDA has classified hydroquinone as a drug and it is no longer approved for use in cosmetics. Hydroquinone use is also reported to increase the risk of developing leukemia, liver cancer, skin irritation, irreversible hyperpigmentation and reproductive damage. The permanent depigmentation produced by hydroquinone photosensitizes the skin and makes it vulnerable to damage by UV-rays thereby increasing the risk of development of skin cancer.

Green tea is also reported to be a competitive tyrosinase inhibitor based on in vitro studies. The gallic acid moiety in the major catechin constituents epicatechin gallate, epigallocatechin gallate and gallic acid is reported to be responsible for this effect<sup>4</sup>. Additionally, the antioxidant, anti-inflammatory and UV protectant effects of green tea catechins are well-documented. Paper mulberry extract (from the root bark of *Broussonetia kazinoki* x *B. papyrifera*) also contains active depigmenting agents, which were shown to be more efficacious than hydroquinone (IC<sub>50</sub> of 2.5 mg/ml against 5.5 mg/ml for hydroquinone)<sup>5</sup>. Soy extract is also reported to have moderate skin lightening action in solar lentigenes (hyperpigmentation due to sun exposure)<sup>6</sup>. An extract from matricaria (*Chamomilla recutita*) is reported to contain an endothelin inhibitor. Endothelin inhibitors are reported to work faster than tyrosinase inhibitors on account of the fact that their mechanism of action is outside the melanocyte cell membrane. Tyrosinase inhibitors on the other hand have to cross four barriers – the stratum corneum (outer epidermal layer), deeper epidermal layers, the melanocyte membrane and the melanosome membrane<sup>3</sup>.

Flavanone derivatives from the roots of *Sophora flavescens*, were found to show significant inhibitory activity on tyrosinase and melanin production<sup>7</sup>. *Sophora flavescens* (Leguminosae) is a Chinese medicinal herb whose leaves and roots have been applied in folk medicine as antipyretic, analgesic, anthelmintic and stomachic. The mechanisms of action of various known skin lightening agents have not been completely elucidated, however some potential pathways have been summarized by researchers<sup>1</sup>. Sunscreens such as titanium dioxide or oxybenzone, do not directly affect pigmentation, but block UVB light, a factor that influences melanogenesis. Aminosugars inhibit tyrosinase synthesis through cytotoxic effects, while tyrosinase inhibitors such

## Natural Cosmeceuticals as Skin Lighteners

The toxicity associated with hydroquinone use, induced researchers to identify less dangerous botanicals with comparable activity. In addition to lightening, these botanical extracts offer multifunctional skin

as hydroquinone, ascorbic acid derivatives, arbutin, kojic acid and tetrahydrocurcuminoids inhibit melanogenesis. Hydroquinone is cytotoxic to melanocytes, and raises safety concerns. Tocopherols, some ascorbic acid derivatives and certain plant derived compounds such as polyphenols from green tea, turmeric (curcuminoids), resveratrol and others potentially inhibit the polymerization of melanin. Endothelin-1 (ET-1) inhibition is reported to be the mechanism of action of *Chamomilla recutita* extract.

Arbutin is a glycosylated hydroquinone (beta-D-glucopyranoside) effective in the topical treatment of various skin hyperpigmentations characterized by hyperactive melanocyte function. It is found that several plants including *Arctostaphylos Uva-Ursi* (bearberry), leaves of pear trees and certain herbs. In *in vitro* studies, it was determined that arbutin inhibited tyrosinase activity of cultured human melanocytes at noncytotoxic concentrations, unlike hydroquinone<sup>8</sup>). Melanin production was significantly inhibited by competitive inhibition of tyrosinase. Additionally, arbutin-rich extracts from several *Arctophylos* species have been shown to exhibit superoxide-dismutase-like activity and moderate absorbance in the UVB area. An *in vitro* evaluation of the depigmenting action is reported (Sugai, T et al, 1992). L-tyrosine solution (0.5 ml) at a concentration of 0.10, 0.25 or 0.50 mg/ml was mixed with 0.5 ml tyrosinase (0.1 mg/ml) in 1/15M Sorensen phos-

phate buffer (pH 6.8), and the mixture was incubated for 5 minutes at  $37\pm 1^\circ$  C. Absorbance at 475 nm of the resulting solution was measured. The 50% inhibitory concentration ( $IC_{50}$ ) was used as the concentration of the inhibitors to express 50% inhibition of tyrosinase activity. The  $IC_{50}$  for arbutin was found to be  $7.48 \times 10^{-3}M$ .

Melasma is a benign hyperpigmentary disorder affecting sun-exposed areas of the face and is most commonly encountered in darker-skinned women. Factors implicated include exposure to UV light, pregnancy, the use of oral contraceptives and racial predisposition<sup>9</sup>). In a clinical trial performed with 28 Japanese women with melasma, it was found that a 3% arbutin-containing skin lotion, milky lotion or cream applied twice daily for three months was effective in reducing melasma intensity and lesion size (good-to-excellent clinical response in 71.4% of the patients). A significant lightening of pigmented macules with a simultaneous reduction in lesional size was observed<sup>10</sup>).

Glabridin, from *Glycyrrhiza glabra* (Licorice) was shown to inhibit both melanogenesis and inflammation (Yokota, T et al, 1998). It was found to have tyrosinase inhibitory activity and demonstrated efficacy in reducing UV radiation induced inflammation in animal models. An *in vitro* study revealed that glabridin inhibits tyrosinase activity in cul-



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tured B16 murine melanoma cells at concentrations of 0.1 to 1 mcg/ml, with no detectable effect on their DNA synthesis. Glabridin was also found to inhibit the superoxide anion production and cyclooxygenase activities, *in vitro*. In animal model studies, topical application of 0.5% glabridin was shown to inhibit UVB induced skin pigmentation and inflammation in guinea pig skin. Through testing synthesized derivatives of glabridin for anti-inflammatory activity, the authors of this study concluded that the hydroxyl groups in the molecule are important in the inhibition of melanin synthesis, more specifically, the hydroxyl group in the 4' position<sup>11,12</sup>.

Kojic acid is reported to inactivate tyrosinase by chelating the copper ions that are essential for its activity and suppressing the conversion of dopachrome to 5,6-dihydroxyindole-2-carboxylic acid in the melanin biosynthesis pathway. A 14-month clinical trial revealed that a cream containing 1% kojic acid produced significant improvement in various types of pigmentary disorders, including chloasma, *Lentigo senilis* and postinflammatory pigmentation, with over 75% of the female patients tested showing marked to moderate improvement in chloasma and postinflammatory pigmentation, and 63% showing marked to moderate improvement in *Lentigo senilis*<sup>1,3</sup>.

## Tetrahydrocurcumin: A Multifunctional Natural Skin Lightener and Brightener

When natural yellow curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin) from *Curcuma longa* (Turmeric) roots are hydrogenated, a color free mixture of Tetrahydrocurcuminoids is obtained<sup>17,18</sup>. This natural blend is valued as a topical antioxidant and anti-inflammatory agent, with superior free radical scavenging and lipid peroxidation inhibition efficacy as compared to vitamin E. Studies indicate that Tetrahydrocurcuminoids, particularly ultrapure Tetrahydrocurcumin (trademarked SabiWhite®) efficiently inhibits tyrosinase. The parent compound Curcumin is a potent inhibitor of protein kinase C, EGF-receptor tyrosine kinase and IkappaB kinase<sup>13</sup>.



Laboratory studies revealed that SabiWhite® is an effective skin lightening agent with multifunctional topical benefits. The extract is safe for topical use with no irritant or sensitization side effects<sup>14-16</sup>. Ingested curcumin is metabolized into tetrahydrocurcumin *in vivo*. Thus tetrahydrocurcumin is a natural biotransformation product of curcumin<sup>19</sup>.

**Antioxidant action:** SabiWhite® offers effective topical antioxidant protection. Its antioxidant action is of a comprehensive "bioprotectant" nature, efficiently preventing the formation of free radicals, while quenching pre-formed ones as well. This dual action protects the skin cells from damage by UV radiation and the resultant inflammation and injury with far reaching beneficial effects on overall health and well being. The free radical scavenging activity of SabiWhite® was found to be superior to that of the synthetic vitamin E analog, Trolox<sup>20</sup>. Curcuminoids (are reported to protect normal human keratinocytes from hypoxanthine/ xanthine oxidase injury *in vitro* studies. This study

suggests that curcuminoids and therefore SabiWhite® offer protection to the skin and could be included in as functional antioxidants in topical preparations<sup>21</sup>). *In vitro* data reveal that SabiWhite® efficiently scavenges free radicals and protects the skin cells<sup>22</sup>)

- Reactive oxygen species scavenging in Swiss 3T3 fibroblast cell line: IC50 : 1.44 µg/ml
- Oxygen Radical Absorbance Capacity (ORAC): 10,815 µmol trolox equivalents/gram.
- Hydroxyl Radical Averting capacity (HORAC): 3,152 µmol gallic acid equivalents/gram.
- Lipid peroxidation inhibition: IC50 : 13.7 µg/ml
- DPPH scavenging: IC50 : 0.93 µg/ml

**Luminosity Booster and Powerful Tyrosinase Inhibitor:** *In vitro* studies indicate that SabiWhite® efficiently inhibits tyrosinase, the rate limiting enzyme in the synthesis of melanin. Its efficacy is superior to that of commonly used natural skin lightening agents such as kojic acid, and of related compounds (Figure 2).

**Anti-inflammatory and UV protectant effects:** Laboratory studies revealed that SabiWhite® offers topical protection against UVB induced inflammation and the resultant damage to the skin. These properties are particularly useful in antiaging, skin lightening, sun care and after sun care formulations. Free radicals on the surface of the skin, generated through exposure to ultraviolet radiation, chemicals or other environmental stress factors catalyze aging of the skin. SabiWhite® scavenges free radicals and prevents their formation. The anti-inflammatory effect of SabiWhite® combined with the efficient antioxidant action is useful in anti-aging formulations and in topical formulations designed to maintain general skin health and integrity. The powerful tyrosinase inhibitory activity of SabiWhite® could also slow down melanogenesis, thereby lightening the skin tone. Use levels range from 0.05 to 2% w/w.

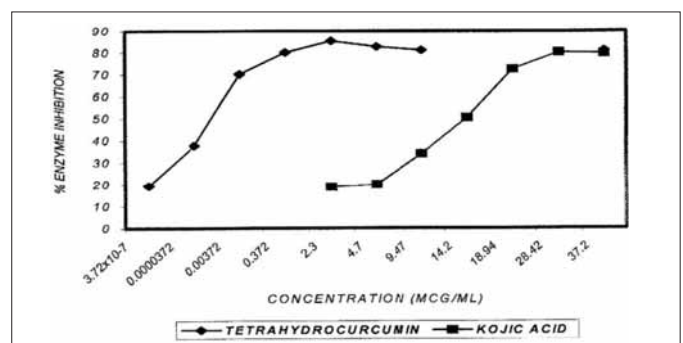


Figure 2: Comparative Luminosity Boosting Property of SabiWhite and Kojic Acid (16)

SabiWhite® is color free, and can be conveniently dispersed into cosmetic formulations.

Combine Part A ingredients as in Table 1 and heat the mixture to 70-75° C. Combine Part B ingredients in a separate vessel and heat it to 70-75° C. Add part A to Part B with continuous agitation. When the temperature is 45° C add Part C. Add Part D and mix to form a homogeneous mixture.

	Ingredients	%w/w	Function
A	Isopropyl palmitate	4.0	Emollient
	Caprylic/Capric triglycerides	5.0	Emollient
	Glyceryl stearate	1.0	Emollient
	Cetearyl octanoate	3.0	Emollient
	Dioctyl adipate	1.0	Emollient
	Dimethicone	1.0	Slip aid
	Steraeth 21 (BRIJ 721)	1.0	Emulsifier
	Stearth 2 (BRIJ 72)	0.5	Emulsifier
B	Glycerin	3.0	Humectant
	Tetrasodium EDTA	0.02	Chelating agent
	Imidurea	0.15	Preservative
	Sodium methylparaben	0.2	Preservative
	Sodium propylparaben	0.02	Preservative
	Deminerlized water	Qs	Diluent
	Citric acid(10%)	Qs	Acidulant
C	SabiWhite™	0.25	Active
	Cosmoperine®	0.05	Permeation enhancer
	Ethanol	2	Solvent
D	FLOCARE ET 30	5.0	Viscosity modifier

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Table 1: Sample Formulation with SabiWhite® (Skin Lightening Cream)

## Conclusions

Tyrosinase inhibitors and other agents that affect the melanin biosynthesis pathway are widely distributed in plant materials. These natural ingredients offer safer alternatives to hydroquinone, for use in topical skin lightening compositions. Such actives would offer addi-

tional functionalities as sunscreen boosters, moisturizers, or “anti-aging” ingredients, thereby supporting skin health, and reducing the appearance of wrinkles.

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