J. Soc. Cosmet. Scientists Korea
Vol. 35 No. 1 March 2009, 1-9

남아시아지역의 천연 미백제의 연구 현황

스마시 바비타† · 신 정 현* · 김 은 기*

피부바이오소재 NRL, 생명화공학부 인하대, *인하대병원 피부과
(2009년 3월 11일 접수, 2009년 3월 17일 수정, 2009년 3월 20일 채택)

Potential Skin Whitening Agents of Natural Origin from South Asian Region

Sumathy Babitha†, Jeong Hyun Shin*, and Eun Ki Kim*

NRL of Skin Bioactive Material Laboratory, Department of Biological Engineering, Inha University, Yonghyun-dong, Nam-gu, Incheon 402-751, Korea
*Department of Dermatology, School of Medicine, Inha University
(Received March 11, 2009; Revised March 17, 2009; Accepted March 20, 2009)

요 약: 남아시아 지역은 문화적, 사회적으로 흰 피부에 대한 관심이 높으며 이로 인해 미백화장품에 대한 요구가 크다. 합성물에 대한 우려 및 거부감으로 천연물중심의 원료가 급증하고 있다. 본 논문에서는 인도를 포함하는 남아시아 지역의 미백소재에 관한 문화, 사회적 배경과 최근 연구 개발 현황을 조사하였다.

Abstract: South Asian's growing obsession with fair skin has made the cosmetic industry into a multibillion-dollar trade over the last decade alone. With reports of toxicity and potential mutagenicity of conventional skin lightening agents, cosmetic industries are looking for plant-based skin whitening formulations. In this review some potential depigmentation agents from South Asian region are discussed, including their historical background, biochemical characteristics and recent findings on their depigmenting activity.

Keywords: *South Asia, depigmenting, natural products, tumeric, saffron*

1. Introduction

Luminous skins have been prized through the centuries as a beautiful trait, from 15th century Venetian painters who used crushed glass in portraits to make subjects' skin glow to 18th century Japanese geishas to 20th century skin bronzers. Furthermore, archaeologists have found records of skin protection creams for pyramid builders in Ancient Egypt more than 3,000 years ago when most Europeans were living in crude huts. In the 19th century, make-up went out of fashion, but white skin continued to be a prized asset. Even though the obsession for white skin is prevalent across Asia there is a growing trend in skin whitening among South Asians (India, Pakistan, Sri Lanka, Bangladesh). Because of geographical proximity to the equator, South East Asians are brown in skin color. In India, the brown skin tone varies from light maple cream to deep chocolate brown color. North Indians are slightly lighter skin than the South Indians because of the distance from the equator. In spite of the growing campaign against the concept that skin color determines how successful you'll be in life, skin lightening creams continue gaining importance. But recent years have seen some ingredients used in skin whitening products from being beyond reproach to being suspect and even banned. For example, FDA proposed a ban on over-the-counter sales of hydroquinone-containing products on August 29, 2006. The reason cited for the proposed ban is that studies in rodents show evidence that hy-

† 주 저자 (e-mail: babisp2003@yahoo.com)

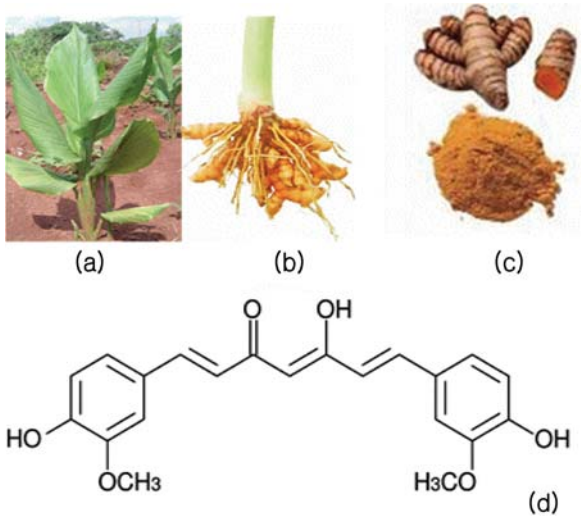

Figure 1. Turmeric (*Curcuma longa*), (a) Plant, (b) Root showing rhizome, (c) Powdered rhizome, (d) Curcumin structure.

droquinone may act as a carcinogen or cancer-causing chemical. Hydroquinone also has been linked with the medical condition known as ochronosis in which the skin becomes dark and thick. This circumstance has inevitably increased demands for highly safe natural counter parts. This article overviews some potential depigmenting plant sources having a long history of traditional use in South Asia region giving emphasis to India.

2. Main Subject

2.1. Turmeric

Turmeric (*Curcuma longa*) is an herbaceous perennial plant, belonging to the Zingiberaceous family. The Curcuma genus contains around 30 species. The plant originates from India and South East Asia. Cultivated in South Asia tropical regions, the earliest use of turmeric dates back nearly 3,000 years of the ancient Vedic culture of India. Turmeric in India was always considered a magical herb. The rhizomes of this plant, when dried and ground, provide a yellow and flavor-rich powder (Figure 1(a), (b)), used for centuries as a natural coloring agent in food, cosmetics and textiles, as a flavoring compound and also as an insect repellent.

Turmeric has been used as an age old ingredient for cosmetic use. Known for its ability to inhibit superfluous body hairs and disinfecting properties and, Indian women, over generations have used turmeric paste scrubs before having their bath. Turmeric paste is applied to bride and groom before marriage in some places of India, Bangladesh, and Pakistan, since it is said to make her skin soft, blemish free and glowing.

The three principal types of turmeric extract are essential oil of turmeric, turmeric oleoresin and curcumin. Curcumin (Figure 1(c)), which gives the yellow color to turmeric, was first isolated almost two centuries ago, and its structure as diferuloylmethane was determined in 1910.

Tetrahydrocurcuminoids have also been found to inhibit the activity of tyrosinase, an enzyme that participates in melanogenesis, thereby preventing melanin formation with resultant lightening of the skin tone. These biological properties of the THC combined with their lack of yellow color render them useful in achromatic cosmetic applications[1]. Kinetic studies showed that the mechanism of tyrosinase inhibition of both mono-demethoxycurcumin and carboxylized curcumin belongs to non-competitive type inhibition. U.S. patent number 6,653,327 was granted to Sabinsa Corporation in 2003. It covers cross-regulin composition of turmeric-derived tetrahydrocurcuminoids (THC) for skin lightening, particularly effective in tyrosinase inhibition, protection against UVB radiation and in affording protection to the skin against UVB radiation and chemical, physical and biological irritants.

Turmeric is also known for its photo-protective activity. In laboratory studies, extract of turmeric was shown to be effective in suppressing inflammation and protecting the epidermal cells from the damages caused by UVB radiation[2]. Turmeric is also currently used in the formulation of some sunscreens.

2.2. Saffron

Saffron is the dried stigmas of the *Crocus sativus*, belongs to the family Iridaceae. It is a small bulbous perennial plant. It has a bitter taste and a penetrating aromatic odor. India is one of the ancient harvesting

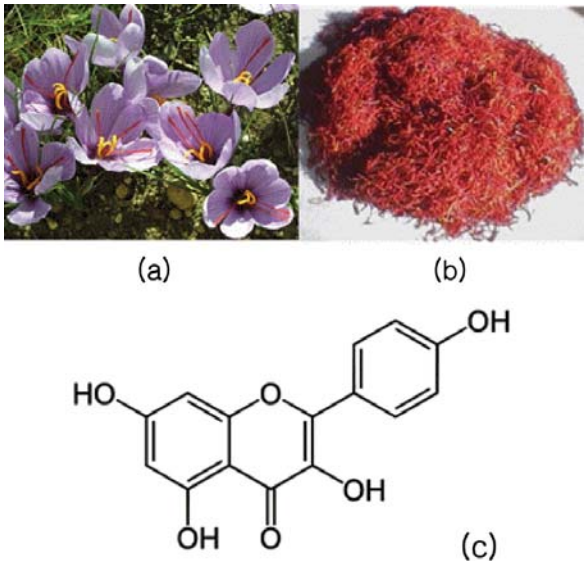

Figure 2. Saffron (*Crocus sativus*). (a) Flower, (b) Stigmas (saffron filaments), (c) Kaempferol structure.

ground of some of the purest saffron in the world. In the beautiful valley of Kashmir, fields of crocus sativus have heralded the dawn for close to 2,000 years. Each flower contains only three stigmas (Figure 2(a), (b)). These threads must be picked from each flower by hand, and more than 75,000 of these flowers are needed to produce just one pound of saffron filaments, making it the world's most precious spice.

It has varied uses ranging from culinary to medicinal and beauty and has been highly valued by man since ancient times. In Ayurveda, saffron is used to cure chronic diseases such as asthma and arthritis. It is also useful in treating cold and cough. Ayurvedic medicines containing saffron are used to treat acne and several skin diseases. Traditionally saffron is believed to promote fair complexion. It is an age-old belief that pregnant women give birth to 'fair' babies, if they consume saffron.

Fehrat (2004) has reviewed the application of saffron extracts from dried saffron stigmas by aqueous ethanol in formulation of cosmetics, skin cares and sun protection products[3]. A flavonol, kaempferol, (Figure 2(c)) isolated saffron was found to inhibit the oxidation of L-3,4-dihydroxyphenylalanine (L-DOPA) catalyzed by mushroom tyrosinase with an ID_{50} of 67 g/mL (0.23 mM). Kaempferol competitively inhibit tyrosinase activity by their ability to chelate the copper in the active site, leading to irreversible inactivation of tyrosinase [4,5]. Being a competitive inhibitor the molecule of kaempferol with its close resemblance with the substrate, fits loosely into the active site of tyrosinase and prevents entry of L-DOPA. On the other hand, a bulky sugar moiety attached to the 3-hydroxyl group in the flavonols hinders their approach to the active site of tyrosinase[5,6]. Recently 4 new compounds crocusatin H, crocin-1, and crocin-3 isolated from stigmas of saffron flower also reported to have significant tyrosinase inhibitory activity[7]. Nowadays use of saffron in the cosmetic industry is increasing owning to its active substances and to the trend to use natural products in cosmetic formulations.

2.3. *Vitex negundo*

Vitex negundo or nirgundi deciduous shrub belongs to family Verbenaceae, chiefly occurring in Pakistan, India and Ceylon[8,9]. Commonly it is cultivated as a hedge plant. A large shrub or rather small tree grows 2 ~ 4 m in height, with quadrangular branches and thin grey bark. The leaves petiolate, smooth, exstipulate, have a typical pungent odor. The flowers are bluish purple in color, lanceolate, in panicles up to 30 cm long. The fruits are ovoid or obovoid, four-seeded drupes, black when ripe. It has been claimed to possess many medicinal properties[10]. In traditional medicinine, the leaves are made into a paste and applied over rheumatic swellings and over painful joints. It is also an important cure for bruises and different kinds of skin infections. Though almost all plant parts are used, the extract from leaves and roots is the most important in the field of medicine and is sold as drugs[11]. The leaf extract is used in Ayurvedic and Unani system of medicine[12].

Ul-Haq *et al.* (2006) have reported the tyrosinase inhibitory potentials of eight lignans isolated from the roots of *V. negundo*[13]. They also made attempts to justify the structure-activity relationships of these 8 lignans from the methanaol extract of the plant; negundin A, negundin B, 6-hydroxy-4-(4-hydroxy-3-

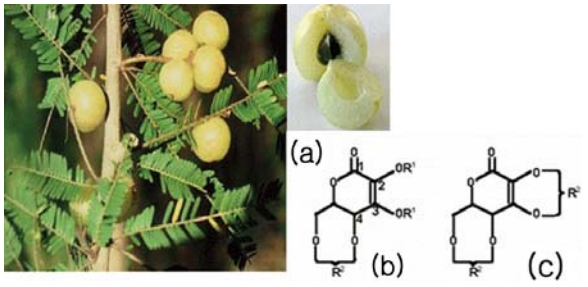

Figure 3. *Phyllanthus emblica*, (a) Fruit, (b) Emblicanin A structure, (c) Emblicanin B structure.

methoxy)-3-hydroxymethyl-7-methoxy-3, 4-dihydro-2-naphthaledehyde, vitrofolal E, (+)-lyoniresinol, (+)-lyoniresinol-3[α]-*O*-[β]-D-glucoside, (+),(-)- pinoresinol, and (+)-diasyringaresinol. It was found that the substitution of functional group(s) at C-2 and C-3 positions and the presence of the -C[H_2]OH group plays a vital role in the potency of the compounds[14]. Proven as an effective tyrosinase inhibitor, extracts of *Vitex negundo* are now one the main ingredients in many skin fairness formulations of cosmetic industry[15].

2.4. *Phyllanthus emblica*

Phyllanthus emblica also known as *Emblica officinalis* (Indian gooseberry) is a deciduous tree of the Euphorbiaceae family (Figure 3). The tree is found growing in the plains and sub-mountain on tracts all over the Indian subcontinent 200 ~ 1,300 m altitude. Its natural habitat, like other members of its family, extends from Burma in the east to Afghanistan in the west and Sri Lanka in the south. This herb has been used for thousands of years in India and is a cornerstone within the traditional healing system of Ayurveda. According to one study, amla is a more potent antioxidant than vitamin C because of other polyphenols, which increases its free radical scavenging[16]. However, there are some *in vivo* studies indicating that antioxidant activities of it cannot be attributed to ascorbic acid alone and that the overall effect is due to other polyphenols such as ellagic acid, gallic acid, tannins, etc[17-19]. Fujii *et al.* (2008) investigated the effects of fruit extract on human skin fibroblasts, especially for production of procollagen and matrix metalloproteinases (MMPs), *in vitro*[20]. The extract stimulated proliferation of fibroblasts in a concentration-dependent manner, and also induced production of procollagen in a concentration and time-dependent manner. From these results, it was proved that *Phyllanthus emblica* extract works effectively in mitigative, therapeutic and cosmetic applications through control of collagen metabolism. The effectiveness of a standardized antioxidant fraction of *Phyllanthus emblica* fruits (Figure 3(a)) as a skin lightener and also as an antioxidant was proven by Chaudhuri (2004) and has granted a patent entitled skin lightening (U.S. Pat. No. 6,649,150). Many patents for skin lightening compositions based on extracts *Phyllantus emblica* have been granted. US Published Application No: 2004/0028642 A1, entitled "Cosmetic composition comprising an extract of emblica officinalis and methods of using same" and filed by Hansenne *et al.*, US Published Application No: 2004/0166069 A1, entitled "Boosting Tyrosinase Inhibiting Activity of Skin Whitening and Sunscreen Compositions" filed by Gupta; US Published Appli- cation No: 2003/0157202, entitled "Lightening compositions and methods of use" filed by Mahalingam *et al.* are few among them. Emblica is the patented composition extracted from the plant. Skin whitening activity of the extract is based on a combination of low molecular tannins that form a cascading system of antio- xidants. The key active ingredients of this cascade system are Emblicanin A (Figure 3(b)) and emblicanin B (Figure 3(c)). Under oxidation, emblicanin A is transformed into emblicanin B. Under continued oxidation, emblicanin B then forms oligomers which themselves act as antioxidants. Emblica also possesses exciting photoprotective properties. The addition of emblica extract to the sunscreen compositions has the advantage of increasing the photostability of these compositions, thereby increasing or prolonging their effectiveness when they or their user are exposed to ultraviolet radiation.

2.5. *Waltheria indica*

Waltheria indica L. (Sterculiaceae) is an rect shrub-by perennial, up to 50 cm native to India now grows throughout the tropics and warmer subtropics[21].

Most parts of the plant are covered in short shiny hairs. Leaves narrowly lanceolate with irregularly toothed margins. Flowers are yellow in dense axillary clusters. As an alternative medicine, it has been used in the treatment of diverse conditions of inflammation, rheumatism, circulatory problems, and immune system deficiencies[22]. Recently the skin whitening ability of the plant has been disclosed in a European patent for formulating skin whitening composition based on *Walteria indica* leaf extract (EP 1 842 530 A1). It has been also reported that *Waltberia indica* extract, ferulic acid and certain other ingredients act synergistically in a whitening complex that that inbibits tyrosinase and provides mild exfoliation[23]. Durawhite, an extract of *Waltheria indica*, is used in a commercial cosmetic for its ability to inhibit melanin synthesis and whiten the skin[24].

2.6. *Tamarindus indica*

Tamarindus indica also called Indian Date is a tree in the family Fabaceae. Tamarind has been cultivated in India for centuries and was taken by the Spanish conquistadores to the West Indies and Mexico in the 17th century. It an economically important tree of India, which grows abundantly in the dry tracts of Central and South Indian States as an ornamental to provide shade as well as for the fruit. The tree produces brown pod-like fruits, which contain pulp and hard-coated seeds. The fruit pulp is the richest natural source of tartaric acid (8 ~ 18 %)[25]. It has a variety of medicinal uses; the bark is used as an astringent, the flowers can reduce blood pressure, the fruit has a laxative effect. The leaves are used in herbal steams as the acidity is thought to help the skin absorb the other herbal ingredients faster. It contains high AHA which is widely used in skin care product as an emollient, peeling action, and relieves hyper-pigmentation. It also has skin lightening and whitening properties and help to adjust skin acidity condition[26]. A patent has been granted to Stanislav (2005) for a cosmetic preparation based on high molecular tamarind antioxidant produced by alkaline extraction of *Tamarindus indica* species seeds coats[27].

2.7. *Artocarpus heterophyllus*

Artocarpus heterophyllus, commonly known as jackfruit is a species of tree of the mulberry family (Moraceae); grows in the evergreen forests of the western hills of India, Sri Lanka, and the Deccan plain of Bangladesh[28]. Its fruit is the largest tree borne fruit in the world. The fruit is popular among the rural people of the Indian subcontinent. Jackfruit seed extract contains a lectin termed jackfruit lectin (JFL), which possesses diverse biological activities. Arung *et al.* (2006) have isolated artocarpanone, from *A. heterophyllus* wood extract which inhibited both mushroom tyrosinase activity and melanin production in B16 melanoma cells[29]. Very recently the same group have isolated a series of prenylated flavone-based polyphenols, compounds 1 ~ 8, from the wood of *Artocarpus heterophyllus*; artocarpin, cudraflavone C, 6-prenylapigenin, kuwanon C, norartocarpin and albanin A. These compounds were found to be active inhibitors of the *in vivo* melanin biosynthesis in B16 melanoma cells, with little or no cytotoxicity without showing tyrosinase inhibiting activity. A structure-activity investigation indicated that the presence of the isoprenoid-substituted moiety that enhanced the inhibitory activity on melanin production[30].

2.8. *Swertia chirayita*

Swertia chirayita is a medicinal plant indigenous to temperate Himalaya. Its medicinal usage is reported in Indian pharmaceutical codex, the British and the American pharmacopoeias and in different traditional systems of medicines such as the Ayurveda, Unani and Siddha[31]. The plant has numerous flowers, pale green in color, tinged with purple, with long white or pink hairs and minute sharp pointed fruits. The whole plant, collected in its flowering stages and dried, constitutes the drug. It is known by an array of names; Anaryatikta, Viktaka, Chirrato, Nilaveppa, Qasabuzzarirah etc. suggesting its widespread use. The trade name of *S. chirayita* is chiretta[32,33]. *S. chirayita* belongs to family Gentianaceae, which records the occurrence of taxonomically informative molecules, namely iridoids, xanthones, mangiferin and *C*-glucoflavones[34]. In a

recent effort to screen Bangladeshi indigenous medicinal plants for tyrosinase inhibitory activity by Khanon (2000), *S. chirayita* has been found to be a potent tyrosinase inhibitor[35].

2.9. *Acacia catechu*

Acacia catechu, is a moderate size deciduous tree with rough dark gray brown bark. It belongs to family Leguminoseae-mimoseae and is a native of India, Myanmar, Nepal, Pakistan, Thailand. *A. catechu* is a multipurpose tree species. The use of *A. catechu* tanning agent in India is believed to go back as far as history relates. Commonly known as Katha is an indispensable ingredient of Pan which is beetle leaf preparation chewed in India. It is highly valuable for its powerful astringent and antioxidant activities making it useful in dental, oral, throat infections[36]. Ancient ayurvedic text recommends *Acacia catechu* as a best herb for countering various skin ailments. It is considered as one among the best rejuvenating herb for skin thus prevents wrinkling of the skin. It is used for contagious skin diseases and skin problems where inflammation and discharge are major symptoms. The chief phytoconstituent of the heartwood are catechin, epicatechin, epicatechin-3-*O*-gallate, and epigallocatechin-3-*O*-gallate [37]. Tannic acid in catechu is used as astringent, which tightens the skin surface making it mechanically stronger and also decreases exudation. A patent has been filed by Millikin *et al.* (2007) for a skin lightening combination based on *Acacia catechu* extract[38]. Jia and Farrow (2005), mentioned the potent antioxidant activity of 7-hydroxychromon isolated from *A. catechu* and chromones reportedly exhibit tyrosinase inhibitory activity[39,40].

2.10. *Pterocarpus marsupium*

Otherwise known as Indian Kino Tree, is a species of Pterocarpus which grows abundantly in leafy forests of southern, western and eastern India and on Sri Lanka. It reaches a height of 15 ~ 25 m. The dark-brown to gray bark shows large cracks and, after damage, secretes a reddish gum-like substance known as kino gum[41]. The leaves are 15 ~ 25 cm in size and the flowers appear yellow. The fruits are flat and round and contain one or two small seeds. The heart of the wood is hard and golden to red-brown in color. *Pterocarpus marsupium* has a high reputation in the traditional system of Indian medicine[42]. The wood and the bark are used as an anti-diabetic and anti-diarrheic. They also show astringent and anti-inflammatory activity. The leaves are used as an animal feed and also for healing wounds and particularly for curing skin diseases. Depigmenting activity of *Pterocarpus marsupium* extracts has been disclosed in United States Patent Application 20040146482 USPTO by Pauly *et al.* (2003). Patent Application 20050267047 discribes the tyrosinase inhibition property of diarylpropanes isolated from *P. marsupium* extracts by Jia and Zhao 2005. Perrier *et al.* (2006) mentioned the melanogenic inhibition activity of aurones from *Pterocarpus marsupium* flowers (USPTO Patent Application 20060228313). Aurones are molecules which belong to the family of flavonoids, and which are structurally isomers of flavones[43].

2.11. *Kaempferia galanga*

Kaempferia galanga is a perennial aromatic herb with very fragrant rhizomes that grows throughout India. It belongs to the family of Zingiberaceae. It is an ingredient of many ayurvedic drug preparations and valued traditionally for their skin protectant action[44]. One patented application of *Kaempferia galanga* pertains to its action against ultraviolet rays and function as a 'booster' that augments the activity of conventional sunscreens. It has been discovered that *Kaempferia galanga* rhizome contains about 1.5 ~ 2.0 % essen- tial oil, whose main components are ethyl cinnamate (25 %), ethyl *p*-methoxycinnamate (30 %) and *p*- methoxycinnamic acid, of which ethyl *p*-methoxycinnamate was shown to inhibit tyrosinase activity in a dose dependent manner[45].

2.12. *Symplocos racemosa*

Symplocos racemosa or lodh tree (Family: Symplocaceae) is an evergreen tree, 6.0 ~ 8.5 m tall, found abundantly in plains and lower hills throughout India.

The useful part of the plant is bark. Bark is astringent, refrigerant, ophthalmic, expectorant, anti-inflammatory, hypothermic, astringent, depurative, febrifuge, haemostatic, stomachic and suppurative[46]. In traditional Indian medicine, *Symplocos racemosa* is known to heal ailments for all types of skin[47]. According to a recent finding topical application of plant extracts of the species belonging to the genera Symplocos shown to have significant skin lightening benefits[48].

3. Conclusion

Increasing consumer interest in skin care products derived from natural sources has driven increased search for potential depigmenting herbs. This has also lead to the renewed study of traditionally known depigmenting herbs such as turmeric and saffron which have recently found applications in skin whitening formulations. Knowledge of depigmenting activity of herbs which are common and available to the region, obtained through recent research in this field may increase the acceptance of cosmetic formulations based on their active components.

Acknowledgements

This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea Government (MEST) R0A-2007-000-10015-0.

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