Cosmeceuticals are topical cosmetic-pharmaceutical hybrids that enhance the beauty through constituents that provide additional health-related benefit. Cosmeceuticals are commonly used for hyperpigmentation. These disorders are generally difficult to treat, hence the need for skin lightening agents including, cosmeceuticals. These agents selectively target hyperplastic melanocytes and inhibit key regulatory steps in melanin synthesis. With the recent safety concern regarding use of hydroquinone, the need for alternative natural, safe and efficacious skin lightening agents is becoming all the more necessary. We carried out a PUBMED search using the following terms “cosmeceuticals, hyperpigmentation, skin lightening agents.” We cited the use of various agents used for the treatment of hyperpigmentation, mainly melasma and post-inflammatory hyperpigmentation. We describe the safety and efficacy of these agents and their advantage over the conventional therapy.

**KEYWORDS**: Cosmeceuticals, hyperpigmentation, melasma

**INTRODUCTION**

The U.S. Food, Drugs and Cosmetic Act defines cosmetics by their intended use, as ‘articles’ intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance.\(^1\) It is important to understand that cosmetics do not alter the structure or function of the skin.\(^2\) Cosmetics can be divided into two broad groups: Make-up and skin care products. Cosmetics are luxury items, which make the user feel better, without any lasting impact on the skin.\(^3\)

Cosmeceuticals are topical cosmetic-pharmaceutical hybrids that provide additional health-related benefit. They are applied topically as cosmetics, but contain ingredients that influence the skin’s biological function.\(^3\) Cosmeceuticals are, in fact, a bridge between personal-care products and pharmaceuticals.

Cosmeceuticals are commonly used for hyperpigmentation. Pigmentary disorders are the most common dermatologic disorder and cause significant psychosocial impairment.\(^4\) These disorders are generally difficult to treat, hence the need for skin lightening agents including cosmeceuticals. These agents selectively target hyperplastic melanocytes and inhibit key regulatory steps in melanin synthesis. With the recent safety concern regarding use of hydroquinone, the need for alternative natural, safe and efficacious skin lightening agents is becoming all the more necessary. This article attempts to review the upcoming and available options for the treatment of hyperpigmentation, mainly melasma and post-inflammatory hyperpigmentation. This was carried out by a PUBMED search using the terms “cosmeceuticals, hyperpigmentation, skin lightening agents.”

Cosmeceuticals for hyperpigmentation can be classified based on the mechanism of action, as shown in Figure 1 and those present in leading brands of cosmetics in India shown in Table 1.

**PHENOLIC COMPOUNDS**

Hydroquinone (HQ) is a dihydric phenol with two important derivatives viz: monobenzyl and monomethyl ether of hydroquinone. Hydroquinone competitively inhibits melanin synthesis by inhibiting sulphydryl
groups and acting as a substrate for tyrosinase. Melanosomes and melanocytes are damaged by the semiquinone free radicals released during the above reaction.\[5-7\] Hydroquinone is considered the gold standard for the treatment of hyperpigmentation. It is commonly used at concentrations of 2-4%. Clinical studies report well to excellent responses induced by 2% hydroquinone. Higher concentrations are effective but can cause irritation. It can be safely combined with retinoids and steroids in the Kligman’s regimen (5% hydroquinone, 0.1% tretinoin, 0.1% dexamethasone) and the modified Kligman’s regimen (4% hydroquinone, 0.05% tretinoin, 1% hydrocortisone acetate). Recently, flucinolone acetonide 0.01% has been used in triple combination creams with results showing superior efficacy without major side effects.

Chronic adverse effects include exogenous ochronosis, cataract, pigmented colloid milia, sclera, and nail pigmentation, loss of elasticity of the skin, impaired wound healing and exuding an offensive fish odour.\[8\] Ochronosis is the most common chronic side-effect related to long-term topical use of hydroquinone. Findlay et al. described this condition first among South-African Bantu women who applied high concentrations of hydroquinone for many years.\[9\] Clinically, ochronosis is characterized by asymptomatic hyperpigmentation, erythema, papules, papulonodules on sun-exposed areas of the body namely, face, upper chest, and upper back. There are very few reports of ochronosis from India. There are reports of nail discoloration from chronic use of hydroquinone. This discoloration occurs due to the oxidation and polymerization of by-products from hydroquinone. The fawn colored pigmentation of all 20 nails is called - “pseudo yellow nail syndrome” as it mimics the yellow nail syndrome.

Hydroquinone can cause DNA damage as demonstrated in studies done in rodent models and cultures. This carcinogenic effect has raised concerns regarding its use. Due to this, the International Agency for Research on Cancer has placed hydroquinone as not classifiable as to its carcinogenicity in humans.\[8\] The Food and Drug Administration (FDA) has even proposed banning over-the-counter skin bleaching agents containing hydroquinone. However, it should be kept in mind that these studies were based on oral and parenteral doses and there have been no clinical studies or cases of skin cancer or internal malignancy related to topical use. Hence, the exaggerated fears of patients should be addressed carefully. Careful medical supervision limiting the duration of exposure and restriction surveillance to prevent adulteration with other mixed-up agents can definitely help.\[10\]

Due to the side-effect and safety profile, hydroquinone is not used as a component of cosmeceuticals available in the market for the treatment of hyperpigmentation [Table 1].

| Brand                        | Ingredients                                      | Cost (INR) |
|------------------------------|--------------------------------------------------|------------|
| Clarins                      | Whitening night cream: Ascorbyl glucoside         | 1800       |
|                              | All spots whitening corrector: Parsley extract, Salicylic acid, Biotin, Fruit extract, Citric acid |           |
| Chambor (softener)           | White lily extract: Vitamin E                     | 435        |
| YSL (whitening cream)        | Grape seed extract: Vitamin C                     | 3550       |
| La Prairie (fairness cream)  | Caviar extract: White truffles, White wine extract, White flower complex, White tea | 25000      |
| Elizabeth Arden              | Vitamin C derivative (emblica)                    | 800        |
| Revlon (fairness cream)      | Dimethicone, Titanium dioxide, Magnesium phosphate | 145        |
| Lakme (fairness cream)       | Titanium dioxide: Aluminium hydoxide, Tocopheryl acetate, Sodium ascorbyl acetate, Lycopene, Lily extract | 175        |
| Olay fairness cream          | Niacinamide, Tocopheryl acetate, Titanium dioxide, Zinc oxide, Citric acid, Grapefruit extract, Lemon extract, Apple fruit extract | 250        |
| Garnier fairness cream       | Ascorbyl glucoside: Orange fruit extract, Lemon extract | 78         |
| Fair and Lovely multivitamin fairness cream | Niacinamide, Ascorbyl phosphate, Tocopheryl acetate, Allantoin | 82         |
| Himalaya fairness cream      | Aloe vera, Citrus reticulata extract               | 65         |
| Ponds fairness cream         | Nicotinamide, Tocopheryl acetate, Allantoin       | 140        |
| Emami fairness cream         | Liquorice distillate: Niacinamide, Grape seed oil, Wheat germ oil, Methoxyccinamate, Titanium dioxide, Zinc oxide | 45         |
Mequinol
4-hydroxyanisole, hydroquinone monomethyl ether, is a derivative of hydroquinone. Its mechanism of action is unclear. It acts as a substrate for tyrosinase, thereby inhibiting the formation of melanin precursors. In a randomized parallel group study involving 216 subjects, mequinol 2%/tretinoin 0.01% solution was found to be highly effective and well tolerated treatment for solar lentigines and related hyperpigmented lesions on the forearms and of similar efficacy for lesions on the face. It is marketed in USA at a concentration of 2% in combination with 0.01% tretinoin. The combination can cause erythema, burning, pruritus, desquamation, skin irritation, halo hypopigmentation. Combination with sunscreens reduces the incidence of adverse effects.

N-acetyl-4-S-cysteaminylphenol (NCAP)
NCAP is a phenolic agent that inhibits tyrosinase activity by acting as an alternative substrate. It is more stable and causes less irritation than hydroquinone. Clinical response is evident after 2-4 weeks. Various studies using 4% NCAP have found marked improvement in patients with melasma.

Non-phenolic agents
Kojic acid
Kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrene) is a naturally occurring hydrophilic fungal product derived from certain species of Acetobacter, Aspergillus, and Penicillium. It reduces hyperpigmentation by inhibiting the production of free tyrosinase and is also a potent antioxidant. Kojic acid (KA) is used at concentrations ranging from 1% to 4%.

Arbutin
Arbutin is one of the most widely prescribed skin-lightening and de-pigmenting agent worldwide. Arbutin, the b-D-glucopyranoside derivative of hydroquinone, is a naturally occurring plant derived compound found in the dried leaves of a number of different plant species including, bearberry (Arctostaphylos uva-ursi), blueberry, cranberry, and pear trees. Arbutin, inhibits tyrosinase activity competitively but at non-cytotoxic concentrations in a dose dependent manner in cultured melanocytes. It also inhibits melanosome maturation and is less cytotoxic to melanocytes than hydroquinone. Although, higher concentrations may be more efficacious, greater risk for paradoxical hyperpigmentation exists.

Deoxyarbutin is a synthesized topical derivative. Studies have shown that it has an enhanced sustained improvement, general skin lightening and a safety profile comparable to hydroquinone.

Vitamin C
Vitamin C is a naturally occurring antioxidant that interacts with copper ions at the tyrosinase active site. Vitamin C acts as a reducing agent at various oxidative steps of melanin formation, hence inhibiting melanogenesis.
Studies have shown that the reduced tyrosinase activity mediated by vitamin C seems to be caused by antioxidant activity, and not by the direct inhibition of tyrosinase activity.[20]

Topical vitamin C products derived from fruits and vegetables is unstable, resulting in questionable efficacy. Hence, stable esterified derivatives have been developed out of which the most popular is magnesium-ascorbyl-phosphate (MAP) followed by ascorbyl-6-palmitate.[21]

A study compared 5% ascorbic acid and 4% hydroquinone in 16 female patients with melasma and found 62.5% and 93% improvement respectively. Side-effects were present in 68.7% with hydroquinone versus 6.2% with ascorbic acid. Although, HQ showed better response, vitamin C may play a role as it is devoid of any side-effects, can be used alone or in combination therapy.[22]

Penetration of vitamin C into the skin is low. One study conducted in Japanese women showed that high-frequency ultrasound radiation when combined with skin lightening gel (ascorbyl glucoside with niacinamide) caused reduction in hyperpigmentation by causing enhanced transepidermal transport of the gel.[23]

Vitamin C is a constituent of many cosmeceuticals and cosmetic creams as shown in Table 1.

MAP is a derivative of vitamin C. It is absorbed through the stratum corneum as it is lipophilic. 10% MAP cream has been found to cause significant skin lightening effect.[24] However, most skin care products contain less than 1% concentration.

**Alpha tocopherol (Vitamin E)**

Vitamin E is the major lipophilic antioxidant in plasma, membranes, and tissues. The term “vitamin E” includes eight naturally occurring molecules (four tocopherols and four tocotrienols) that have vitamin E activity. In humans, alpha tocopherol is the most abundant vitamin E derivative, followed by gamma tocopherol.[25]

Controlled studies with vitamin E show insufficient evidence of effectiveness in treatment of specific dermatologic disorders. However, there is a large body of experimental evidence proving its photo-protective effects. It has been shown to cause depigmentation by interference with lipid peroxidation of melanocyte membranes, increase in intracellular glutathione content, and inhibition of tyrosinase.[26] Another clinical double-blinded study showed a significant improvement of melasma and pigmented contact dermatitis lesions using topical vitamins E and C, with the combination showing better results compared to the single-vitamin treatment groups.[27]

Although, topical alpha-tocopherol is mostly used at concentration of 5% or less, products with varying concentrations have been marketed. Side-effects such as allergic or irritant reactions are rare with topical vitamin E and hence, it is a component of cosmeceuticals preparations.

**Niacinamide**

Furthermore, known as nicotinamide (3-pyridine-carboxamide) is the physiologically active amide of niacin (vitamin B3). Niacin is involved in the synthesis of the enzymes Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) required for cellular metabolism.

Study done on pigmented reconstructed epidermis (PREP) showed that niacinamide interferes with the interaction between keratinocytes and melanocytes, thereby inhibiting melanogenesis. It also modulates the protease-activated receptor (PAR-2) that is involved in the transfer of melanosomes from melanocytes to surrounding keratinocytes. Clinical trials using 2% niacinamide have shown that it significantly reduces the total area of hyperpigmentation and increases skin lightness after 4 weeks of treatment. There is a plateau in treatment effect which could be due to balance between the up-regulation of melanogenesis in the hyperpigmented area and the down-regulation by niacinamide. Alternatively, the plateau could reflect the fraction of the hyperpigmented area that is sensitive to niacinamide treatment. The study also showed that the daily use of niacinamide with sunscreen was effective in reducing hyperpigmentation and in increasing lightness of basal skin colour compared with sunscreen alone.[28]

Niacinamide is the main ingredient of the most popular cosmeceutical used for hyperpigmentation in the Indian market, that is Fair and Lovely fairness cream where it is combined with sunscreen for additional benefits [Table 1]. In another variety of the same product, niacinamide is used along with Vitamin C.

**Botanical/plant extracts**

Due to the potential side-effects of existing therapies, there is a rising trend towards development of natural derived extracts for hyperpigmentation [Table 1]. Various plant extracts are being studied for their role in melasma. Hwang et al. conducted an in vitro study with 101 plant extracts and evaluated their effect on melanin synthesis in B16 melanoma cells.[29] They found that Broussonetica kazwoki, B. Papyrifera, Cornus officinalis, Rhus javanica and Pinus densiflora inhibited tyrosinase and Dihydroxyphenylalanine (DOPA) oxidation in a dose dependent manner. Due to the lack of side-effects, various plant extracts are being used in various cosmeceuticals.
creams [Table 1]. Few of the botanical extracts used for hyperpigmentation are mentioned below.

**Grape seed extract**
Grape seed extract contains proanthocyanidin, which is a powerful antioxidant. Although, there are no studies on the topical use of grape seed extract, but oral intake for 6 months has been found beneficial in patients with melasma in a study conducted by Yamakoshi, et al.[30]

**Orchid extract**
Tadokoro et al. conducted a study in 48 female patients to evaluate the efficacy of a cosmetic formulation containing orchid extract and compared it to 3% vitamin C derivative.[31] The authors found that orchid extract has efficacy similar to vitamin C in melasma and lentigines.

**Aloe vera extract**
Study conducted in animals found that the leaf extract of A. Vera and its active ingredient aloin induced powerful, dose-dependent, physiologically significant melanin aggregating effects leading to skin lightening via adrenergic receptor stimulation.[32] Aloe vera extract is an ingredient of various market preparations.

**Pycnogenol**
Pycnogenol obtained from the bark of French maritime pine Pinus pinaster is evolving for its use in hyperpigmentation. Its main constituents are procyanidins, polyphenolic monomers, phenolic or cinnamic acids. It has antioxidant and anti-inflammatory properties and hence scavenges free radicals. Pine extract has been used in various market preparations. Oral pynogenol has been found to reduce melasma severity although, studies on topical use are lacking.[33]

**Marine algae extract**
Cha, et al. evaluated the effect of 43 marine algae extracts on melanin synthesis and found that few extracts evidenced potent tyrosinase inhibitory activity similar to that of positive control, kojic acid without causing any side effects.[34] Hence, these extracts can be used as an ingredient in skin lightening cosmeceuticals.

**Cinnamic acid**
It is a phenyl propanoid derivative occurring in plants that inhibits tyrosinase activity as demonstrated in studies conducted on human and guinea pig melanocytes. Study conducted by Tan et al. found that cinnamic acid (2 mmol/L; 0.5 mmol/L) showed greater inhibition of tyrosinase activity compared to hydroquinone (0.5 mmol/L).[35]

**Flavonoids**
Flavonoids are naturally occurring polyphenolic compounds with anti-inflammatory, antioxidant, antiviral and anti-carcinogenic properties. Various plant derived flavonoids still under investigation include catechin conjugated with gallic acid (from green tea leaves), ellagic acid (from green tea, eucalyptus, strawberry, etc.) and aloesin (from aloe tree).

**Green tea extracts**
Green tea extracts contain polyphenolic compounds that act on various biochemical pathways hence causing anti-inflammatory, anti-oxidant and anti-carcinogenic effects. Epigallocatechin-3-gallate is the main active ingredient contained in green tea. Study conducted by No, et al. has shown that green tea extracts cause in vitro inhibition of mushroom tyrosinase, which may be responsible for the de-pigmenting effect.[36] However, more in vivo studies are needed to substantiate this action.

**Aloesin**
Aloesin is a natural derivative of aloe vera that inhibits tyrosinase at non-cytotoxic concentrations.[37,38] Aloesin is a competitive inhibitor of Dopa oxidation and a non-competitive inhibitor of tyrosine hydroxylase activity.[39] Aloesin is an experimental product and is not available clinically.

**Coffeeberry**
Coffeeberry extract is known to have anti-oxidant properties. However, its de-pigmenting action is yet to be proven. Study conducted by McDaniel et al. in 30 patients with photo-damage showed improvement in hyperpigmentation following 6 weeks of coffeeberry extract application.[40]

**Mulberry extract**
Mulberry extract is derived from the plant Morus alba L from the Moraceae family. The leaves of this plant have anti-hyperglycaemic activity. The derivatives of its root bark have been found to have skin lightening effect. This could be due to inhibition of dopa oxidase activity of tyrosinase and superoxide scavenging activity.

IC50 (concentration causing 50% inhibition of activity of tyrosinase) is very low (0.396%) as compared to 5.5% for hydroquinone and 10.0% for kojic acid.[41] However, clinical trials regarding skin lightening effects are lacking. A patch test using 1% paper mulberry extract revealed no significant skin irritation at 24 h and 28 h.

**Soy (glycine soja)**
The major components of soy are phospholipids (45-60%), and essential fatty oils (30-35%). It also contains active ingredients like isoflavones, vitamin E and serine protease inhibitors-soybean trypsin inhibitor (STI) and Bowman-Birk protease inhibitor (BBI). The protease inhibitors inhibit PAR-2 activation, thereby inhibiting melanosome transfer.[42]
The fatty acids in soy inhibit trypsin which is a known activator of PAR-2. Furthermore, the isoflavones inhibit the DOPA oxidase activity thus inhibiting melanogenesis.\[^{43}\]

Soy has proven to be both efficacious and safe. Several skin care products containing soy are available to improve hyperpigmentation. Skin lightening benefit can be seen after 12 weeks of twice daily application. The de-pigmenting effect of soy milk is reversible and daily topical treatments for 7 months result in no adverse effects.\[^{44}\]

**Licorice extract**

Licorice extract is obtained from the root of Glycyrrhiza Glabra Linnera. It is cultivated extensively in India. Licorice extract improves hyperpigmentation by dispersing the melanin, inhibition of melanin biosynthesis and inhibition of cyclooxygenase activity thereby decreasing free radical production. Glabridin, a polyphenolic flavonoid is the main component of licorice extract. Studies have shown that glabridin prevents Ultraviolet B (UVB) induced pigmentation and exerts anti-inflammatory effects by inhibiting superoxide anion and cyclooxygenase activity.\[^{45}\] However, more studies are needed to prove its de-pigmenting action.

**Umbelliferone**

Umbelliferone (UMB) or 7-hydroxycoumarin, a widespread natural product of the coumarin family, is a phenolic compound of plant origin, for which many biological activities have been reported. It occurs in many plants from the Apiaceae (Umbelliferae) family such as carrot, coriander. UMB absorbs ultraviolet light strongly at several wavelengths (300, 305, 325 nm) and is used in sunscreens. It is also used as an antioxidant with minimal toxicity. It also has anti-inflammatory activity as it decreases lipid peroxidation.

Thus, UMB is a phytochemical with sun-blocking, antioxidant and anti-inflammatory properties.

**Boswellia**

Boswellia (BAs) are pentacyclic triterpenes, with strong anti-inflammatory activity, extracted from the gum resins of the tropical tree Boswellia serrata that grows in India and Africa. Until recently, work on Boswellia focussed on the immunomodulatory properties of the resin. In numerous clinical trials and *in vitro* and *in vivo* studies boswellic acids are found to exert significant anti-inflammatory and pro-apoptotic activity.\[^{46}\] The mechanism of action in hyperpigmentation is not clear although, it is used in many cosmetic products.

**N-Acetyl Glucosamine**

N-Acetyl Glucosamine (NAG) reduces the amount of melanin in melanocytes, thereby improving hyperpigmentation and skin tone. It inhibits the conversion of pro-tyrosinase to tyrosinase and also affects the genes involved in hyperpigmentation. In a study conducted by Bessett, 2% NAG was found to reduce facial hyperpigmentation after 8 weeks of application.\[^{47}\] Its combination with niacinamide has been found to have greater de-pigmenting effect in various clinical studies.\[^{48}\] It is a component of various over-the-counter products used for hyperpigmentation.

**Retinoids and retinoid combination therapy**

Retinoids, that are derivatives of vitamin A, are used to treat various pigmentation disorders like melasma and post-inflammatory hyperpigmentation. It causes inhibition of tyrosinase and epidermal melanin dispersion. Retinoids may also interfere with pigment transfer to keratinocytes and accelerate pigment dispersion by causing the epidermis to be shed more quickly. Retinoids use over prolonged period causes increased stratum corneum compaction and decreased melanin content.

Griffiths, *et al.* used tretinoin in 38 patients with melasma over a 40 week period and observed 68% improvement.\[^{49}\] However, side-effects in the form of erythema and desquamation were seen in 88% patients.

Studies have demonstrated good improvement in melasma with triple combinations of corticosteroids, hydroquinone and retinoic acid. Retinoids reduce the atrophy of the corticosteroid and facilitate epidermal penetration and delivery of hydroquinone. However, irritant reaction causes paradoxical hyperpigmentation. Retinoids are not used in the commercial preparations used for hyperpigmentation.

**Role of sun-protection**

Broad spectrum sunscreens are the cornerstone of hyperpigmentation therapy. Avobenzone absorbs light in the UVA range. However, it is unstable. The stability of avobenzone is increased by combining with oxybenzone. Many cosmeceuticals have physical sunscreens like titanium dioxide, zinc oxide in the same formulation for added benefits [Table 1].

**CONCLUSION**

Cosmeceuticals for hyperpigmentation are in great demand in the Indian market. These agents target the key regulatory steps in melanin synthesis. Although, hydroquinone remains the gold standard of treatment, various botanicals are being increasingly used in the various commercial preparations due to the lack of any side-effects. There is paucity of literature regarding their efficacy and side effect profile. More studies are needed to evaluate their role. It is important to realize that patient
follow-up and compliance is very necessary in any cosmeceutical use as they are slower than conventional therapies. Furthermore, good sun-protection is a must for good outcome.

REFERENCES

1. Dureja H, Kaushik D, Gupta M, Kumar V, Lather V. Cosmeceuticals: An emerging concept. Indian J Pharmacol 2005;37:153-9.
2. Sinclair R. How credible is the science behind cosmetic skin creams? West J Med 1999;171:35-6.
3. Grace R. Cosmeceuticals: Functional food for the skin. Natural Foods Merch 2002;23:92-9.
4. Halder RM, Nootheti PK. Ethnic skin disorders overview. J Am Acad Dermatol 2003;48:5143-8.
5. Denton CR, Lerner AB, Fitzpatrick TB. Inhibition of melanin formation by chemical agents. J Invest Dermatol 1952;18:119-35.
6. Jimbow K, Obata H, Pathak MA, Fitzpatrick TB. Mechanism of depigmentation by hydroquinone. J Invest Dermatol 1974;62:436-49.
7. Findlay GH. Ochronosis following skin bleaching with hydroquinone. J Am Acad Dermatol 1982;6:1092-3.
8. Nordlund JJ, Grimes PE, Ortonne JP. The safety of hydroquinone. J Eur Acad Dermatol Venereol 2006;20:781-7.
9. Findlay GH, Morrison JG, Simson IW. Exogenous ochronosis and pigmented colloid milium from hydroquinone bleaching creams. Br J Dermatol 1975;93:613-22.
10. Tse TW. Hydroquinone for skin lightening: Safety profile, duration of use and when should we stop? J Dermatol Treat 2010;21:272-5.
11. Draefos ZD. Cosmetic therapy. In: Welleron SE, editor. Comprehensive Dermatologic Drug Therapy. 2nd ed. Philadelphia: Saunders; 2007. p. 761-74.
12. Jarratt M. Mequinol 2%/tretinoin 0.01% solution: An effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines. Cutis 2004;74:319-22.
13. Colby SI, Schwartzel EH, Huber FJ, Highton AD, Altman DJ, Epinette WW, et al. A promising new treatment for solar lentigines. J Drugs Dermatol 2002;3:147-52.
14. Jimbow K. N-acetyl-4-S-cysteaminylphenol as a new type of depigmenting agent for the melanoderma of patients with melasma. Arch Dermatol 1991;127:1528-34.
15. Kahn V. Effect of kojic acid on the oxidation of DL-DOPA, norepinephrine, and dopamine by mushroom tyrosinase. Pigment Cell Res 1995;8:234-40.
16. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. Dermatol Surg 1999;25:282-4.
17. Garcia A, Fulton JE Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. Dermatol Surg 1996;22:443-7.
18. Maeda K, Fukuda M. Arbutin: Mechanism of its depigmenting action in human melanocyte culture. J Pharmacol Exp Ther 1996;276:765-9.
19. Boissy RE, Visscher M, DeLong MA. DeoxyArbutin: A novel reversible tyrosinase inhibitor with effective in vivo skin lightening potency. Exp Dermatol 2005;14:601-8.
20. Choi YK, Rho YK, Yoo KH, Lim YY, Li K, Kim BJ, et al. Effects of vitamin C vs. multivitamin on melanogenesis: Comparative study in vitro and in vivo. Int J Dermatol 2010;49:218-26.
21. Farris PK. Cosmeceutical vitamins: Vitamin C. In: Draefos Z, editor. Procedures in cosmetic dermatology series: Cosmeceuticals. Philadelphia: Elsevier; 2005. p. 51-6.
22. Espinal-Perez LE, Moncada B, Castanedo-Cazares JP. A double-blind randomized trial of 5% ascorbic acid vs. 4% hydroquinone in melasma. Int J Dermatol 2004;43:604-7.
23. Hakozaki T, Takihaki H, Miyamoto K, Sato Y, Arase S. Ultrasound enhanced skin-lightening effect of vitamin C and niacinamide. Skin Res Technol 2006;12:105-13.
24. Kameyama K, Sakai C, Kondo H, Yonemoto K, Nishiyama S, Tagawa M, et al. Inhibitory effect of magnesium L-ascorbyl-2-phosphate (VC-PMG) on melanogenesis in vitro and in vivo. J Am Acad Dermatol 1996;34:29-33.
25. Thiele J, Hsieh SN, Ekanayake-Mudiyanselage S. Vitamin E: Critical review of its current use in cosmetic and clinical dermatology. Dermatol Surg 2005;31:805-13.
26. Badreshia-Bansal S, Draelos ZD. Insight into skin lightening cosmeceuticals for women of color. J Drugs Dermatol 2007;6:32-9.
27. Hayakawa R, Ueda H, Nozaki T, Izawa Y, Yokotake J, Yasaki K, et al. Effects of combination treatment with vitamins E and C on chloroasia and pigmented contact dermatitis. A double blind controlled clinical trial. Acta Vitaminol Enzymol 1981;3:31-8.
28. Hakozaki T, Minwalla L, Zhuang J, Chhoa M, Matsubara A, Miyamoto K, et al. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. Br J Dermatol 2002;147:20-31.
29. Hwang JH, Lee BM. Inhibitory effects of plant extracts on tyrosinase, L-DOPA oxidation, and melanin synthesis. J Toxicol Environ Health A 2007;70:393-407.
30. Yamakoshi J, Sano A, Tokutake S, Saito M, Kikuchi M, Kubota Y, et al. Oral intake of proanthocyanadin-rich extract from grape seeds improves chloasma. Phytother Res 2004;18:895-9.
31. Tadokoro T, Bonté F, Archambault JC, Cauchard JH, Neveu M, Ozawa K, et al. Whitening efficacy of plant extracts including orchid extracts on Japanese female skin with melasma and lentigo senilis. J Dermatol 2010;37:522-30.
32. Ali SA, Galgut JM, Choudhary RK. On the novel action of melanolysis by a leaf extract of Aloes vera and its active ingredient aloin, potent skin depigmenting agents. Planta Med 2012;78:767-71.
33. Ni Z, Mu Y, Gulati O. Treatment of melasma with pycnogenol. Phytother Res 2002;16:567-71.
34. Cha SH, Ko SC, Kim D, Jeon YJ. Screening of marine algae for potential tyrosinase inhibitor: Those inhibitors reduced tyrosinase activity and melanin synthesis in zebrafish. J Dermatol 2011;38:354-63.
35. Tan C, Zhu W, Lu Y. Aloin, cinnamic acid and sophorcarpine are potent inhibitors of tyrosinase. Chin Med J (Engl) 2002;115:1859-62.
36. No JK, Soung DY, Kim YJ, Shin KH, Jun YS, Rhee SH, et al. Inhibition of tyrosinase by green tea components. Life Sci 1999;65:PL241-6.
37. Choi S, Lee SK, Kim JE, Chung MH, Park YJ. Aloesin inhibits hyperpigmentation induced by UV radiation. Clin Exp Dermatol 2002;27:513-5.
38. Jones K, Hughes J, Hong M, Jia Q, Orndorff S. Modulation of melanogenesis by aloesin: A competitive inhibitor of tyrosinase. Pigment Cell Res 2002;15:335-40.
39. Rendon MI, Gaviria J. Review of skin-lightening agents. Dermatol Surg 2005;31:886-9.
40. Rendon MI, Gaviria J. Review of skin-lightening agents. Dermatol Surg 2005;31:886-9.
41. McDaniel DH. Clinical safety and efficacy in photoaged skin with coffeeberry extract, a natural antioxidant. Cosmet Dermatol 2009;22:610-6.
42. Lee SH, Choi SY, Kim H, Hwang JS, Lee BG, Gao J, et al. Mulberryoside F isolated from the leaves of Morus alba inhibits melanin biosynthesis. Biol Pharm Bull 2002;25:1045-8.
43. Thornfeldt C. Cosmeceuticals containing herbs: Fact, fiction, and future. Dermatol Surg 2005;31:873-80.
44. Leyden J, Wallo W. The mechanism of action and clinical benefits of soy for the treatment of hyperpigmentation. Int J Dermatol 2011;50:470-7.
45. Wallo W, Nebus J, Leyden J. Efficacy of a soy moisturizer in photoaging: A double-blind, vehicle-controlled, 12-week study. J Drugs Dermatol 2007;6:917-22.
46. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. Pigment Cell Res 1998;11:355-61.
47. Moussaieff A, Mechoulam R. Boswellia resin: From religious ceremonies

Journal of Cutaneous and Aesthetic Surgery - Jan-Mar 2013, Volume 6, Issue 1
to medical uses; a review of in-vitro, in-vivo and clinical trials. J Pharm Pharmacol 2009;61:1281-93.

47. Bissett DL, Robinson LR, Raleigh PS, Miyamoto K, Hakozaki T, Li J, et al. Reduction in the appearance of facial hyperpigmentation by topical N-acetyl glucosamine. J Cosmet Dermatol 2007;6:20-6.

48. Kimball AB, Kaczvinsky JR, Li J, Robinson LR, Matts PJ, Berge CA, et al. Reduction in the appearance of facial hyperpigmentation after use of moisturizers with a combination of topical niacinamide and N-acetyl glucosamine: Results of a randomized, double-blind, vehicle-controlled trial. Br J Dermatol 2010;162:435-41.

49. Griffiths CE, Finkel LJ, Ditre CM, Hamilton TA, Ellis CN, Voorhees JJ. Topical tretinoin (retinoic acid) improves melasma. A vehicle-controlled, clinical trial. Br J Dermatol 1993;129:415-21.

How to cite this article: Sarkar R, Arora P, Garg KV. Cosmeceuticals for hyperpigmentation: What is available?. J Cutan Aesthet Surg 2013;6:4-11.

Source of Support: Nil. Conflict of Interest: None declared.

Author Help: Online submission of the manuscripts

Articles can be submitted online from http://www.journalonweb.com. For online submission, the articles should be prepared in two files (first page file and article file). Images should be submitted separately.

1) First Page File:
Prepare the title page, covering letter, acknowledgement etc. using a word processor program. All information related to your identity should be included here. Use text/rtf/doc/pdf files. Do not zip the files.

2) Article File:
The main text of the article, beginning with the Abstract to References (including tables) should be in this file. Do not include any information (such as acknowledgement, your names in page headers etc.) in this file. Use text/rtf/doc/pdf files. Do not zip the files. Limit the file size to 1 MB. Do not incorporate images in the file. If file size is large, graphs can be submitted separately as images, without their being incorporated in the article file. This will reduce the size of the file.

3) Images:
Submit good quality color images. Each image should be less than 4 MB in size. The size of the image can be reduced by decreasing the actual height and width of the images (keep up to about 6 inches and up to about 1200 pixels) or by reducing the quality of image. JPEG is the most suitable file format. The image quality should be good enough to judge the scientific value of the image. For the purpose of printing, always retain a good quality, high resolution image. This high resolution image should be sent to the editorial office at the time of sending a revised article.

4) Legends:
Legends for the figures/images should be included at the end of the article file.