REVIEW ARTICLE

Cosmeceuticals for Hyperpigmentation: What is Available?

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 and the article attempts to look at other alternative cosmeceuticals available or maybe upcoming in the future. 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.[2]

Cosmeceuticals are topical cosmetic-pharmaceutical hybrids that enhance the beauty through constituents 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.

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Cosmeceuticals are commonly used for hyperpigmentation. Pigmentary disorders are the third 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 sulfhydryl

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Table 1: Cosmeceuticals for hyperpigmentation in leading brands in Indian market

Brand	Ingredients	Cost (INR)
Clarins		1800
Whitening night cream	Ascorbyl glucoside	
All spots whitening corrector	Parsley extract Salicylic acid Biotin Fruit extract Citric acid	
Chambor (softener)	White lily extract Aloe vera extract Vitamin E	435
YSL (whitening cream)	Vitamin C Grape seed extract	3550
La Prairie (fairness cream)	Caviar extract White truffles White wine extract White flower complex White tea	25000
Elizabeth Arden	Vitamin C derivative (emblica) New marine mineral extract	800
Revlon (fairness cream)	Cinnamate Dimethicone Titanium dioxide Magnesium phosphate	145
Lakme (fairness cream)	Titanium dioxide Aluminium hydroxide 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 Sugarcane extract Benzyl salicylate	78
Fair and Lovely multivitamin fairness cream	Niacinamide Ascorbyl phosphate Tocopheryl acetate Allantoin Titanium dioxide	82
Himalaya fairness cream	Aloe vera Citrus reticulata extract	65
Ponds fairness cream	Niacinamide Tocopheryl acetate Allantoin Titanium dioxide	140
Emami fairness cream	Liquorice distillate Niacinamide Grape seed oil Wheat germ oil Methoxycinnamate Titanium dioxide Zinc oxide	45

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].

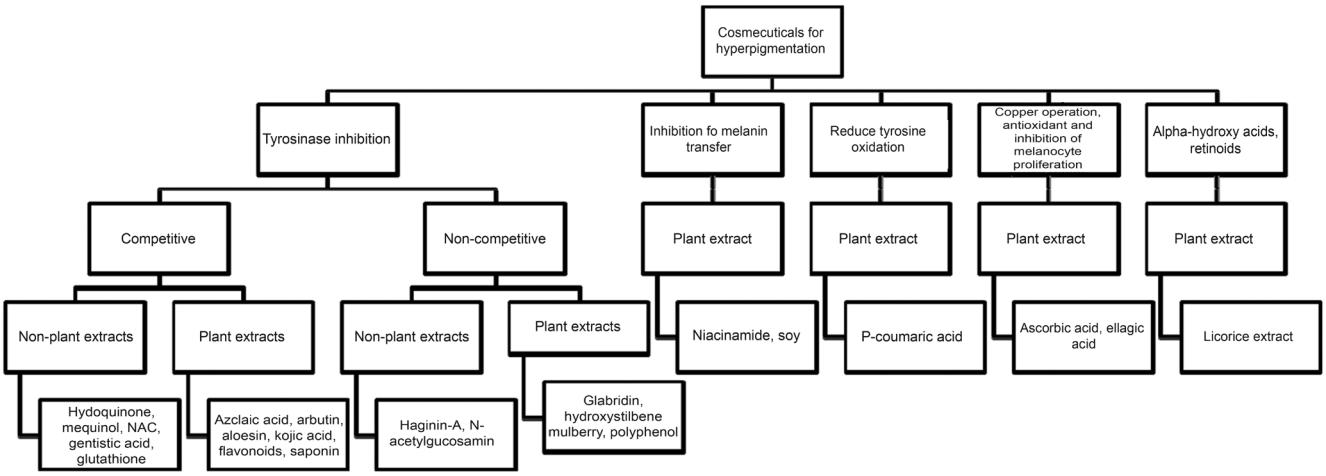

Figure 1: Cosmeceuticals based on their mechanism of action

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.[11] 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.[12] 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.[13]

N-acetyl-4-S-cysteaminylphenol

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.[14]

Non-phenolic agents

Kojic acid

Kojic acid (5-hydroxy-2 hydroxymethyl-4-pyrone) 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.[15] Kojic acid (KA) is used at concentrations ranging from 1% to 4%.

There are no RCTs available comparing KA to other treatments. However, because both KA and HQ are tyrosinase inhibitors, the combination augments efficacy as demonstrated in the study by Lim JT where 2% kojic acid in a gel containing 10% glycolic acid and 2% hydroquinone was compared with the same application but without kojic acid.[16] Thus, patients who do not respond to HQ may benefit from the addition of Kojic Acid to the treatment regimen.[16,17] Table 1 shows that kojic acid does not find a place in the cosmeceuticals available. This could be due to the side effect profile of this drug.

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.[18] 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.

Controlled trials on treating hyperpigmentation are lacking. However, several studies have shown that arbutin is less effective than kojic acid for hyperpigmentation. 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.[19]

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 soymilk 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 Glycyrrhia 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 loss 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.

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