ABSTRACT

UV radiation (UV) is considered as a complete carcinogen as it is both a mutagen and a non-specific damaging agent. It is the most important risk factor for skin cancer and many other skin disorders like Hyperpigmentation. There is a need of long-term topical skin care treatments (both cosmetic and cosmeceutical) to address problems associated with hyperpigmentation. Synthetic depigmenting agents, such as hydroquinone, mequinol, although highly effective, can raise several safety concerns (for example, ochronosis, cataract, impaired wound healing, desquamation, and other local or systemic side effects) with long-term exposure. The benefits of phytochemicals and natural extracts offer opportunities to develop new formulations to treat pigmentation problems. Cosmeceuticals are topical cosmetic-pharmaceutical preparations containing active ingredients which improve the appearance of skin. Among cosmeceuticals, the phytochemicals have been known to have a multitude of cellular actions for various dermatological diseases. Plant-derived compounds and their effectiveness in the treatment of hyperpigmentation disorders (Melasma) are discussed.

Keywords: UV radiation, Hyperpigmentation, Phytochemicals, Cosmeceuticals

1. INTRODUCTION

Human skin is the superficial layer which is exposed to various environmental stimuli such as humidity, dust, microbes and UV radiation. Due to day-to-day change in environmental conditions, these UV rays are affecting epidermis as well as dermis of the skin. UV radiation can be classified into UV-A, -B and -C. UV-A has the least energetic photons with the longest wavelength, lying between 315-400nm, UV-C has the highest energetic photons with the shortest wavelength lying between 100-280nm, while UV-B lies in between. On the basis of their exposure, UV affects skin physiology, causing acute or delayed pigmentation.

The cosmetic and pharmaceutical industries aim to achieve the needed therapy for treatment of skin pigmentation. Relating to cosmetic and aesthetic role, skin lightening formulations help to provide action against hyperpigmentation, melasma, post inflammatory hyperpigmentation, photo ageing, skin cancer and phototoxicity. Skin-lightening agents, derived from herbal sources are considered as safe and efficient ingredients, certified for use in cosmetics.

Hyperpigmentation is a skin disorder that occurs due to an increase in cutaneous melanin deposition either through rise in melanin synthesis or melanocytes, the specialized cells producing melanin. Based on the location of deposition of melanin granules, hyper pigmentation can be divided into epidermal and dermal hyperpigmentation. Epidermal hyperpigmentation occurs due to melanin pigmentation and is visualized as brownish blue, while, dermal pigmentation k/a ‘ceruloderma’ or ‘blue hyper pigmentation’ occurs due to melanin or non-melanin pigments. The melanocytes are located at basal layer which on increased activity results in hyperpigmentation. However, in some cases melanin formation may be transferred to the dermis. In these instances, a rise in activity or number of melanocytes leads to dermal hyperpigmentation.

2. MECHANISM

The damage at cellular level initiates transcription of the pro-opiomelanocortin (POMC) gene, leading to production and secretion of melanocyte stimulating hormone (α-MSH). In the basal epidermis, binding of α-MSH with melanocortin 1 receptor (MC1R) on melanocyte, produces cAMP through interaction between MC1R and adenylyl cyclase. This results
in activation of cAMP responsive binding element (CREB), microphthalmia transcription factors (Mitf) and protein kinase A. CREB and Mitf accelerate melanin production by elevating tyrosinase level. Rise in tyrosinase level produces melanin, leading to hyperpigmentation of skin\(^{1,9,10}\) (Fig. 1).

Figure 1: Mechanism of hyperpigmentation

### 3. APPROACHES FOR TREATMENT OF HYPERPIGMENTATION BY PHYTOCHEMICALS

#### 3.1 Tyrosinase inhibition and related enzyme expression

The expression of tyrosinase and other melanogenic enzymes is modified in the initial stage i.e the transcriptional level\(^{11}\). Research and formulation of novel skin lightening agents from natural sources needs various phytoconstituents to be analyzed, that inhibit formation of tyrosinase, tyrosinase related protein-1 (TRP1) and tyrosinase related protein-2 (TRP-2)\(^{12}\).

Cho et al. studied and demonstrated that isoimperatorin and imperatorin obtained from ethanolic extract of Angelica dабurica showed inhibition of tyrosinase synthesis in Bl6 melanoma cells by reducing the level of tyrosinase m-RNA, leading to skin whitening\(^{13}\).

#### 3.2 Inhibition of tyrosinase activity

Majority of the herbal depigmenting compounds act by interfering in the melanin synthesis pathways by inhibiting tyrosinase activity\(^{12}\). These types of tyrosinase inhibitors are prevalent and herbal extracts serve as good source of naturally occurring tyrosinase inhibitors which are used as traditional therapies for pigmentation disorders\(^{14,15}\).

Based on the in vitro studies, Green tea is known to be a competitive tyrosinase inhibitor. The major catechin constituents: epicatechin gallate, epigallocatechin gallate and gallocatechin gallate are responsible for this effect\(^{16}\).

As studied by Picardo and Carrera, aloesin from Aloe vera acts as a non-competitive inhibitor of tyrosinase, affecting the tyrosinase complex, resulting in the conversion of DOPA into melanin.\(^{17}\).

Tan et al. reported that aloin isolated from Aloe vera leaf extract serves as a natural skin lightening agent which binds to the enzyme- substrate complex in addition to tyrosinase enzyme, thus inactivating the enzyme that results in lightening of skin\(^{18}\).

Glycyrrhiza glabra is a commonly used compound in the skin lightening industry, which inhibits tyrosinase and reduces the formation of pigment in melanocyte cells. Studies of Nerya et al. and Fu et al revealed that glabridin and isoliquiritigenin, the main constituents of the licorice extract inhibit tyrosinase activity in B16 murine melanoma cells\(^{19,20}\). Research showed that skin lightening potential of glabridin is greater than that of hydroquinone, the artificial depigmentation agent widely used\(^{20,21}\).

Hesperidin, a bioflavonoid also exhibits dose-dependent antityrosinase activity in B16 melanoma cells that results in inhibition of melanin synthesis without any cytotoxicity\(^{22}\).

#### 3.3 Inhibition of Melanin dispersion

Several studies have analyzed the regulatory factors of the melanosome movement and the interaction between keratinocytes and melanocytes during the transfer process\(^{23,24}\).

Hence, various compounds are known to have an effect on the melanin transfer from melanocytes to keratinocytes, leading to skin lightening and therefore can treat hyperpigmentation disorders\(^{13}\).

Recent studies revealed that Aloe vera extract aids in skin lightening through stimulation of adrenergic receptors of various subtypes in different melanophore models\(^{25}\).
3.4 Melanin degradation control and removal

Some compounds increase the degradation and removal of pigment granules from the skin. They remove excessive melanin and are used as cosmetic and therapeutic agents. Studies conducted by Amer and Metwalli, demonstrated that liquiritin isolated from Licorice root extracts, exhibited potent skin lightening benefits in melasma patients, by removing keratinocytes, shortening the cell cycle and facilitating rapid pigment loss.

4. ROLE OF PHYTOCHEMICALS FOR TREATMENT OF HYPERPIGMENTATION

Phytochemicals and natural products with skin-lightening properties are meeting demands of consumers and researchers due to their mild, safe, and healthy action than synthetic alternatives. Botanicals are extensively being used in skin lightening cosmetics and are promising agents with great potential for future use, because scope of natural treatments is considered efficient for treatment of hyperpigmentation. The phytochemicals used to treat hyperpigmentation are listed in Fig. 2. Since, hydroquinone is one of the standard treatments, however, a number of adverse effects have been reported such as skin irritation, cutaneous and contact dermatitis. Due to adverse drug reaction, hydroquinone has been banned in several countries including European Union. Advancement in cosmeceuticals and phytochemical industry led to an investigation of natural plant extracts. Active plant compounds are found to be potent inhibitors of melanin formation than hydroquinone as they do not involve any cytotoxicity. The clinical prospects and the activity of different phytochemical compounds have been listed below in Table 1.

Figure 2: Classification of depigmenting Phytochemicals

4.1 Aloesin

Aloesin is a botanical compound obtained from aloe plant. It competitively inhibits tyrosinase level from human and murine sources. It significantly inhibits 3,4-dihydroxyphenylalanine (DOPA) oxidase, which further inhibit tyrosinase activity.

Wang et al., using reconstituted human skin, studied the effects of aloesin on melanogenesis and found that aloesin had direct inhibitory effects on melanogenesis and exhibited dose-dependent reductions in tyrosinase activity and melanin content.

In a study by Jones et al., aloesin is shown to modulate melanogenesis via competitive inhibition of tyrosinase enzyme and is considered as an effective alternative for treating pigmentation for cosmetic or therapeutic applications.

4.2 α-bisabolol

α-bisabolol, the primary constituent of the Matricaria chamomilla plant is a monocyclic sesquiterpene alcohol. This compound has tremendous application including anti-inflammatory, antibiotic, analgesic and gastric protection. The anti-inflammatory effect of bisabolol masks photoprotection. Moreover, it was found that α-bisabolol also inhibits α-MSH induced melanogenesis by suppressing cyclic adenosine monophosphate level. This is mediated by blocking CREB phosphorylation induced by protein kinase A (PKA). Hence it is considered as an effective inhibitor of hyperpigmentation.

In a double blind, vehicle control study by Lee et al., α-bisabolol was evaluated for its efficacy on hyperpigmentation. The cream containing 0.5% α-bisabolol and vehicle control was tested on Korean women of age 32-52 years for about 2 months. A stronger whitening effect was observed with α-bisabolol than control vehicle. As per the in vivo studies, alpha-bisabolol was essentially utilized as an adjunctive therapy for the treatment of hyperpigmentation.
4.3 Arbutin

Arbutin, a hydroquinone-\(\alpha\)-\(\beta\)-D glucopyranoside, from leaves of plant named bearberry, obtained from the fruit *Aesculus californica Nutt.*, and cranberry. Arbutin acts by inhibiting the activity of melanosomal tyrosinase and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) at nontoxic concentrations. Therefore, arbutin inhibited tyrosinase activity.\(^{37,38}\)

In a randomized, prospective, open label study by Ertam et al., the efficiency of ellagic acid (EA) and arbutin in melasma was studied. Women with the ages ranging 26–50 years were selected. Fifteen of 20 patients were found to have epidermal melasma, while five had a mixed type of melasma. Ten patients each were tested with natural EA, synthetic EA and arbutin. Reduction in pigmentation was observed by using arbutin and natural EA. Arbutin efficiency is proven for treating melasma and it was concluded that natural EA had same efficiency as that of arbutin.\(^{39}\)

4.4 Ellagic acid

Ellagic acid is a polyphenolic compound obtained from green tea, strawberry, cherries, walnut and geranium. It helps in providing relief from pigmentation caused by UV radiation. In vitro studies proved reduction in melanogenesis by inhibition of tyrosinase at cellular level by using EA. The inhibition is found to be caused by chelation of copper molecules on tyrosinase.\(^{40,41}\)

Shimoğalı et al., conducted study on the efficacy of ellagic acid on melanogenesis inhibition and performed *in vitro* and *in vivo* evaluation. Tyrosinase activity in the B16 medium melanoma cells was found to recover in a dose-dependent manner when copper ions were added to the medium containing ellagic acid.\(^{42}\)

Kasai et al. analyzed the effects of oral administration of ellagic acid-rich pomegranate extract on UV-induced pigmentation in the skin. It had a protective effect on slight sunburn even at low doses. Hence it can be concluded that ellagic acid-rich pomegranate extract proved to be a whitening health food.\(^{41}\)

4.5 Liquiritin

Liquiritin is an active compound of Liquorice extract (*Glycyrrhiza glabra*). Liquiritin generally has no effect on tyrosinase but it helps in melanin dispersity and thereby causing epidermal removal. Amer and Metwali, demonstrated effect of licorice cream applied 1g daily for 4 weeks showing the benefit in melasma.\(^{42}\)

Zuhair and Mujtaba, analyzed the effect of topical licorice application on 90 patients for melasma. A formulation of 2% and 4% liquiritin along with 4% hydroquinone was analyzed. The study showed that 4% liquiritin showed better result on melasma as compared to 2% liquiritin and 4% hydroquinone.\(^{43}\)

4.6 Silymarin

Silymarin, a natural polyphenolic flavonoid is a biologically active component with antioxidant properties. Derived from the milk thistle plant *Silybum marianum*, it prevents melanin production in a dose-dependent manner without affecting cell viability and reduces and suppresses hazardous effects of UV.\(^{44,45}\)

Silymarin is also involved in the inhibition of L-DOPA oxidation activity of tyrosinase, the rate limiting melanogenic enzyme. It was also determined that silymarin decreased the expression of tyrosinase protein by western blot analysis. Hence it was concluded that silymarin may be useful as a natural skin-lightening agent.

In a double-blind, placebo-controlled study by Altaei, the safety and efficacy of topical silymarin cream was assessed at two different doses for treatment of 96 melasma patients. Both the creams were reported to reduce the Melasma Area and Severity Index score to 0.\(^{46}\)

4.7 Glabridin

Glabridin, a pyranosiflavan is an active ingredient in liquorice extract derived from *Glycyrrhiza glabra*. It exerts an anti-inflammatory action and is a potent inhibitor of melanogenesis.

Yokota et al investigated *in vitro* the inhibitory effects of glabridin on melanogenesis and inflammation by using cultured B-16 murine melanoma cells and guinea pig skin. The depigmentation was studied with a colorimeter and number of melanocytes were determined by histochemical analysis. It was concluded that glabridin inhibits tyrosinase activity but has no effect on DNA synthesis.\(^{47}\)

Chen et al determined the inhibitory kinetics of glabridin on tyrosinase along with their binding mechanisms by spectroscopic, zebrafish model and molecular docking techniques. It was observed that glabridin reversibly inhibits tyrosinase in a noncompetitive manner through a multiphase kinetic process.\(^{49}\)

4.8 Hesperidin

Hesperidin is a predominant flavonoid derived from citrus fruits. Zhu and colleagues studied and demonstrated hesperidin’s potent ability to inhibit melanin synthesis without cytotoxicity.\(^{48,49}\) This study led to dose-dependent inhibition of tyrosinase activity (vs control) of hesperidin in melanoma B16 cells and human primary melanocytes.\(^{50}\)

Proteggente found that hesperidin protected against oxidative damage of collagen and UVA-induced damage of fibroblasts.\(^{51}\) Hence, hesperidin has potential skin-lightening benefits, along with improved overall skin tone and anti-yellowing effects.

Recent studies showed that hesperidin induces melanogenesis in murine melanoma cells when added to the culture medium, which, if extrapolated to *in vivo* conditions, would lead to hyperpigmentation.

Furthermore, in a study by Usach et al, it was found that hesperidin concentrations of 25 and 50 μM induced melanin synthesis and tyrosinase activity in human melanocytes in a concentration-dependent manner. Both these results suggest that hesperidin increases melanin in human skin.\(^{52}\)

4.9 Procyanidin

Procyanidin, the main active component of *Pinus pinaster* bark extract is a promising therapeutic compound for treatment of pigmentation. It has both anti-inflammatory and antioxidant action. The mechanism of action lies in inhibition of the proliferation of melanocytes and melanin synthesis by tyrosinase in melanocytes.\(^{53}\)

Handog et al conducted a double-blind, placebo-controlled prospective using 30 healthy female volunteers who were treated with procyanidin for 30 days. Variations in pigmentation were recorded using a mexameter. The study revealed improvement in level of lightening of melasma in the treatment group.\(^{54}\)
Clark and Sivamani carried out a randomized, double-blind, placebo-controlled trial lasting 8 weeks, involving 60 Filipino patients with bilateral epidermal melasma, the safety and efficacy of procyanidin along with vitamins A, C, and E was evaluated. Mexameter measurements showed a significant decrease in the degree of pigmentation, suggesting that procyanidin combination with vitamins A, C, and E is safe and well tolerated, with minimal adverse events\textsuperscript{55,56}. Syed et al studied the clinical efficacy, safety, and tolerability of 2% analogue of green tea extract (EGGC) in a hydrophilic cream for melasma treatment in women. 60 subjects, aged 18 to 50 years with centrofacial, malar, and mandibular types of lesions were selected. Patients were randomized according to sequence into two parallel groups. A substantial improvement was observed in both the groups. Therefore, the cream was observed to highly reduce mean lesion count than placebo. In terms of clearing lesions, therapeutic success was observed in 60% of the active group and 3% in placebo subjects\textsuperscript{57}. Elmets evaluated the effect of polyphenols on cutaneous photoprotection along with its analysis. Skin of volunteers was treated with green tea extract or one of its constituents. Thirty minutes later, the treated locations were exposed to a 2 minimal erythema dose solar simulated radiation. UV-treated skin was observed clinically for UV-induced erythema, histologically for the presence of Langerhans cell distributions, or biochemically for UV-induced DNA damage. Polyphenolic extracts of green tea were proved to be effective chemopreventive agents against adverse effects of UV on human health and may thus serve as natural alternatives for photoprotection\textsuperscript{58}.

### 4.10 Green tea

Green tea extracts, comprising multiple polyphenolic antioxidants, of which epigallocatechin-3-gallate (EGCG) is the main constituent\textsuperscript{55,56}. Syed et al studied the clinical efficacy, safety, and tolerability of 2% analogue of green tea extract (EGGC) in a hydrophilic cream for melasma treatment in women. 60 subjects, aged 18 to 50 years with centrofacial, malar, and mandibular types of lesions were selected. Patients were randomized according to sequence into two parallel groups. A substantial improvement was observed in both the groups. Therefore, the cream was observed to highly reduce mean lesion count than placebo. In terms of clearing lesions, therapeutic success was observed in 60% of the active group and 3% in placebo subjects\textsuperscript{57}. Elmets evaluated the effect of polyphenols on cutaneous photoprotection along with its analysis. Skin of volunteers was treated with green tea extract or one of its constituents. Thirty minutes later, the treated locations were exposed to a 2 minimal erythema dose solar simulated radiation. UV-treated skin was observed clinically for UV-induced erythema, histologically for the presence of Langerhans cell distributions, or biochemically for UV-induced DNA damage. Polyphenolic extracts of green tea were proved to be effective chemopreventive agents against adverse effects of UV on human health and may thus serve as natural alternatives for photoprotection\textsuperscript{58}.

### Table 1: Overview of depigmenting action of phytochemicals

<table>
<thead>
<tr>
<th>Phytochemical</th>
<th>Plant source</th>
<th>Mechanism</th>
<th>Uses</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe vera</td>
<td>Aloe vera</td>
<td>Inhibition of tyrosinase, Decrease DOPA oxidase</td>
<td>UV radiation hyperpigmentation</td>
<td>Jones et al., 2002 Choi et al., 2002</td>
</tr>
<tr>
<td>Chamomile</td>
<td>California buckeye, bearberry, cranberry, and blueberry</td>
<td>Inhibits DHICA polymerase and tyrosinase</td>
<td>Solar lentigines</td>
<td>Boissy et al., 2005</td>
</tr>
<tr>
<td>Green tea</td>
<td>Green tea, geranium, strawberry, grapes, walnuts and cherries</td>
<td>Decrease melanocyte proliferation, Copper chelation</td>
<td>Melasma</td>
<td>Ertam et al., 2008</td>
</tr>
<tr>
<td>Liquorice</td>
<td>Liquorice</td>
<td>Dispersion of Melanin, epidermal removal</td>
<td>Melasma</td>
<td>Zubair and Muijtba, 2009</td>
</tr>
<tr>
<td>Silymarin</td>
<td>Silybum marianum (standardized extract)</td>
<td>Inhibits l-DOPA oxidation activity of tyrosinase</td>
<td>Melasma</td>
<td>Atlai, 2012</td>
</tr>
<tr>
<td>Liquorice</td>
<td>Liquorice</td>
<td>Tyrosinase inhibition</td>
<td>UBV-induced pigmentation</td>
<td>Yokota et al., 1998</td>
</tr>
<tr>
<td>Citrus fruits</td>
<td>Collagen antioxidant, tyrosinase inhibition Inhibits melanin synthesis</td>
<td>UV-A induced and oxidative damage of collagen</td>
<td>Usach et al., 2015</td>
<td></td>
</tr>
<tr>
<td>Pinus pinaster</td>
<td>Anti-inflammatory and antioxidant</td>
<td>Melasma</td>
<td>Handog et al., 2009</td>
<td></td>
</tr>
<tr>
<td>Camellia sinensis</td>
<td>Antioxidant Tyrosinase inhibition</td>
<td>Melasma</td>
<td>Liang et al., 2014</td>
<td></td>
</tr>
</tbody>
</table>

5. ALTERNATIVES TO PHYTOCHEMICALS

5.1 Phenolic compounds

a) Hydroquinone (HQ)

Hydroquinone is a dihydric phenolic compound with two important constituents namely monobenzyl and monomethyl ether of hydroquinone. Hydroquinone competitively inhibits sulfhydryl groups that act as a substrate for tyrosinase, thereby inhibiting melanin formation\textsuperscript{59,60,61}. HQ is commonly used in the concentration of 2-4%\textsuperscript{62}. Higher concentrations are found to be effective but can cause irritation.

**Limitation:** Although having advantages, HQ has got so many limitations. Chronic adverse effects have been reported including exogenous ochronosis, pigmented colloid milia, sdera, cataract, nail pigmentation, loss of skin elasticity and impaired wound healing\textsuperscript{63}. HQ can even cause DNA damage and therefore, international agency for research on Cancer has placed hydroquinone as non classifiable agent. A proposal was also passed by Food and Drug administration (FDA) on banning of skin bleaching agent containing hydroquinone\textsuperscript{64}.

b) Mequinol

Mequinol (4-hydroxyanisole) is a phenolic compound that competitively inhibits tyrosinase without damaging melanocytes\textsuperscript{85}. A study conducted by Jarrett, involving 216 volunteers, analyzed the effect of 2% mequinol and 0.01% tretinoin. The solution was effective and well tolerated for hyperpigmentation and solar lentigines\textsuperscript{86}.

**Limitation:** Mequinol causes erythema, burning, desquamation and hypopigmentation.
c) N-acetyl-4-S-cysteaminylphenol (NCAP)

It is a phenolic substrate which inhibits tyrosinase activity. It is safer than hydroquinone and shows clinical response after 2-4 weeks for melasma.

5.2 Laser treatments

Fractional laser therapy, for melasma is the only laser treatment approved by US Food and Drug Administration. As observed in a study, evaluating the efficacy of lasers in 10 female subjects, it showed promising results.

**Limitation:** Q-switched ruby, Erbium-yttrium-aluminum garnet, and Q-switched alexandrite 755-nm lasers, are not generally recommended because of ineffectiveness and increased risk of adverse events.

5.3 Chemical peels

Chemical peels such as alpha hydroxyl acids and beta hydroxyl acids have been used for many years in the treatment of melasma. A cream containing 10% glycolic acid and 2% hydroquinone in combination with glycolic acid peel (at 3-weeks interval) showed lightening of melasma and fine facial wrinkling.

**Limitation:** Although improvement in melasma was observed by using glycolic acid, but adverse effect of a painful burn in the glycolic acid peel group was analyzed with ensuring post-inflammatory hyperpigmentation for 2 months in one case.

6. APPLICATION OF NANOTECHNOLOGY IN HYPERPIGMENTATION

Nanoparticles are small substances which act and react as a whole unit having dimension between 1 to 100 nm. These are widely used in the field of dermatology. Nanoparticles such as liposomes, niosomes, dendrimers, solid lipid nanoparticles as well as silver and gold nanoparticles are advantageous due to their high stability along with providing moisturizing effect.

Hydroquinone is well known for its anti-hyperpigmentation activity but due to its adverse effect on skin, its application is limited. Since hydroquinone has hydrophilic structure, it does not penetrate easily in to the skin. Moreover, it oxidizes rapidly. Ghanbarzadeh et al. formulated solid lipid nanoparticle of hydroquinone. The optimized hydroquinone loaded solid lipid nanoparticles indicated better localization of hydroquinone into the skin making it promising drug carrier for topical administration of HQ in the treatment of hyperpigmentation.

In another study, Tokton et al., developed ellagic acid rich pomegranate peel extract (EPP) loaded nanostructure lipid carrier (NLCs). EPP was formulated using warm microemulsion technique having anti tyrosinase value with IC50 28.54 ± 1.34 µg/ml. It had high entrapment efficiency and better penetrability. This denotes that apart from treating hyperpigmentation, nanoparticles are efficacious for promoting product stability and functionality.

7. FUTURE PROSPECTS

Since the global population continues to age, and years of sun damage along with influence of fluctuating hormones, results in uneven pigmentation. This tends to continuously increase worldwide. Today’s consumers are not only looking to treat Melasma, but to create a more even skin tone with enhanced luminosity.

Formulation development of anti-hyperpigmentation products is a challenging phenomenon.

Various studies have been performed and nano formulations have been developed. However, many phyto components exist in which micro and nano formulations have still not been explored.

Development of novel formulations such as SMEDDs, nano, micro, artificial intelligence can be further included. Additionally, sprays and mists for melasma can be obtained so that drug can easily diffuse through the skin.

The effectiveness of depigmenting formulations can be enhanced by incorporating sun screen boosters like titanium dioxide, kaolin, t alc, zinc oxide, carbonate. Newer chemical compounds, such as bemotrizinol, avobenzone, bisoctizole, oxybenzone, and oxyoctylene, are broadband-spectrum agents and are effective against a broad range of solar spectrum.

In addition moisturizers or “antiaging” ingredients can support skin health thereby reducing the appearance of wrinkles. Hence, by incorporating these compounds, an effective depigmenting action along with a photosprotection effect can be obtained.

8. CONCLUSION

Treatment of pigmentation poses a challenge to skin care experts and a broader field is necessary to improve treatments for hyperpigmentation. A huge dimension of safe and effective de-pigmenting botanicals exists as promising alternatives to current drugs, such as hydroquinone.

Phytochemical extracts represent a large area for skin-lightening formulations. Further studies that integrate botanicals with standard treatments are desirable for the treatment of Melasma.

Nanotechnology has primarily gained importance in dermatology, in relation to manufactured products, especially in the cosmetics industry, leading to innovation in the treatment of inflammatory and immunomodulated dermatoses through more effective medications involving less side effects.

**In vitro** studies show that these agents may prove to be an additional potential for protective cosmeceutical use, through antioxidant effect and protection of macromolecules, such as collagen from UV irradiation. So, natural plant extracts may offer the potential to significantly expand the choices for skin-lightening formulations and address the need for better ways to treat Melasma.

REFERENCES


Jarratt MR, Mequinal %/tretinoin 0.1% solution: An effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines. Cutis 2004; 74:319-22.