Current clinical use of depigmenting agents

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ABSTRACT
A variety of topical depigmenting agents have been used clinically, with varying degrees of success. To date, the most effective topical treatment is a triple-combination agent containing hydroquinone (HQ), tretinoin, and fluocinolone acetonide. However, its use is associated with relatively high frequencies of adverse reactions, and therefore there is a necessity to produce effective topical depigmenting agents with fewer adverse effects. Several processes can be targeted for the treatment of hyperpigmentation; specifically, regulation of melanogenesis by inhibiting tyrosinase activity, a key enzyme in melanin synthesis, represents a major therapeutic target. Another option is regulation of melanosomes by manipulation of their formation or transfer. In addition, depigmenting agents can act through antioxidant or anti-inflammatory activities. We compared the tyrosinase inhibitory activity and cytotoxicity of HQ with those of other cosmetic ingredients. The results showed that although HQ was a strong tyrosinase inhibitor, it was cytotoxic at high concentrations. By contrast, 4-α-butyleresorcinol effectively controlled tyrosinase activity without showing toxicity at high concentrations. These findings indicated that 4-α-butyleresorcinol had the potential to act as an effective depigmenting agent, while producing less irritation than the currently available agents.

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Introduction
Recently, many topical depigmenting agents have been developed and widely applied for the amelioration of pigmentary dermatoses. Depigmenting formulations can be classified as either pharmacological agents or cosmetic agents. Hydroquinone (HQ) is a main component of topical pharmacological agents, which exhibits great efficacy, but has a relatively high rate of adverse side effect.1–4 For this reason, most of these formulations require a doctor’s prescription. By contrast, cosmetic agents place more importance on safety, and therefore reduce adverse reactions by using nonirritant ingredients or using lower concentrations of irritant ingredients. Although these cosmetic agents can be used safely without a prescription, they are generally less effective than HQ-based pharmacological agents. The present article reviews current clinical usage of pharmacological and cosmetic depigmenting agents, as well as the current status of emerging depigmenting ingredients. In addition, we present laboratory data on the efficacy and safety of HQ and other cosmetic ingredients.

Pharmacological depigmenting agents

1,4-dihydroxybenzene (commonly known as HQ)
Most pharmacological depigmenting agents target the activity of tyrosinase, a key enzyme in melanin synthesis. Tyrosinase is a copper-containing transmembrane glycoprotein that is the rate-limiting enzyme in melanogenesis.5 HQ, a powerful tyrosinase inhibitor, is the most extensively investigated antimelanogenic agent.6,7 HQ competes with the tyrosinase substrate (i.e., tyrosine) and prevents its enzymatic oxidation to dihydroxyphenylalanine. In addition, oxidative products of HQ cause oxidative damage to membrane lipids and proteins, including tyrosinase.8 In a randomized, double-blind, placebo-controlled trial, Ennes et al9 reported that 38% of patients treated with 4% HQ achieved clinical clearance of melasma in 12 weeks, compared with only 8% of patients in the control group (Table 1). In another randomized, double-blind trial, Haddad et al10 compared the efficacy of 4% topical HQ with a skin-whitening complex consisting of Arctostaphylos uva-ursi, biofermented Aspergillus, grapefruit extract, and rice extract in 30 patients with melasma. HQ showed a 77% improvement,
whereas the skin-whitening complex showed a 67% improvement (Table 1).

Although HQ is proven to be a highly effective depigmenting agent, the safety issue is still controversial. Amer and Metwalli demonstrated that HQ had a “good” to “excellent” effect on melasma and postinflammatory hyperpigmentation, but most participants experienced skin irritation (Table 1). In addition, Haddad et al reported that 25% of patients treated with HQ reported itchy eruption, whereas none of the patients treated with the skin-whitening complex reported any side effects (Table 1). Although the most common adverse events associated with HQ usage in these investigations were mild and tolerable, the use of topical medication with such a high rate of side effects is burdensome for patients, especially in cosmetic conditions. Furthermore, some rare but serious side effects have also been reported with HQ use, such as exogenous ochronosis and permanent depigmentation. Exogenous ochronosis was caused by the accumulation of homogentisic acid in the dermis, resulting in degeneration of collagen and elastic fibers, followed by the irreversible deposition of ochre-colored fibers. Permanent depigmentation can be triggered by the destruction of melanocytes after prolonged use of HQ. Considering these possible long-term complications, the European Committee (24th Directive 2000/6/EC) banned the use of HQ. However, Nordlund et al reviewed the evidence related to the safe use of HQ in 2006 and concluded that it was reasonable to use HQ for the treatment of hyperpigmentation.

**Table 1** Summary of efficacy and safety of topical depigmenting agents.

<table>
<thead>
<tr>
<th>Topical agent</th>
<th>Study</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroquinone (HQ)</td>
<td>1998, Amer and Metwalli</td>
<td>“Good” to “excellent” response in 89.5%, 75%, and 44.4% of patients with melasma, postinflammatory hyperpigmentation, and freckles, respectively</td>
<td>Local irritation was noted in most patients</td>
</tr>
<tr>
<td></td>
<td>2003, Haddad et al</td>
<td>76.9% of patients with melasma showed improvement</td>
<td>25% of patients experienced adverse events</td>
</tr>
<tr>
<td></td>
<td>2000, Ennes et al</td>
<td>38.1% of the melasma patients showed total improvement, 57.2% showed partial improvement</td>
<td>28.6% of patients reported adverse events</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>1993, Griffiths et al</td>
<td>“Improved” or “much improved” in 68% of patients with melasma</td>
<td>Moderate cutaneous side effects occurred in 88% of patients</td>
</tr>
<tr>
<td></td>
<td>1994, Kimbrough-Green et al</td>
<td>“Improved” in 32% of melasma patients</td>
<td>Mild retinoid dermatitis occurred in 67% of patients</td>
</tr>
<tr>
<td>Triple-combination cream (TCC)</td>
<td>2003, Taylor et al</td>
<td>75% reduction in &gt;70% of patients with melasma</td>
<td>63% of patients experienced adverse events such as erythema and desquamation</td>
</tr>
<tr>
<td></td>
<td>2005, Torok et al</td>
<td>“Completely” or “nearly completely” cleared in &gt;90% of patients with melasma</td>
<td>57% of patients experienced adverse reaction</td>
</tr>
<tr>
<td></td>
<td>2007, Ferreira Cestari et al</td>
<td>Improvement of &gt;75% was achieved in 73% of melasma patients using TCC, whereas improvement (&gt;75%) was achieved in only 49% of patients using HQ</td>
<td>No significant difference between the incidence of adverse events in these two groups (15% in TCC vs. 9% in HQ)</td>
</tr>
<tr>
<td></td>
<td>2008, Chan et al</td>
<td>“Cleared” or “significantly improved” in 49.6% of patients with melasma</td>
<td>48.8% of patients had related adverse events</td>
</tr>
<tr>
<td>Arbutin</td>
<td>2008, Ertam et al</td>
<td>All of 10 melasma patients showed a significant decrease of melanin level</td>
<td>No side effects were observed</td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>1991, Balinta et al</td>
<td>64.8% of melasma patients achieved a “good” or “excellent” result</td>
<td>Local irritation was reported in 11.0% of patients</td>
</tr>
<tr>
<td>Kojic acid</td>
<td>2013, Monteiro et al</td>
<td>Mean Melasma Area and Severity Index score was decreased by 2.403 after 12 wks of application</td>
<td>One patient (3.3%) experienced erythema and burning sensation</td>
</tr>
<tr>
<td>4-n-butylresorcinol</td>
<td>2010, Huh et al</td>
<td>Mean melanin index was decreased by 4.87% after 8 wks of application</td>
<td>No adverse events were observed after 8 wks</td>
</tr>
<tr>
<td></td>
<td>2010, Huh et al</td>
<td>Mean melanin index was decreased by 7.51% after 8 wks of application</td>
<td>No adverse events were observed throughout the study</td>
</tr>
</tbody>
</table>

* Combination of 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide.

**Tretinoin**

Tretinoin is another topical pharmacological agent that acts by inhibiting the activity of tyrosinase. This topical retinoid was first used in combination with HQ to enhance its penetration; however, it was later recognized that retinoid alone has an effect on pigmentation by inhibiting the activities of tyrosinase and dopachrome conversion factor. Concentrations ranging from 0.025% to 0.1% have been used to treat pigmentation disorders and skin aging. In 1993, a randomized controlled trial evaluating the efficacy of topical 0.1% tretinoin was conducted in patients with melasma by Griffiths et al (Table 1). After 40 weeks of using tretinoin, 68% of the patients were rated as “much improved” or “improved”, whereas only 5% of the vehicle group showed “improvement”. However, the rate of adverse reaction was also high in the study groups. Moderate cutaneous adverse effects (erythema and irritation) occurred in 88% of patients in the tretinoin group and in 29% of the vehicle group. In another study performed by Kimbrough-Green et al, tretinoin also exhibited good clinical efficacy with a high rate of adverse events (Table 1). Moreover, a review article by Kang et al reported that topical retinoids were effective for the treatment of pigmentary disorders, either as monotherapy or in combination with other topical agents.

**Triple-combination cream**

Triple-combination cream (TCC), which contains 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide, is the most effective topical treatment for melasma reported to date. TCC is the only HQ-containing drug approved by the United States Food and Drug Administration for the treatment of melasma. As mentioned earlier, HQ and tretinoin show depigmenting effects by inhibiting the activity of tyrosinase. Fluocinolone acetonide is a corticosteroid that reduces levels of cytokines, including endothelin-1 and granulocyte-macrophage colony-stimulating factor, which mediate UV-induced pigmentation. Apart from their individual depigmenting effects, each ingredient of the TCC can help in reducing the potential side effects of the other ingredients. Steroids reduce the irritation caused by HQ, and tretinoin ameliorates corticosteroid-induced epidermal thinning.

Ferreira Cestari et al demonstrated that TCC was more effective than 4% HQ for the treatment of melasma (Table 1). In that study, clearance of melasma lesions was observed in 35% of the
patients in the TCC group, compared with 5% of the patients in the HQ group. The incidence of adverse events, including erythema, burning sensations, and desquamation, was similar in both study groups. Although TCC treatment has been reported to show a high efficacy in many clinical studies, it is also associated with high rates of adverse reactions. Torok et al\(^1\) reported that >90% of 173 patients studied experienced “complete” or “nearly complete” clearance of melasma after a 12-month treatment with TCC. However, 129 patients (57%) experienced at least one treatment-related adverse reaction, although these were generally mild and transient in nature (Table 1).\(^16\) In another investigation, Taylor et al\(^2\) also demonstrated high efficacy and a high rate of adverse events in patients treated with TCC (Table 1).

Asian patients have been reported to have a high potential for skin irritation. A clinical trial was therefore conducted to determine the efficacy and safety of TCC in Asian patients. The results of the clinical trial revealed that TCC effectively improved melasma but had a considerable rate of adverse events (Table 1).\(^21\) Interestingly, Asian patients reported more symptomatic complaints, such as skin discomfort or irritation, than did individuals with other skin types.

In conclusion, although pharmacological depigmenting agents such as HQ cream, tretinoin cream, and TCC have been shown to be effective for the treatment of hyperpigmentation, adverse reactions are common. These adverse reactions were mild and transient in most cases, but a high rate of adverse effects may reduce patient compliance and satisfaction. Thus, effective topical agents with fewer adverse effects are urgently needed.

**Cosmetic depigmenting agents**

**Regulation of melanogenesis by controlling tyrosinase activity**

This section considers cosmetic depigmenting agents that inhibit tyrosinase activity, and classifies them by their mechanism of action (Table 2).

**Inhibition of tyrosinase activity**

Arbutin, derived from the bearberry plant, is a naturally occurring HQ beta-D-glucopyranoside. It is commonly used in the production of cosmetic agents and is known to exhibit depigmenting activity at nontoxic concentrations.\(^22\) Arbutin has been demonstrated to suppress tyrosinase activity without affecting its messenger RNA expression, and to inhibit 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase activity.\(^23\) In a randomized, open-label study conducted by Ertam et al,\(^24\) melanin level was significantly decreased in 10 melasma patients treated with 1% arbutilin for 6 months.

Azelaic acid is a naturally derived dicarboxylic acid present in *Malassezia furfur*. It inhibits tyrosinase activity, leading to the hypopigmented macules commonly observed in tinea versicolor. Balina and Graupe\(^25\) compared the efficacy of 20% azelaic acid and HQ in the treatment of melasma. In that 24-week trial, 64.8% of patients treated with azelaic acid exhibited “good” or “excellent” results, whereas 72.5% of patients treated with 4% HQ also reported the same results. Thus, it was concluded that there was no significant difference in efficacy between these two treatments, and severe side effects (e.g., allergic sensitization or exogenous ochronosis) were not observed with azelaic acid.

Kojic acid [5-hydroxy-2-(hydroxymethyl)-4-pyrene], an antibotic produced by species of *Aspergillus* and *Penicillium*, produces bleaching by chelating the copper in tyrosinase and inhibiting nuclear factor-κB (NF-κB) activity in keratinocytes.\(^26\) Monteiro et al\(^2\)\(^7\) compared the efficacy of 4% HQ and 0.75% kojic acid cream (including 2.5% vitamin C) in the treatment of melasma. After 12 weeks, the mean Melasma Area and Severity Index score was decreased to 2.403 in the kojic acid group, whereas it was 11.423 in the HQ group. These findings indicated that the 4% HQ cream is a more effective topical depigmenting agent, with a rapid rate of clinical improvement, when compared with the 0.75% kojic acid cream.

4-n-Butylresorcinol also directly inhibits the activities of tyrosinase and tyrosinase-related protein-1 (TRP-1).\(^28\) We have demonstrated the efficacy of this compound in several previous clinical trials.\(^29\),\(^30\) In a randomized controlled split-face trial, 0.1% 4-n-butylresorcinol cream showed rapid efficacy with excellent tolerability in patients with melasma (Table 1).\(^28\) In another randomized, double-blind, vehicle-controlled, split-face study, liposome-encapsulated 4-n-butylresorcinol had significantly reduced the melanin index after 8 weeks of application, without any occurrence of adverse events (Figure 1 and Table 1).\(^30\)

**Reduction of tyrosinase production**

Microphthalmia transcription factor (MITF) is a key factor controlling the transcription of tyrosinase and TRP-1 genes.\(^31\) It is crucial for both melanocyte proliferation and melanogenesis. Mutations in human MITF result in hypopigmentation and deafness in type 2A Waardenburg syndrome.\(^32\) Sphingosine-1-phosphate sustains extracellular signal-regulated kinase (ERK) activation, and induces MITF phosphorylation and degradation, which are responsible for reducing melanin synthesis.\(^33\) Transforming growth factor-β1 also induces significant delay in ERK activation and ERK-induced MITF downregulation, which could contribute to hypopigmentation.\(^34\) We found that lysophosphatidic acid and C2 ceramides could induce MITF degradation or block MITF expression through an initial effect on Akt/protein kinase B or ERK.\(^35\) We also found that another signaling lipid mediator, sphinigosylphosphorylcholine, may inhibit melanogenesis by transcriptional regulation of the tyrosinase gene.\(^36\)

**Increase of tyrosinase degradation**

Several topical fatty acids including linolenic, linoleic, and oleic acids showed a depigmenting effect on guinea pig skin after UV irradiation.\(^37\) The bleaching effects of these compounds may be due to their stimulation of tyrosinase ubiquitination and proteasomal degradation, because they did not influence the number of melanosomes or the level of tyrosinase expression.\(^38\) Phospholipase D2, an unsaturated fatty acid, also reduces melanogenesis through a similar mechanism.\(^39\)

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**Table 2** Classification of cosmetic depigmenting agents based on their mechanisms.

<table>
<thead>
<tr>
<th>Controlling tyrosinase</th>
<th>Inhibition of melanosome transfer</th>
<th>Antioxidant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibition of tyrosinase activity</strong></td>
<td>Centaureidine</td>
<td>Ascorbic acid</td>
</tr>
<tr>
<td>Arbutin</td>
<td>Niacinamide (vitamin B₃)</td>
<td>α-Tocopherol</td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>Lectins</td>
<td>6-Hydroxy-3,4-</td>
</tr>
<tr>
<td>Kojic acid</td>
<td>Neoglycoproteins</td>
<td>6-Hydroxy-3,4-</td>
</tr>
<tr>
<td>4-n-Butylresorcinol</td>
<td>(α-lipoic acid)</td>
<td>Thyrolic acid</td>
</tr>
<tr>
<td><strong>Reduction of tyrosinase production</strong></td>
<td>Resveratrol</td>
<td></td>
</tr>
<tr>
<td>Sphingosine-1-phosphate</td>
<td>Lysophosphatidic acid</td>
<td></td>
</tr>
<tr>
<td>Lyso sphingomyelin</td>
<td>Ceramide</td>
<td></td>
</tr>
<tr>
<td>Sphingosylphosphorylcholine</td>
<td>Increase of tyrosinase degradation</td>
<td>Linolenic acid</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Oleic acid</td>
<td></td>
</tr>
<tr>
<td>Phospholipase D2</td>
<td>Increase of tyrosinase degradation</td>
<td>Linoleic acid</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Increase of tyrosinase degradation</td>
<td>Linoleic acid</td>
</tr>
<tr>
<td>Phospholipase D2</td>
<td>Increase of tyrosinase degradation</td>
<td>Linoleic acid</td>
</tr>
</tbody>
</table>
Inhibition of melanosomal transfer

Melanosomes are specialized subcellular organelles in which melanin is synthesized and deposited. A reduction in the transfer of melanosomes from melanocytes to keratinocytes results in hypopigmentation, as it blocks the dispersion of pigment to keratinocytes. Serine protease inhibition results in impaired activation of protease-activated receptor 2 in keratinocytes, resulting in the accumulation of melanosomes within melanocytes. In a previous study, centaureidine (a flavonoid glucoside isolated from yarrow) and niacinamide (vitamin B3) were demonstrated to inhibit melanosomal transfer to keratinocytes (Table 2). Furthermore, glycosylated residues on melanocyte and keratinocyte membranes are critical for receptor-mediated endocytosis, and thus for facilitating melanosome transfer. Lectins and neoglycoproteins have also been shown to inhibit melanosome transfer (Table 2).

Antioxidants

Compounds with antioxidant properties exhibit hypopigmenting effects by interacting with o-quinones or copper at the active site of tyrosinase, thus reducing the oxidative polymerization of melanin intermediates. Moreover, antioxidant agents regulate the signaling process enabling stimulation of epidermal melanogenesis, by scavenging reactive oxygen species generated in the skin after UV exposure. Cosmetic depigmenting agents that act through antioxidant properties are summarized in Table 2.

Ascorbic acid interferes with different steps involved in melanin production by interacting with copper ions, reducing dopaquinone, and by blocking the oxidation of DHICA.

α-Tocopherol and its derivative, α-tocopherol ferulate, interfere with membrane lipid peroxidation and increase intracellular glutathione content, thus leading to depigmentation.

6-Hydroxy-3,4-dihydrocoumarins are novel antioxidants recently reported to exert antimalanogenic effects in cultured human melanocytes at noncytotoxic concentrations. These compounds might act by accelerating glutathione synthesis and inhibiting tyrosinase transfer.

Thiolic acid (α-lipoic acid), a disulfide derivative of octanoic acid, has been reported to prevent UV-induced oxidative damage, mainly by the downmodulation of NF-κB activation. It is also known to inhibit tyrosinase activity, probably by copper ion chelation.

Resveratrol, a natural extract derived from the roots of Fallopia japonica, has strong antioxidant properties. We performed a clinical trial to evaluate the efficacy of a whitening agent containing 0.05% resveratrol. A total of 30 patients applied the agent twice daily and significant improvements were observed in the melanin index and in clinical photographic assessments after 8 weeks (p < 0.05, unpublished data).

Comparative laboratory study of HQ and cosmetic ingredients

Speculation on depigmenting agents

When preparing topical drugs for pigmentary disorders, HQ is often used as the main ingredient to inhibit tyrosinase activity. Although HQ is a potent tyrosinase inhibitor, frequent adverse effects present a major drawback in clinical practice. In the cosmetic industry, many agents have been used to produce depigmenting cosmetics. Because these agents are used at low and safe concentrations, their efficacy has not been extensively compared with that of HQ. A comparative study is therefore necessary to develop effective and safe topical agents for the treatment of pigmentary disorders.

Comparison of the efficacy of HQ and other ingredients commonly used to make cosmetics

We compared the tyrosinase-inhibition activities of various depigmenting compounds using cultured normal human melanocytes (Table 3). At 100 μM, HQ inhibited the tyrosinase activity of normal human melanocytes by 65%. However, protein concentrations also decreased in a dose-dependent manner and reached 70.9% of the control level at 100 μM HQ (Table 3). These results suggest that HQ is an effective tyrosinase inhibitor while also being safe topical agents for the treatment of pigmentary disorders.

Table 3 Tyrosinase activity in normal human melanocytes.

<table>
<thead>
<tr>
<th></th>
<th>Hydroquinone</th>
<th>Azelaic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1μM</td>
<td>10 μM</td>
</tr>
<tr>
<td>Protein concentration</td>
<td>86.7</td>
<td>74.1</td>
</tr>
<tr>
<td>Tyrosinase activity</td>
<td>65.7</td>
<td>68.1</td>
</tr>
<tr>
<td>Arbutin</td>
<td>86.7</td>
<td>74.1</td>
</tr>
<tr>
<td>Kojic acid</td>
<td>86.7</td>
<td>74.1</td>
</tr>
</tbody>
</table>

|                | 1μM          | 10 μM        | 100 μM       | 1μM          | 10 μM        | 100 μM       |
| Protein concentration | 109.6 | 109.8 | 114.5 | 110.2 | 98.3 | 113.9 |
| Tyrosinase activity | 88.8 | 78.8 | 63.7 | 94.8 | 95.3 | 84.9 |
| Ascorbic acid    | 88.8 | 78.8 | 63.7 | 94.8 | 95.3 | 84.9 |
| l-glutathione    | 88.8 | 78.8 | 63.7 | 94.8 | 95.3 | 84.9 |

|                | 1μM          | 10 μM        | 100 μM       | 1μM          | 10 μM        | 100 μM       |
| Protein concentration | 105.1 | 105.6 | 96.4 | 90.8 | 98.5 | 101.4 |
| Tyrosinase activity | 93.1 | 89.8 | 97.1 | 97.1 | 105.3 | 98.2 |
| Hinokitiol       | 93.1 | 89.8 | 97.1 | 97.1 | 105.3 | 98.2 |
| 4-n-butylresorcinol | 93.7 | 84.6 | 77.2 | 119.0 | 116.0 | 118.6 |

*p % of control by Bradford assay

*p % of control.
toxic at high concentrations. These results may also explain why adverse effects are so commonly observed with HQ-containing formulations. In the cosmetic market, azelaic acid, arbutin, and kojic acid are frequently used to produce depigmenting products. Our results indicated that these agents did not show cytotoxicity at high concentrations, but neither did they produce significant tyrosinase inhibition. This means that although they are relatively safe, they may lack significant depigmenting effects. Nevertheless, because their cytotoxicity is very low, azelaic acid, arbutin, and kojic acid can be used at high concentrations to achieve depigmenting effects. As mentioned earlier, antioxidants may theoretically be used to prepare good depigmenting agents. However, our results showed that ascorbic acid and L-glutathione did not significantly inhibit tyrosinase activity (Table 3). Although hinokitiol decreased protein levels at high concentrations, 4-n-butylresorcinol did not affect the protein levels, even at 100 μM concentrations. These findings indicated that 4-n-butylresorcinol can be used as an effective depigmenting agent with an excellent safety profile.

New approaches to developing depigmenting agents

The data described herein indicate that HQ is not a safe tyrosinase inhibitor and that it is necessary to develop novel topical agents for the treatment of pigmentary disorders. 4-n-Butylresorcinol may be used to produce a safe cosmetic agent, with the clinical efficacy required of a pharmaceutical agent. Furthermore, a multitarget approach is necessary because the combined use of two agents with different mechanisms of action can produce more powerful, additive effects. For example, 4-n-butylresorcinol acts mainly by inhibition of tyrosinase activity and has no effect on MITF. However, when combined with hinokitiol, an additive effect is produced which reduces MITF expression.28 The combination of two agents with different mechanisms may therefore be another useful strategy for increasing the efficacy of these agents.

Conclusion

Although HQ is most commonly used to treat pigmentary disorders, a literature review and our laboratory results strongly suggested that new topical pharmaceutical depigmenting agents are required to enable safer and more effective treatment of pigmentary disorders.

Acknowledgments

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References