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REVIEW ARTICLE

Topical Hypopigmenting Agents for Pigmentary Disorders and Their Mechanisms of Action

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Melanin is produced in melanocytes and stored in melanosomes. In spite of its beneficial sun- protective effect, abnormal accumulation of melanin results in esthetic problems. Hydroquinone, competing with tyrosine, is a major ingredient in topical pharmacological agents. However, frequent adverse reactions are amongst its major limitation. To solve this problem, several alternatives such as arbutin, kojic acid, aloesin, and 4-n-butyl resorcinol have been developed. Herein, we classify hypopigmenting agents according to their mechanism of action; a) regulation of enzyme, which is subdivided into three categories, i) regulation of transcription and maturation of tyrosinase, ii) inhibition of tyrosinase activity, and iii) post-transcriptional control of tyrosinase; b) inhibition of melanosome transfer, and c) additional mechanisms such as regulation of the melanocyte environment and antioxidant agents. **(Ann Dermatol 24(1) 1～6, 2012)**

-Keywords-
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INTRODUCTION

Melanin plays an important role in protecting the skin from ultraviolet light. It also determines skin color and influences phenotypic appearances. However, abnormal accumulation of melanin may lead to esthetic problems. Hydroquinone (HQ) is a major ingredient in topical pharmacological agents that are used for hyperpigmentary disorders. However, HQ is frequently associated with a high rate of adverse effects[1,2].
Therefore, several topical hypopigmenting agents have been developed and widely used (Table 1). This review summarizes the different approaches that have been implemented to achieve hypopigmentation and classify them on the basis of their mechanisms.

TOPICAL HYPOPIGMENTING AGENTS HQ IN MELASMA

Treatment of melasma is difficult and a number of agents have been used for this intractable condition. To date, the most effective treatment is a triple-combination cream that contains 4% HQ, 0.05% tretinoin and 0.01% fluocinolone acetonide[3]. HQ is the most commonly used tyrosinase inhibitor. Oxidation products of HQ result in oxidative damage of membrane lipids and proteins, including tyrosinase, and depletion of glutathione[4]. However, HQ is not commonly used in cosmetics because of long-term complications[5]. Tretinoin is used as an anti-wrinkle agent. However, it is also reported that topical retinoid is effective in the treatment of pigmentary disorders or can be combined with other topical agents[6]. The third ingredient featured in triple combination products is corticosteroids. Steroids are effective in the suppression of cytokines such as endothelin-1 and granulocyte macrophage colony-stimulating factor (GM-CSF), which mediate ultraviolet (UV)-induced res-

Table 1. Classification of hypopigmenting agents. Compounds are divided on the basis of their reported mechanism of interference with melanogenesis[5]

Before melanin synthesis
Regulation of tyrosinase transcription
TGF-β1, TNF-α, IL-1α, β, IL-6, lysophosphatidic acid, C2-ceramides, sphingosine-1-phosphate Sphingosylphosphorylcholine, tretinoin
Inhibition of tyrosinase maturation
Glucosamine, tunicamycin, glycosphingolipid, calcium d-pantetheine- S-sulphonate
During melanin synthesis
Inhibition of tyrosinase activity
Hydroquinone, arbutin, kojic acid, 4-n-butylresorcinol, phenolic compounds, 4-hydroxy-anisole, methyl gentisate, 4-S-CAP & derivatives, ellagic acid, oxyresveratrol, resveratrol, aloesin, azelaic acid
After melanin synthesis
Posttranscriptional control of tyrosinase
Linoleic acid, α-linolenic acid, phospholipase D2
Inhibition of melanosome transfer
Niacinamide (Vitamin B3), serine protease inhibitors, lecthins and neoglycoproteins, RW-50353, soybean.milk extracts
Regulation of melanocytes environment
Corticosteroids, glabridin
Antioxidant agents
α-Tocopherol, ascorbic acid, ascorbic acid palmitate, D, L-α TF, VC-PMG, methimazole, hydrocoumarins (6-hydroxy-3,4-dihydrocoumarins), thioctic acid (α-lipoic acid), phenol/catechol

TGF: transforming growth factor, TNF: tumor necrosis factor, IL: interleukin, TF: α-tocopherol ferulate, VC-PMG: magnecium-Ascorbyl-2-phosphate.

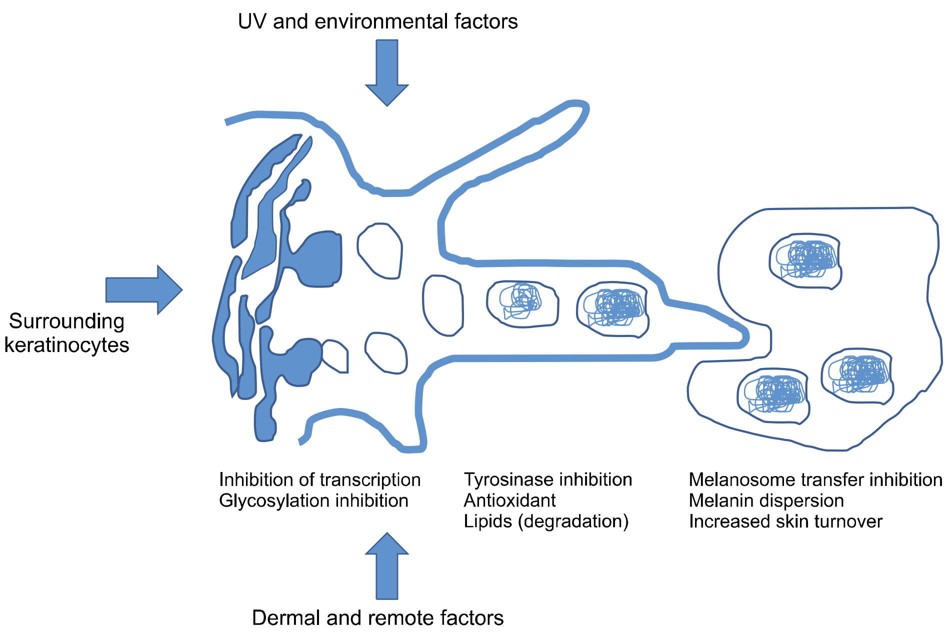

Fig. 1. Schematic illustration of possible strategies for inhibition of melanogenesis. UV: ultraviolet.

ponses[7,8]. By using a triple-combination cream, combined effects can be expected for the treatment of pigmentary conditions.

The efficacy and safety of triple-combination creams have been reported in several studies[9]. In one study, 26.1% showed a complete clearing of melasma by week 8[10]. In another multicenter study, global evaluations revealed that 75% of patients showed "moderate or marked improvement" or were "almost clear" or "clear" by week 8. These results showed that a triple-combination cream is a rapidly effective topical agent for the treatment of melasma[11]. However, in one study, 57% of patients experienced at least one treatment-related adverse reaction, although it was claimed to be mild and transient in nature[12]. In particular, post-inflammatory hyperpigmentation should be expected in darker-skinned patients[13]. A multicenter study was also performed to compare the efficacy and safety of a triple-combination cream in Asian patients. The results showed that a triple-combination cream was also effective in Asian patients with tolerable adverse reactions. Although most adverse events were mild, almost 50% of patients reported the incidence of related adverse events[14]. Thus, it should be noted that triple-combination creams are effective for melasma, but can have a high frequency of adverse reactions.

CLASSIFICATION OF TOPICAL AGENTS FOR PIGMENTARY CONDITIONS

At present, the most effective hypopigmenting agents are tyrosinase inhibitors. However, melanogenesis can be controlled by regulating (i) the transcription and activity of enzymes such as tyrosinase, tyrosinase-related protein-1 (TRP-1), tyrosinase-related protein-2, and/or peroxidase; (ii) the uptake and distribution of melanosome in keratinocytes and (iii) melanin and melanosome degradation and turnover of "pigmented" keratinocytes[5]. However, it is very clear that hypopigmenting agents can work by different combined mechanisms. Furthermore, melanogenesis is controlled by additional factors via keratinocytes, fibroblasts and also by local and/or systemic conditions (Fig. 1).

Regulation of enzymes

1) Regulation of transcription and maturation of tyrosinase

Transcription of genes encoding tyrosinase and TRP-1 is under the control of the microphthalmia transcription factor (MITF)[15]. Mitf is a critical transcription factor for both melanocyte proliferation and melanogenesis. As Mitf is regulated by the Wnt signaling pathway as well as cAMP, and by both p38 signaling and the MAP kinase pathway, any agents that can potentially regulate these signaling pathways will also affect Mitf and melanogenesis. Although it is not clinically available, sustained extracellular signal regulated kinase (ERK) activation by sphingosine-1-phosphate (S1P) can lead to MITF phosphorylation and degradation, which in turn are responsible for decreased melanin synthesis[16]. Transforming growth factor (TGF-β1) also plays an inhibitory role in melanogenesis. TGF-β1 induced a significant delay in ERK activation and ERK-induced down-regulation of Mitf[17]. Furthermore, lysophosphatidic acid and C2 ceramides are able to induce Mitf degradation or decrease Mitf expression[18-20]. These are examples that inhibit melanogenesis by transcriptional regulation of the tyrosinase gene. Tyrosinase is a glycosylated protein. Therefore, glucosamine or tunicamycin, which are specific inhibitors of lipid carrier-dependent glycosylation, can induce hypopigmentation[21]. In addition, calcium D-pantetheine-S-sulphonate ($PaSSO_3Ca$) causes an inhibition of melanogenic enzymes possibly through the alteration of tyrosinase and TRP-1 glycosylation without affecting their expression[22].

2) Inhibition of tyrosinase activity

There are several tyrosinase inhibitors that have been used to produce hypopigmenting topical agents or cosmetics. Arbutin, a naturally occurring HQ beta-D-gluconopyranoside is commonly used[23]. Arbutin decreases tyrosinase activity without affecting mRNA expression and inhibits 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase activity[24]. Kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one) was also a commonly used antibiotic agent produced by species of *Asperigillus* and *Penicillum*[25].
Among these, 4-n-butylresorcinol has been characterized as a strong tyrosinase inhibitor[26]. We compared the hypopigmenting effects of HQ and 4-n-butyl resorcinol and showed that HQ (100 μM) and 4-n-butyl resorcinol (10 μM) had similar tyrosinase inhibition activities. These finding suggests that 4-n-butyl resorcinol is a more potent tyrosinase inhibitor than HQ. Thus, the hypopigmenting effect can increase if the concentration of 4-n-butyl resorcinol is increased. However, a cautious increase will be necessary to ensure both efficacy and safety. Positive hypopigmenting effects of 4-n-butyl resorcinol have previously been demonstrated[27].
Generally, phenolic compounds are known as hypopigmenting agents because of their ability to serve as alternative substrates for tyrosinase[28].

3) Post-transcriptional control of tyrosinase

There are examples of agents that inhibit melanogenesis by the increased degradation of tyrosinase proteins. Unsaturated linoleic acid decreases tyrosinase activity, whereas saturated palmitic or stearic acids increases tyrosinase activity. Also, topical application of linolenic, linoleic and oleic acids produce a hypopigmenting effect on guinea pig skin stimulated with UV light[29]. It is reported that linoleic acid decreases the amount of tyrosinase through increased tyrosinase ubiquitination and degradation by the proteasome[30,31]. In addition, other agents like phospholipase D2 decrease melanogenesis through the same ubiquitin-mediated degradation of tyrosinase[32].

Inhibition of melanosome transfer

Melanosomes are specialized organelles in which melanin is synthesized and deposited. The addition of TGF-β1 to cultured melanocytes produced less pigmented melanosomes even when the cells were concomitantly treated with αMSH to increase their fully melanized melanosomes[33]. It is also reported that ERK activation by S1P can lead to hypopigmentation[16]. Interestingly, decreased melanization of melanosomes was also found in S1P treated melanocytes (unpublished data). Moreover, S1P-treated cells showed undifferentiated early stage melanosomes, whereas control cells showed internal fibrils and dense pigments in melanosomes. These findings suggest that inhibition of melanosome formation can be a good strategy to control melanogenesis. However, there are no agents that are currently available to meet this requirement.

Melanosome formation is an important step in melanognesis and melanosomes need to be transferred to keratinocytes from melanocytes for the completion of this step. Thus, the inhibition of melanosome transfer can produce a hypopigmenting effect. Theoretically, the inhibition of serine protease can result in an impaired activation of protease-activated receptor 2 on the keratinocyte leading to the accumulation of melanosomes within the melanocyte[34]. Clinically, niacinamide (Vitamin B3), which is commonly used to manufacture cosmetics, has been found to inhibit melanosome transfer to keratinocytes both *in vitro* and *in vivo*[35].

Additional mechanisms

1) Regulation of melanocytes environment

Endothelin 1 (ET-1), which is produced by keratinocytes after exposure to inflammatory stimuli or UV exposure, stimulates melanogenesis. ET-1 has strong stimulatory effects both on DNA synthesis and melanization in human melanocytes. Thus, topical application of *M. chamomilla* extract inhibits ultraviolet B (UVB)-induced pigmentation by inhibiting ET-1 effects[36].

Clinically, it is well-known that topical corticosteroids have strong anti-inflammatory effects. They have been used for the treatment of melasma to decrease irritation caused by hypo-pigmenting agents[37], and work by the suppression of cytokines through the inhibition of nuclear factor kappa B (NF-κB) activation. Topical steroids can be effective by the suppression of cytokines such as endothelin-1 and GM-CSF, which mediate UV-induced pigmentation[7,8].

There are several ingredients with anti-inflammatory activity. Glabridin, the main component of hydrophobic fraction of licorice extracts decreases tyrosinase activity in B16 melanoma cells and inhibits UVB-induced skin pigmentation as well as erythema. The capability to inhibit cyclooxygenase activity and superoxide anion production implies that this anti-inflammatory effect requires an interference with the arachidonic acid cascade. Consequently, protection against oxidative stress plays a key role in controlling melanogenesis[38].

2) Antioxidant agents

In general, antioxidants exhibit hypopigmenting effects by interacting with *o*-quinones, thus avoiding the oxidative polymerization of melanin intermediates, or with copper at the active site of tyrosinase. In addition, antioxidant agents can regulate the signaling process by scavenging ROS in the skin[39]. For example, ascorbic acid can interfere with melanization by interaction with copper ions at tyrosinase and reduction of dopaquinone and DHICA oxidation[40,41]. α-Tocopherol and its derivatives can also regulate melanogenesis. The antioxidant property affects the lipid peroxidation of membranes and increases the intracellular glutathione content[42]. 6-Hydroxy-3,4-dihydrocumarins, another novel type of antioxidant, have an anti-melanogenic activity in cultured normal human melanocytes at non-cytotoxic concentrations without interfering with tyrosinase activity[43]. The acceleration of glutathione synthesis and the inhibition of tyrosinase transfer may be the mechanism of action[44]. α-lipoic acid, a disulfide derivative of octanoic acid, has been reported to prevent UV-induced oxidative damage, mainly through the down-modulation of NF-κB activation. In addition, this agent is known to inhibit tyrosinase activity by possibly chelating the copper ions[45]. Peroxidase is involved in the polymerization of melanogenic intermediates[46]. Based on this, the inhibition of peroxidase can decrease melanogenesis by reducing the polymerization of eumelanin[47]. Methimazole, an antithyroid agent belonging to the thionamide group, shows inhibitory action towards tyrosinase and peroxidase[48]. Mild to moderate inhibition of melanization can be expected with morphological changes of melanocytes in animal models.

3) Combination of multifunction hypopigmenting agents

Recently, we reported that terrein, a bioactive fungal metabolite isolated from a *Penicillium* species, reduces melanin synthesis by reducing tyrosinase production via ERK activation, and that this is followed by MITF downregulation[49]. Interestingly, we also found that terrein decreases melanogenesis through ubiquitin-dependent proteasomal degradation as well as decreased expression of its mRNA[50]. Thus, terrein can be an example of a hypopigmenting agent that inhibits melanogenesis by dual action including the down-regulation of transcription and up-regulation of degradation.

In contrast to terrein with multifunction, the combined use of two agents with different action mechanisms can be additive in terms of total effects. As already described, 4-n-butylresorcinol did not induce ERK or Akt activation, or MITF degradation, and also had no effect on cAMP response element binding protein phosphorylation, which stimulates MITF expression[26]. However, 4-n-butylresorcinol showed an additive effect in combination with hinokitiol, which reduces MITF expression. Thus, the combination of these two agents with different action mechanisms can be another strategy to increase the efficacy of these agents.

CONCLUSION

Recently, melanocyte biology has made remarkable progress. However, the pathogenic mechanisms underlying acquired hyperpigmentation have not been completely understood. Even though these mechanisms need to be explored further, our present understanding has improved greatly, which has contributed to the enhancement of diagnosis and treatment of pigmentary conditions. In particular, the finding that the dermal microenvironment can affect epidermal pigmentation through dermal degeneration or vascular dilatation has had a significant influence. These findings suggest that environmental effects on melanogenesis are very important. In addition, the combined use of multiple agents with different actions can show additive effects. As already described, 4-n-butylresorcinol is a strong tyrosinase inhibitor, whereas a signal regulator such as terrain affects pigmentation through ERK-induced MITF degradation. Thus, the combination of multiple agents with different mechanisms of action can be another strategy to increase the efficacy of these agents.

REFERENCES

1. Gupta AK, Gover MD, Nouri K, Taylor S. The treatment of melasma: a review of clinical trials. J Am Acad Dermatol 2006;55:1048-1065.
2. Amer M, Metwalli M. Topical hydroquinone in the treatment of some hyperpigmentary disorders. Int J Dermatol 1998;37: 449-450.
3. Rendon MI. Utilizing combination therapy to optimize melasma outcomes. J Drugs Dermatol 2004;3(5 Suppl):S27-34.
4. Bolognia JL, Sodi SA, Osber MP, Pawelek JM. Enhancement of the depigmenting effect of hydroquinone by cystamine and buthionine sulfoximine. Br J Dermatol 1995;133:349-357.
5. Briganti S, Camera E, Picardo M. Chemical and instrumental approaches to treat hyperpigmentation. Pigment Cell Res 2003;16:101-110.
6. Kang HY, Valerio L, Bahadoran P, Ortonne JP. The role of topical retinoids in the treatment of pigmentary disorders: an evidence-based review. Am J Clin Dermatol 2009;10:251-260.
7. Kim DS, Kim HJ, Choi KH, Chung JH, Kim KH, Par KC. UVB-induced GM-CSF production is suppressed by dexamethasone in HaCaT cells. Photodermatol Photoimmunol Photomed 2001;17:121-125.
8. Lee IW, Lee SC, Kim DS, Kim HJ, Park KC. Effects of dexamethasone on endothelin-1 (ET-1) production by keratinocytes. Ann Dermatol 2001;13:148-152.
9. Torok HM. A comprehensive review of the long-term and short-term treatment of melasma with a triple combination cream. Am J Clin Dermatol 2006;7:223-230.
10. Taylor SC, Torok H, Jones T, Lowe N, Rich P, Tschen E, et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. Cutis 2003;72:67-72.
11. Grimes P, Kelly AP, Torok H, Willis I. Community-based trial of a triple-combination agent for the treatment of facial melasma. Cutis 2006;77:177-184.
12. Torok HM, Jones T, Rich P, Smith S, Tschen E. Hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%: a safe and efficacious 12-month treatment for melasma. Cutis 2005;75:57-62.
13. Hexsel D, Arellano I, Rendon M. Ethnic considerations in the treatment of Hispanic and Latin-American patients with hyperpigmentation. Br J Dermatol 2006;156 Suppl 1:7-12.
14. Chan R, Park KC, Lee MH, Lee ES, Chang SE, Leow YH, et al. A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma. Br J Dermatol 2008;159:697-703.
15. Yasumoto K, Yokoyama K, Takahashi K, Tomita Y, Shibahara S. Functional analysis of microphthalmia-associated transcription factor in pigment cell-specific transcription of the human tyrosinase family genes. J Biol Chem 1997;272:503-509.
16. Kim DS, Hwang ES, Lee JE, Kim SY, Kwon SB, Park KC. Sphingosine-1-phosphate decreases melanin synthesis via sustained ERK activation and subsequent MITF degradation. J Cell Sci 2003;116:1699-1706.
17. Kim DS, Park SH, Park KC. Transforming growth factor-beta1 decreases melanin synthesis via delayed extracellular signal-regulated kinase activation. Int J Biochem Cell Biol 2004; 36:1482-1491.
18. Kim DS, Park SH, Kwon SB, Youn SW, Park KC. Effects of lysophosphatidic acid on melanogenesis. Chem Phys Lipids 2004;127:199-206.
19. Kim DS, Kim SY, Moon SJ, Chung JH, Kim KH, Cho KH, et al. Ceramide inhibits cell proliferation through Akt/PKB inactivation and decreases melanin synthesis in Mel-Ab cells. Pigment Cell Res 2001;14:110-115.
20. Kim DS, Kim SY, Chung JH, Kim KH, Eun HC, Park KC. Delayed ERK activation by ceramide reduces melanin synthesis in human melanocytes. Cell Signal 2002;14:779-785.
21. Mishima Y, Imokawa G. Selective aberration and pigment loss in melanosomes of malignant melanoma cells in vitro by glycosylation inhibitors: premelanosomes as glycoprotein. J Invest Dermatol 1983;81:106-114.
22. Franchi J, Coutadeur MC, Marteau C, Mersel M, Kupferberg

A. Depigmenting effects of calcium D-pantetheine-S-sulfonate on human melanocytes. Pigment Cell Res 2000;13:165-171.
23. Sugai T. Clinical effects of arbutin in patients with chloasma (in Japanese). Hifu (Skin Res) 1992;34:522-529.
24. Chakraborty AK, Funasaka Y, Komoto M, Ichihashi M. Effect of arbutin on melanogenic proteins in human melanocytes. Pigment Cell Res 1998;11:206-212.
25. Moon KY, Ahn KS, Lee J, Kim YS. Kojic acid, a potential inhibitor of NF-kappaB activation in transfectant human HaCaT and SCC-13 cells. Arch Pharm Res 2001;24:307-311.
26. Kim DS, Kim SY, Park SH, Choi YG, Kwon SB, Kim MK, et al. Inhibitory effects of 4-n-butylresorcinol on tyrosinase activity and melanin synthesis. Biol Pharm Bull 2005;28: 2216-2219.
27. Huh SY, Shin JW, Na JI, Huh CH, Youn SW, Park KC. Efficacy and safety of liposome-encapsulated 4-n-butylresorcinol 0.1% cream for the treatment of melasma: a randomized controlled split-face trial. J Dermatol 2010;37:311-315.
28. Fenoll LG, Rodríguez-López JN, Varón R, García-Ruiz PA, García-Cánovas F, Tudela J. Action mechanism of tyrosinase on meta- and para-hydroxylated monophenols. Biol Chem 2000;381:313-320.
29. Ando H, Ryu A, Hashimoto A, Oka M, Ichihashi M. Linoleic acid and alpha-linolenic acid lightens ultraviolet-induced hyperpigmentation of the skin. Arch Dermatol Res 1998; 290:375-381.
30. Ando H, Funasaka Y, Oka M, Ohashi A, Furumura M, Matsunaga J, et al. Possible involvement of proteolytic degradation of tyrosinase in the regulatory effect of fatty acids on melanogenesis. J Lipid Res 1999;40:1312-1316.
31. Ando H, Wen ZM, Kim HY, Valencia JC, Costin GE, Watabe H, et al. Intracellular composition of fatty acid affects the processing and function of tyrosinase through the ubiquitin-proteasome pathway. Biochem J 2006;394:43-50.
32. Ando H, Watabe H, Valencia JC, Yasumoto K, Furumura M, Funasaka Y, et al. Fatty acids regulate pigmentation via proteasomal degradation of tyrosinase: a new aspect of ubiquitin-proteasome function. J Biol Chem 2004;279:15427-15433.
33. Martínez-Esparza M, Ferrer C, Castells MT, García-Borrón JC, Zuasti A. Transforming growth factor beta1 mediates hypopigmentation of B16 mouse melanoma cells by inhibition of melanin formation and melanosome maturation. Int J Biochem Cell Biol 2001;33:971-983.
34. Seiberg M, Paine C, Sharlow E, Andrade-Gordon P, Costanzo M, Eisinger M, et al. Inhibition of melanosome transfer results in skin lightening. J Invest Dermatol 2000;115:162-167.
35. 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. Dermatol 2002;147:20-31.
36. Imokawa G, Kobayashi T, Miyagishi M, Higashi K, Yada Y. The role of endothelin-1 in epidermal hyperpigmentation and signaling mechanisms of mitogenesis and melanogenesis. Pigment Cell Res 1997;10:218-228.
37. Kligman AM, Willis I. A new formula for depigmenting human skin. Arch Dermatol 1975;111:40-48.
38. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. Pigment Cell Res 1998;11:355-361.
39. Karg E, Odh G, Wittbjer A, Rosengren E, Rorsman H. Hydrogen peroxide as an inducer of elevated tyrosinase level in melanoma cells. J Invest Dermatol 1993;100(2 Suppl):209S-213S.
40. Gukasyan GS. Study of the kinetics of oxidation of monophenols by tyrosinase. The effect of reducers. Biochemistry (Mosc) 2002;67:277-280.
41. Ros JR, Rodríguez-López JN, García-Cánovas F. Effect of L-ascorbic acid on the monophenolase activity of tyrosinase. Biochem J 1993;295:309-312.
42. Ichihashi M, Funasaka Y, Ohashi A, Chacraborty A, Ahmed NU, Ueda M, et al. The inhibitory effect of DL-alpha-tocopheryl ferulate in lecithin on melanogenesis. Anticancer Res 1999;19:3769-3774.
43. Nishiyama T, Ohnishi J, Hashiguchi Y. Fused heterocyclic antioxidants: antioxidative activities of hydrocoumarins in a homogeneous solution. Biosci Biotechnol Biochem 2001;65: 1127-1133.
44. Yamamura T, Onishi J, Nishiyama T. Antimelanogenic activity of hydrocoumarins in cultured normal human melanocytes by stimulating intracellular glutathione synthesis. Arch Dermatol Res 2002;294:349-354.
45. Saliou C, Kitazawa M, McLaughlin L, Yang JP, Lodge JK, Tetsuka T, et al. Antioxidants modulate acute solar ultraviolet radiation-induced NF-kappa-B activation in a human keratinocyte cell line. Free Radic Biol Med 1999;26:174-183.
46. d'Ischia M, Napolitano A, Prota G. Peroxidase as an alternative to tyrosinase in the oxidative polymerization of 5,6-dihydroxyindoles to melanin(s). Biochim Biophys Acta 1991; 1073:423-430.
47. Kasraee B. Peroxidase-mediated mechanisms are involved in the melanocytotoxic and melanogenesis-inhibiting effects of chemical agents. Dermatology 2002;205:329-339.
48. Kasraee B. Depigmentation of brown Guinea pig skin by topical application of methimazole. J Invest Dermatol 2002; 118:205-207.
49. Park SH, Kim DS, Kim WG, Ryoo IJ, Lee DH, Huh CH, et al. Terrein: a new melanogenesis inhibitor and its mechanism. Cell Mol Life Sci 2004;61:2878-2885.
50. Park SH, Kim DS, Lee HK, Kwon SB, Lee S, Ryoo IJ, et al. Long-term suppression of tyrosinase by terrein via tyrosinase degradation and its decreased expression. Exp Dermatol 2009;18:562-566.