Editorial

Skin-lightening agents: New chemical and plant extracts -ongoing search for the Holy Grail!

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Skin-lightening agents (SLA) are used to treat hyperpigmentation. Dermatologists, pharmacists, applied botanists, and allied health care researchers have discovered and undertaken various *in vivo* and *in vitro* studies on SLA. Hydroquinone, its derivatives, several plant extracts, either monotherapy or in combination are tried to achieve the skin-lightening effect and are being used in cosmetics. Each approach has its advantages and disadvantages with adverse side effects. This article analyzes the latest developments of SLA with reference to *in vivo* studies and clinical trials.

SLA interferes in the following important steps involved in melanogenesis and reduces pigmentation.[1-3] SLA inhibits the conversion of tyrosine to melanin. Tyrosinase is the rate-limiting enzyme in melanin synthesis. It is a copper-containing binuclear enzyme that catalyzes three steps of melanin biosynthesis: the hydroxylation of tyrosine to 3, 4-dihydroxyphenylalanine (DOPA), oxidation of DOPA to DOPA quinone, and oxidation of 5, 6-dihydroxyindole to indolequinone. Tyrosinase inhibitors play a vital role as a SLA.[2] SLA mostly act as tyrosinase inhibitors[3] and tyrosinase is a potential target in the search for a newer SLA.

Hydroquinone, alpha hydroxy acids, retinoid, and topical steroids: benefits and side effects

The gold-standard SLA is hydroquinone.[4] Hydroquinone covalently binds to histidine or interacts with copper at the active site of tyrosinase. Besides tyrosinase inhibition, alteration of melanosome functions, depletion of glutathione, generation of reactive oxygen species, and subsequent oxidative damage of membrane lipids and proteins may play a role in the hypopigmenting effect of hydroquinone.[2]

Hydroquinone is very unstable and rapidly gets oxidized. It can induce erythema, skin irritation, contact dermatitis, and permanent skin depigmentation. Its cytotoxic effects prevent its usage in cosmetics. Exogenous ochronosis,[5] cataract, pigmented colloid millium, sclera and nail pigmentation, loss of skin elasticity, and impaired wound healing of skin are the adverse effects of hydroquinone.[5] Ochronosis commonly presents as asymptomatic blue-black macules on the malar areas, temples, inferior cheeks, and neck. Chronic usage of cosmetics containing this SLA exudes an offensive fish odor in the sweat that is described as "fish odor syndrome." This is due to excretion of a chemical, trimethylamine in the breath, urine, sweat, saliva, and vaginal secretions.[5] Phenols, resorcinol, and quinine are also associated with ochronosis.[5] Therefore, many countries have legislation on the usage of concentration of phenolic derivatives in cosmeceuticals.

Glycolic acid or retinoids shortens the cell cycle and facilitates rapid pigment loss, interferes with pigment transfer, and enhances penetration of other SLA.[2] Potency of hydroquinone is increased by adding of glycolic acid or tretinoin.[3] Alpha-hydroxy acids, retinoid, and topical steroids are usually used in combination rather than monotherapy. They cause peeling, erythema, and hyper pigmentation. Retinoids cause scaling, erythema, stinging, and burning (retinoid dermatitis).[6] Rosacea-like eruption (persistent erythema, papules and pustules) distributed in a centro-facial pattern, perioral dermatitis, allergic contact dermatitis, persistent itching, atrophy, and telangiectasia are the complications of prolonged use of steroid monotherapy.[6]

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Withdrawal of hydroquinone from the USA, European, and Japanese markets has motivated interest in developing alternative and safer SLA.[3] Research on newer SLA involving *in vivo* and *in vitro* studies have confirmed the role of following chemical and plant extracts. They can be classified[1-3,7,8] on the basis of their interfering mechanisms that regulate melanin synthesis. SLAs act on more than one step of the melanin synthesis pathway; however, the most common interference of a SLA is highlighted below.

1. Competitive tyrosinase inhibitors

Non-plant extracts

A) Hydroquinone and its derivatives:
   1) Hydroquinone (2-5%)
   2) Mequinol (2%) (4-hydroxyanisol, monobenzyl ether of hydroquinone)
   3) *N*-acetyl-4-S-cysteaminylphenol
   4) Gentisic acid (methyl gentisate)
B) Glutathione (thiol)
C) Epicatechin gallates.

Plant extracts

A) Azelaic acid (15-20%)[9] (9-carbon dicarboxylic acid)
B) Arbutin (3%)
C) Alpha arbutin[10]
D) Deoxyarbutin
E) Aloesin
F) Kojic acid[11] (2-4%)
G) Flavonoids, flavones, flavonols, hesperidins
H) Kuraninone
I) Saponin
J) Oregonin
K) Yohimbine

2. Non-competitive tyrosinase inhibitors:

Non-plant extracts

A) Haginin A
B) *N*-acetyl glucosamine

Plant extracts

A) Glabirdin (10-40%) (Licorice extracts)
B) Hydroxystilbenes: (1) resveratol, (2) oxyresveratol, (3) ginetol
C) Piceatannol
D) Mulberry (mulberroside)
E) Polyphenols (procyanidins)

3. Newer tyrosinase inhibitors (require further *in vivo* and *in vitro* studies)

Non-plant extracts

A) Hydroxyphenyl naphthol
B) Calycosin
C) Quinolines: chloroquine and quinine[12]

Plant extracts

Diarylpropane

4. Reduces the transfer of melanosomes from melanocytes to keratinocytes or melanin transfer (serine protease inhibitors)

Plant extracts

(A) Niacinamide (5%); (B) Soy (soybean trypsin inhibitor)[13]

5. Reduces tyrosine oxidation

Plant extracts

A) P-coumaric acid

6. Copper chelation, anti-oxidant, and inhibits melanocyte proliferation

Plant extracts

A) Ascorbic acid (5-10%) (Magnesium L-ascorbic acid-2- phosphate)
B) Ellagic acid.

7. Removes keratinocytes (desquamation), shortens the cell cycle and facilitates rapid pigment loss, interferes with pigment transfer and enhances penetration of other SLA

Non-plant extracts

A) Alpha hydroxy acids: Glycolic acids[14] (6-12%)
B) Retinoids: Tretinoin[15] (Retinoic acid) (0.05 and 0.1%), adapalene[16] (0.1%).

Plant extracts

A) Liquirtin (Licorice extracts)[17]

Hydroquinone, magnesium-L-ascorbyl-2-phosphate (MAP), mequinol, *N*-acetyl-4-S-cysteaminylphenol and arbutin are the most widely used SLA.[8]

Combination of SLA therapy

An ideal SLA should interrupt one of the key steps in melanogenesis, should be safe, should have least side effects, should be nontoxic or less toxic to melanocytes, and should penetrate the stratum corneum. One SLA cannot meet all the above requirements. SLA interfering with different steps of melanin synthesis improves clinical efficacy, reduces the duration of therapy, and minimizes the risk of adverse effects. SLA that exerts its action *in vivo* may not be that effective *in vitro* due to poor bioavailability and penetration into the melanosome.[2] Therefore, transdermal agent delivery plays a significant role. A suitable combination of SLA

is designed considering the above factors to produce a synergistic hypopigmenting effect, and various clinical trials are undertaken.[18-22]

Combinations (established by clinical trials)[18-22]

Alternate use of hydroquinone with any of the plant extracts, combination of hydroquinone with steroids or sequential application achieves hypopigmentation and minimizes the side effects caused by hydroquinone. Addition[18] or sequential treatment[19] of glycolic acid with hydroquinone enhances better penetration of the pharmacological agent.

Combination therapies increase the efficacy as compared to monotherapy.[6] The following are the important combinations of SLA: (1) hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%, (Kligman's formula[20]) combination is the most used combination treatment. Various modifications changing the concentration or changing steroid or retinoids are done with varying better results. (2) Azelaic acid 20% and tretinoin 0.05 or 0.1%.[19] (3) Mequinol 2% and tretinoin 0.01% (penetrates and enhance action with other SLA).[21,22] (4) Hydroquinone 2%, kojic acid 2% and glycolic acid 10% in a gel.[11] (5) Mequinol 2% in combination with 0.01% tretinoin, functioning as a penetration enhancer and magnesium ascorbyl phosphate. These active agents are dissolved in an ethyl alcohol vehicle.[3]

In Kligman's formula[20] besides the synergistic therapeutical effect, dexamethasone decreases the irritative effects of hydroquinone and produces mild hypopigmentation, through an antimetabolic action,[23] whereas tretinoin reduces the epidermal atrophy caused by corticosteroids and improves stratum corneum penetration. Serial glycolic acid peels can significantly improve the clinical efficacy of a modified Kligman's formula.[19]

Newer combinations

The following SLA combination treatment are tried with good hypopigmentation

1) Arbutin (deoxyarbutin) and aloesin synergistically inhibit melanin synthesis by combined mechanisms of competitive inhibitions of tyrosinase.[24,25] Aloesin is hydrophilic molecule and therefore it has a limited ability to penetrate the skin.[3]
2) Licorice extract, soy, and ascorbic acid (magnesium ascorbyl phosphate).[3]
3) Kojic acid, phytic acid, and buthyl methoxy dibenzoyl methane for melasma have been assessed in a double-blind controlled comparative study.[26]
4) Hydroquinone and kojic acid.[4]

Efficacy and safety of newer SLA as compared to hydroquinone

Hydroquinone, mequinol, and azelaic acid are the potent SLAs.[3] These potent tyrosinase inhibitors are toxic and have limited solubility and low stability in formulations.[2] The irritation profiles of hydroquinone and retinoids are a major concern. Azelaic acid has an excellent safety profile, but causes burning and transient stinging on topical application. It can be safely combined with retinoids to yield an additive benefit, but it is not as effective as hydroquinone for the treatment of hyperpigmentation. Combination of azelaic acid and hydroquinone is ideal than compared to azelaic acid and glycolic acid.[27] Azealiac acid (20%) is superior to 2% hydroquinone and comparable to 4% hydroquinone.[6,27] Intercomparison of plant extracts reveals potency of arbutin, kojic acid, aloesin, and leucorice in the descending order with respect to skin-lightening action and safety.[3]

Advantages of a newer SLA

Arbutin and kojic acids are safe and currently used as cosmetic additives.[24] Arbutin shows good photo stability.[2] Plant extracts are generally safe without cytotoxicity and cause least irritation. Licorice is the safest pigment-lightening agents with the fewest side effects and most commonly used SLA in cosmetics.[3] The soybean trypsin inhibitor is the most commonly used SLA in cosmeceutical moisturizers.[28] Beta carotene, a vitamin A analogue is used.[29] Kojic acid is a good tyrosinase inhibitor; however it may cause allergy.[30]

CONCLUSION

Hydroquinone and mequinol are potent chemical SLAs with irritation. Adverse effects of hydroquinone limit its usage. SLA should be advised to apply strictly in the night and to the affected areas only to minimize the side effects. Newer chemical and plant extracts are promising and proven by *in vivo* studies; however, double-blind clinical trials need to be undertaken to prove their efficacy. Plant extracts arbutin, kojic acid, azelaic acid, and aloesin show a good skin-lightening potential with no cytotoxic effects and are much safer; however, they have the least penetrative action. Glycolic acid and retinoids enhance penetration of these plant extracts therefore suitable combination of chemical and newer plant

extracts needs to be designed and evaluated on a large-scale clinical trial.

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