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Review Article

Biochemistry of selected skin lightening agents: A REVIEW

*[1]Yusuf, R. S., [2, 3]Busari, M. B., [4]Yahaya, A. S. and [5]Yunusa, I. O.

[1]Department of Biochemistry, Sa'adu Zungur University Bauchi State, Nigeria
[2] Centre for Genetic Engineering and Biotechnology, Federal University of Technology Minna, Nigeria
[3]Department of Biochemistry, Federal University of Technology Minna, Nigeria
[4]Department of Biochemistry and Molecular Biology, Federal University Dutsin-Ma Katsina State, Nigeria
[5]Department of Biotechnology, Abdulkadiri Kure University Minna, Nigeria

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ABSTRACT

Skin whitening or lightening refers to the practice, deeply embedded in many ethnic groups using natural or synthetic substances to lighten the skin tone or provide an even complexion by reducing the melanin concentration in the skin. Example of such of chemicals include mercury, Hydroquinone, Kojic acid, Azeleic acid, Arbutin, Aloesin, N-acetyl glucosamine, Glabiridin (Liquorice), α-Hydroxyacids, ascorbic acid and its derivatives among others. Biochemically, these set of whitening agents target melanin production and many of them serve as competitive inhibitors to tyrosinase which is one of the key enzymes in melanogenesis. Skin bleaching has been associated with a variety of known adverse health effects ranging from dermatitis to exogenous ochronosis, steroid acne, mercury (Hg) poisoning,acne, stretch marks, hypopigmentation, cancer and nephrotic syndrome among others. Hence, biochemistry of all these bleaching agents needs to be elucidated to expose and prevent the adverse effects being caused by them.

Keywords: Skin whitening, Hydroquinone, Kojic acid, Melanin, Hypopigmentation, Cancer
***Corresponding author's email**: ruqayyahsyusuf@sazu.edu.ng, +2347042021335

INTRODUCTION

Skin whitening or lightening refers to the practice, deeply embedded in many ethnic groups [1], of using natural or synthetic substances to lighten the skin tone or provide an even complexion by reducing the melanin concentration in the skin [2]. Skin-bleaching practices, such as using skin-lightening creams and soaps to achieve a lighter skin tone or to "whiten" skin, are common among non-White populations throughout the world, triggered by deep historical, economic, sociocultural, and psychosocial roots [3]. For instance, Chinese myth believes that pearls can lighten one's complexion by taking a small amount of pearl powder together with hot water every day. In West

Country, aristocrats and rich people in the seventeenth and eighteenth centuries kept their skin white by applying lead oxide powder to their faces to differentiate themselves from the working masses [4]; the Indian women used painful processes to bleach their skin, trying to become more attractive to colonizers [5]. Many African, afro-Carribean [6] and Asian [7] women love to keep their skin toned and beautiful but unfortunately most of them end up indulging in skin care products that bleach the skin and eventually pose potential risk to their health. Landor *et al*. [8] shows that top three most common perceptions are that lighter skin tone increases woman's chance of getting married (63.4%), men consider woman with lighter skin to be more beautiful (62.6%), and lighter skin tone is more beautiful (62.3%). The least perception they have is that lighter skin tone implies that woman belongs to a higher social class (19.7%).

Skin-bleaching practices have transitioned from historically "being a response to economic and complexion-related oppression of the darker-skinned working class and poor populations to a current expression of fashion and ungendered rites of beauty." [9]. Most of these bleaching products contain different kinds of chemicals that may be harmful and affect the health of women. Examples of chemicals in these products include mercury, hydroquinone, Kojic acid, Azeleic acid, Arbutin, Aloesin, N-acetyl glucosamine, Glabiridin (Liquorice), α-Hydroxyacids, ascorbic acid and its derivatives, and many more [10]. Skin bleaching has been associated with a variety of known adverse health effects ranging from dermatitis to exogenous ochronosis, steroid acne, mercury (Hg) poisoning, and nephrotic syndrome, which are linked to ingredients such as hydroquinone, corticosteroids, and Hg [11]. Due to health concerns, some of these chemicals are regulated [12]. Skin lightening products are readily available from major cosmetics companies, from local convenience stores, and widely over the internet. These types of products are marketed as skin-evening creams, skin lighteners, skin brighteners, skin whiteners, skin toners, fading creams, or fairness creams [13].

In Africa, voluntary depigmentation is performed for multiple reasons (aesthetic, sociological, political, etc.) [14]. Hence, the intensive use of whitening agents in many cultures constitutes a real public health risk and can lead to severe pathologies including burns, acne, stretch marks, hypopigmentation, and even cancer [15]. Clinically, these chemicals are also used for treatment of hyperpigmentary disorders such as melasma, café au lait spot and solar lentigo. All of these target naturally melanin production, and many of the commonly used agents are known as competitive inhibitors of tyrosinase, one of the key enzymes in melanogenesis [16].

Melanogenesis

Melanogenesis is the physiological process of producing melanin, the light-absorbing pigment that is responsible for the human skin and hair coloration, together with other biochromes [17].

Human skin colour stems from the outermost layer of the skin, the epidermis where the pigment-producing cells melanocytes are localized to produce melanin which is the polymeric, amorphous, non-proteinaceous pigment that dictates the colour of our skin [18]. Melanogenesis takes place in melanosomes. Two types of melanin are synthesized within melanosomes:

eumelanin and pheomelanin [19]. Eumelanin is a dark brown-black insoluble polymer, whereas pheomelanin is a light red-yellow sulphur-containing soluble polymer [20]. The difference in skin color between fair people and dark people is due not to the number (quantity) of melanocytes in their skin, but to the melanocytes' level of activity (quantity and relative amounts of eumelanin and pheomelanin). In skin that exhibits a dark color the melanosomes are well distributed in the keratinocytes, which absorb radiation [21]. Upon exposure of the skin to UV radiation, melanogenesis is enhanced by the activation of the key enzyme of melanogenesis, tyrosinase.

Tyrosinase catalyses the first two steps of melanin production: the hydroxylation of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) and the subsequent oxidation of this *o*-diphenol to the corresponding quinone, L-dopaquinone [10]. Even though L-tyrosine is the building stone for melanin, it is transported into the melanosome by facilitated diffusion [22]. It is also noteworthy to know that the concentration of L-tyrosine for melanogenesis depends on the conversion of the essential amino acid L-phenylalanine by intracellular phenylalanine hydroxylase (PAH) activity and in contrast to L-tyrosine, L-phenylalanine is actively transported through the melanosomal membrane to ensure high content of L-tyrosine inside this organelle [10].

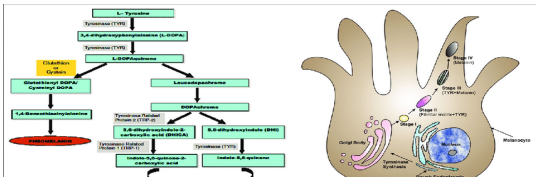


Figure 1: Melanin Synthetic Pathway [23].

Melanin synthesis begins with catalysation of the substrates L-phenylalanine and L-tyrosine to produce L-DOPA via phenylalanine hydroxylase (PAH), tyrosinase and partly tyrosinase hydroxylase 1 (TH-1). The pathways are then divided into eumelanogenesis or pheomelanogenesis. The other melanogenic enzymes are TRP-2 (DCT) and TRP-1 for eumelanogenesis. No specific enzymes have been found that are involved in pheomelanogenesis so far [10].

The melanin polymer functions in quenching of free-radicals and acting as a physical barrier against UV radiation, and through its negatively charged properties, has the ability to bind amines and heavy metals [24].

The Biochemical Properties of Skin Lightening Ingredients

There are today many known substances that can reduce the level of pigmentation in the skin. Many of these substances have a tyrosinase-inhibiting effect leading to reduced total melanin production, some are known to have an effect on the transfer of melanin from melanocytes to keratinocytes while others increase the desquamation of the skin and thus, remove excessive; melanin content within the skin.

Hydroquinone

Hydroquinone, also chemically known as 1,4-dihydroxybenzene, is a ubiquitous chemical that occurs naturally in our environment [25]. It is the oxidation product of certain aromatic compounds. It is found in cigarette smoke, in diesel engine lubricants, etc. [26]. It has use in diverse industrial sectors including photograph development, antioxidant for protecting oils and fats, polymerization inhibitor in processes involving

monomers such as vinyl acetate or acrylic monomers, paint stabilizers and so on [27].

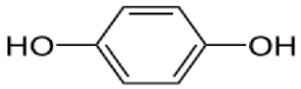


Figure 2: The Structure of Hydroquinone

Hydroquinone (1,4-dihydroxybenzene, HQ) has been the gold standard for treating hyperpigmentation for decades and has been successfully used to treat melanosis [28]. It is a strong oxidant that is rapidly converted to p-benzoquinone and hydroxybenzoquinone, both of which are melanocyte toxic [29]. Hydroquinone is an effective inhibitor of melanogenesis in vitro and in vivo, inhibiting both DNA and RNA synthesis, as well as reducing tyrosinase activity primarily in melanocytes [30].

Hydroquinone interacts with tyrosinase by binding histidines at the active site of the enzyme resulting in reduction in skin pigmentation [31]. Hydroquinone induces generation of reactive oxygen species, and as typical with quinones, leads to oxidative damage of membrane lipids and proteins such as tyrosinase [32]. With topical use it is known to cause ochronosis, and its metabolite has been implicated in bone marrow toxicity [33]. Hydroquinone toxicity can also lead to severe side effects such as kidney and liver malfunction, blood poisoning, nausea, abdominal pains, convulsion and even coma [34].

Arbutin

Arbutin is a naturally occurring β,D-glycopyranoside derivative of hydroquinone. It is obtained from various plants in the Ericaceae (bearberry, strawberry tree, huckleberry, heather), Saxifragaceae, Asteraceae, Rosaceae, Lamiaceae, and Apiaceae families [26]. Although it shows tyrosinase inhibition, it is not found to affect RNA synthesis as does hydroquinone. The alpha isomer has the greatest inhibitory activity against mammalian tyrosinases [35]. Numerous studies show that arbutin is just as effective as hydroquinone, but less toxic [36].

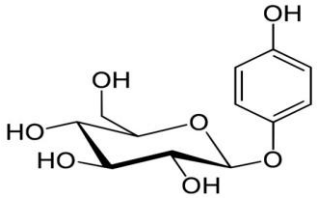


Figure 3: The Structure of Arbutin

Arbutin exhibits different levels of toxicity depending on the cell type and exposure time, but 1 mM is considered as a boundary concentration between cytotoxicity and safety. When arbutin is treated in vivo, its concentration in contact with cells must be maintained at 1 mM or lower, so that beneficial efficacy without the risk of serious side effects can be expected [36].

Mercury

Mercury salts produce their cutaneous depigmenting effect via inhibition of melanin formation. This occurs because mercury salts compete with copper in tyrosinase [37]. Mercury is a volatile element that is harmful to the skin when used in an effort to lighten the skin [38]. However, chronic exposure of the body to mercury at very low concentration can cause long-lasting neurological and kidney impairment [39] as shown in Table 1. Mercury in bleaching preparations can be absorbed through the skin and accumulates in body organs giving rise to severe toxicity [38].

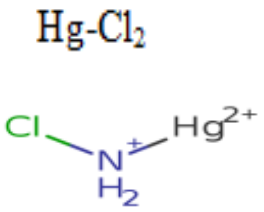


Figure 4 and 5: The Structures of Mercury II Chloride and Ammoniated Mercury

The features of mercury toxicity, also known as the 'hatters disease', as immortalized in Alice in Wonderland by Lewis Carroll, consists of psychiatric (disturbance of recent memory, impairment of intellectual function, inattention and depression) and neurological (irritability, memory loss and neuropathies) problems [40]. Another adverse reaction noted with mercury toxicity is a paradoxical increase in skin pigmentation [41].

Kojic acid

Kojic acid was discovered in 1907 through isolation from the mycelia of Aspergillus oryzae grown on steamed rice (the term koji means steamed rice in Japanese) [42]. It is a powerful tyrosinase inhibitor.

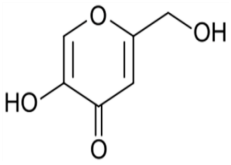


Figure 6: The Structure of Kojic Acid

It functions by the chelation of copper at the active site of the enzyme tyrosinase [31] and suppressing the conversion of dopachrome to 5,6-dihydroxyindole-2-carboxylic acid in the melanin biosynthesis pathway [43]. It is found to be unstable in formulations and may also cause discoloration [44]. Some stable derivatives, such as kojic acid dipalmitate, are being used to enhance effectiveness by enhanced skin penetration [45].

Aloesin

Aloesin is a low molecular weight glycoprotein extracted from various species of plants in the genus Aloe, in which it can be found in significant amounts [46]. It competitively inhibits the function of tyrosinase by inhibiting the hydroxylation of tyrosine to DOPA and oxidation of DOPA to dopaquinone [47].

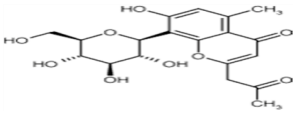


Figure 7: The Structure of Aloesin

Studies completed by Jones *et al.* [48] on normal human melanocytes treated with aloesin, showed a dose dependent decrease in tyrosinase activity. The hydrophilic nature of the compound reduces the skin penetration of aloesin. Hence, combination treatment of aloesin with arbutin has been studied to assess the synergistic effects on tyrosinase activity. The two adhere to different mechanisms of action where aloesin exhibits noncompetitive inhibition while arbutin inhibits competitively [47]. Testing of aloesin revealed no cytotoxicity, which makes it a good alternative to hydroquinone [46]. From the standpoint of its toxicology profile, aloesin is evidently safe to use. This molecule, is non-genotoxic and has a high No Observable Adverse Effect Level (NOAEL) (2000 mg/Kg/day via the oral route) [49].

Azelaic Acid

Azelaic acid is a C9-dicarboxylic acid. This acid is produced naturally by a yeast, Malassezia furfur. Its inhibitory activity against tyrosinase is reflected in the appearance of depigmented maculae on the skin of subjects suffering from a

mycosis, Pityriasis versicolor [50]. This fungus produces lipoxygenases that are capable of acting on the unsaturated fatty acids present on the skin surface. In culture, this fungus is capable of oxidizing oleic acid into azelaic acid [51].

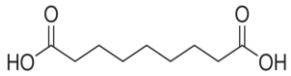


Figure 8: The Structure of Azelaic Acid

There is unanimous agreement regarding its efficacy and absence of undesirable effects. However, some mild undesirable effects (burning, tingling) were reported [52]. The anti-inflammatory, anti-keratinizing and bacteriostatic activity of azelaic acid justifies its use in treating diseases such as rosacea or acne [53]. Azelaic acid apparently behaves differently, depending on the characteristics of the cells concerned [53].

N-acetyl glucosamine

N-acetyl glucosamine (NAG), an amino hexose, found throughout nature and in all human tissues, is known for its function as a precursor to hyaluronic acid.

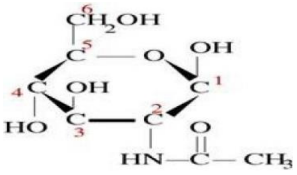


Figure 9: Structure of N-acetyl Glucosamine

The role of this polymer is in the forming of the structure of extracellular matrix in joints and skin (dermis and epidermis) and keeping them hydrated [54]. Research has shown that NAG and glucosamine are able to reduce production of melanin in human cell culture systems [55]. These agents inhibit the glycosylation of tyrosinase to prevent activation of this enzyme and reduce melanin formation [55].

Glabridin

Glabridin is present in the hydrophobic fraction of licorice root extract (licorice) and is capable of reducing the activity of tyrosinase on melanocytes in culture, and of inhibiting the induction of pigmentation by UVB and erythema formation in guinea pigs [56].

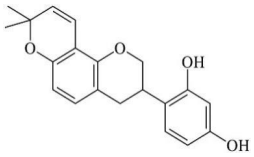


Figure 10: Structure of Structure of Glabridin

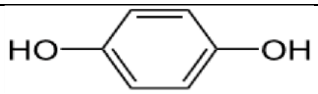
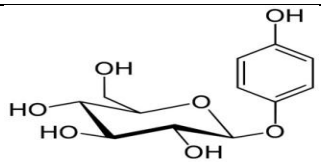
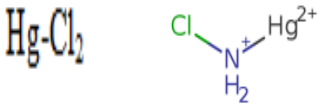
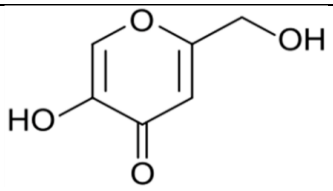
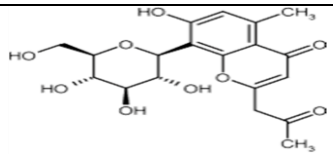
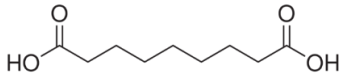
Glabridin, from Glycyrrhiza glabra (Licorice) was shown to inhibit both melanogenesis and inflammation [57]. It was found to have tyrosinase inhibitory activity and demonstrated efficacy zin reducing UV radiation induced inflammation in animal models. An in vitro study revealed that glabridin inhibits tyrosinase activity in cultured B16 murine melanoma cells at concentrations of 0.1 to 1 mcg/ml, with no detectable effect on their DNA synthesis. Glabridin has been shown to prevent UVB-induced pigmentation and to inhibit tyrosinase activity (Table 1), superoxide anion production and cyclo-oxygenase activity. This suggests an influence of glabridin extract on both melanogenesis and inflammation of the skin [58].

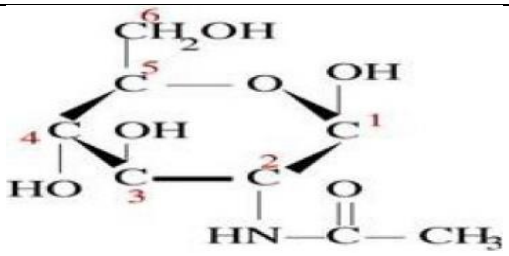
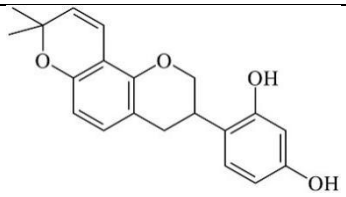
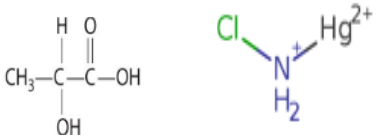
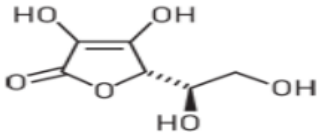
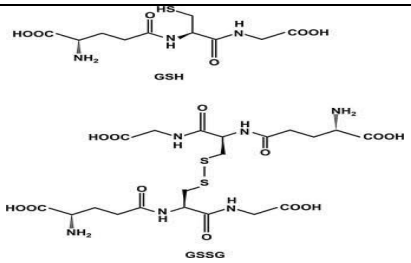
α-Hydroxyacids

α-Hydroxyacids (AHA) are weak organic acids found in fruits, plants and milk sugars [59]. For centuries, α-hydroxyacids have been one of the most commonly utilized peeling agents used to treat dry skin, acne, actinic damage and to improve

skin color/texture [60]. AHAs are also reported to effectively treat pigmentary lesions such as solar ntigenes, melasma and post inflammatory hyperpigmentation (PIH)

.Table 1: A summary of some selected skin lightening agents and their modes of action

S/N	AGENT	STRUCTURE	ACTIONS	SIDE EFFECTS	REFERENCES
1.	Hydroquinone		interacts with tyrosinase by binding histidines at the active site of the enzyme resulting in reduction in skin pigmentation	known to cause ochronosis, and its metabolite has been implicated in bone marrow toxicity	[33]
2.	Arbutin		shows tyrosinase inhibition	Generally safe at at a concentration of 1 mM or lower	[36]
3.	Mercury		inhibition of melanin formation	chronic exposure of the body to mercury at very low concentration can cause long-lasting neurological and kidney impairment	[39]
4.	Kojic acid		functions by the chelation of copper at the active site of the enzyme tyrosinase	may cause discoloration	[44]
5.	Aloesin		It competitively inhibits the function of tyrosinase by inhibiting the hydroxylation of tyrosine to DOPA and oxidation of DOPA to dopaquinone	no cytotoxicity	[46]
6.	Azelaic acid		Possesses anti-inflammatory, anti-keratinizing and bacteriostatic activity	mild undesirable effects such as burning and tingling	[52]

7.	N-acetyl glucosamine (NAG)		inhibit the glycosylation of tyrosinase to prevent activation of this enzyme and reduce melanin formation		[55]
8.	Glabridin		have tyrosinase inhibitory activity		
9.	α-Hydroxyacids (AHA)		desquamation of the stratum corneum by AHAs is complemented by a direct inhibition of tyrosinase	redness, swelling, burning, and pruritus	[63]
10.	Vitamin C and its derivatives		act as reducers and block the chain of oxidations transforming tyrosine into melanin at different points	does not have the harmful effects	[65]
11.	Glutathione		Possesses antimelanogenic effects	Gastrointestinal symptoms, such as flatulence and loose stools, were the most common side effects of oral glutathione	[72]

At low concentrations AHAs promotes exfoliation by decreasing corneocyte cohesion and stimulating new growth in the basal layer, while at higher concentrations AHAs promote epidermolysis and dispersed basal layer melanin.

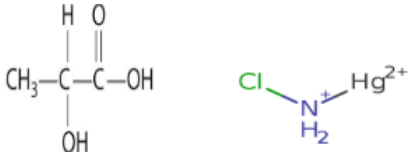


Figure 11 and 12: The Structure of Lactic acid and Glycolic acid

The accelerated desquamation of the stratum corneum by AHAs is complemented by a direct inhibition of tyrosinase, without influencing mRNA or protein expression [61]. Lactic acid (LA) and glycolic acid (GA) are AHAs derived from sour milk and sugarcane juice, respectively [62]. However, caution is required in relation to adverse reactions to AHA products, which can include redness, swelling, burning, and pruritus [63].

Ascorbic Acid and Its Derivatives

Vitamin C and its derivatives act as reducers and block the chain of oxidations transforming tyrosine into melanin at different points [64]. Furthermore, the interaction of ascorbic acid with copper, an essential cofactor in tyrosinase activity, explains the tyrosinase inhibitor effect observed in vitro. Although less effective than hydroquinone, ascorbic acid does not have the harmful effects of the latter [65]. Ascorbic acid or vitamin C is readily degraded by oxidation, especially in aqueous media. For this reason, it is preferable to use more stable derivatives such as ascorbyl palmitate and magnesium-L-ascorbyl-2-phosphate (MAP) [66]. Its use is not regulated and vitamin C is found in cosmetics in concentrations ranging from 4% to 20% [67].

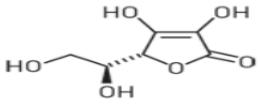


Figure 13: Structure of Structure of Ascorbic Acid

Glutathione

Glutathione, one of the skin-whitening agents in cosmetic industries [68], is an antioxidant commonly found in the human body [69] Glutathione is commonly found in two forms: reduced glutathione (GSH) and oxidized glutathione (GSSH). Several in vitro experiments demonstrated that glutathione showed antimelanogenic effects; thus, it is associated with melanin production [69]. It is known that glutathione may promote pheomelanin synthesis, inhibit intracellular melanogenic enzymes, and demonstrate antioxidative as well as antiaging effects [69.70]. Glutathione may affect skin pigmentation by inhibiting tyrosinase activity during melanogenesis, either directly or indirectly. Direct inactivation is done by binding to the active site of enzymes containing copper ion, while indirect inactivation eliminates free radicals and peroxides in antioxidative manners. During melanogenesis, glutathione converts eumelanin to pheomelanin and modulates depigmentation of melanocytotoxic agents [71]. Gastrointestinal symptoms, such as flatulence and loose stools, are the most common side effects of oral glutathione [72].

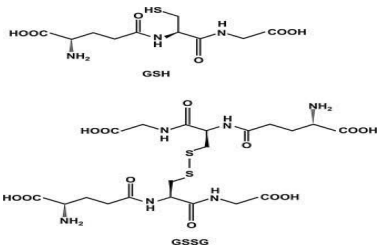


Figure 14: Structure of GSH and GSSH

CONCLUSIONS

Skin, the organ of study, is the largest organ of the human body which accounts for about 15% of the human body weight and its health could be affected by topical agents. Skin lightening or skin bleaching agents though are essential tools in the management of disorders of hyperpigmentation have been used to lighten the skin for beauty purposes. Some skin lightening agents contain harmful products such as hydroquinone, kojic acid, and mercury while others contain less harmful substances such as azelaic acid, arbutin and aloesin. Generally, skin lightening agents should be used with caution due to some undesirable side effects that may occur.

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