### Alpha Arbutin as a Skin Lightening Agent: A Review

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ABSTRACT
For decades, possessing a lighter skin color has been known as a characteristic of elegance and superiority. The use of skin lighten agents is still prevalent across the globe despite strict regulations and public health campaigns against them. This can be attributed to the misleading marketing of harmful skin bleaching agents under the name of skin brighteners, skin toners, or dark spot removal creams that are readily available. In an effort to find a safer alternative to hydroquinone and other harmful skin lighteners, extensive research culminated in the discovery of α-arbutin. It acts by inhibiting tyrosinase activity and melanosome maturation. It is one of the most popular skin lightening ingredients in the world at present and has been used in the treatment of many hyperpigmentation disorders. α-arbutin has a high market value due to its wide applicability in the cosmetics and pharmaceutical industries. In this review, we have discussed the physiochemical properties of α-arbutin and safety profile, its mechanism of action, recent advances in the delivery of α-arbutin for skin lightening, various combination treatments, and current market status. This literature review presents a futuristic scope of α-arbutin as a safer alternative to other harmful skin lightening agents.

Keywords: Alpha arbutin, skin lightening, cosmetic, hyperpigmentation, melanogenesis

INTRODUCTION
Hyperpigmentation conditions including melasma (Cardinali et al., 2012), solar lentigines (Davis et al., 2010), and post-inflammatory hyperpigmentation are common causes for dermatology visits. Hyperpigmentation is also associated with UV exposure (Tran et al., 2008), skin aging (Ortonne, 1990), hormonal imbalance (Mahmood et al., 2016), and skin irritation (Saeedi et al., 2019). Dyschromatosis is another skin condition that is marked by hypo or hyperpigmented skin lesions giving a mottled appearance (Namitha et al., 2015). It can occur due to changes in different biochemical processes controlling melanogenesis. Melanogenesis is the complicated mechanism by which melanocytes produce pigment melanin in melanosomes (Videira et al., 2013). Such changes in the melanogenesis process may result in increased melanocytes, melanosome production, melanin synthesis, or melanocyte hyperplasia, leading to greater deposition of melanin in the skin (Hollinger et al., 2018). In the last decade, pathophysiological studies on hyperpigmentation disorders have evolved considerably owing to the high prevalence of hyperpigmentation. This has led to newer treatment options, resulting in a range of investigations and developments of several skin lightening agents to reduce the concentration of melanin in the epidermis layer of the skin. Melanin is a natural skin pigment that plays a vital role in skin pigmentation, and the biological synthesis of melanin is primarily regulated by the enzyme tyrosinase (Solano, 2014). Tyrosinase enzyme inhibitors have thus become essential components in cosmetic skin whitening formulations. Skin lightening for cosmetic purposes has been associated with significant harmful effects on well-being, and negative impact on the skin, which pose enormous challenges for dermatologists (Charles, 2003). Skin lightening cosmetics continue to dominate the cosmetic market, amid existing regulations. Skin lightening agents are possibly underestimated for cutaneous and systemic side effects, since a complete list of ingredients, illegal ingredient, is rarely disclosed. Skin lightening agents do not have high side effects with minimal use. However, when used for extended periods or under occlusion, the risk of adverse reactions is increased. Traditional first-line skin lightening
agents like hydroquinone, corticosteroids, mercury, kojic acid, etc. are highly effective but their long-term exposure can potentially cause serious adverse effects on the skin such as ochronosis, atrophy, carcinogenesis, and other local or systemic side effects (Rendon et al., 2012). Hydroquinone, often considered as the gold standard for the topical treatment of hyperpigmentation disorders may cause a condition called exogenous ochronosis which is characterized by paradoxical blue-gray hyperpigmentation due to deposition of homogentisic acid in the skin (Gandhi et al., 2012). Squamous cell carcinoma has also been reported after long-term use of hydroquinone (Faye et al., 2018). Systemic absorption may cause peripheral neuropathy (Karamagi et al., 2001), conjunctival pigmentation (Anderson, 1947), corneal melanosis and degeneration (DeCaprio, 1999; Naumann, 1966), impaired wound healing (Ajose, 2005; Olumide et al., 2008) and fish odor syndrome (trimethylaminuria) (Tse, 2010). Super-potent corticosteroids (e.g., clobetasol) may lead to bacterial, viral, and fungal skin infections due to local immunosuppression (Valencia et al., 2003). However, a compromised hypothalamic-pituitary adrenal axis is one of the concerning side effects that result due to the systemic absorption of corticosteroids (Broersen et al., 2015). Cushing syndrome (Broersen et al., 2015), adrenal insufficiency (Sobngwi et al., 2003), diabetes (Sobngwi et al., 2003), and hypertension (Bwomda et al., 2005) are other distressing side-effects of the use of corticosteroids. Ophthalmologic side-effects include glaucoma (Phulke et al., 2017) and cataracts (Fanny et al., 2014). Mercury-containing skin lightening formulations have been reported to cause neuropsychiatric toxicity (Sun et al., 2017) and nephrotoxicity (Agrawal et al., 2015), as well as nail dyschromia, pneumonitis, and mercurial baboon syndrome (Hamann et al., 2014). Glutathione is a significant health issue in many countries now due to its potential adverse effects (Sonthalia et al., 2018). For various alcoholic liver diseases, glutathione infusions are approved in India whereas, in the Philippines, glutathione is approved to be used in conjunction with cisplatin chemotherapy. However, the FDA has not approved their use for skin lightening (Sonthalia et al., 2018). Significant complications of glutathione include renal, hepatic, neurologic toxicity, air emboli, and Stevens-Johnson syndrome (Dadzie, 2016). Oral and topical treatment with tranexamic acid, a synthetic derivative of amino acid lysine has also been carried out for skin lightening and it may cause bloating, abdominal pain, and vascular thrombosis (Ebrahimi et al., 2014; Tan et al., 2017). The oral and topical use of retinoids (e.g., tretinoin) (Griffiths et al., 1993) has shown to cause erythema, peeling retinoid dermatitis, photosensitivity, teratogenic effects, fetal complications, thyroid dysfunction, and hepatic toxicity (Mukherjee et al., 2006). Based on the above data, there is clearly a need for better tolerated, yet effective, skin lightening agents that could be used by a wider population and have led to the investigation of several potential botanical/natural compounds.

Arbutin is a naturally occurring skin lightening agent and has been found in the species of various plant families such as marjoram, cranberry, blueberry, and several pear species. The production of melanin is effectively reduced by arbutin by inhibiting the tyrosinase enzyme. Arbutin exists in its two isoforms, namely α-arbutin (4-hydroxyphenyl-α-D-glucopyranoside) and β-arbutin (4-hydroxyphenyl-β-D-glucopyranoside). Both α and β-arbutin have different rotation configurations but the same chemical formula structure (Couteau et al., 2016). β-arbutin is generally extracted from leaves of various plants and fruit peels. However, α-arbutin does not occur naturally and can be biosynthesized by microbial enzymes or microorganisms. Interestingly, α-arbutin is much more efficient in inhibiting tyrosinase activity than natural arbutin (Garcia-Jimenez et al., 2017). At the active site of tyrosinase, the α-glucoside bond displays greater affinity than the β-glucoside bond. The 50% inhibitory concentration (IC 50) of α-arbutin in human tyrosinase is 2.0 mM, whereas, for natural arbutin, it is higher than 30 mM (Sugimoto et al., 2007; Sugimoto et al., 2003). In the cultured melanoma cell and the human skin model, the α-arbutin inhibitory effects on melanin biosynthesis were examined, and findings showed that α-arbutin effectively inhibited melanin synthesis without any cytotoxicity (Sugimoto et al., 2004). α-arbutin has been shown to inhibit the tyrosinase enzyme from mouse melanoma, and the inhibition was found to be 10 times stronger than β-arbutin. α-arbutin did not inhibit the growth of cultured human melanoma cells, HMV-II, but effectively inhibited melanin synthesis, suggesting that α-arbutin can be effective and safe for treating hyperpigmentation disorders (Sugimoto et al., 2004). Because of its molecular structure, α-arbutin works similarly to hydroquinone, but with less irritation and melanoctyotoxicity. It also does not cause exogenous ochronosis and is less likely to cause irritation and sensitization, making it a
more tolerable alternative to hydroquinone. This protects skin from sun-induced pigmentation and free radicals without increasing the skin’s sensitivity to sun exposure. It lightens skin tone by fading discoloration caused by inflammation and environmental stress. It also addresses glycation, sugar-induced skin sallowness, and loss of elasticity (Notaroberto, 2017). Commercially, α-arbutin is synthesized by using an enzyme that catalyzes alpha-anomer selective transglycosylation reaction between a glucosyl donor and hydroquinone as an acceptor. In addition to enzymatic biosynthesis, α-arbutin can be synthesized from hydroquinone with the help of some microbial species (Kitao et al., 1994). In this review, we present a novel look at α-arbutin as a safer alternative to other harmful skin lightening agents. The benefits of α-arbutin as a skin lightening agent are represented in Figure 1.

**Physiochemical Properties of α-arbutin and safety profile:** α-Arbutin, (2R,3S,4S,5R,6R)-2-(hydroxymethyl)-6-(4-hydroxyphenoxy)oxane-3,4,5-triol has a molecular weight of 272.25 g/mol and appears as a white to off-white powder (Sugimoto et al., 2007). It has a melting point between 195° – 196°C and a boiling point of 561.6 ± 50.0 °C (Sugimoto et al., 2007). The solubility of α-arbutin in water and DMSO (Dimethyl sulfoxide) is 151 g/L at 20 ± 5 °C and 54 mg/mL (198.34 mM), respectively (Degen, 2016). It has a log P value of -1.49 (Pati et al., 2011) and a log S value of -0.84. Although α-arbutin has a strong inhibitory effect on human tyrosinase activity, its high hydrophilicity causes low percutaneous absorption. This limits its permeation into the stratum basale where melanocytes reside. The chemical structure of α-arbutin is shown in Figure 2. The analysis of α-arbutin can be performed by using high-performance liquid chromatography (HPLC) (Jeon et al., 2014). The stability of α-arbutin is pH-dependent in a buffered aqueous solution, with maximum stability at pH 5.0. The Scientific Committee on Consumer Safety (SCCS) has suggested concentrations of α-arbutin i.e., up to 2% in face creams and up to 0.5% in body lotions for the safety of consumers that use α-arbutin based cosmetic products (Degen, 2016). The clinical studies supporting the safety of α-arbutin for the treatment of hyperpigmentation are represented in Table 1.
**Fig.2: The chemical structure of α-arbutin**

Alpha Arbutin

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### Table 1: Clinical Studies Supporting Safety of α-arbutin (Degen, 2016)

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<tr>
<th>Test</th>
<th>Model</th>
<th>Concentration</th>
<th>Observation</th>
</tr>
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<tbody>
<tr>
<td>Acute oral toxicity test</td>
<td>Rat/Sprague-Dawley CD</td>
<td>5% cream 10% cream</td>
<td>LD50 &gt; 125 mg/kg of α-arbutin LD50 &gt; 2500 mg/kg of α-arbutin</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>New Zealand White rabbits</td>
<td>0.5 g moistened with 0.5 mL water</td>
<td>Non-irritant to skin</td>
</tr>
<tr>
<td>Mucous membrane irrigation / Eye irritation</td>
<td>New Zealand White rabbits</td>
<td>10% solution</td>
<td>Minimally irritant to rabbit eye</td>
</tr>
<tr>
<td>Skin sensitization</td>
<td>Dunkin Hartley guinea pigs</td>
<td>50% (w/w) solution</td>
<td>Non-sensitizing to the skin</td>
</tr>
<tr>
<td>Mutagenicity / Genotoxicity</td>
<td><em>Salmonella typhimurium</em> and <em>Escherichia coli</em> strain, Mice</td>
<td>50, 150, 500, and 5000 μg/plate 500, 1000 and 2000 mg/kg bodyweight</td>
<td>Non-mutagenic in bacteria Non-genotoxic (clastogenic and/or aneugenic) in bone marrow cells of mice.</td>
</tr>
<tr>
<td>Photo-induced toxicity</td>
<td>Dunkin Hartley guinea pigs</td>
<td>10% in distilled water</td>
<td>Non-phototoxic and non-photosensitizing</td>
</tr>
<tr>
<td>Stability</td>
<td>Human female</td>
<td>3% gel</td>
<td>Conversion to hydroquinone was negligible.</td>
</tr>
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**Cellular and Molecular Mechanisms of α-arbutin**

Tyrosinase (Polyphenol oxidase, EC 1.14.18.1) is a copper-containing mixed-function enzyme. It is widely distributed in nature, including animals, plants, fungi, and microorganisms (Sánchez-Ferrer et al., 1995). It contributes to melanin production, which induces skin pigmentation and protects the skin from UV-induced skin damage. The enzyme tyrosinase has been reported to catalyze two types of reaction. Firstly, it triggers the ortho-hydroxylation of monophenols (tyrosine), converting them into o-diphenols (L-DOPA) (monophenolase activity). Secondly, it catalyzes the oxidation of o-diphenols, transforming them into o-quinones (diphenolase activity) (Burton, 2003; Mataba et al., 2006). During the production of melanin, the tyrosinase enzyme plays a vital role. Melanin protects the skin from UV-induced skin damage and is responsible for the formation of skin color (Korner et al., 1982; Taylor, 2002). Pigmentation disorders (melasma, freckles, etc.), however, can create a severe aesthetic problem in humans (Priestley, 1993). α-arbutin is a synthetic substance produced from enzymatic glycosylation of hydroquinone. It inhibits the melanosomal tyrosinase activity directly or competes with tyrosinase for the active site by acting as a substrate, thereby causing skin lightening effects. The mechanism of action of α-arbutin is represented in Figure 3. Qin et al., 2014 studied the mechanism of action of α-arbutin by investigating the impact of mushroom tyrosinase on the monophenolase and diphenolase activities. The authors reported that α-arbutin exhibits dual effects on monophenolase and diphenolase activities of mushroom tyrosinase. α-arbutin inhibited the reduction of the enzyme activity in the steady-state (suicide inactivation of the active sites of tyrosinase) during the monophenolase reaction. Also, a characteristic lag period was observed during the oxidation of tyrosine during the monophenolase reaction. The lag time showed a dose-dependent increase with the increasing concentration of α-arbutin. However, during the diphenolase reaction, α-arbutin acted as an activator due to the interaction of α-arbutin with residues located at the entrance to the active site. Herein, no lag
period was observed during the oxidation of L-Dopa. Furthermore, it also decreased the effect of suicide inactivation. In light of the above findings, Garcia-Jimenez et al., 2017 carried out experiments to gain in-depth insights into the mechanism of action of α-arbutin. The authors reported that the α-arbutin did not completely inhibit tyrosinase and proposed that α-arbutin acts as an alternative competitive substrate to the enzyme since the enzyme is able to hydroxylate it and does not function as an inhibitor. In another study, Sugimoto et al., 2004 studied the inhibitory effects of α-arbutin on melanin biosynthesis in cultured human melanoma cells and a 3D (three-dimensional) human skin model. The authors reported a concentration-dependent inhibition of melanin synthesis by α-arbutin on human melanoma cells, HMV-II. The inhibitory effect on melanogenesis was achieved at noncytotoxic concentrations of α-arbutin. The authors concluded that direct inhibition of melanosomal tyrosinase activity by α-arbutin hampered the melanogenesis process, rather than suppressing tyrosinase gene expression or cell growth. Another mechanism was proposed by Chakraborty et al., 1998 that the inhibition of tyrosinase activity by α-arbutin might be due to its influence at the post-translational level.

![Diagram of skin lightening mechanism](image)

**Fig. 3:** Mechanism of action of α-Arbutin for skin lightening
Recent advances in the delivery of α-arbutin to skin

α-Arbutin is one of the most widely used skin lightening agents and less toxic as compared to hydroquinone. It is hydrophilic in nature and has a log P value of −1.49 and therefore exhibits poor permeation across the skin. Since the stratum corneum is more exclusive to hydrophobic substances, it is difficult for hydrophilic α-arbutin to penetrate across the skin and reach the melanocytes. Owing to the advantages offered by α-arbutin as compared to the other harmful skin lightening agents, there is an urgent demand to improve the penetration and permeation of α-arbutin across the skin by developing various novel delivery systems such as microneedles, nanosystems, microsystems, lipidic systems, etc. Various approaches that can serve as a promising platform for the effective delivery of α-arbutin are represented in Figure 4.

The microneedle-based delivery system has gained the attention of many researchers due to its non-invasive nature and high skin penetration property. Microneedles are being exploited by research scientists to deliver therapeutics that need to bypass the stratum corneum without causing any discomfort. They are micron-sized needles of less than 1000 μm and promote penetration of the active compound across the skin by creating micro-channels through the stratum corneum without harming the skin. Microneedles can be dissolvable or hydrogel-forming. Dissolving microneedles (DMNs), as the name suggests dissolve completely after the insertion of microneedles and release the encapsulated active moiety after coming in contact with the interstitial fluid in the skin. Hydrogel-forming MNs (HMNs) are fabricated by using swellable polymers. HMNs, upon skin insertion, pass the stratum corneum and come in contact with the interstitial fluid within the skin. Therein, they swell and enlarge several times, thus releasing the active compound.

To overcome poor permeability issues of α-arbutin, very recently, Aung et al., 2020 attempted to develop dissolvable and hydrogel-forming microneedles using polyvinyl alcohol (PVA) and poly (acrylic acid-co-maleic acid) copolymer (PAMA). DMNs containing α-arbutin showed complete dissolution within 45 min, whereas the highest HMN swelling was observed at 4 h. As compared to the gel and commercial cream preparations, the developed DMNs and HMNs showed 4.5- and 2.8-times superior permeation, respectively. The in vivo studies also confirmed the superior intradermal delivery of α-arbutin by both formulations (DMNs and HMNs) compared to the gel preparation and commercial cream. The results suggested that DMNs and HMNs can offer superior transdermal delivery of α-arbutin to achieve an enhanced skin lightening effect. In another study, Aung et al., 2020 fabricated DMNs to promote transepidermal delivery of α-arbutin using hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone K-90 (PVP) for effective skin lightening. The HPMC/PVP DMNs demonstrated 4.7 times superior permeation of α-arbutin across the skin than the gel formulation. DMNs developed using HPMC/PVP for the delivery of α-arbutin were proven to be a promising delivery platform to achieve enhanced penetration of α-arbutin. Polymeric nanoparticles have also been exploited due to their ability to alter the drug release rate, increase the therapeutic duration of action, and enhance site-specific drug delivery. Ayumi et al.,
2019 developed chitosan nanoparticles (CNPs) for topical delivery of both α-arbutin and β-arbutin. Chitosan interacts with epidermal tight junction proteins providing a penetration barrier in the stratum granulosum, which is located beneath the lipid barrier in the stratum corneum, thus enhancing skin penetration (Ali et al., 2017). Also, chitosan possesses a cationic charge, which facilitates interaction with negatively charged cell surfaces and tissues. It is reported that slightly acidic formulations appear to be more acceptable for dermal use because the acid mantle of normal human skin will not be disrupted (Rajan et al., 2012). The developed chitosan-based α-arbutin nanoparticles ranged from 147 to 274 d.nm. It was observed that increasing the concentration of α-arbutin increased the size of the nanoparticles. The α-arbutin loaded CNPs demonstrated significantly higher release as compared to their free form. CNPs could be a promising carrier system for the delivery of α-arbutin across the skin in order to improve its efficacy as a skin lightening agent. In another study, Patrojanasophon et al., 2020 fabricated highly aligned cellulose acetate nanofibers containing α-arbutin for its application as a face mask. Ideally, a nanofibers-based face mask should provide instant release of the active compound with a high skin penetration rate owing to its high surface area. Electrospun nanofibers have outstanding characteristics, making them desirable as carriers for several therapeutics. The characteristics feature of nanofibers is their high surface area which easily overcomes the constraint of the traditional delivery systems. Manufacturing ultrafine electrospun nanofibers not only increase the solubility of the drug but also promotes faster drug release. The developed highly arranged nanofibers showed 80.0% of α-arbutin release in 1.77 min which was significantly faster as compared to partially aligned (4.2 mins) and randomly aligned nanofibers (9.4 mins). The authors successfully demonstrated the crucial role of the orientation of nanofibers in controlling drug release. It was achieved due to the network meshes present in the nanofibers with different degrees of entanglement, which directly affected the diffusion of drugs across the skin.

α-arbutin is one of the most popular skin brightening compounds and less toxic as compared to hydroquinone. With a massive growth in the skin brightening industry today, the supply and demand of α-arbutin are increasing considerably. Therefore, exploring various delivery systems such as nanoparticles, microparticles, nanogels, nanoemulsion for improving the efficacy of α-arbutin as a skin brightening agent is needed.

**Combination Therapy of α-arbutin**

Combined active compounds with different targeting mechanisms are used to enhance the effectiveness of the skin lighting agent. Skin formulations containing α-arbutin along with other skin brighteners such as kojic acid, vitamin C, or niacinamide have been reported to demonstrate synergistic effects. A combination of 2% α-arbutin and 3% tranexamic acid, 2% galactomyces ferment filtrate, and 4% niacinamide has proven to be a safe and effective alternative to enhance skin lightening with no significant side effects (Santoso et al., 2018). α-arbutin combined with 4-n-butyresorcinol, and licorice extract has been used in the therapeutic management of melasma with improved safety, efficacy, and tolerability (Kolbe et al., 2013). Combination therapy with 7% α-arbutin solution and Q-switched Nd:YAG laser demonstrated an effective and well-tolerated treatment for refractory melasma (Polnikorn, 2010). Very recently, Wang et al., 2021 prepared a dissolving microneedles array (DMNA) containing α-arbutin and Vitamin C in a 1:1 ratio. It was observed that this ratio exhibited maximum inhibition effects on melanogenesis and tyrosinase activity.

**Market Status of α-arbutin**

Natural and herbal beauty products are becoming extremely popular, particularly in the United States (U.S.) and Europe. These areas are expected to provide profitable opportunities for α-arbutin producers. Furthermore, because of its excellent antioxidant properties, α-arbutin has seen an increase in demand in the pharmaceutical industry, which is expected to create highly profitable opportunities for manufacturers in the coming years. North America is the largest consumer of α-arbutin, followed by Europe and the Asia Pacific. Consumers’ increasing preference for eco-friendly products has prompted several US cosmetic manufacturers, including L’Oreal and Garnier, to develop newer and more innovative cosmetic products. As a result, it is expected to boost market growth in North America. In 2018, Europe had the highest consumption of α-arbutin. An increase in regulations aimed at reducing the use of synthetic ingredients in cosmetic products, as well as a rise in the geriatric population, are the two factors that are expected to boost the market growth (FutureWise Market Research and Reports; 2019).

**CONCLUSION**
α-arbutin has emerged as a popular alternative to other harmful skin lightening agents because of its outstanding capability to reduce hyperpigmentation without any unwanted side effects. Today, with massive growth in the cosmetic and pharmaceutical industry, its supply and demand are increasing exponentially. Currently, α-arbutin is found as the main ingredient in a wide range of skin lightening products such as creams, serums, face washes, gels, and lotions. However, owing to the hydrophilic nature of α-arbutin, more studies are urgently needed to enhance the penetration of α-arbutin across the skin to achieve maximum skin lightening effect. Lastly, more comprehensive research investigating the long-term effects and complexities of α-arbutin products is recommended since they can pose a risk to the population using skin lightening products. In this review, we have aimed to highlight α-arbutin as a safer alternative to many other harmful skin lightening agents as the abuse of skin bleaching agents remains prevalent worldwide.

Conflict of Interest: The authors declare that they have no competing interests.

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