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REVIEW

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A comprehensive review of the therapeutic potential of α-arbutin

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Cosmetic dermatology preparations such as bleaching agents are ingredients with skin-related biological activities for increasing and improving skin beauty. The possibility of controlling skin hyperpigmentation disorders is one of the most important research goals in cosmetic preparations. Recently, cosmetics containing herbal and botanical ingredients have attracted many interests for consumers of cosmetic products because these preparations are found safer than other preparations with synthetic components. However, high-quality trial studies in larger samples are needed to confirm safety and clinical efficacy of phytotherapeutic agents with high therapeutic index. Arbutin (*p*-hydroxyphenyl-β-D-glucopyranoside) is a bioactive hydrophilic polyphenol with two isomers including alpha-arbutin (4-hydroxyphenyl-α-glucopyranoside) and β-arbutin (4-hydroxyphenyl-β-glucopyranoside). It is used as a medicinal plant in phytopharmacy. Studies have shown that alpha-arbutin is 10 times more effective than natural arbutin. A comparison of IC50 values showed that α-arbutin (with concentration 2.0 mM) has a more potent inhibitory activity on human tyrosinase against natural arbutin (with higher concentration than 30 mM). A review of recent studies showed that arbutin could be beneficial in treatment of various diseases such as hyperpigmentation disorders, types of cancers, central nervous system disorders, osteoporosis, diabetes, etc. This study was designed to describe the therapeutic efficiencies of arbutin.

KEYWORDS
arbutin, hyperpigmentation disorders, nanoparticles, skin whitening agents, therapeutic mechanisms

1 | INTRODUCTION

Due to the growing interest in topically applied cosmetics, research on different types of skin depigmenting and lightening agents has also increased (Khezri, Saeedi, Morteza-Semnani, Akbari, & Hedayatizadeh-Omran, 2021; Khezri, Saeedi, Morteza-Semnani, Akbari, & Rostamkalaei, 2020; Lee et al., 2018). Cosmetic dermatology preparations such as bleaching agents (Khezri, Saeedi, & Dizaj, 2018) are ingredients with skin-related biological activities for increasing and improving skin beauty (Kusumawati & Indrayanto, 2013). The main function of skin whitening preparations is the treatment of skin hyperpigmentation disorders through increase in skin-bleaching (Li, Yin, Zhai, Lu, & Mi, 2019). The possibility of controlling skin hyperpigmentation disorders (especially in the face and neck) is a most cosmetically important research aim (Napolitano & Ito, 2018). Melasma is the most common form of facial hyperpigmentation (Passeron & Picardo, 2018). Other types of hyperpigmentation disorders have been reported in studies including erythromelanosis follicularis of the face and neck, Riehl's melanosis, linea fusca, poikiloderma of Civatte, cosmetic hyperpigmentations, and erythrose peribuccale pigmentaire of Brocq (Perez-Bernal, Munoz-Perez, & Camacho, 2000). Recently, cosmetics with herbal and botanical ingredients have attracted many

interests for consumers of cosmetic products because these preparations are found safer than preparations containing synthetic and animal components (Aburjai & Natsheh, 2003).

Nevertheless, a review of various studies including meta-analyses, systematic reviews, double-blind randomized clinical trial (RCTs), prospective cohort studies, case–control studies (retrospective), case reports and case series, unsystematic observations, and expert opinions showed that some of several medicinal plants have serious side effects for consumers. In this regard, researchers designed main guidelines associated with clinical trials to obtain high levels of efficacy and safety of herbal medicine, including evaluation of herbs and herb–drug interactions, precautions for the use of herbal compounds in pregnancy and breastfeeding women, the pediatric, adolescent, and geriatric population (Izzo, Hoon-Kim, Radhakrishnan, & Williamson, 2016). Also, it is necessary to check the following items before using any herbal medicines: standardization of the extracts, the accurate identification of plant species, adulteration of herbal medicines, adverse effects associated with plant food supplements and botanical preparations, extraction methods, and the type of solvent used in the extraction process (Andrew & Izzo, 2017).

Arbutin (*p*-hydroxyphenyl-β-D-glucopyranoside) is a bioactive hydrophilic polyphenol with two isomers including alpha-arbutin (4-hydroxyphenyl-α-glucopyranoside) and β-arbutin (4-hydroxyphenyl-β-glucopyranoside) (Couteau & Coiffard, 2016). It has been used as a medicinal plant in phytotherapy and phytocosmetics (Migas & Krauze-Baranowska, 2015). It is obtained from various types of natural and synthetic sources including various species of plants, enzymatic processes, and metabolic engineering of microorganisms (Figure 1 and Table 1). The formation of these isomers depends on how the hydroquinone binds to the anomeric carbon atom in the glucose molecule

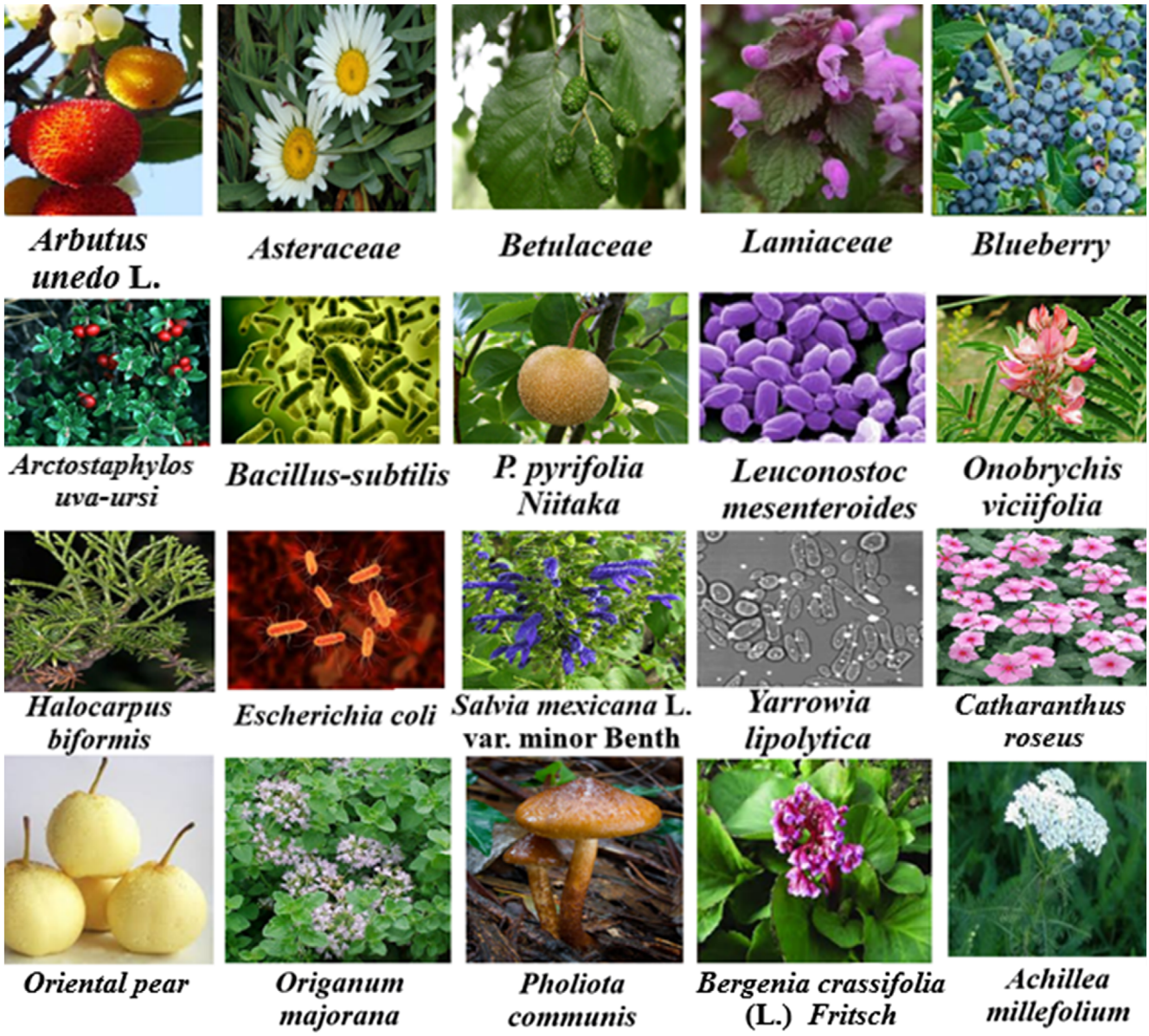

FIGURE 1 Types of natural and synthetic sources of arbutin [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 A list of natural and synthetic sources of arbutin derived from various species of plants, enzymatic processes, and metabolic engineering of microbes

Sources	Plant families/bacterial species	References
Japanese pear trees	*Pyrus pyrifolia* cv. Kousui	Sasaki, Ichitani, Kunimoto, Asada, and Nakamura (2014)
Bearberry	*Arctostaphylos uva-ursi*	Parejo, Viladomat, Bastida, and Codina (2001)
Majoram	*Origanum majorana*	Lukas, Schmiderer, Mitteregger, and Novak (2010)
Fruit peel	*P. pyrifolia* Nakai	Cho et al. (2011)
Fruit peel	*P. pyrifolia* Niitaka	Lee and Eun (2012)
Leaves	*P. biossieriana* Buhse	Shahaboddin et al. (2011)
Oriental pear	*P. Bretschnrideri*	Cui, Nakamura, Ma, Li, and Kayahara (2005)
Oriental pear	*P. pyrifolia*	Cui et al. (2005)
Oriental pear	*P. ussuriensis*	Cui et al. (2005)
Oriental pear	*P. sinkiangensis*	Cui et al. (2005)
Occidental pear	The flowers, buds, and young fruits of *Pholiota communis*	Cui et al. (2005)
Leaves	*Bergenia crassifolia* (L.) Fritsch	Carmen, Vlase, and Tamas (2009)
Leaves	A number of Lamiaceae species	Rychlinska and Nowak (2012)
Leaves	A number of Ericaceae species	Rychlinska and Nowak (2012)
Leaves	A number of Saxifragaceae species	Rychlinska and Nowak (2012)
Leaves	A number of Rosaceae species	Rychlinska and Nowak (2012)
Pear	*P. serotina* Rehder	Lee, Choi, et al. (2018)
Pear	*Achillea millefolium*	Lee, Choi, et al. (2018)
Strawberry tree leaves	*Arbutus unedo* L.	Jurica et al. (2017)
Leaves	Asteraceae	Thogchai and Liawruangrath (2013)
Leaves	Betulaceae	Thogchai and Liawruangrath (2013)
Leaves	Lamiaceae	Migas and Krauze-Baranowska (2015)
Leaves	Apiaceae	Migas and Krauze-Baranowska (2015)
Bacteria	*Bacillus subtilis* and *Leuconostoc mesenteroides*	Migas and Krauze-Baranowska (2015)
Metabolic engineering of microbes (engineering shikimate pathway)	*Pseudomonas chlororaphis* P3	Wang et al. (2018)
Fed-batch fermentation	*Escherichia coli*	Wu, Nair, Chu, and Wu (2008)
Shoot culture	*Origanum majorana* L. (Lamiaceae)	Skrzypczak-Pietraszek, Kwiecień, Gołdyn, and Pietraszek (2017)
Metabolic engineering of microbes (engineering shikimate pathway)	*Yarrowia lipolytica*	Shang et al. (2020)
Blueberry	—	Program (2006)
Cranberry	—	Program (2006)
Cowberry	*Vaccinium vitis-idaea* L., Ericaceae	Program (2006)
Juvenile foliage of the New Zealand tree	*Halocarpus biformis*, *Salvia mexicana* L. var. minor Benth, *Rhodiola sacra* S H Fu, *Onobrychis viciifolia* (Sainfoin), and *Origanum majorana*	Program (2006)
By the incubation of HQ with enzyme extracts from bean or wheat plants	—	Program (2006)
The germination of seeds	*Viguna mungo* seeds	Program (2006)
Plant tissues in the presence of HQ	—	Program (2006)
Biotransformation of HQ	*Catharanthus roseus* cells	Misawa (1994)

(Continues)

TABLE 1 (Continued)

Sources	Plant families/bacterial species	References
It can be synthesized from acetobromglucose and HQ or from the reaction of β-D-glucose pentaacetate and HQ monobenzyl ether in the presence of phosphorus oxychloride	—	Program (2006)
Sucrose phosphorylase + hydroquinone	*L. Mesenteroides*	Kitao and Sekine (1994)
Sucrose isomerase + hydroquinone	*E. rhapontici*	Zhou et al. (2011)
Dextransucrase + hydroquinone	*L. Mesenteroides*	Seo et al. (2009)
α-Glucosidase + hydroquinone	*S. cerevisiae*	Prodanović et al. (2005); Prodanović, Milosavić, Sladić, Veličković, and Vujčić (2005)
CGTase + hydroquinone	*Thermoanaerobacter* sp.	Mathew and Adlercreutz (2013)
Amylosucrase + hydroquinone	*D. Geothermalis*	Seo et al. (2012)
Amylosucrase + hydroquinone	*C. Carboniz*	Yu et al. (2018)
α-Amylase + hydroquinone	*B. subtilis X-23*	Nishimura, Kometani, Takii, Terada, and Okada (1994)
α-Glucosidase + hydroquinone	*X. campestris WU-9701*	Kurosu et al. (2002)

(Hazman, Sarıova, Bozkurt, & Ciğerci, 2021). It has been shown that alpha-arbutin is 10 times more effective than natural arbutin. A comparison of IC50 values showed that α-arbutin (with concentration 2.0 mM) has a more potent inhibitory activity on human tyrosinase in comparison with natural arbutin (with higher concentration than 30 mM) (Zhu et al., 2018). In a study, tyrosinase inhibitory capacity of α-arbutin has been evaluated using cultured human melanoma cells and a human skin model. It revealed that α-arbutin can potentially inhibit melanin formation without the induction of cytotoxicity (Sugimoto, Nishimura, & Kuriki, 2007; Sugimoto, Nishimura, Nomura, Sugimoto, & Kuriki, 2004). Therefore, α-arbutin synthesis is very much valuable and useful for cosmetic and pharmaceutical industrials (Zhu et al., 2018).

Recent studies show that seven microbial enzymes are able to synthesize alpha-arbutin, including sucrose isomerase, cyclodextrin glycosyltransferase, alpha amylase, amylosucrase sucrose phosphorylase, dextransucrase, and α-glucosidase (Hazman et al., 2021). Arbutin as a hydroquinone glycoside has various biological functions in cosmetics and pharmaceutical preparations (Lee & Kim, 2012). It is widely used in cosmetic products as a skin bleaching agent and antiaging agent (Zhou et al., 2017). Furthermore, a review of recent studies showed that arbutin could be beneficial in the treatment of various diseases (Table 2).

In accordance with the presented practical guidelines by Izzo et al. and to provide new perspectives in research studies of herbal medicine (Izzo et al., 2020), this review aims to update and describe applications and the therapeutic benefits of arbutin in the treatment of various diseases. Also, a search method of study was performed by searching the electronic databases, including Scopus, Google Scholar, PubMed, Science Direct, Web of Science, using search keywords such as arbutin, hyperpigmentation disorders, and therapeutic mechanisms, skin whitening agents, arbutin nanoparticles. In this study, literature searches were carried out with no restrictions on publication date and language.

2 | CHEMICAL CHARACTERIZATIONS AND THERAPEUTIC EFFECTS OF ARBUTIN IN COSMETIC AND PHARMACEUTICAL PREPARATIONS

In recent years, herbal and medicinal plant extracts such as arbutin have attracted special attention due to multiple biological and pharmacological properties and their unique therapeutic benefits (Shang, Wei, Zhang, & Ye, 2020; Zhu et al., 2018). Kawalier discovered arbutin (in the leaves of *Uva ursi*) in 1851. It is identified as a glucoside and can convert into sugar, hydroquinone ($C_6H_6O_2$) (arctuvin of kawalier) (Maisch, 1874).

Arbutin is a white powder (pure synthetic) with crystal structure and it is classified in polyphenolic compounds. Its IUPAC name is (2R,3S,4S,5R,6S)-2-hydroxymethyl-6-(4-hydroxyphenoxy) oxane-3,-4,5-triol. It is also called hydroquinone β-D-glucopyranoside. It is used as a skin whitening agent (in skin care and cosmetic preparations) for the inhibition of melanin synthesis in patients with hyperactive melanocyte and hyperpigmentation disorders (Araujo-Andrade, Lopes, Fausto, & Gómez-Zavaglia, 2010). In vitro studies on dermal penetration showed that the hydrolysis of alpha-arbutin to hydroquinone is done in two ways including human skin microbe interactions and enzymatic activity (Bang, Han, & Kim, 2008; Degen, 2016). Trade brand of arbutin is Aqua lotion (Amarte) (Couteau & Coiffard, 2016). Absorbance measurements of arbutin by UV–Vis spectrophotometer showed that it has two main absorbance peaks at approximately 230–280 nm (Yang et al., 2013). Because arbutin does not have

TABLE 2 A list of biological activities of alpha-arbutin

Functions	Results	Model	References
Wound healing	This study represents wound healing effects of arbutin on human dermal fibroblast cell cultures with the downregulated ROS expression, inhibition of the forkhead box protein O1 and sirtuin 1 genes, upregulating type I procollagen, the matrix metallopeptidase 3, epidermal growth factor receptor genes, and insulin/IGF-1 signaling pathway.	In silico and in vitro	Polouliakh et al. (2020)
Cytotoxicity and hypopigmentation effects from UVB-irradiated arbutin	The results of this study revealed that arbutin has effective toxic and brightening effects on Detroit 551 human fibroblast cells B16-F10 mouse melanoma cells. It can decrease the melanin synthesis in melanoma cells by activating caspase-3 pathway.	In vitro	Chang et al. (2017)
Arbutin effects on bone cells and the development of antioxidant titanium implants	Arbutin showed protective role on osteoblast-like cells (Saos-2) and periosteum-derived progenitor cells (PDPCs) with the high biocompatibility and upregulation of the expression of PDPC differentiation markers and it can use as a promising strategy for the development of antioxidant titanium implants.	In situ and in vitro	Bonifacio et al. (2020)
Cytoprotective effects	Arbutin demonstrated the good antioxidative and cytoprotective activities with high cell viability.	In vitro	Seyfizadeh et al. (2012)
Decrease of potentially toxins produced in human blood neutrophils	Arbutin exhibited anti-inflammatory activity through downregulation of the expression of phospholipase D, myeloperoxidase, elastase activity, suppression of the synthesis of superoxide, and reactive oxygen species.	In vitro	Pečivová, Nosáľ, Sviteková, and Mačičková (2014)
Estrogen-like effects	Arbutin identifies as a phytoestrogen ingredient with estrogen-like effects.	In vitro and in vivo	Zeng et al. (2018)
Pro-apoptotic effects	Arbutin and its derivatives indicated potential skin brightening and anti-malignant melanoma activities.	In vitro	Jiang et al. (2018)
Stability of membranes	Arbutin acts as stabilizing cellular membranes and increases plant stress tolerance via presence of different lipid composition such as the non-bilayer-forming chloroplast lipid monogalactosyldiacylglycerol.	In vitro	Hincha, Oliver, and Crowe (1999)
Inhibitory effects on melanin biosynthesis	Arbutin inhibits melanin formation through downregulation of the expression of α-melanocyte-stimulating hormone.	Ex vivo and in vitro	Lim et al. (2009)
Anti-inflammatory effects	Arbutin revealed anti-inflammatory activity through inhibition of BV2 microglial cells activation in response to LPS stimulation.	In vitro	Lee and Kim (2012)
Effects on immuno-inflammation	It can be concluded that arbutin was effective in inhibiting activity of dexamethasone and prednisolone on picryl chloride and sheep red cell delayed type hypersensitivity.	In vivo	Matsuda et al. (1990)
Effects on radiation-induced micronuclei	Experiments showed that arbutin has anti-clastogenic and radioprotective activities against gamma radiation.	In vivo	Nadi, Msc, Mozdarani, Mahmodzade, and Pouramir (2016)
Hepatoprotective effects	Hepatoprotective effects confirmed by antioxidant and free radical scavenger activities of arbutin.	In vivo	Mirshahvalad et al. (2016)
Cardiac hypertrophy	Arbutin exhibited an anti-hypertrophic effect by decreasing TLR-4/NF-κb pathway.	In vivo	Nalban et al. (2020)

(Continues)

TABLE 2 (Continued)

Functions	Results	Model	References
Anti-ulcerogenic activities	Arbutin acts as an anti-ulcer through anti-oxidant and lipid peroxidation inhibitory, immuno modulatory and lipid peroxidation inhibitory mechanisms.	In vitro and in vivo	Taha et al. (2012)
Epilepsy	Arbutin showed anti-epilepsy effect via inhibiting glial activity, downregulate in the expression of memory impairment markers, and suppressing inflammatory cytokine release.	In vitro and in vivo	Ahmadian et al. (2019)
Hypoglycemic activity	Results confirmed the potential anti-diabetic effects of arbutin through inhibitory activities on α-amylase and α-glucosidase.	In vitro	Yousefi, Mahjoub, Pouramir, and Khadir (2013)
Diuretic	The availability in urine is about 65% of the administered dose of arbutin.	Clinical trial	Schindler et al. (2002)
Enhanced antimicrobial activities	Findings of this research confirm that phenolic groups of polymers increased the antimicrobial activity of polymeric arbutin than monomeric arbutin.	In vitro	Kajiwara et al. (2019)
Parkinson's disease (PD)	These results suggested that arbutin can act as a neuroprotective agent and can considerably decrease behavioral deficits, oxidative and nitrosative stress in PD animal models both in vitro and in vivo.	In vitro and in vivo	Dadgar et al. (2018), Ding et al. (2020)
Antitussive activities	Finding of this study showed that arbutin formulations in doses of 50 and 100 mg/kg b.w.p.o. and i.p. can effectively reduce intensity of cough attack and cough frequency in cats.	In vivo	Strapkova, Jahodar, and Nosal'ova (1991)
Increase of longevity and stress resistance	Arbutin considerably increases lifespan and improves stress resistance of nematodes.	In vitro and in vivo	Zhou et al. (2017)
Decrease of intracellular ROS	Arbutin as an antioxidant and anti-inflammatory agent can inhibit the activity of the intracellular ROS, the expression level of IL-1β and TNF-α gene.	In vitro	Safari et al. (2020)
Alzheimer's disease	These results suggested that arbutin has neuroprotective activities against memory impairment and oxidative damage in the brain.	In vitro and in vivo	Dastan et al. (2019)
Chronic bacterial prostatitis	This study reveals that arbutin is effective strategy in treatment of chronic bacterial prostatitis.	Clinical trial	Busetto et al. (2014)
Positively regulate DAF-16 expression in nuclear	Arbutin regulates nuclear localization of DAF-16 by activating antioxidant signaling pathways.	In vitro and in vivo	Zhou et al. (2017)
Radioprotective effect	Arbutin at dose of 50 mg/kg revealed potent radioprotective properties.	In vitro and in vivo	Nadi et al. (2019)
Enhance recovery and osteogenic differentiation in dried and rehydrated human mesenchymal stem cells	Arbutin- loaded dehydrated human mesenchymal stem cells increases the stabilizing activities of trehalose through activation mechanisms of endogenous heat shock proteins.	In vitro	Jamil et al. (2005)
Anti-myocardial infarction effects	Arbutin at dose 50 mg/kg bw showed effective anti-myocardial infarction effects in animal model against mitochondrial, hyperlipidemia, and DNA and lysosomal membrane damages.	In vivo	Sivasangari, Asaikumar, and Vennila (2020)
Sperm cryoprotective agent	Arbutin increased sperm longevity by increasing the membrane fluidity.	In vitro	Aboagla and Maeda (2011)

TABLE 2 (Continued)

Functions	Results	Model	References
Multiple sclerosis (MS)	Arbutin showed high therapeutic capacity for demyelinating disorders such as multiple sclerosis by reducing expression of inflammation markers, astrocyte activation, and oxidative stress.	In vivo	Ebrahim-Tabar et al. (2020)
Optic nerve injury	Arbutin has a protective role in retinal ganglion cells injured due to oxidative stress through up-regulation of miR-29a and suppressing p38MAPK and MEK/ERK signaling pathways.	In vivo	Zhao et al. (2019)
Antioxidant activity	The present findings suggested that arbutin has a potent antioxidant activity in the skin.	In vitro	Takebayashi et al. (2010)
Prostate cancer	Arbutin showed a prostate anticancer effect by increasing apoptosis and reducing expression of pro-inflammatory markers and ROS.	In vitro	Safari et al. (2020)
Breast cancer	Results indicate that arbutin has a breast anticancer activity.	Clinical trial	Cacchio, Prencipe, et al. (2019)
Human bladder cancer	Arbutin plays an antiproliferation role on TCCSUP human bladder carcinoma cells by suppressing ERK signaling pathway and p21 up-regulation.	In vitro	Li, Jeong, Kim, Kim, and Kim (2011)
Antidiabetic and anti-glycation activities	Arbutin showed antidiabetic and anti-glycation activities via JNK and mTOR-signalling pathways and up-regulating miR-27a.	In vitro	Lv et al. (2019)
Osteoporosis treatment	Arbutin has effective role in osteoporosis treatment by Wnt/β-catenin signaling pathway and increasing osteoblastic proliferation and differentiation of MC3T3-E1 cells.	In vitro	Man et al. (2019)
Acute lung injury	Finding of this study reveals that arbutin is a promising therapeutic strategy in inflammation-related lung injury via regulating the Nrf-2/HO-1/NF-κB signaling pathway.	In vitro and in vivo	Ye et al. (2019)
Post-trauma/surgery persistent hand edema	Arbutin was an effective method in the management of patients with post-trauma/surgery persistent hand edema.	Clinical trial	Cacchio, Di Carlo, Vincenza, and Elisabetta (2019)
Antiapoptotic role and radio-protector	Arbutin showed an anti-apoptotic effect via downregulation of the expression of intracellular hydroxyl radical formation, activation of the JNK/p38 MAPK pathway and suppression of Bax-mitochondria pathway.	In vitro	Wu et al. (2014)

chromophores that are absorbed at wavelengths above 290 nm (Lyman, Reehl, & Rosenblatt, 1990), it is found that maximum absorbance peak of arbutin is in 267 nm. Arbutin shows the most stability at pH 5–7 (Couteau & Coiffard, 2000). It has very high solubility in water with logP value −1.49 and this causes insufficient absorption from the skin layers (Wen, Choi, & Kim, 2006). Its physical state is needle-shaped crystals and it can be transformed into a white or gray powder. It has high solubility in methyl alcohol, ethyl alcohol, acetonitrile, and tetrahydrofuran, but it does not dissolve in some solvents such as DMSO, chloroform, petroleum, diethyl ether, and cyclohexane. It is unstable in acidic medium and is easily hydrolyzed. The chemical structure of arbutin contains a hydrophilic anhydroglucose functional group and a phenolic group (as a melanin inhibitor) (Zhou et al., 2017). Chemical structure and multiple biological activities of arbutin ($C_{12}H_{16}O_7$) are shown in Figure 2.

In various studies, it is revealed that arbutin formulations can be useful for the treatment of various diseases due to its multi-target biological effects such as treatment of hyperpigmentation disorders (Ayumi, Sahudin, Hussain, Hussain, & Samah, 2019; Park et al., 2019), anti-diabetic (Lv et al., 2019), wound healing (Polouliakh et al., 2020), anti-osteoporosis (Bonifacio et al., 2020), treatment of acute lung injury (Ye et al., 2019), management of cardiac hypertrophy (Nalban et al., 2020), anticancer (Jiang et al., 2018; Safari et al., 2020; Wang, Wang, Li, Zhang, & Wang, 2020), antioxidant activity (Bonifacio

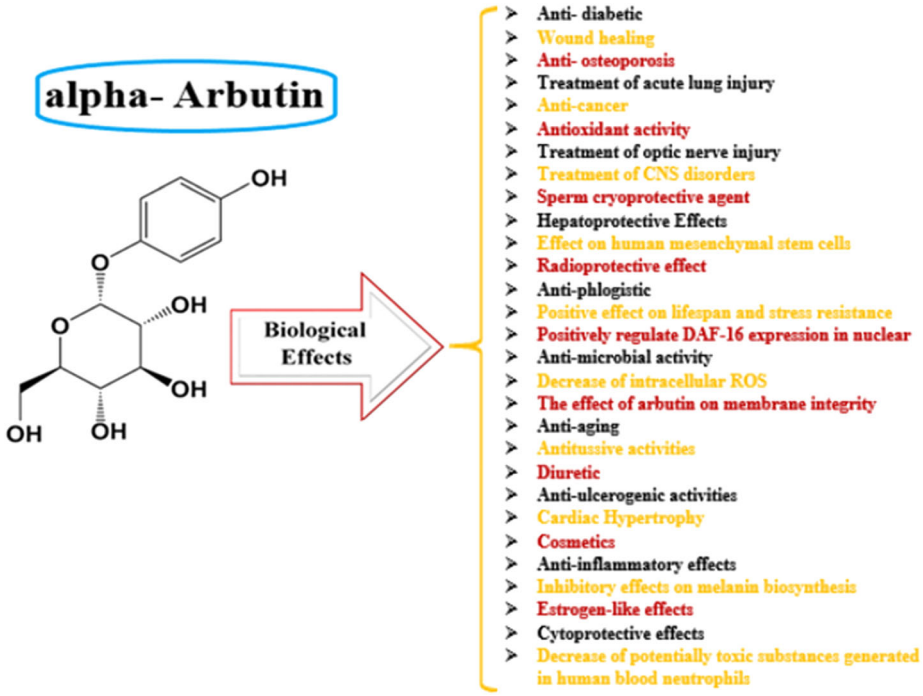

FIGURE 2 Chemical structure and multiple biological activities of arbutin [Colour figure can be viewed at wileyonlinelibrary.com]

et al., 2020), treatment of optic nerve injury (Ebrahim-Tabar, Nazari, Pouramir, Ashrafpour, & Pourabdolhossein, 2020; Zhao, Wang, Qin, & Wang, 2019), treatment of central nervous system disorders (Ahmadian, Ghasemi-Kasman, Pouramir, & Sadeghi, 2019; Dastan et al., 2019; Ding et al., 2020), hepatoprotective activity (Mirshahvalad et al., 2016), effect on human mesenchymal stem cells (Bonifacio et al., 2020; Jamil, Crowe, Tablin, & Oliver, 2005), radioprotective effect (Nadi, Elahi, Moradi, & Banaei, 2019), antimicrobial (Nadi et al., 2019), antiaging (Zhou et al., 2017), antitussive (Koul, Kumar, Yadav, & Jin, 2020), diuretic (Myagchilov, Mineev, Sokolova, Gerdasova, & Gorovoi, 2020), anti-inflammatory (Lee & Kim, 2012; Zhou, Zhao, Li, & Reetz, 2019), inhibitory effects on melanin formation (Li, Du, & Du, 2018), estrogen-like effects (Zeng et al., 2018), and cytoprotective effects (Seyfizadeh et al., 2012) etc.

In the study by Takii et al., it showed that arbutin was able to delay hyperglycemia after postprandial. The results of this investigation suggested that arbutin could be used as an effective supplement to control blood sugar in diabetes (Takii, Matsumoto, Kometani, Okada, & Fushiki, 1997).

It has been shown that the alpha form has photostable property with the highest inhibitory activity against mammalian tyrosinase. But it is unstable to heat and decomposes, and must be formulated at low temperatures (Couteau & Coiffard, 2000; Sugimoto et al., 2005). Poor stability of arbutin has limited its application. Glycosylation process is a very common and key structural modification for enhancement of light and oxidation stability. This process improves hydrophilicity, pharmacokinetic, and physicochemical properties of bioactive phenolic substances (Nakano et al., 2002). In a study, Li et al. designed a complex of arbutin and hydroxypropyl-β-cyclodextrin. They showed that this complex can considerably improve the heat stability of arbutin and has capacity for developing arbutin applications in pharmaceuticals, chemicals, food products, and cosmetics (Li et al., 2016). According to the studies reported in Table 2, arbutin seems to be a promising therapeutic agent in management of various diseases.

3 | HYPERPIGMENTATION DISORDERS AND SIGNALING PATHWAYS ASSOCIATED WITH MELANIN PRODUCTION

Hyperpigmentation is one of the most common skin disorders (Khezri et al., 2020, 2021) in dermatology clinics that results from excessive synthesis of melanin or melanin deposition on various skin layers (Kaur, Aggarwal, & Nagpal, 2019). Excessive synthesis of melanin and its accumulation can cause disorders such as acanthosis melasma, skin cancer risk, periorbital hyperpigmentation, cervical poikiloderma, lentigines, neurodegeneration associated with Parkinson's disease, and nigricans (Zolghadri et al., 2019). Various agents such as UV radiation, inflammatory mediators, hormones disorders, and radicals caused upregulated expression of melanogenesis process and hyperpigmentation (Kanlayavattanakul & Lourith, 2018a). Currently, melanin pigmentary disorders are a cosmetic problem that causes mental and psychological damage to patients (Sarkar, Arora, & Garg, 2013).

A literature review showed that changes in the serum levels of female sex hormones (estrogen and progesterone) during the menstrual cycle play main role in catamenial hyperpigmentation of the skin (Mobasher et al., 2020). Hyperpigmentation disorders can be classified as acquired, congenital, or inherited (Jimbow & Minamitsuji, 2001).

Recent advances in cellular and molecular sciences such as transcriptome analysis, sequencing technologies, and genome sequencing and epigenetic analysis to evaluation of various skin diseases have upgraded our understanding of melanogenesis. Discovering more details of the different cell signaling pathways associated with melanin

synthesis can be useful in the control of melanogenesis process (D'Mello, Finlay, Baguley, & Askarian-Amiri, 2016).

Excitation of keratinocytes by ultraviolet radiation causes the synthesis of proopiomelanocortin-derived α-melanocyte stimulating hormone (α-MSH) peptide. The surface receptor of melanocyte cells attaches to α-MSH. By doing this reaction, the melanogenesis process expresses multiple signaling pathways including protein kinase A (PKA), microphthalmia-associated transcription factor (MITF) activity, and cAMP (cAMP response element-binding protein [CREB]) (Kanlayavattanakul & Lourith, 2018b). MITF as a main transcriptional regulator plays a key role in the replication of multiple melanogenic enzymes (tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (TRP-2)) (Shin et al., 2020). There are three main subgroups of mitogen-activated protein kinases (MAPKs) including p38, stress-activated protein kinases (SAPKs) also known as c-Jun NH2-terminal kinases (JNK), and extracellular signal-regulated kinases (ERKs) (Johnson & Lapadat, 2002). Pro-inflammatory cytokines and factors such as heat, UV radiation, and hydrogen peroxide stimulate P38 and SAPKs kinases and eventually damage DNA (Kanlayavattanakul & Lourith, 2018b). Activation of the ERK signaling pathway suppresses melanogenesis process in the melanocytes by downregulating MITF expression (Kim et al., 2003). Therefore, sufficient knowledge about these signaling pathways can lead to better understand the factors influencing melanogenesis process.

4 | CLINICAL FEATURES AND PATHOPHYSIOLOGY OF HYPERPIGMENTATION DISORDERS

Histological studies have shown that pigment disorders can occur in the dermis and epidermis layers or both layers. These disorders can occur with an increase in the number of melanocytes (i.e., melanocytosis), an upregulation of melanin synthesis without any changes in the number of melanocytes (i.e., melanosis), and/or existence of non-melanin pigments (e.g., tattoo pigment) (Jimbow & Minamitsuji, 2001). In the management of hyperpigmentation disorders, it is important to identify the type of dermal and epidermal pigmentation disorder by clinical tests such as using a wood's lamp. Using wood lamp, disorders of epidermal pigmentation are usually seen prominently, which shows dark brown or black fluorescence. But, disorders of dermal pigmentation using wood lamps usually appeared less prominent, which emits often a slate gray or blue fluorescence (Lawrence & Al Aboud, 2020). These findings can be used as a powerful tool to better clinical management of hyperpigmentation disorders.

5 | TREATMENT STRATEGIES FOR SKIN HYPERPIGMENTATION

In recent years, studies have significantly increased on the biological function of melanocytes and melanin synthesis processes. In this regard, new treatment strategies have been designed to inhibit melanogenesis and melanocyte dysfunction (Pillaiyar, Manickam, & Jung, 2015). Hyperpigmentation disorders have therapeutically been challenging and discouraging (Khezri et al., 2020). In this regard, various therapeutic approaches have been developed to improve the treatment of hyperpigmentation disorders including topical therapies, combination therapy, emerging topical agents, chemical peels, microdermabrasion, microneedling, lasers, oral agents, botanical agents, emerging oral treatments, and intravenous agents (Cheng & Vashi, 2017). These studies offered that developing new treatment approaches for inhibiting skin hyperpigmentation could lead to modulate these disorders and provide new perspectives on the management of melanogenesis and melanocyte dysfunction.

6 | A BRIEF OVERVIEW OF TYROSINASE AND ITS APPLICATIONS

Tyrosinase as a bifunctional metalloenzyme is a protein complex with two copper atoms in its active site (Cabanes, Chazarra, & GARCIA-CARMONA, 1994). The first research of tyrosinase was performed on the mushroom *Russula nigricans* in 1895. Because this mushroom turned red after being cut and then changed its color to black (Bourquelot & Bertrand, 1895), an attempt was made to find the reason for this color change (Van Gelder, Flurkey, & Wichers, 1997). In agricultural products such as raisins, tea, and cocoa, the tyrosinase activity is used for the production of distinct organoleptic properties. It is also reported that tyrosinase has applications in food and animal feed, monitoring environmental pollution and dye production (Nunes & Vogel, 2018). Tyrosinase has a key role in melanin biosynthesis in mammalian (Ma et al., 2019). Skin melanin is a biological pigment that is synthesized through melanogenesis in the melanocytes (Khezri et al., 2020). It removes ROS (Kim & Uyama, 2005) and acts as a photoprotective agent against harmful rays of the sun and skin photocarcinogenesis (Brenner & Hearing, 2008). It is also applied as natural antibacterial substance for the treatment of wounds (Nunes & Vogel, 2018). Tyrosinase has capacity in various biotechnological applications such as formation of L-DOPA, synthesis of novel mixed melanins, biocatalysis, protein crosslinking, phenol and dye removal, and phenolic biosensors (Fairhead & Thöny-Meyer, 2012). Extracted tyrosinase of *Streptomyces glausescens*, the fungi *Neurospora crassa* and *Agaricus bisporus* have the best properties (Parvez, Kang, Chung, & Bae, 2007). Increasing and decreasing melanin synthesis (hyperpigmentation and hypopigmentation, respectively) can cause serious problems in human's quality of life and skin beauty (Khezri et al., 2020). Also, it is showed that tyrosinase has the main role in physiologically vital processes of invertebrates such as defense reactions (immunity), producing pigmentation, wound healing and cuticular solidify (sclerotization), and structural proteins formed in the process of hard cuticle formation (Zaidi, Ali, Ali, & Naaz, 2014). In the fungal studies, it has been shown that melanin acts as a virulence factor in pathogenic fungi and is associated with the formation of sexual organs and spores and the protection of tissue after damage (Molloy et al., 2013).

Thus, these studies highlight key and main considerations in developing and designing future preclinical and clinical investigations associated with biological activities of tyrosinase.

7 | TYROSINASE INHIBITION

Tyrosinase plays a key and main role in the melanogenesis process. In this regard, many studies have been done to find effective inhibitors from natural (fungi, bacteria, plants) and synthetic sources (Muñoz-Muñoz et al., 2010). To evaluate the potency of tyrosinase inhibitors, they are assayed by a monophenolic substrate (such as tyrosine) or a diphenolic substrate (such as L-dopa) and ultimately their activity evaluates based on the rate of dopachrome formation (Khezri et al., 2020, 2021). Therefore, inhibition of tyrosinase activity and preventing oversynthesis and accumulation of melanin in skin are the most important cosmetic goals in clinical treatment of hyperpigmentation disorders.

8 | MELANOGENESIS PROCESS AND INHIBITION MECHANISMS OF DEPIGMENTATION AGENTS

Melanogenesis is known as a biosynthetic pathway. It has a key role in skin melanin synthesis. Regulation of melanogenesis expression occurs through intracellular signaling pathways related with the enzymes tyrosinase (TYR), tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (Chang, 2012). Tyrosinase initiates the melanogenesis process by performing three basic reactions including the tyrosine hydroxylation to L-DOPA, L-DOPA oxidation, and finally its conversion to dopaquinone. After this step, dopaquinone forms melanin through a series of complex reactions involving cyclization and oxidative polymerizations (Olivares, Jiménez-Cervantes, Lozano, Solano, & García-Borrón, 2001; Raper, 1928). A review of patents since 2009 shows that melanogenesis inhibitors are effective for the treatment of cutaneous hyperpigmentation disorders by two mechanisms including direct inhibition of catalytic activity or reduction of tyrosinase production. Studies on oligopeptides and siRNA have shown that these compounds are effective candidates for tyrosinase inhibition (Pillaiyar et al., 2015). A review of the literature shows that herbal inhibitors can be extracted from plant sources containing polyphenols (arbutin and quercetin), aldehydes (transcinnamaldehyde and cumic acid), fungi derived materials (azelaic acid and kojic acid), and other derivatives. Tyrosinase inhibitors are used in cosmetic, agriculture, and food industries (Parvez et al., 2007). In this regard, effort to find potential tyrosinase inhibitors from natural and herbal sources is very important. Because, as mentioned above, these natural compounds can cause serious side effects for consumers, it is necessary to check their safety before consumption.

The studies indicated that depigmentation agents can inhibit the melanin synthesis through various mechanisms including free-radical trapping agents (glycyrrhetinic acid, topical steroids), inhibition of tyrosinase transcription (*N*-acetyl glucosamine, glucosamine, tretinoin, retinaldehyde, retinol), epidermal turnover accelerant (liquiritin, retinoids, vitamin C, lactic acid, thioctic acid, vitamin E, glycolic acid, salicylic acid), tyrosinase inhibition (arbutin, hydroquinone, kojic acid, resveratrol, ellagic acid, mequinol, oxyresvaretrol, azelaic acid), anti-inflammatory (soy milk, niacinamide), and inhibition of melanosome transfer (linoleic acid) (Couteau & Coiffard, 2016). Figure 3 presents the mechanism of melanogenesis inhibition of α-Arbutin.

In summary, identifying and understanding cellular mechanisms regulating human melanogenesis can help the management and inhibition of melanogenesis process and the development of potential bleaching agents.

9 | USE OF ZEBRAFISH MODEL (IN VIVO) FOR SCREENING OF ALPHA-ARBUTIN AND OTHER SKIN LIGHTENING AGENTS IN COSMETIC

Recently, a zebrafish model (in vivo model) is proposed as a preclinical and animal model to study antimelanogenic efficacy of skin lightening agents. Using this model, special tests have been designed for this purpose including melanin content, gene expression, phenotype based test, tyrosinase test, and protein expression (Lajis, 2018). Several studies have been performed using zebrafish embryo model for screening of skin lightening agents in cosmetic preparations (Lajis, Hamid, Ahmad, & Ariff, 2017; Lajis, Hamid, & Ariff, 2012). This animal model is used for bioactive and depigmenting agents such as arbutin and kojic acid too. Depigmenting assay by in vitro (i.e., melanocytes) and in vivo (i.e., mice) models along with zebrafish

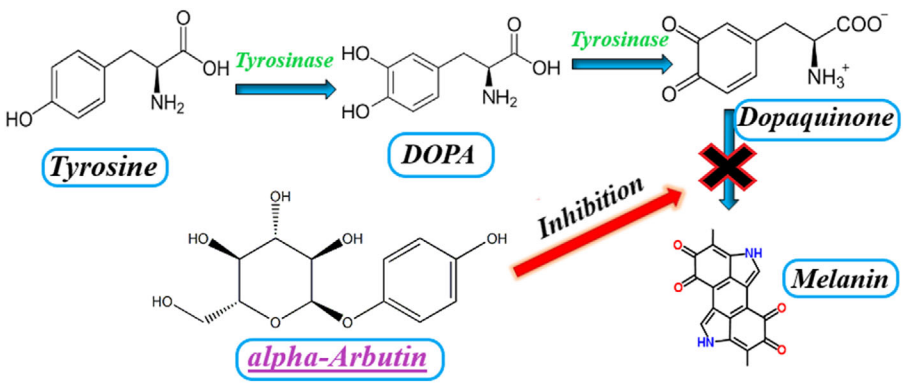

FIGURE 3 Mechanism of melanogenesis inhibition of α-arbutin [Colour figure can be viewed at wileyonlinelibrary.com]

model can lead to a better understanding of the effectiveness of antimelanogenic agents and better and safe development of these lightening agents (Lajis et al., 2012; Lee et al., 2018; Park et al., 2019). Findings from these investigations highlighted the importance of zebrafish used as an alternative model in the anti-melanogenic evaluations of cosmetics ingredients because of similar gene sequences to humans.

10 | SYNERGISTIC/ANTAGONISTIC EFFECTS WITH COMBINATION THERAPY OF ARBUTIN

In an investigation, Kubo et al. designed a combination therapy containing arbutin and prednisolone/dexamethasone. Effects of this co-therapy evaluated in a mice model induced by picryl chloride and sheep red blood cell delayed type hypersensitivity. The results of this study showed that this formulation is able to increase the inhibitory potency against swelling of contact dermatitis induced in mice compared to either of the two chemicals alone (Kubo, Ito, Nakata, & Matsuda, 1990). In this regard, Matsuda et al. developed co-delivery systems using arbutin plus indomethacin (on carrageenin-induced edema and adjuvant-induced arthritis) and arbutin plus dexamethasone ointment (on picryl chloride and carrageenin-induced paw edema). The findings of these studies demonstrated stronger inhibitory effect of these co-delivery systems than arbutin, indomethacin, and dexamethasone alone in these models (Matsuda, Nakata, Tanaka, & Kubo, 1990; Matsuda, Tanaka, & Kubo, 1991). In another study, it showed that co-delivery of arbutin with nonsteroidal anti-inflammatory drugs such as ibuprofen and indomethacin can increase the anti-inflammatory effects (Program, 2006). In an in vivo study on UV-induced pigmentation in human skin, Choi et al. have investigated anti-tyrosinase activity of aloesin (an anti-inflammatory) alone and combined with arbutin. They showed that combined therapy could be considerably effective (63.3% suppression of pigmentation) in treating hyperpigmentation disorders by synergistic inhibition mechanism of tyrosinase compared to therapy of aloesin (34%) and arbutin (43.5%) alone (Choi, Park, Lee, Kim, & Chung, 2002). Also, in another study, it is revealed that co-therapy with arbutin can suppress UV-induced nuclear factor-kappa B activation in human keratinocytes (Ahn, Moon, Lee, & Kim, 2003). In a mouse skin model system induced using 12-O tetradecanoylphorbol-13-acetate, Nakamura et al. indicated that coadministration of arbutin can effectively prevent oxidative stress (Nakamura et al., 2000). These results suggest that combination therapies of arbutin can be considered with positive effects through synergistic and antagonistic interactions.

11 | SAFETY ASSESSMENT OF ARBUTIN IN COSMETICS AND PHARMACEUTICAL PREPARATIONS

Cosmetic products, especially preparations containing skin lightening ingredients, are very popular. Breast cancer is one of the most common diseases among women. Therefore, it is necessary to make sure that cosmetics ingredients such as arbutin are safe and their beneficial/harmful effects on breast cancer should be carefully studied and monitored ("disorders.eyes.arizona.edu,"). It is reported that arbutin is widely used in a variety of cosmetic products in Japan, Korea, and United States (Davis & Callender, 2010). An evaluation of recent studies showed that arbutin is identified as a safe and effective strategy for treating breast cancer (Berdowska et al., 2013; Cacchio et al., 2019; Hazman et al., 2021).

Experimental studies using animal models have demonstrated that arbutin metabolites such as hydroquinone have a high potential for carcinogenic, nephrotoxic, hepatotoxic, and mutagenic (Nowak, Shilkin, & Jeffrey, 1995; Peters, Jones, Monks, & Lau, 1997). Therefore, the use of the glycosylation process for arbutin stability can lead to the formation of new compounds with unknown properties, which require tests to determine their safety before use in food and medicine (Liu et al., 2012). It is reported that arbutin is widely absorbed from the gastrointestinal tract and is available as hydroquinone in liver (Deisinger, 1996). In various studies, evaluation of oral administration of arbutin showed that arbutin and other arbutin-rich herbal preparations can metabolize into hydroquinone and glucose in the liver by the process of β-glucosidase. It then forms conjugations with glucuronic and sulfuric acids that are rapidly eliminated through urine and it is not a significant threat (Jurica, Benković, Sikirić, Kopjar, & Brčić Karačonji, 2020; Migas & Krauze-Baranowska, 2015; Schindler et al., 2002).

Several investigations demonstrate that arbutin is less toxic than hydroquinone. It is reported that arbutin is a suitable alternative to hydroquinone in treating hyperpigmentation disorders (Draelos, Deliencourt-Godefroy, & Lopes, 2020; Nordlund, Grimes, & Ortonne, 2006). A review of the studied cases with different concentrations of arbutin (3, 5, and 7%) in the patch tests showed that treated patients with these formulations developed various symptoms of contact dermatitis including edematous pruritic erythema, infiltrated small erythema, depigmented spot, pruritic erythema, oedematous erythema in different areas of facial skin such as cheek, eyelid, and forehead (Li et al., 2018; Numata, Tobita, Tsuboi, & Okubo, 2016). The Scientific Committee on Consumer Safety (SCCS) has expressed that the best range of safe and effective concentrations of α-arbutin is concentrations greater than 0.5% for body lotions and concentrations higher than 2% in facial creams (Degen, 2015, 2016). These reports confirm that formulations containing alpha-arbutin are considered as a safe health care product for consumers.

12 | CLINICAL STUDIES OF ARBUTIN IN COSMETICS PREPARATIONS

One of the successful treatments for hyperpigmentation disorders is long-term therapy using depigmenting and bleaching agents, either alone, or in combination with other skin lightening agents at various concentrations (Saeedi, Eslamifar, & Khezri, 2019). Several clinical studies suggested the use of arbutin with other depigmenting agents in melasma therapies and other hyperpigmentation disorders

(Table 3). However, in some studies, side effects such as contact dermatitis (with arbutin alone) (Numata et al., 2016), allergic contact dermatitis in a combination therapy (containing arbutin and dipotassium glycyrrhizate) (Oiso, Tatebayashi, Hoshiyama, & Kawada, 2017) and a monotherapy (with arbutin alone) (Matsuo, Ito, Masui, & Ito, 2015), erythema, burning, and irritation (the combination of arbutin 5% + glycolic acid 10% + kojic acid 2%) (Fragoso-Covarrubias, Tirado-Sánchez, & Ponce-Olivera, 2015) have been reported due to the use of arbutin in combination therapy. According to Table 3, it is revealed that combination of arbutin with other lightening agents can be considered to be better than monotherapy.

13 | NANO-PHYTOTHERAPY—A POTENTIAL STRATEGY FOR INCREASING BIOAVAILABILITY OF ARBUTIN

As previously mentioned, high hydrophilicity and hygroscopicity properties of arbutin cause its insufficient absorption from the skin layers and, therefore, reduce the therapeutic effectiveness of arbutin in topical products (Aung et al., 2020). The review of the literature shows that attempts have been made to develop delivery systems of herbal medicines (Fathi, Lotfipour, Dizaj, Hamishehkar, & Mohammadi, 2020; Negahdari et al., 2020; Sharifi et al., 2020). Recently, nanotherapy-based herbal drugs (nano-phyto therapy) have emerged as a promising strategy to overcome the poor biopharmaceutical properties of herbal and botanical ingredients including highly soluble in water, low absorption, loss of bioavailability and efficacy, poor membrane permeability, poor physicochemical stability, extensive metabolism in the gut, very low biosolubility at acidic and physiological pH, short half-life in plasma, rapid fecal elimination, poor oral bioavailability, redox instability, etc. (Dewanjee, Chakraborty, Mukherjee, & De Feo, 2020; Murthy, Monika, Jayaprakasha, & Patil, 2018). Actually, nano-phyto therapy has been reported as a simple, eco-friendly, improved cellular uptake, rapid, controlled release, stable, enhanced dissolution rates, safe, cost-effective, excellent blood stability, and novel treatment approach for synthesis of herbal nanoformulations (Thangadurai, Sangeetha, & Prasad, 2020; Sarli & Ghasemi, 2020). In this regard, the strategy using arbutin nanoformulations (as a nano-phyto therapy agent) has been reported in various studies. In an investigation, to obtain efficient drug loading, Wen et al. designed nanoliposomes containing arbutin. They found that high encapsulation of arbutin in liposomes was dependent on the amount of lipid in liposomal formulations (Wen et al., 2006). In the study by Cho et al., it is revealed that the stability of combined formulation by liposomal arbutin and phosphatidylcholine cholesterol in o/w emulsion was effectively improved by adding poly (methacrylic acid–co-stearyl methacrylate) (Cho, Lim, Shim, Kim, & Chang, 2007). In an in vivo study, Park et al. designed arbutin–gold nanoparticle complexes. They exhibited that these nanoparticles have very stronger whitening effect than arbutin and can be used as a new therapeutic strategy for the development of novel anti-pigmenting agents (Park et al., 2019).

In another study, the whitening capacity of chitosan-sodium triphosphate-nanoparticles containing α- and β-arbutin were investigated by Ayumi et al. In this formulation, chitosan has the positive charge due to having amine functional groups and arbutin, and TPP

TABLE 3 Melasma therapies (clinical trials) using arbutin alone and in various combinations

Treatment formulation given	Patients	Duration	Results	Reference
A topical serum formulation containing a combination of tranexamic acid (containing tranexamic acid 3%, galactomyces ferment filtrate 4%, niacinamide 2%, and α-arbutin 4%)	30	4 weeks	Serum combination can be considered as a safe and effective option to increase skin brightness with no significant side effect	Santoso et al. (2018)
2% arbutin	54	8 weeks	The arbutin mask scored better than the control in patient satisfaction and investigator assessment	Han et al. (2011)
A novel cream formulation containing nicotinamide 4%, arbutin 3%, bisabolol 1%, and retinaldehyde 0.05% for treatment of epidermal melasma	33	60 days	This formulation has proven to be an effective, safe, and tolerable treatment option for patients with epidermal melasma	Crocco, Veasey, Boin, Lellis, and Alves (2015)
7% arbutin in conjunction with laser therapy	35	24 weeks	Combination therapy with the MedLite C6 and 7% α-arbutin solution is an effective and well-tolerated treatment for refractory melasma	Polnikorn (2010)
1% arbutin	10	6 months	Melanin level was significantly decreased	Ertam et al. (2008)
Arbutin (5%) + glycolic acid (10%) + Kojic acid (2%) cream	33	3 months	The triple combination was equally effective than hydroquinone, although with more frequent occurrence of side effects. Side effects were erythema, burning, and irritation in both groups, mainly in A group	Fragoso-Covarrubias et al. (2015)

TABLE 4 List of arbutin patents for cosmetic applications

Patent/application number	Title of the patent	Inventors	Current assignee	Number of claims	References
US9883998B2	Methods for lightening skin using arbutin compositions	Judy Hattendorf, Steve Carlson	Obagi cosmeceuticals LLC	15	Hattendorf and Carlson (2018)
US7056742B2	High level production of arbutin in green plants	Knut Meyer, Paul V. Viitanen, Dennis Flint	University of North Texas	12	Meyer, Viitanen, and Flint (2006)
US7431949B2	Topical cosmetic compositions containing α-arbutin	Arnold Neis, Robert Neis, Jerry Whittemore	Browne E T drug co Inc	16	Neis, Neis, and Whittemore (2008)
US6306376B1	Use of arbutin monoesters as depigmenting agents	Michel Philippe	LOreal SA	14	Philippe (2001)
US20090069253A1	Whitening cosmetic composition containing arbutin nanoparticles	Teruyuki NANBU	ASKA Corp co ltd	2	Nanbu (2009)
US20060188559A1	Topical cosmetic compositions comprising α-arbutin	Arnold Neis, Robert Neis, Jerry Whittemore	Browne E T drug co Inc	4	Neis, Neis, and Whittemore (2006)
US7217810B2	High level production of arbutin in green plants and microbes	Meyer Knut, Dennis Flint, Paul V. Vitanen	University of North Texas	3	Knut, Flint, and Vitanen (2007)
US20040042984A1	Skin whitening composition containing arbutin and glucosidase as active ingredients	Deok Park, dong Il Jang, Kuk Hyun Kim	COTDE Inc	12	Park, Jang, and Kim (2004)
US3201385A	Synthesis of arbutin	Arthur D Jarrett	Polaroid Corp	1	Jarrett (1965)
US6388103B2	Preparation method of arbutin intermediates	Yeon Soo Lee, bum Tae Kim, Yong Ki Min, no Kyun Park, Ki ho Kim, Jae Seob Lee, see Wha Jeoung, Ki Soo Kim	Korea research institute of chemical technology KRICT, Biolano co ltd SK, Bioland co ltd	8	Lee et al. (2002)
US20010053350A1	Cosmetic composition comprising *N*-ethyloxycarbonyl-4-amino-phenol and arbutin or its derivatives and/or ellagic acid or its derivatives	Veronique Chevalier, dang-Man Pham	LOreal SA	27	Chevalier and Pham (2001)

has negative charge. These polymeric nanoparticles were prepared via ionic cross-linking of chitosan and sodium triphosphate. The findings of this study showed that the positively charged nanoparticles are able to improve the delivery of arbutin through skin compared to the negatively charged nanoparticles because the skin has a negative charge in neutral pH (Ayumi et al., 2019). In another study, Huang et al. designed a co-delivery system using hydrocolloid gelatin networks of arbutin (as hydrophilic ingredient) and coumaric acid (as hydrophobic ingredient). They indicated that this multiphase nanoemulsion (w/o/w) can be used to improve stability and bioaccessibility of important phenolic compounds such as arbutin and coumaric acid (Huang, Belwal, Liu, Duan, & Luo, 2019). According to these results, it can be concluded that nano-phyto therapy as a modern therapeutic approach has open promising pharmaceutical perspectives in better and safer health care. Also, a list of arbutin patents for cosmetic applications is provided in Table 4.

14 | CONCLUSION

Recently, cosmetics with natural and bioactive ingredients have attracted many interests for consumers of cosmetic products because these preparations are found safer than preparations containing synthetic components. However, high-quality trial studies in larger samples are needed to confirm safety, and clinical efficacy of

phytotherapeutic agents with high therapeutic index. The studies indicated that depigmentation agents can inhibit the melanin synthesis through various mechanisms including free radical trapping agents, inhibition of tyrosinase transcription, epidermal turnover accelerant, tyrosinase inhibition, anti-inflammatory, etc. The present review focuses on therapeutic potentials of arbutin in broad spectrum of various diseases such as hyperpigmentation disorders.

The Scientific Committee on Consumer Safety has expressed that the best range of safe and effective concentrations of α-arbutin is concentrations greater than 0.5% for body lotions and concentrations higher than 2% in facial creams. It has been shown that the alpha form has photostable property with the highest inhibitory activity against mammalian tyrosinase. But it is unstable to heat and decomposes and must be formulated at low temperatures. Several investigations demonstrate that arbutin is less toxic than hydroquinone. High hydrophilicity and hygroscopicity properties of arbutin cause arbutin insufficient absorption from the skin layers and, therefore, reduce the therapeutic effectiveness of arbutin in topical products. The review of the literature shows that attempts have been made to develop delivery systems of arbutin. In this regard, expert opinions on arbutin nanoformulations have effectively increased its bioavailability and therapeutic efficacy. These studies exhibited that arbutin nanoparticles have very stronger whitening effect than arbutin and it can be used as a new therapeutic strategy for the development of novel anti-pigmenting agents. Nevertheless, it appears that more detailed studies are required for clinical and industrial applications.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interests in this study.

DATA AVAILABILITY STATEMENT

The data for this study can be requested from the corresponding author via email.

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