INTRODUCTION

Melanin is a biopolymer synthesized by the melanocyte cells in the cell organelles called melanosomes in epidermal layers of the skin [1-3]. Mature melanosomes are then transferred via intermediary dendrites into keratin, resulting in the dark-colored coating on the corneum layer of skin epidermis [4-7]. Naturally, melanin serves as a protective agent that protects DNA from damage due to UV radiation [8-10].

Melanin synthesized process is a combination of enzymatic catalysis and chemical reactions with tyrosinase [11-14] as the major enzyme. Moreover, tyrosinase can cause enzymatic browning in raw fruits, vegetables, and beverages.

This enzyme plays a critical role in changing substrates in the form of L-tyrosine into L-dihydroxyphenylalanine (L-DOPA) via hydroxylation reaction, and the change of L-DOPA becomes highly reactive and can polymerize spontaneously that at the end of the reaction it forms the melanin compounds. The formation of melanin is responsible for skin pigmentation condition that would interfere with the aesthetics of human [17-19]. Moreover, hyperpigmentation is caused by the accumulation of excess melanin production. It can cause quite serious skin problems, such as melasma, post-inflammatory melanoderma, solar lentigo, ochronosis exogenous, and dermatosis papulosa nigra [20-23]. Inhibition of the enzymatic activity of tyrosinase, both competitive and non-competitive, is widely used as a key strategy in the development of depigmentation agent, either as cosmetics or the treatment of hyperpigmentation problems [24-27].

Some of the most used tyrosinase enzyme inhibitor agents are hydroquinone [11, 28, 29], kojic acid [30-33], and arbutin [34-38]. Hydroquinone is a tyrosinase inhibitor agent that has been used for a long time and become the gold standard in the treatment of hyperpigmentation in the USA [39, 40]. However, the use of hydroquinone in cosmetic preparations has been banned by FDA, and only allowed for the use of physician prescription. The FDA requested the use of hydroquinone is not exceeded more than 1.5-2.0% in skin cosmetics product. This is due to the effect that hydroquinone can cause ochronosis exogenous and cytotoxic in the presence of reactive metabolites, such as, hydroxyl benzoquinone and p-benzoquinone [41-45].

Natural product that contains stilbenes, uses tyrosinase inhibitors as skin whitening agents [46]. Sapindus mukorossi that grows in tropical and sub-tropical regions of Asia has weak bioactivity against tyrosinase with IC\textsubscript{50} values of 17.8% and 12.3% at 10 μg/ml [47]. Curcumin-Mn and Zn has a potent as anti-tyrosinase capacity as a depigmentation agent [48] that can be studied further.

In the previous study, Celastrus paniculatus seed oil exhibited superior tyrosinase inhibition activity than the standard ascorbic acid, kojic acid and arbutin [49]. Senol et al. found natural anti-tyrosinase from the aerial parts of 33 Turkish Scutellaria species. However, the plant's activity is moderate, ranged from 39.57% to 51.58% inhibition [50]. The plants from common tropical plant species in the Indian subcontinent and Southeast Asia have been observed as a skin whitening treatment, and it has sub-nano molar activity. However, the IC\textsubscript{50} is 60 times higher than kojic acid [51]. Tyrosinase inhibitory activity also is shown by the enzymatic hydrolyses of the collagen that obtained from the skin of squid (Todarodes pacificus) [52].

Hydroquinone has very effective to inhibit melanosynthesis thus can be used as a depigmentation agent. However, metabolite results from oxidation of hydroquinone by tyrosinase cause seriously adverse effects. DNA is damaged by hydroquinone as showed in studies against rodent models [53]. Furthermore, hydroquinone is banned in European Union, US FDA, and also in Indonesia for the cosmetic active ingredient.

Some derivatives of hydroquinone has become much better than hydroquinone due to the decreasing its cytotoxicity, such as arbutin derivatives [54].

Kojic acid is an effective tyrosinase inhibitor agent both in vitro and in vivo [55-58]. However, these compounds have been banned in Japan for causing allergies and mutagenic [59]. Arbutin has been traditionally used by Japanese people to treat skin pigmentation disorders [60]. It is known to be an effective agent to address skin hyperpigmentation disorders. Its cytotoxic properties against melanocyte cells are lower than...
hydroquinone, but depigmentation activity of arbutin is still far below hydroquinone depigmenting activity [61, 62]. In 2005, Roissy and his team synthesized a tyrosinase inhibitor agent and used arbutin as the parent compound, dA (4-[Tetrahydro-2H-Pyrans-2-yl] oxy) phenol), by removing the hydroxy group on the compound of arbutin. This compound is proved to be more effective than other tyrosinase agent inhibitors and more secure [63, 64]. There are known two form of arbutin, α- and β-arbutin. The both form of arbutin is hydroxylated by oxytrosinase in ortho position of the catechol group thus to give rise to a complex formed by met-tyrosinase with hydroxylated [37]. β-arbutin is naturally compound from Ericaceae and Saxifragaceae [65]. On the other hand, α-arbutin is synthesized from hydroquinine using enzymatic or chemical synthesis [66, 67]. In many study, α- and β-arbutin has inhibit the formation melanin in B16 cell induced by α-melanocyte stimulating hormone (α-MSH) and inhibit tyrosinase activity [68, 69]. Sugimoto et al. [62] explained that the α-arbutin has an effective and safe to use skin lightening that decrease the cellular tyrosinase activity of HMV-II (Human Melanoma cell). The molecular mechanism of α-arbutin against tyrosinase activity is studied by Gilbro et al. [69]. However, arbutin has some side effect to human skin in some cases. Arbutin cause allergic dermatitis caused by arbutin from Japan patients [71, 73].

The other derivative of hydroquinone is deoxyarbutin (dA) that has more effective and safe clinically than arbutin to therapy hyperpigmentation. dA is second generation derivatives of hydroquinone [74]. dA is less cytotoxic than the others hydroquinone derivatives. This review summarized melanogenesis process and the role of tyrosinase inhibitor through the latest effective and safety compound, dA [75].

The arrangement is automatically carried out by a substrate-induced melanogenic pathway (L-tyrosine and/or L-DOP). This arrangement will also regulate the function of melanocytes by structural or regulatory protein activity and through mediating melanogenesis and melanin itself [76].

Melanogenesis
Melanin is produced in the melanocytes cells through the process of melanogenesisin enzymatic or chemical reactions. Melanogenesis occurs in specialized organelles within melanocytes cells called melanosomes [77-80]. In normal circumstances, melanin serves to protect the skin from the damaging effects of UV radiation. The accumulation of abnormal melanin will cause aesthetic effects and disrupt health [75]. One of the clinical manifestations of abnormally accumulated melanin is the incidence of melasma, i.e. hyperpigmentation on the epidermis or dermis in the facial area that affects mainly the individual light-skinned, which included skin types III-IV, according to the classification of Fitzpatrick. It is more prevalent in women than associated with hormonal factors [81]. The auto regulate automatically itself is carried out by a substrate-induced melanogenic pathway (L-tyrosine and/or L-DOP) and this arrangement will also regulate the function of melanocytes by structural or regulatory protein activity and through mediating melanogenesis and melanin itself [15].

The main targets are developed for depigmentation that inhibits the activity of tyrosinase enzyme, which is a precursor for the melanin synthesis [82]. Tyrosinase is a glycoprotein located on the membrane of melanosomes, and also dominated inside melanosomes, trans membrane, and in the cytoplasm of melanocyte cells. It is a monooxidase copper-dependent enzyme that has a role in catalyzing the conversion of monoeneic compound (L-tyrosine) into dieneolic compound (L-DOPA) through hydroxidation process, and convert dieneolic compound to quinone (benzoquinone) compound through an oxidation process [83]. The role of tyrosinase enzyme in melanin formation mechanism in the melanosomes within melanocytes cells and the processes that occur during melanogenesis itself [84].

The main substrate on melanogenesis enzymatic reaction is tyrosine. Tyrosine is hydroxylated by tyrosinase enzyme to be dopaquinone as a product of them. Dopaquinone will react with the cysteine-S to produce 5-cysteinyllopa and 2-S-cysteinyllopa in limited quantities. Cysteinyllopa is oxidized to produce benzothiazine followed by pheomelanin, a red pigment that causes blond hair. The absence of cysteine causes additional intramolecular amino groups for dopaquinone changed to be cyclodopa (Leucodopa-chrome). This compound then undergoes auto-oxidation and turned into dopa and dopachrome. Dopa is a substrate of tyrosinase, but tyrosinase will oxidize back into dopaquinone. Next, dopachrome decomposes gradually and forms DHQ and DHICA in very small amounts. The process is catalyzed by the tyrosinase-related enzyme protein-2 (Typr2), which is now known as dopachrome tautomerase (Dct). Finally, hydroxyl indole compound is oxidized to eumelanin. Tyrosinase-related protein-1 (Typr1) catalyzes the conversion of partially enzyme DHICA into eumelanin. Eumelanin is a black brown pigment that produces skin hyperpigmentation [85].

After the formation of melanin, melanin-shrouded melanosomes will be taken by melanocytes and transferred to the keratocytes cells, namely keratinocytes that have undergone differentiation. The transfer from melanocytes to keratinocytes is made through the tentacles of melanocyte (dendrites) approaching keratinocytes in the stratum above the basal layer. In the basal stratum 1, melanocytes are surrounded by 30-40 keratocytes cells [86, 87].

Melanogenesis at a subcellular level
In subcellular level, melanogenesis encoded by the melanogenesis-related enzyme, including tyrosine, Typr1 and Typr2 that are regulated through intracellular pathways. The signal of this pathway is initiated by some kinds of hormones including interleukin, growth factor, and prostaglandin. Some hormones also respond to a complex signal for their exposure to UV radiation or other stimulation that comes from the environment outside the body. Fig. 2 shows several signaling pathways that have been known to be actively involved in the process of melanogenesis at the subcellular level. All three of the signaling pathway involving microphthalmias-associated transcription factor (MITF), which is a transcription factor with the domain structure of basic helix-loop-helix leucine zipper. In addition, its role in the proliferation and differentiation of melanocyte cell survival, MITF is also an important regulator that regulates the expression of genes for the formation of tyrosiase, Typr1, and Typr2. Up-regulation of MITF activity will activate the expression of the melanogenesis-related enzyme, which in turn will stimulate melanogenesis and vice versa, while down-regulation of MITF activity will suppress the expression of this enzyme that would inhibit melanogenesis [24, 88].

Alpha-melanocyte stimulating hormone (α-MSH) is a peptide derived from proopio melano cortine (POMC) [89], which regulates melanogenesis through cAMP pathway. α-MSH is released into the systemic circulation of the pituitary. It is related to melanocortin peptides, derived from the precursor POMC, which also expressed in numerous CNS and peripheral structures. When bound to its receptor namely melanocortine 1 receptor (MC1R) on melanocytes cell membrane, these hormones activate adenylyl cyclase (AC) to produce intracellular cAMP as the second messenger through the activation of G-protein-coupled receptors (GPRC). cAMP activates protein kinase A (PKA), which subsequently activate the MITF gene expression through phosphorylase A complex, element-binding protein (CREB). Afterwards, MITF efficiently activates the melanogenesis-related enzyme and stimulates melanogenesis. Once α-MSH is bound to the MC1R, the increase of melanogenesis will increase by more than 100 times. Likewise with other POMC peptides are β-MSH and adrenocorticotropine hormone (ACTH), will stimulate melanogenesis via the same pathways [90]. Other signaling pathways that also activate MITF gene expression are the Wnt signaling pathway. The main key to this pathway is namely intracellular level of β-catenin. When the Wnt signal is absent, β-catenin is phosphorylated by glycogen synthase kinase-3β (GSK-3β). This phosphorylation recognized by the ubiquitin ligase complex, will degrade β-catenin [91]. Conversely, the signal Wnt-activated would regulate GSK-3β, causing the accumulation of β-catenin cytoplasmic translocate to the nucleus and forms a complex with the T-cell factor (TCF) and lymphocyte enhancer factor-1 (LEF), to download the up-regulation of gene expression MITF which in turn activates melanogenesis reaction via the same pathways [92]
In the opposite of the aforementioned path, the path of an extracellular signal-regulated kinase (ERK) regulates melanogenesis through MITF protein degradation. ERK activates the phosphorylation of MITF through serine 73, followed by MITF ubiquination and proteasome-mediated degradation. As the result, the ERK pathway activation will inhibit melanogenesis, associated with down-regulation of MITF activity [34, 93].

The internal and external factors of melanogenesis

Melanocytes produce POMC peptides, cytokines, NO, prostaglandins, and leukotrienes that are activated through autocrine or paracrine pathway, associated with the production of adenylcyclase and cAMP as shown fig. 1. Those receptors are within the immune response and inflammatory response, which are also involved in the process of pigmentation of the skin [20]. This creates some incidences of melanoderma post-inflammatory, hyperpigmentation after an injury to the skin, and hyperpigmentation post-infection as in the case of chikungunya; as for other receptors in the melanocyte cells that are tied to the production of adenylylase and cAMP as muscarinic receptor and estrogen receptor α and β. Therefore, increased production of estrogen during pregnancy can cause hyperpigmentation such as melasma, hyperpigmentation areolar, and line nigricans [20].

Many extrinsic factors can trigger the occurrence of hyperpigmentation, such as the use of several kinds of drugs, chemicals, and even substances that are commonly used for the treatment of anti-aging and melisma, for example, hydroquinone which causes oncronosis exogenous—the formation of the blue to black pigment on skin tissue [34]. UV radiation is the main cause of skin hyperpigmentation. Rapid pigmentation can occur 5-10 min after exposure to UVR and disappear after a few minutes or days later. It usually occurs because of UVA radiation or delayed pigmentation in 3-4 d after exposure to UVR, and disappear after a few weeks due to UVA and UVB radiation [20].

UV radiation induces DNA damage which will be activated by p53 (tumor protein suppressor). p53 stimulates the POMC gene undergone the post-translational, such as ACTH, α-MSH, and β-endorphin. The POMC peptide binds to MC1R on melanocytes, which further regulates melanogenesis through cAMP pathway [94]. Melanin is produced and transferred back to the keratinocytes. It has been mentioned that one POMC peptides bound to the MC1R, it lead a hundred times of melanogenesis incidence [34] that cause hyperpigmentation due to exposure of UV radiation.

Deoxyarbutin synthesis

dA compound (4-[Tetrahydro-2H-Pyran-2-yl] oxy) phenol) designed by Boissy and his team for the first time in 2005, used quantitative structure-activity relationships (QSAR). This method is used as an approach to understanding the structural characteristics of the compounds. Although many techniques can be used in QSAR methods, but a basic understanding of this method is to convert the structure of a molecule or a part of the molecular structure to become a value numerically. In consequence, the value will be correlated with traits desired in an unknown compound [64].

The properties are optimized in this design. It is the competitive inhibition [at the binding site] of mushroom tyrosinase enzyme, inhibitor resistance to oxidation by the enzyme tyrosinase (thus can be an alternative substrate) and the molecule’s ability to penetrate the skin. dA compounds are synthesized by eliminating the hydroxyl groups of the side chains of glucose group from arbutin as the parent compound as shown in fig. 2 [64]. The facile and highly efficient preparation of deoxyarbutin is recommended using a one-step catalyst-free continuous-flow etherification protocol. The one-step direct etherification obtains dA from hydroquinone through a continuous-flow, catalyst-free process [95].
The activity, efficacy and safety of deoxyarbutin
dA is safer and less cytotoxic compared with hydroquinone [96]. Based on in vitro experiments against mushroom tyrosinase, it turns out that dA effectively inhibits mushroom tyrosinase with Ki 10 times lower than hydroquinone and 350 times lower than arbutin. The inhibition coefficient of dA, hydroquinone, kojic acid, and arbutinin µM is 0.05, 0.54, 7.70, 17.60, respectively. In another study, dA is still stronger than hydroquinone that becomes the gold standard for melasma treatment. IC50 of dA (17.5±0.5 µmol/l) is lower than hydroquinone (73.7±9.1 µmol/l) when using mushroom tyrosinase assay and an inhibition coefficient of dA and hydroquinone at Ki 21.6±1.0 µmol/l and 83.1±5.9, respectively [97]. dA also could fight against tumour in vitrod and in vivo. dA inhibits the proliferation and metastasis of tumour via a p38-mediated mitochondria [98].

Furthermore, dA in hairless guinea pigs shows skin lightening activity immediately and extended, where this activity is reversible after 8 w of discontinuation of topical application of dA. In contrast to the same study, hydroquinone skin-lightening activity has shorter onset but not extended, whereas kojic acid and arbutin show in significant skin lightening effect during the test [97]. Hydroquinone has some side effects with long-term application, such as melanocyte destruction, ochronosis and contact dermatitis [35].

In clinical trials conducted human subjects, topical application of dA in 12 w resulted in significant skin lightening on the subject who has light skin and improvements in solar lenities experienced in the dark-skinned population [64].

Other clinical trials conducted on the subject of 25 men and women ranged from 18-60 y old, for 5 w experiment, with the type of post-exposure test (subjects were given prior to UV exposure for 7 d (tanning process) with a dosage test). The result showed that the percentages of the final tanning in control subjects (who were not given dosage), the subjects who had hydroquinone therapy and the subjects with dA treated are 44.6%, 51.6% and 37.3% respectively [63].

dA is a reversible inhibitor of the tyrosinase enzyme. It shows that the dA does not permanently damage the melanocytes. In further

In an attempt to increase the stability of dA in preparations, some studies have observed dA stability in the system anhydrous emulsion formula with a base polyol-in silicone. The quantity of dA and the accumulation of hydroquinone as dA degradation products in aqueous solution are measured using HPLC [104]. The developed HPLC analytical method meets the validation criteria made by ICH. Muchtaridi et al. perform the analysis of dA using column C-18, UV detector 225 nm, methanol: water (60:40 v/v) as the mobile phase with isocratic elution; the flow rate is at 1 ml/min and the running time is 8 min.

The research demonstrates that the anhydrous emulsion systems with a polyol-in silicone as a base (oil based), improve the stability dA in preparations and lead to delays degradation of deoxyarbutin becoming hydroquinone at temperatures of 25 °C and 45 °C [102].

As well as being thermolabile, arbutin and dA in aqueous solution are photolabile and create degradation products, such as hydroquinone. The concentration of hydroquinone increases during UV radiation in an aqueous solution containing arbutin and dA [101]. The release of the o-diphenol product forming deoxyarbutin is predicted be slower than in the case of β-arbutin using molecular modeling methods [105]. It contributes to its oxidation to a quinone before released from the protein into the water phase.

In an effort to increase the stability of arbutin and dA against UVR exposure, Yang and his team (2013) in their study, added Benzoophenone-4 in dA aqueous solutions and arbutin aqueous solutions. The treatment proved that it can increase the stability of the two substances against UV radiation exposure although not significant [101]. dA is insoluble in water, but it easily degrades in aqueous conditions. Tofani et al. (2016) formulates nanomaterials to improve topical delivery of dA to inhibit tyrosinase during melanogenesis [106].

CONCLUSION
The prospective of dA agent as a depigmentation agent has a good efficacity, safety and stability. dA is tyrosinase inhibitor with good efficacity and relatively safe. It has higher potential as depigmentation agent than hydroquinone, which has been the gold standard of treatment of hyperpigmentation in the last decade. It has been demonstrated both in vitro and in vivo that the inhibition constants of dA and that IC50 are lower than hydroquinone. In terms of security, dA is safer than hydroquinone, which has low potential to be

Fig. 3: The dA degradation mechanisms in an aqueous solution becomes hydroquinone (colorless) and benzoquinone (brown)
cytotoxic. In addition, based on other toxicity tests, dA is known to be more secure. However, dA is the removable and photo labile. Several attempts have been made to improve the stability, such as making anhydrous emulsion formulations and adding sunscreen agents into the formula preparations. The development strategy and more advanced formulations of dA is required to improve the stability Therefore, not only preparations with dA have good potential and security but also good quality and stability during in storage, due to the effectiveness and safety of an active compound that cannot be achieved in unstable or degraded preparation in storage condition.

CONTRIBUTION
Muchtaridi Muchtaridi give the main idea of this article and also write the substances of this paper. Mentari Luthfika Dewi drafted of Muchtaridi Muchtaridi give the main idea of this article and also write the substances of this paper. Mentari Luthfika Dewi drafted of

ABBREVIATION

dA: deoxyarbutin, Ki: Inhibition constant, UV: Ultra violet

FUNDING
Nil

AUTHORS CONTRIBUTIONS
All the authors have contributed equally.

CONFLICT OF INTERESTS
Conflict of interest declared none.

REFERENCES
1. Ali SA, Nazir I. Biochemical aspects of mammalian melanocytes and the emerging role of melanocyte stem cells in dermatological therapies. Int J Health Sci 2018;12:69-76.
2. Mahantsy S, Kawai AA, Dakappa SS, Mahendradas P, Kurian M, Kharbanda V, et al. Aqueous humor tyrosinase activity is indicative of iris melanocyte toxicity. Exp Eye Res 2017;162:79-85.
3. Zhang Y, Heike KL, Coelho SG, Valencia JC, Hearing VJ, Sun S, et al. Essential role of the molecular chaperone gp96 in regulating melanogenesis. Pigment Cell Melanoma Res 2014;27:82-9.
4. Ando H, Niki Y, Ito M, Akiyama K, Matsui MS, Yarosh DB, et al. Melanosomes are transferred from melanocytes to keratinocytes through the processes of packaging, release, uptake, and dispersion. J Invest Dermatol 2012;132:1222-9.
5. Chekerik E, Wachulda M, Stasiewicz A, Tymińska A. Skin melanocytes: biology and development. Postepy Dermatologii I Alergologii 2017;30:30-41.
6. Serre C, Busuttil V, Botto JM. Intrinsic and extrinsic regulation of human skin melanogenesis and pigmentation. Int J Cosmet Sci 2018;40:328-47.
7. Scott G. Demonstration of melanosomes transfer by a shedding microvesicle mechanism. J Invest Dermatol 2012;132:1073-4.
8. Coelho SG, Yin L, Smuda C, Mahns A, Kolbe I, Hearing VJ. Photobiological implications of melanin photoprotection after UVB-induced tanning of human skin but not UVA-induced tanning. Pigment Cell Melanoma Res 2015;28:210-6.
9. D’Orazio J, Jarrett S, Amaro Ortiz A, Scott T. UV radiation and the skin. Int J Mol Sci 2013;14:12222-48.
10. Abdassah M, Aryani R, Surachman E, Muchtaridi M. In vitro assessment of effectiveness and photostability avobenzone in cream formulations by combination ethyl ascorbic acid and alpha tocopherol acetate.] J Appl Pharm Sci 2015;5:70-4.
11. Pillayyar T, Manickam M, Namasivayam V. Skin whitening agents: medicinal chemistry perspective of tyrosinase inhibitors.] Enzyme Inhib Med Chem 2017;3:430-43.
12. Zaidi KU, Ali AS, Ali SA, Nazir I. Microbial tyrosinases: promising enzymes for pharmaceutical, food bioprocessing, and environmental industry. Biochem Res Int 2014. p. 16. https://doi.org/10.1155/2014/854687
13. Bang E, Noh SG, Ha S, Jung HJ, Kim DH, Lee AK, et al. Evaluation of the novel synthetic tyrosinase inhibitor (2)-3-(3-bromo-4-hydroxybenzylidene) thiocroman-4-one (MHY1490) in vitro and in silico. Molecules [Basel, Switzerland] 2018;23:5307.
14. Singb BK, Park SH, Lee HB, Goo YA, Kim HS, Cho SH, et al. Kojic acid peptide: a new compound with anti-tyrosinase potential. Annals Dermatol 2016;28:555-61.
15. Slomiński A, Zmięwski MA, Pawełek J. L-tyrosine and L-dihydroxyphenylalanine as hormone-like regulators of melanocyte functions.] Pigment Cell Melanoma Res 2012;25:14-27.
16. Pajak M, Palka K, Winiwcka E, Katska M. The chemo-enzymatic synthesis of labeled l-amino acids and some of their derivatives.] J Radiat Nucl Chem 2018;317:643-66.
17. Araji S, Grammer TA, Gertzen R, Anderson SD, Mikuń Petkowsk M, Veberič R, et al. Novel roles for the polyphenol oxidase enzyme in secondary metabolism and the regulation of cell death in walnut. Plant Physiol 2014;164:1191-203.
18. Sugumaran M. Reactivities of quinone methides versus o-quinones in catecholamine metabolism and eumelanin biosynthesis.] Int J Mol Sci 2016;17:1576.
19. Klopke I, Solher Dolenc M. Chemicals and drugs forming reactive quinone and quinone imine metabolites. Chem Res Toxicol 2018;32: DOI: 10.1021/acs.chemrestox.8b00213
20. Videira IFDS, Moura DFL, Magina S. Mechanisms regulating melanogenesis. An Bras Dermatol 2013;88:76-83.
21. Vandercaustje SJ, De Ceulder J, Wittouck E. Tigecycline induced hyperpigmentation of the skin. Open Forum Infect Dis 2016;3:3-9.
22. Yamaguchi Y, Hearing VJ. Physiological factors that regulate skin pigmentation. BioFactors (Oxford, England) 2009;35:193-9.
23. Vandercaustje SJ, De Ceulder J, Wittouck E. Tigecycline induced hyperpigmentation of the skin. Open Forum Infect Dis 2016;3:dfw033-dfw033.
24. D’Mello SAN, Finlay GJ, Baguley BC, Askanian-Amir ME. Signaling pathways in melanogenesis. Int J Mol Sci 2016;17:1144.
25. Wang Y, Hao MM, Sun Y, Wang LF, Wang H, Zhang YJ, et al. Synergistic promotion on tyrosinase inhibition by antioxidants. Molecules [Basel, Switzerland] 2018;23:106.
26. Alam BM, Bajpai VK, Lee J, Zhao P, Byeon JH, Ra JS, et al. Inhibition of melanogenesis by jineol from scopolendra subspecies mutlans via MAP-Kinase mediated MITF downregulation and the proteasomal degradation of tyrosinase.] Sci Reports 2017;7:45880.
27. Cho BR, Jun HJ, Thach TT, Wu C, Lee SJ. Betaine reduces cellular melanin content via suppression of microphthalmia-associated transcription factor in B16-F1 murine melanocytes. Food Sci Biotechnol 2017;26:1391-7.
28. Chen WC, Tseng TS, Hsiao NW, Lin VL, Wen ZH, Tsai CC, et al. Inhibition of melanogenesis by jineol from scopolendra subspecies mutlans via MAP-Kinase mediated MITF downregulation and the proteasomal degradation of tyrosinase.] Sci Reports 2017;7:45880.
29. Strait TS. Natural melanogenesis inhibitors are acting through the down-regulation of tyrosinase activity. J Invest Dermatol 2014;134:1391-4.
30. Lee YS, Park JH, Kim MH, Seo SH, Kim HJ. Synthesis of tyrosine inhibitory kojic acid derivative. Arch Pharm [Weinheim] 2006;339:11-4.
31. Saeedi M, Eslamifar M, Khezri K. Kojic acid applications in cosmetic and pharmaceutical preparations. Biomed Pharmacother 2019;110:582-93.
32. Laijs ABF, Hamid M, Arif A.B. Depigmenting effect of Kojic acid esters in hyperpigmented B16/F1 melanoma cells.] J Biomed Biotechnol 2012. Doi:10.1155/2012/952452
33. Burnett CL, Bergfeld WF, Beliso DV, Hill RA, Klaassen CD, Liebler DG, et al. Final report of the safety assessment of kojic acid as used in cosmetics. Int J Toxicol 2010;29:2445-2738.
34. Chang TS. Natural melanogenesis inhibitors are acting through the down-regulation of tyrosinase activity. Materials 2012;5:1661-85.
35. Ghawla S, deLong MA, Visscher MO, Wickett RR, Manga P, Boissy RE. Mechanism of tyrosinase inhibition by deoxy arbutin and its second-generation derivatives. Br J Dermatol 2008;159:1267-74.
36. Tada M, Kohn M, Niwano Y. Alleviation effect of arbutin on oxidative stress generated through tyrosinase reaction with L-tyrosine and L-DOPA. BMC Biochem 2014;15:523-5.
37. Garcia Jimenez A, Teruel Puche JA, Berna J, Rodriguez Lopez JN, Tudela J, Garcia Canovas F. Action of tyrosinase on alpha and beta-arbutin: a kinetic study. PLoS One 2017;12:e0177330-e0177340.
38. Lee SY, Baek N, Nam TG. Natural, semisynthetic and synthetic tyrosinase inhibitors. J Enzyme Inhibition Med Chem 2016;31:1-13.
39. Ni-Komatsu L, Tong C, Chen G, Brindzei N, Orlow SJ. Identification of quinolines that inhibit melanogenesis by altering tyrosinase family trafficking. Mol Pharmacol 2010;74:557-60.
40. Palumbo A, d’Ischia M, Misuraca G, Prota G. Mechanism of inhibition of melanogenesis by hydroquinone. Biochim Biophys Acta 1991;1073:85-90.

41. Al-Saleh I, Elkhatib R, Al-Rouqi R, Al-Enazi S, Shiwari N. The dangers of skin-lightening creams. Toxicol Environ Chem 2012;94:219-23.
42. Westerhof W, Kooyers TJ. Hydroquinone and its analogues in dermatology-a potential health risk. J Cosmet Dermatol 2005;4:455-9.
43. Hutt AM, Kaf F. Inhibition of human DNA topoisomerase II by hydroquinone and p-benzoquinone, reactive metabolites of benzene. Environ Health Perspect 1996;104 Suppl 6:1265-9.
44. DeCaprio AP. The toxicology of hydroquinone—relevance to dermatology—a potential health risk. J Cosmet Dermatol 2007;29:283-330.
45. Al-Saleh I, Elkhatib R, Al-Rouqi R, Al-Enazi S, Shiwari N. The occupational and environmental exposure. Crit Rev Toxicol 2012;42:270-7.
46. Loizzo MR, Tundis R, Menichini F. Natural and synthetic tyrosinase inhibitors as antibrowning agents: an update. Compr Rev Food Sci Food Saf 2010;9:129-77.
47. Nisakorn S, Anongnuch T, Ampa J, Krisada K. Antityrosinase and antimicrobial activities of curcumin-metal complexes. Int J Biol Macromol 2010;47:57-64.
48. Sapindus mukorossi extracts. J Taiwan Institute Chem Eng 2017;77:51-5.
49. Eastwood K, Kaldor J, Lack I, et al. Anti-tyrosinase and antimicrobial properties of Curcuma Longa L. extract. J Ethnopharmacol 2010;129:145-9.
50. Noh JM, Kwak SY, Kim DH, Lee YS. Kojic acid-tripeptide amide as a new tyrosinase inhibitor. Biopolymers 2007;88:300-7.
51. Saruno R, Kato F, Ikemo T. Kojic Acid, a tyrosinase inhibitor from aspergillus albus. Agric Biol Chem 1979;43:1337-8.
52. Hashemi SM, Emami S. Kojic acid-derived tyrosinase inhibitors: synthesis and bioactivity. Pharm Biomed Res 2015;5:1-17.
53. Azami F, Tazikheh Lemeski E, Mahmoud Janlou MA. Kojic acid effect on the inhibitory potency of tyrosinase. J Chem Health Risks 2017;7:7. doi:10.22034/JCHR.2017.544176
54. Nakagawa M, Kawai K, Kawai K. Contact allergy to kojic acid in skin care products. Contact Dermatitis 1995;32:9-13.
55. Ando H, Matsu MS, Ichihashi M. Quinacridone pigments: a case report of hyperpigmentation caused by arbutin. Case Rep Dermatol 2015;7:65-7.
56. Mann T, Gerwat W, Batzer J, Eggers K, Schernher C, Wenck H, et al. Inhibition of human tyrosinase requires molecular motifs distinctively different from mushroom tyrosinase. J Invest Dermatol 2010;138:1601-8.
57. Sugimoto K, Nishimura T, Nomura K, Sugimoto K, Kuriki T. Inhibitory effects of alpha-arbutin on melanin synthesis in cultured human melanoma cells and a three-dimensional human skin model. Exp Dermatol 2009;18:457-63.
58. Hamed SH, Sriwiriyapanot P, DeLong MA, Vischer MO, Wickett RR, Boissy RE. Comparative efficacy and safety of deoxyarbutin, a new tyrosinase-inhibiting agent. J Cosmet Sci 2006;57:291-308.
59. Boissy RE, Vischer M, DeLong MA. DeoxyArbutin: a novel reversible tyrosinase inhibitor with effective in vivo skin lightening potency. Exp Dermatol 2005;14:601-8.
60. Chandrashekar B, Chaitim S, Lakshmi NN. Effectiveness and safety of a novel topical depigmenting agent in epidermal pigmentation: an open-label, non-comparative study. Int J Res Dermatol 2018;4:1-9.
61. Liu CQ, Deng L, Zhang P, Zhang SR, Liu L, Xu T, et al. Screening of high alpha-arbutin producing strains and production of alpha-arbutin by fermentation. World J Microbiol Biotechnol 2013;29:1391-8.
62. Seo DH, Jung JH, Lee JE, Jeon EJ, Kim W, Park CS. Biotechnological production of arbutins (alpha-and beta-arbutins), skin-lightening agents, and their derivatives. Appl Microbiol Biotechnol 2012;95:417-25.
63. Lim YJ, Lee EH, Kang TH, Ha SK, Oh MS, Kim SM, et al. Inhibitory effects of arbutin on melanin biosynthesis of alpha-melanocyte stimulating hormone-induced hyperpigmentation in cultured brownish guinea pig skin tissues. Arch Pharm Res 2009;32:367-73.
64. Gilbro JM, Olsson MJ. The melanogenesis and mechanisms of skin-lightening agents—existing and new approaches. Int J Cosmet Sci 2011;33:210-21.
65. Numata T, Tobita R, Tsukahara R, Okubo Y. Contact dermatitis caused by arbutin and dipotassium glycyrrhizinate in skin-lightening products. Contact Dermatitis 2017;75:71-3.
66. Matsuoka Y, Ito A, Masuy I, Ito M. A case of allergic contact dermatitis caused by arbutin. Contact Dermatitis 2015;72:404-5.
67. Matsuoka Y, Ito A, Masuy I, Ito M. A case of allergic contact dermatitis caused by arbutin. Contact Dermatitis 2015;72:404-5.
68. Martin C, Portet C, Bantz P, Brun JP, Ruperti A, Mallet MN, et al. Pharmacokinetics and tissue penetration of single-dose netilmicin used for antibiotic prophylaxis during colo-rectal surgery. Pathol Biol (Paris) 1991;39:507-10.
69. Yang CH, Chang NF, Chen YS, Lee SM, Lin PJ, Lin GC. Comparative study on the photostability of arbutin and deoxyarbutin: sensitivity to ultraviolet radiation and enhanced photostability by the water-soluble sunscreen, benzophenone-4. Biosci Biotechnol Biochem 2013;77:127-30.
70. Sauriarai R, Azizah N, Bashah K. Tyrosinase inhibition, 2,2'-diphenyl-1-picrylhydrazyl radical scavenging activity, and phytochemical screening of fractions and ethanol extract from leaves and stem bark of matoa (Pomertia pinnata). Asian J Pharm Clin Res 2017;10:85-9.
71. Hirobe T. Keratinocytes regulate the function of melanocytes. Dermato Sinica 2014;32:200-4.
72. Nishimura EK. Melanocyte stem cells: a melanocyte reservoir in hair follicles for hair and skin pigmentation. Pigment Cell Melanoma Res 2011;24:401-10.
73. Tachibana M. Sound needs sound melanocytes to be heard. Pigment Cell Res 2014;27:32-44.
74. Steel KP, Barkway C. Another role for melanocytes: their importance for normal stria vascularis development in the mammalian inner ear. Development 1989;107:453-63.
75. Vashi NA, Kundu RV. Facial hyperpigmentation: causes and treatment. Br J Dermatol 2013;169 Suppl 3:41-56.
76. Bae Harboe YS, Park HY. Tyrosinase: a central regulatory protein for cutaneous pigmentation. J Investigative Dermatol 2012;132:2678-80.
83. Uchida R, Ishikawa S, Tomoda H. Inhibition of tyrosinase activity and melanine pigmentation by 2-hydroxytyrosol. Acta Pharm Sinica B 2014;4:141-5.

84. Ito S. A chemist’s view of melanogenesis. Pigment Cell Res 2003;16:230-6.

85. Kobayashi T, Urabe K, Winder A, Jimenez Cervantes C, Imokawa G, Brevignon T, et al. Tyrosinase related protein 1 (TRP1) functions as a DHICA oxidase in melanin biosynthesis. EMBO J 1994;13:5818-25.

86. Chen H, Weng QY, Fisher DE. UV signaling pathways within the skin. J Invest Dermatol 2014;134:2080-5.

87. Li PH, Liu LH, Chang CC, Gao R, Leung CH, Ma DL, et al. Silencing stem cell factor gene in fibroblasts to regulate paracrine factor productions and enhance c-kit expression in melanocytes on melanogenesis. Int J Mol Sci 2018;19:1475.

88. Hsiao JJ, Fisher DE. The roles of microphthalmia-associated transcription factor and pigmentation in melanoma. Arch Biochem Biophys Suppl 2012;563:28-34.

89. Monga SPS. Role and regulation of β-catenin signalling during physiological liver growth. Gene Expression 2014;16:51-62.

90. Huang HC, Chang SJ, Wu CY, Ke HJ, Chang TM. [6]-Shogaol inhibits α-MSH-induced melanogenesis through the acceleration of ERK and PI3K/Akt-mediated MITF degradation. BioMed Res Int 2014. Doi:10.1155/2014/842569.

91. Muchtaridi M, Ida M, Ahmad F. Method development and validation for analysis of deoxyarbutin in anhydrous emulsion system using high-performance liquid chromatography. Int J Mol Sci 2010;11:3977-87.

92. Garcia Jimenez A, Teruel Puche JA, Garcia Ruiz PA, Saura Sammartin A, Bena J, Garcia Canovas F, et al. Structural and kinetic considerations on the catalysis of deoxyarbutin by tyrosinase. PloS One 2017;12:e0187845-e0187845.

93. Muchtaridi M, Ida M, Ahmad F. Mobile phase development and validation of analysis of deoxyarbutin in anhydrous emulsion system using high-performance liquid chromatography. Int J Appl Pharm 2019;11:172-5.

94. Garcia Jimenez A, Teruel Puche JA, Garcia Ruiz PA, Saura Sammartin A, Bena J, Garcia Canovas F, et al. Structural and kinetic considerations on the catalysis of deoxyarbutin by tyrosinase. PloS One 2017;12:e0187845-e0187845.

95. Muchtaridi M, Ida M, Ahmad F. Mobile phase development and validation of analysis of deoxyarbutin in anhydrous emulsion system using high-performance liquid chromatography. Int J Appl Pharm 2019;11:172-5.