Published by
NIGERIAN SOCIETY OF PHYSICAL SCIENCES
Available online @ https://asr.nsps.org.ng/index.php/asr

African Scientific Reports 2 (2023) 95

African Scientific Reports

Natural Skin Whitening Compounds: Types, Source and Mechanism of Action: A Review

Chiagoziem Wisdom Chidiebere[a,*], Ugochukwu Aniefuna Azuka Anthonia[b]

[a]*Surface Chemistry and Environmental Technology(SCENT) Research Unit , Department of Chemistry, Imo State University, Owerri, Imo State , Nigeria*
[b]*Department of Pure and Industrial Chemistry, Nnamdi Azikiwe University Awka, Nigeria*

Abstract

Skin whitening, also known as skin lightening or skin bleaching, is utilizing chemical compounds to lighten or even out the skin's colour by lowering the skin's melanin concentration. The biosynthetic process of melanogenesis and the related main regulatory signaling pathways are summarized in this paper. It also addresses the efficacy of natural skin-whitening treatments based on their mode of action on melanogenesis and their compound classification. The review's goal is to provide useful information and create awareness on the effects of bleaching cream.

DOI:10.46481/asr.2023.2.1.95

Keywords: Skin whitening, Bleaching, Melanin, Melanogenesis

Article History :
Received: 19 February 2023
Received in revised form: 24 March 2023
Accepted for publication: 25 March 2023
Published: 29 April 2023

Communicated by: Tolulope Latunde

1. Introduction

Empirical research regularly shows that individuals in less developed nations view light or "white" complexion as more desirable or superior, particularly among women [1]. Skin whitening, also known as skin lightening or skin bleaching, is the process of utilizing chemical compounds to lighten the skin's colour by lowering the skin's melanin concentration. Several compounds have been proven useful in skin whitening, whereas others are toxic or have safety concerns. Mercury compounds, for example, have been linked to neurological and kidney issues [2]. In the past several years, multinational corporations have heavily marketed the idea that lighter skin leads to more prosperity.

*Corresponding author tel. no: +234 8165827252
Email address: oraclewizzy@gmail.com (Chiagoziem Wisdom Chidiebere)

As a result, dangerous skin bleaching has become a public health crisis, according to the World Health Organization (WHO) [3]. In response, the East African Legislative Assembly (EALA) recently passed a resolution recommending a regional ban on cosmetics containing hydroquinone, a skin-bleaching agent, a ban that looks likely to pass. Several countries, including Ghana, Rwanda, South Africa, and Sudan, have also banned bleaching cosmetics recently [4].

Despite these warnings and bans, the skin-whitening industry has experienced phenomenal growth in parts of Asia and Africa in recent years. Skin lightening products are unbelievably popular in Nigeria. The World Health Organization (WHO) published a report in 2011 estimating that 77 % of Nigerian women use skin-lightening products regularly [5]. This is compared to 59 % in Togo, 35 % in South Africa, and 27 % in Senegal [5]. Bleaching products are reportedly African women's fourth most sought-after household item, alongside essentials like soap, milk, and tea [6]. In many Asian cultures, lighter skin tones have traditionally been associated with youth and beauty. Investment in skin-whitening products is expanding yearly, fueled by Asian markets, particularly those in China, India, and Japan.

Skin colour is controlled by various intrinsic and extrinsic factors, including skin types and genetic background, as well as the amount of sunshine exposure and pollution [7]. The number of melanosomes and the extent to which they are dispersed in the skin affect skin colour. Pigmentation can protect the skin from serious ultraviolet injury under certain physiological conditions. Excessive melanin production, on the other hand, can cause various aesthetic issues, including melasma, ephelides pigmentation, and post-inflammatory hyperpigmentation [8]. Traditional pharmacological drugs, such as corticosteroids, hydroquinone, and aminomercuric chloride, lighten skin tone by inhibiting or interfering with melanocyte development or melanogenesis. Prickling sensations, contact dermatitis, irritation, high toxicity, and sensitivity are all common side effects of most, if not all, drugs, as mentioned earlier. As a result, cosmetic corporations and research institutions have recently focused on developing innovative whitening treatments that selectively suppress tyrosinase (TYR) activity to diminish hyperpigmentation while avoiding cytotoxicity in normal, healthy melanocytes. As a result, the cosmetic and medical industries are paying close attention to natural skin whitening substances [9].

2. Types of natural skin whitening compounds

Tyrosinase inhibition is the most popular target for skin-lightening actions, and some of the most often used inhibitors are listed below [10].

2.1. Quinone-related Compounds

For over 40 years, hydroquinone (1, 4-dihydroxybenzene) has been the gold standard for treating hyperpigmentation. Tea, wheat, fruits, beer, and coffee contain this chemical. Hydroquinone interacts with tyrosinase by binding histidines at the enzyme's active site, causing skin pigmentation to fade. In addition, hydroquinone causes reactive oxygen species to form, and quinones cause oxidative damage to membrane lipids and proteins like tyrosinase. Hydroquinone is also hypothesized to decrease pigmentation by depleting glutathione, reducing DNA and RNA production while degrading melanosomes and causing melanocyte damage. However, hydroquinone's heyday appears to be over. This powerful skin-lightening drug can cause permanent melanocyte loss due to oxidative damage to membrane lipids, resulting in irreversible loss of inherited skin colour. Furthermore, it was discovered that this chemical is swiftly carried from the epidermis into the vascular system and is detoxified into inert compounds in the liver. Hydroquinone has been banned by the European Committee [11] because of the possibility of long-term adverse effects such as irreversible depigmentation and exogenous ochronosis.

Arbutin, a derivative of hydroquinone (hydroquinone-O-D-glucopyranoside) found in cranberries, blueberries, wheat, and pears, is another extensively used quinone for skin whitening. Arbutin is an excellent treatment for hyperpigmentation problems that is less damaging to melanocytes than hydroquinone. Arbutin, like hydroquinone, inhibits melanogenesis by binding tyrosinase competitively and reversibly without affecting tyrosinase RNA transcription. The glycoside derivative of arbutin requires the glycosidic link to be cleaved before it can impact tyrosinase, resulting in a lesser effect than its mother molecule, hydroquinone. Deoxyarbutin, a synthetically created arbutin derivative, is an effective and safer skin-lightening agent. Inhibitory effects of hydroquinone, arbutin, and deoxyarbutin on tyrosinase activity showed that all three substances had similar inhibitory effects [12]. Arbutin and hydroquinone did not influence the protein expression of tyrosinase, while deoxyarbutin affected the protein level. Deoxyarbutin also showed less cytotoxicity in melanocytes than the other two quinones. In a 12-week human clinical experiment, topical

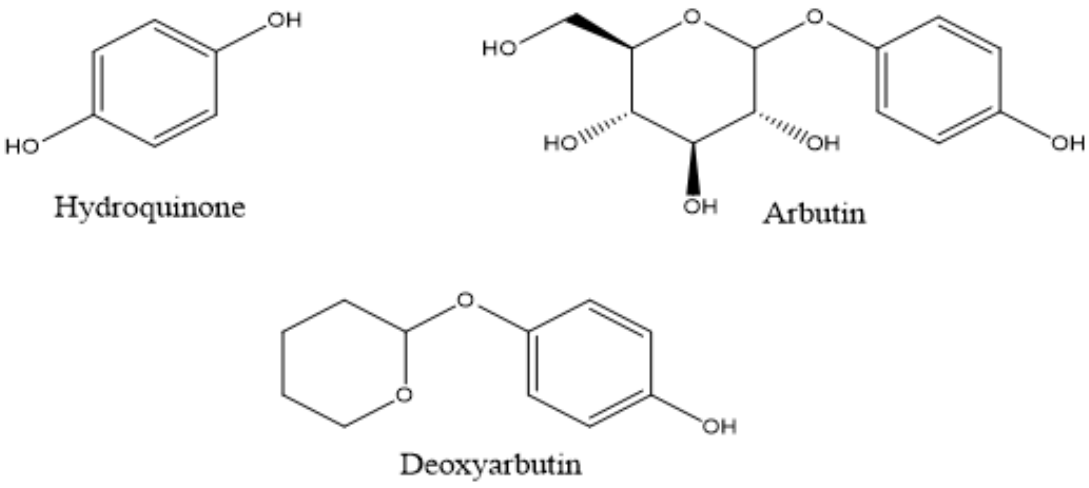

Figure 1. Structures of hydroquinone, arbutin and deoxyarbutin [12]

deoxyarbutin treatment significantly reduced overall skin lightness and improved solar lentigines in a population of light- and dark-skinned people, respectively. Structures of hydroquinone, arbutin, and deoxyarbutin would have been inserted here in Figure 1.

Intriguingly, the mechanism for in vivo modulation of quinone-mediated stress, the antioxidant systems thioredoxin/thioredoxin reductase isoenzyme I/II and tetrahydrobiopterin can electrochemically reduce quinones inside the epidermis, protecting the skin from quinones-containing topical treatments, according to the scientists [13]. However, because fair-skinned people have low thioredoxin reductase/thioredoxin activity as well as low epidermal tetrahydrobiopterin levels, it has been suggested that these people are more vulnerable to topical quinones. Hence, melanocyte toxicity may be more evident in this group.

2.2. Skin-Lightening Activities Originating from Microorganisms

Other non-quinone-related drugs that inhibit tyrosinase, such as kojic acid, are also available (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one). Acetobacter, aspergillus, and penicillium species produce kojic acid, a naturally occurring hydrophilic fungal metabolite. Kojic acid is thought to have activity by chelating copper atoms in the active site of tyrosinase and preventing dopachrome tautomerization to 5, 6-dihydroxyindole-2-carboxylic acid. Despite its popularity as a melasma therapy, kojic acid can induce contact dermatitis, hypersensitivity, and erythema [14].

The saturated dicarboxylic acid, azelaic acid (1,7-heptanedicarboxylic acid), is found naturally in wheat, rye, and barley. It is a natural chemical made by the yeast strain *Pityrosporum ovale*. Acne, rosacea, skin pigmentation, freckles, nevi, and senile lentigines are all treated with it. The chemical can bind amino and carboxyl groups and hence operates as a competitive inhibitor by preventing tyrosine from interacting with the active site of tyrosinase. Azelaic acid has been demonstrated to inhibit thioredoxin reductase in guinea pig and human skin, human keratinocytes, melanocytes, melanoma cells, and murine melanoma cells, as well as purified enzymes from *Escherichia coli*, rat liver, and human melanoma. As thioredoxin reductase, the creation of deoxyribonucleotides, and the substrate for DNA synthesis in the S-phase of the cell cycle, could explain azelaic acid's antiproliferative and cytotoxic effects [15]. Structures of Kojic and Azelaic acid is shown in Figure 2.

2.3. Flavonoid-like Agents

Flavonoids are plant polyphenols found in leaves, bark, and flowers. There are over 4000 flavonoids documented so far. They are said to have anti-inflammatory, antiviral, antioxidant, and anticarcinogenic qualities, among other things. The ability of flavonoids to chelate metals at the active site of metalloenzymes and their ability to scavenge

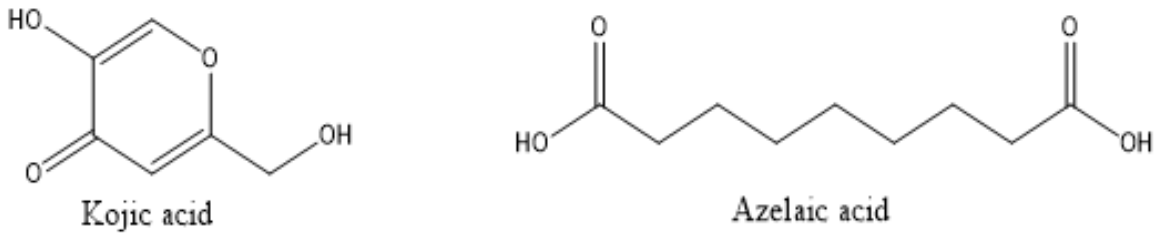

Figure 2. Structures of kojic acid and azelaic acid [15]

Figure 3. Effects of bleaching cream on human skin[17]

reactive oxygen species (ROS) may be the fundamental mechanism behind their pigment-reducing impact. Aloesin, hydroxystilbene derivates, and licorice extracts are among the flavonoids commonly employed in skin-lightening products. Aloesin not only inhibits tyrosinase competitively but also the activities of tyrosine hydroxylase (TH) and dihydroxyphenylalanine (DOPA) oxidase. The hydroxystilbene chemicals, such as resveratrol, are some of the most effective pigment-lightening flavonoid subclasses. Red wine contains resveratrol, which has been demonstrated to lower tyrosinase activity and microphthalmia-associated transcription factor (MITF) expression in B16 murine melanoma cells. Licorice, notably glabiridin, the primary constituent in the hydrophobic portion of licorice extract, is another flavonoid. In B16 murine melanoma cells, this component has been demonstrated to suppress tyrosinase activity.

There are, however, some concerns about using flavonoids in skin-lightening products because some flavonoids are known to enhance melanogenesis. The citrus flavonoid naringenin, which has been demonstrated to enhance melanogenesis and the production of melanogenic enzymes, is a notable illustration of this contradiction. Another example is quercetin, which stimulated melanogenesis in a reconstructed three-dimensional human epidermal model, with significantly enhanced melanin concentration and tyrosinase expression. Taxifolin and luteolin, two antagonistic flavonoids, have efficiently blocked tyrosinase-catalyzed oxidation of L-dihydroxyphenylalanine in cell-free extracts and living cells, lowering melanogenesis. They found a stimulatory effect on tyrosinase protein levels, even though overall pigmentation was reduced. Further research is needed to determine why flavonoids provide contradictory responses [16].

Most of these inhibiting agents have shown some side effects, which led to damaging the epidermal layer of the skin. Figure 3 describes the effect of bleaching skin.

3. Melanogenesis

Melanin is primarily produced by melanocytes, found in the epidermis, the skin's outermost layer, which also controls skin colour in humans. Melanin is made largely in melanosomes, which are specialized organelles found in

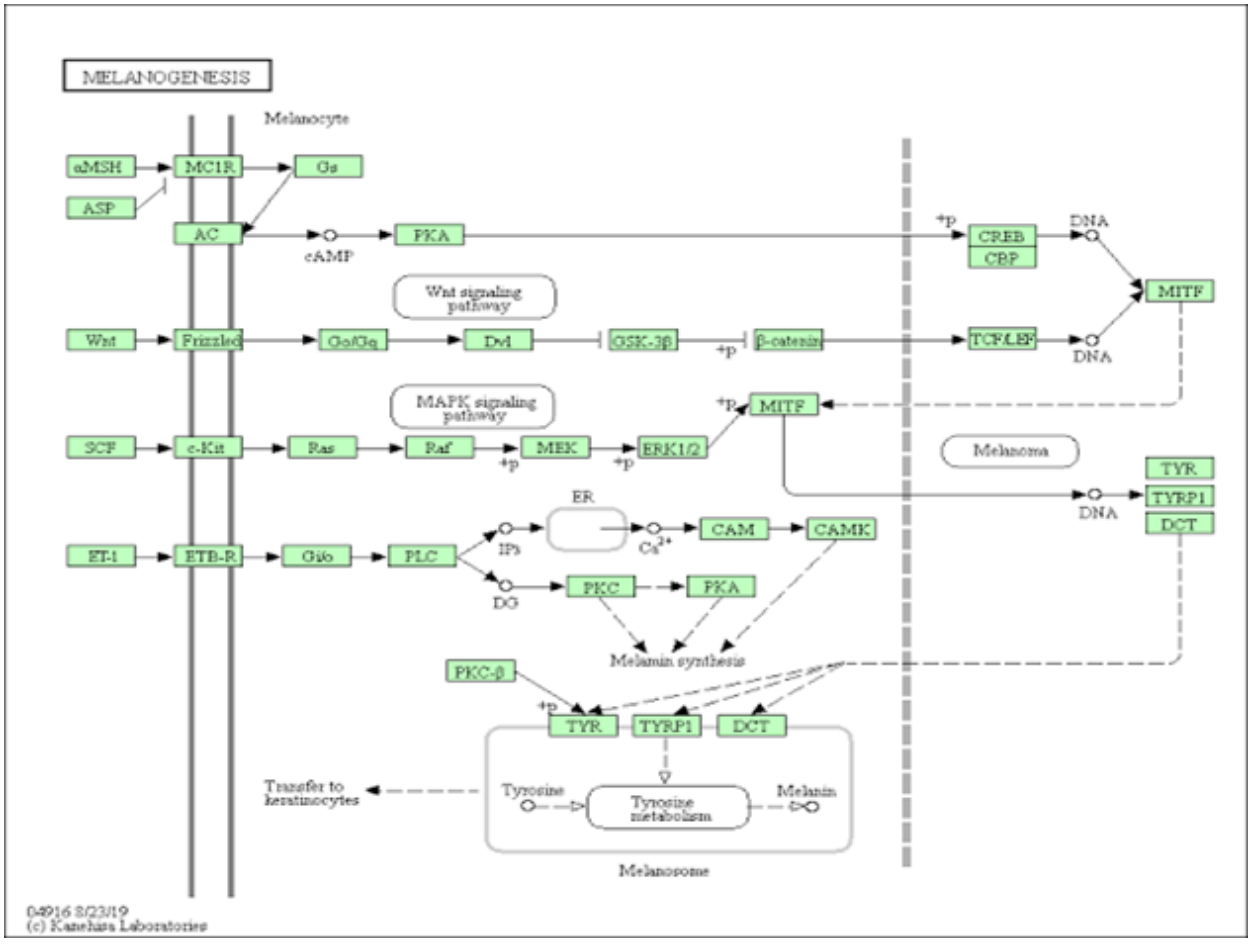

Figure 4. Chart flow of the signaling pathways associated with skin melanogenesis [20]

melanocytes. Melanogenesis is a complex process involving a series of enzymatic and chemical processes within the melanosomes that results in the creation of two types of melanin: eumelanin and pheomelanin [18]. Pheomelanin is a soluble polymer with bright red-yellow colour and contains sulphur, whereas eumelanin is an insoluble polymer with a dark brown-black colour. The conjugation of cysteine or glutathione produces eumelanin and pheomelanin. A review of the signaling pathways linked with skin melanogenesis is shown in (Figure 4) to help understand how whitening agents work. The first step in the pigmentation process is the oxidation of L-tyrosine to L-dopaquinone (DQ) in the presence of the rate-limiting enzyme TYR. The resultant quinone undergoes intramolecular cyclization and oxidation after DQ production, and it acts as a substrate for the synthesis of eumelanin and pheomelanin. The rate-limiting stage in the melanogenesis process is the hydroxylation of L-tyrosine to create L-3, 4-dihydroxyphenylalanine (L-DOPA), which is mediated by TYR [19]. Figure 4 describes the flow chart of melanogenesis.

3.1. Mechanism of Action of Tyroxinase Activities Inhibition

The presence of melanin pigment in the skin is reduced using skin whitening treatments. There are various probable methods of action to accomplish this. Tyrosinase activity is inhibited by the skin whitening agent [21], which inhibits the catalytic action of tyrosinase. The antimelanogenic agent inhibits the expression or activation of tyrosinase, causing less tyrosinase to be produced or preventing tyrosinase from being activated to its functional state, preventing the transfer of melanosomes to keratinocytes and thus directly eliminating existing melanin and melanocyte scavenges intermediate components of melanin formation.

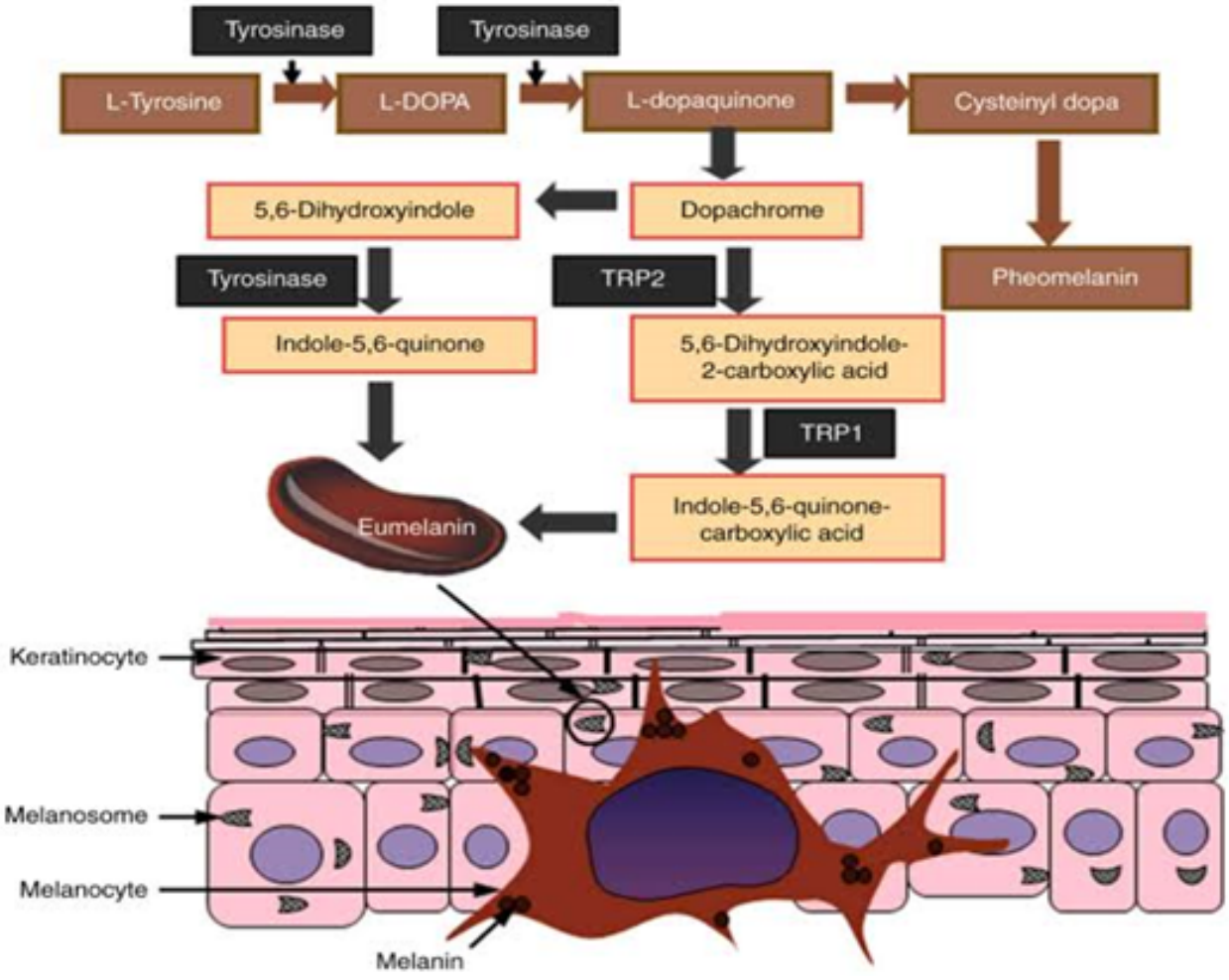

Figure 5. Inhibition process of tyroxinase [22]

3.2. Inhibition of Tyroxinase

Microphthalmia-associated transcription factor (MITF) is a master transcription factor that regulates the production of TYR, TRP1 and TRP2, MART1, PMEL17, and a slew of other melanocyte-related proteins. Down-regulation of MITF reduces melanogenesis and is one of the mechanisms by which some skin whitening treatments work. The expression of MITF is influenced by various signaling pathways and genetic alterations [22]. Several skin whitening drugs, including tyrosinase inhibitors, have been discovered to promote an increase in the expression of tyrosinase, which would boost melanin synthesis on its own. The action of quinone and tyrosinase shows that quinone tends to bind the active site of tyrosinase causing the malfunctioning activity of the tyrosinase. Figure 5 describes the Inhibition process of tyroxinase by hydroquinone which tends to bind at the active sites of tyrosinase thus forming ligand – receptor complex that functions differently from tyrosinase which tends to lead in depigmentation of the skin.

3.3. MC1R Receptor and cAMP

The melanocortin 1 receptor (MC1R) is a G-protein coupled transmembrane receptor found in melanocytes. The melanogenesis regulator MC1R is an important target. The MC1R antagonist raises the ratio of eumelanin to pheomelanin and enhances total melanin production. The MC1R and cAMP signaling pathway begins with the activation of MC1R, which causes the activation of adenylyl cyclase (AC), which produces cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA), which activates cAMP response element-binding protein (CREB)

through protein phosphorylation, which upregulates MITF, of which CREB is. Endogenous agonists of MC1R include alpha-melanocyte-stimulating hormone (α-MSH), beta-melanocyte stimulating hormone (β-MSH), and adrenocorticotropic hormone. The only endogenous antagonist of MC1R appears to be the Agouti signaling protein (ASIP). The peptides afamelanotide and melanotan II have been designed as synthetic MC1R agonists. Red hair, white skin, and an increased risk of skin cancer are all linked to MC1R gene mutations, which are at least largely responsible [23].

3.4. Transfer of Melanosomes

Melanocytes are found in the basal layer of the skin's epidermis, and dendrites from these melanocytes reach keratinocytes. When the number of keratinocytes in the epidermis is minimal, melanosomes and the melanin they contain are transferred from melanocytes to keratinocytes. Keratinocytes carry melanosomes as they progress toward the surface. Keratinocytes play a role in skin pigmentation by storing melanin produced by melanocytes and stimulating melanogenesis via chemical signals sent to melanocytes. The transfer of melanosomes to keratinocytes requires skin colour to be apparent. Some skin whitening treatments work by preventing this transfer from happening [24]. The protease-activated receptor 2 (PAR2) is a G-protein coupled transmembrane receptor expressed in keratinocytes and implicated in melanocyte transfer. PAR2 agonists limit the transfer of melanosomes and whiten the skin, whereas PAR2 antagonists have the reverse effect [25]. Some chemicals are known to damage melanocytes, and this method of action is frequently utilized to remove the remaining pigmentation in vitiligo instances [26, 27].

4. Conclusion

The quest to acquire beauty through fairness has resulted in enhancing skin colour by applying chemicals that contain bleaching agents. These bleaching agents tend to inhibit the production of melanin. This article reviewed several important lightening agents reported in literature for use in skin-lightening products. From the literature reviewed, a derivative of Arbutin – deoxyarbutin showed to be more effective and safer skin lightening agent. An extra study is needed to find alternatives to the existing bleaching agents that could not cause much damage to the skin.

References

[1] S. N. Bukhari, J. Ibrahim, U. T. Oya, S. Muhammad, M. Naeem & H. L. Qin, "Biological activity and molecular docking studies of curcumin-related α, β-unsaturated carbonyl-based synthetic compounds as anticancer agents and mushroom tyrosinase inhibitors", Journal of agricultural and food chemistry **62** (2014) 5538.

[2] Y. Sheng, X. Jing, J. L. Lu, J. H. Ye, Z. J. Chen, J. W. Zhao, Y. R. Liang & X. Q. Zheng, "Protective effects of gallocatechin gallate against ultraviolet B induced skin damages in hairless mice", Scientific Reports **12** (2022) 1.

[3] R. Mustarichi, J. Levita & D. Febriani, "In-silico study of curcumin, demethoxycurcumin, and xanthorrizol as skin whitening agents", World Journal of Pharmaceutical Sciences **1** (2013) 72.

[4] P. Manish, K. P. Mrunmaya & T. Hrudayanath, "Developing Hispolon-based novel anticancer therapeutics against human (NF-κβ) using in silico approach of modelling, docking and protein dynamics", Journal of Biomolecular Structure and Dynamics **23** (2018) 200.

[5] D. Rupsa, M. H. Tiffany, J. T. Sharick, A. A. Gillette & M. C. Skala, "Fluorescence lifetime imaging microscopy: fundamentals and advances in instrumentation, analysis, and applications", Journal of biomedical optics **25** (2020) 071.

[6] C. A. Dehelean, I. Marcovici, S. Codruta, M. Marius, D. Coricovac, S. Iurciuc, M. Octavian & L. Pinzaru, "Plant-derived anticancer compounds as new perspectives in drug discovery and alternative therapy", Molecules **26** (2021) 1109.

[7] B. S. Madhura & T. Tewin, "The protective effect of some Thai plants and their bioactive compounds in UV light-induced skin carcinogenesis", Journal of Photochemistry and Photobiology B: Biology **185** (2018) 80.

[8] L. Carmen, "Purification and biological activity of oregonin, a novel bioactive diarylheptanoid found in the leaves and bark of Alnus rubra (red alder)", University of Victoria **23** (2017) 12.

[9] J. O. Faronbi, O. O. Oyediran, M. A. Adebiyi, S. C. Adereti, G. O. Faronbi & T. T. Famakinwa," Perceived risk and consequences of bleaching practices among university students in Southwest Nigeria", *International Journal of Basic, Applied and Innovative Research* **7** (2018) 1.

[10] C. Arghya, A. R. Gulzar, A. Ali, A. B. Basharat, S. S. Sankar, N. Abhishek & A. Nanda, "Nano approach: Indian spices as antimicrobial agents", Ethno pharmacological investigation of Indian spices **205** (2020) 241.

[11] T. S. Chang, "An updated review of tyrosinase inhibitors", Int. J. Mol. Sci. **10** (2009) 2440.

[12] J. Sharifi-Rad, Y. E. Rayess, A. A. Rizk, C. Sadaka, R. Zgheib, W. Zam, S. Sestito, S. Rapposelli, K. Neffe-Skoci´nska & D. Zieli´nska, "Turmeric and its major compound curcumin on health: Bioactive effects and safety profiles for food, pharmaceutical, biotechnological and medicinal applications", Front. Pharmacol. **11** (2020) 01021.

[13] K. Jakubczyk, A. Druzga, J. Katarzyna & K. Skonieczna-Zydecka, "Antioxidant potential of curcumin–A meta-analysis of randomized clinical trials", Antioxidants **9** (2020) 1092.

[14] K. H. Lee, F. H. Aziz, A. Syahida, F. Abas, K. Shaari, D. A. Israf & N. H. Lajis, "Synthesis and biological evaluation of curcumin-like diarylpentanoid analogues for anti-inflammatory, antioxidant and anti-tyrosinase activities", Eur. J. Med. Chem. **44** (2009) 3195.
[15] M. A. Tomeh, R. Hadianamrei & X. Zhao, "A review of curcumin and its derivatives as anticancer agents", Int. J. Mol. Sci. **20** (2019) 1033.
[16] D. Zheng, C. Huang, H. Huang, Y. Zhao, M. R. U. Khan, H. Zhao & L. Huang, "Antibacterial mechanism of curcumin: A review", Chem. Biodivers. **17** (2020) e2000171.
[17] A. Adamczak, M. Ozarowski & T. M. Karpin´ ski, "Curcumin, a natural antimicrobial agent with strain-specific activity", Pharmaceuticals **13** (2020) 153.
[18] M. R. Jennings & R. J. Parks, "Curcumin as an antiviral agent", Viruses **12** (2020) 1242.
[19] S. Nistico, F. Tamburi, L. Bennardo, S. Dastoli, G. Schipani, G. Caro, M. C. Fortuna & A. Rossi, "Treatment of telogen effluvium using a dietary supplement containing Boswellia serrata, Curcuma longa, and Vitis vinifera: Results of an observational study", Dermatol. Ther. **32** (2019) e12842.
[20] L. Vollono, M. Falconi, R. Gaziano, F. Iacovelli, E. Dika, C. Terracciano, L. Bianchi & E. Campione, "Potential of curcumin in skin disorders", Nutrients **11** (2019) 2169.
[21] C. E. Duru, I. A. Duru & C. W. Chidiebere, "Virtual screening of selected natural products as humantyrosinase-related protein 1 blocker", J. Niger. Soc. Phys. Sci. **3** (2021) 154.
[22] Y. Panahi, O. Fazlolahzadeh, S. L. Atkin, M. Majeed, A. E. Butler, T. P. Johnston & A. Sahebkar, "Evidence of curcumin and curcumin analogue effects in skin diseases: A narrative review", J. Cell Physiol**. 234** (2019) 1165.
[23] Z. Y. Du, Y. F. Jiang, Z. K. Tang, R. Q. Mo, G. H. Xue, Y. J. Lu, X. Zheng, C. Z. Dong & K. Zhang, "Antioxidant and tyrosinase inhibition of polyphenolic curcumin analogs", Biosci. Biotechnol. Biochem. **75** (2011) 2351.
[24] K. S. Bhullar, A. Jha, D. Youssef & H. P. V. Rupasinghe, "Curcumin and its carbocyclic analogs: Structure-activity in relation to antioxidant and selected biological properties", Molecules **18** (2013) 5389.
[25] Y. Jiang, Z. Du, G. Xue, Q. Chen, Y. Lu, X. Zheng, A. H. Conney & K. Zhang, "Synthesis and biological evaluation of unsymmetrical curcumin analogues as tyrosinase inhibitors", Molecules **18** (2013) 3948.
[26] S. N. Bukhari, I. Jantan, O. Unsal Tan, M. Sher, M. Naeem-ul-Hassan & H. L. Qin, "Biological activity and molecular docking studies of curcumin-related-unsaturated carbonyl-based synthetic compounds as anticancer agents and mushroom tyrosinase inhibitors", J. Agric. Food Chem. **62** (2014) 5538.
[27] S. Shirota, K. Miyazaki, R. Aiyama, M. Ichioka & T. Yokokura, "Tyrosinase inhibitors from crude drugs", Biol. Pharm. Bull. **17** (1994) 266.