International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

# Depigmenting Molecules in Cosmeceuticals

**Kiran Arora**

Department of Chemistry, Kirori Mal College, University of Delhi, India
Email: *kiran[at]kmc.du.ac.in*

**Abstract:** ***Excess of melanin synthesis which is primarily caused because of the increase in the tyrosinase activity in melanocyte results in hyperpigmentation. For the pigmentation tyrosine inhibition is a crucial step; to achieve this a number of compounds of different classes have been screened and various research groups have studied their inhibition strength. Some of the potent inhibitors found by various researchers worldwide are Hydroquinone, Arbutin, Deoxyarbutin, Kojic acid, Tranexamic acid, Vitamin C, Azelaic acid, Tretinoin, n-butyl resorcinol etc. The use of these potential inhibitors along with their concentrations in some of the cosmetic products have been reported.***

**Keywords:** Hyperpigmentation, Tyrosinase, Tyrosinase inhibition, Inhibitors, HQ, Arbutin, Kojic acid, Azelaic acid

## 1. Introduction

Topical products that promise to improve the appearance of the skin are known as cosmetics [1–5]. The 1938 Drug and Cosmetics Act made a clear distinction between "drugs" and "cosmetics." According to this document, utilizing ingredients or raw materials in cosmetic products for "cleaning, beautifying and promoting the attractiveness" or "altering the appearance" without a government agency's clearance is allowed; nevertheless, such product(s) may make therapeutic claims. According to Kilgman, who first used the term "cosmeceuticals," it should refer to a product that appears to improve skin tone, texture, and appearance while costing significantly less than a prescription medication [6]. Because of this, the cosmeceutical industry has grown significantly in the last several decades due to consumer desire for multipurpose skincare products. This demonstrates unequivocally how cosmeceuticals bridge the gap between dermatology and skincare (cosmetics). Cosmeceuticals are basically an amalgam of cosmetics and pharmaceutical. They offer physiologically active compounds that help to rejuvenate the skin and have the opposite impact of aging. These untested goods which are considered medications are based on the research on few active compounds. In the cosmetic industry their formulations, mode of action, therapeutic application and synergistic use have produced a niche with notable growth. Cosmetics are used for a variety of conditions and target different parts of the body. One such condition of skin is hyperpigmentation [7], where high melanin production takes place in the skin. Hyperpigmentation may occur due to age spots or melasma or post inflammatory reasons. In fact, sometimes some health condition or some medication may also need to hyperpigmentation. This most common skin condition can affect all skin types.

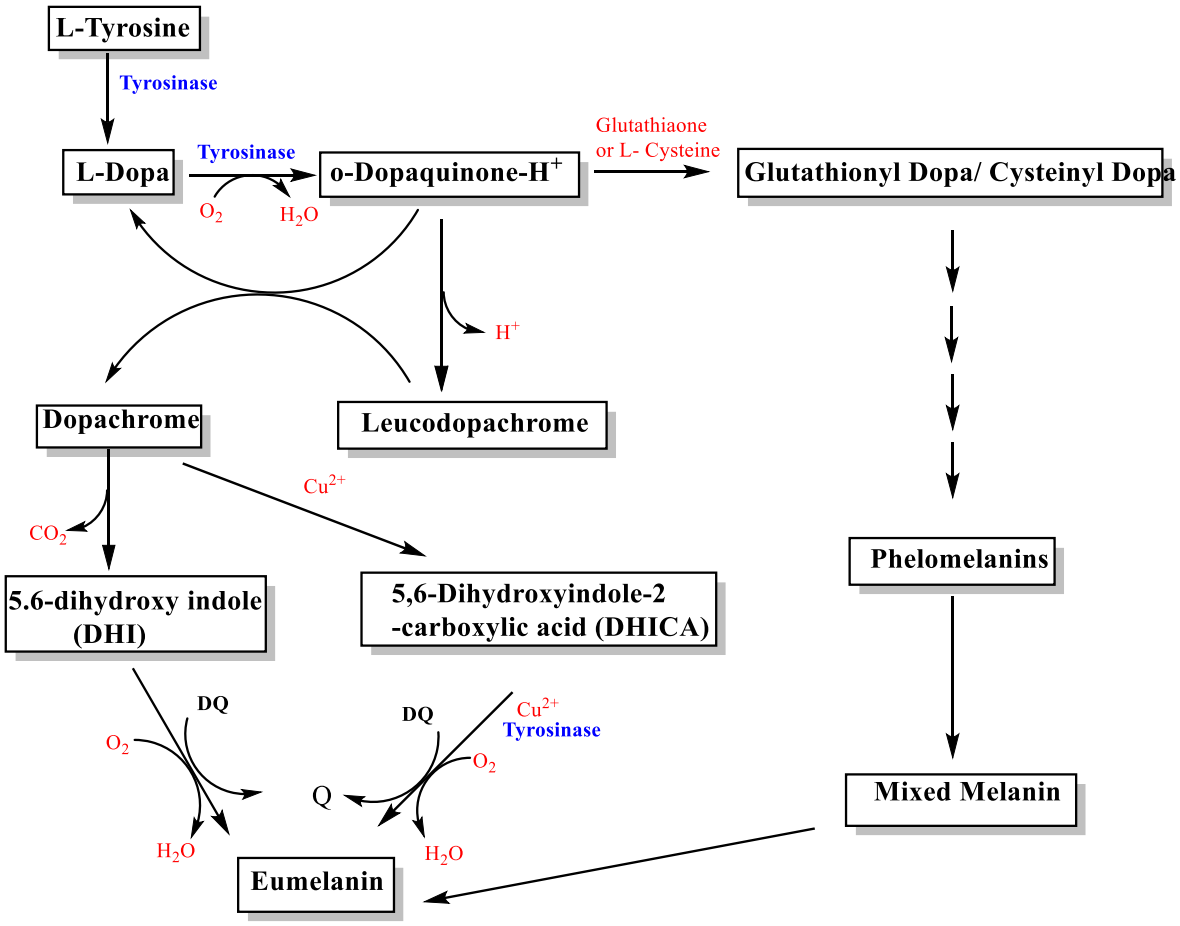
1) Age spots sunspots or liver spots: These spots turn skin brown tan and they appear on the area with over exposure of UV rays of sun. Usually, they appear on elderly or those with extended UV/sun exposure. Most commonly, these are observed on the hands, face and sun exposed areas of the body.
2) Melasma: This condition is also called the mask of pregnancy. In this condition large patches of dark spots are observed. Women with medium to darker skin tone and or who are pregnant or taken by birth tablets suffer from this. These spots are often observed on forehead, face and stomach.
3) Post inflammatory patches: They are the patches of pigmented skin usually seen after an inflammatory skin condition like acne etc. They have no specific location on the body.

Hyperpigmentation is usually harmless but due to aesthetic reasons people prefer to remove it. It can be removed by various topical treatment with skin lightening creams like use of Vitamin C, Hydroquinone or its derivatives deoxyarbutin, α- and β-arbutin, glycolic acid peels, retinoids like tretinoin, niacinamide, soy or some home remedies like applying aloe vera, licorice extract, green tea etc [8-12]. All these chemicals primarily work by inhibiting the rate limiting enzyme tyrosinase of melanin production [12].

Tyrosinase is a multipurpose metalloenzyme that contains dinuclear copper ions and functions as a rate limiting enzyme in the melanin production process [13]. Additionally, tyrosinase is instrumental for the excess melanin production as well as the undesirable browning of fruits and vegetables [8]. Consequently, tyrosinase inhibitors are crucial tool for treating enzymatic fruit and fungal browning as well as hypopigmentary diseases in mammals. As of now several efficient inhibitors have been found and created for use in food bioprocessing agriculture medical and cosmetic product sector as well as environmental sector. However, only a small number of chemicals are known to function as safe and effective tyrosinase inhibitor.

## 2. Enzyme Action

Tyrosinases from different plant and animal sources have been isolated and purified, and some of them have been sequenced also. However, among the different sources of tyrosinases, mushroom tyrosinase has a high similarity and homology with that of human tyrosinase. Tyrosinase catalyzes a sequence of oxidative events involving the amino acid tyrosine (**1**) result in the formation of melanin. In the biosynthesis pathway of melanin in melanocytes, tyrosinase catalyzes three distinct reactions: Hydroxylation of tyrosine to L-Dopa, oxidation of L-Dopa to dopaquinone, and oxidation of 5,6-dihydroxyindole-2-carboxylic acid to Eumelanin [12] (Scheme I). Eumelanin is primarily made up of oligomers of 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA).

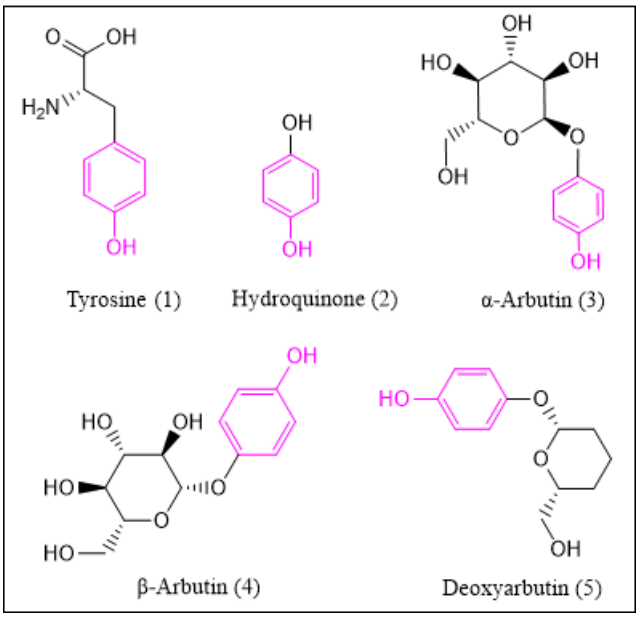



**Scheme I:** Production of Melanin

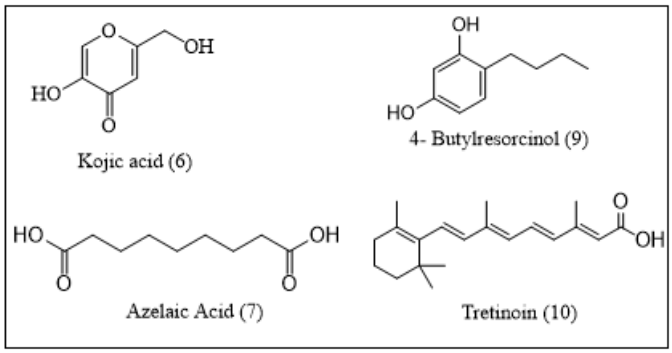
The X-ray crystallography of tyrosine [13] suggests that the active site has empty region surrounded by six histidine residues connected by copper ions, imparting flexibility to the enzyme. The substrate binding pocket in the enzyme's active site can orient according to the position of the substrate [14]. While signaling pathways regulate the expression of the enzymes involved in the melanin synthesis melanosome count help in understanding the regulation of melanin generation at the cellular level [15].

## 3. Tyrosine inhibitors and their mode of action

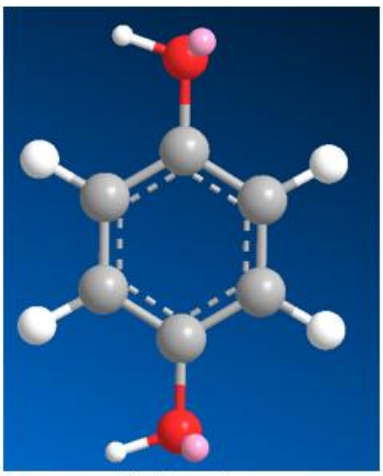
In addition to the mechanism of inhibition, enzyme kinetic studies and inhibitor screening to compute the inhibitors inhibitory strength is important. The inhibitor strength is represented by IC50 value, i.e., the concentration of the inhibitor at which 50% of the target is inhibited. In order to compare the inhibitory strength of defect inhibitors a positive control can be employed for this purpose however the IC50 values might not be comparable because of the different assays used. A number of compounds like Hydroquinone (HQ) (2) and its derivative α-arbutin (3), β-arbutin (4) and deoxyarbutin (5), Kojic acid (6), Azelaic acid (7), n-Butyl resorcinol (9), Tretinoin (10), Ascorbic acid, Tranexamic acid and even class of compounds Thiazoles, flavones, Chalcones, Retinoids, Stilbenes have been studied and screened as a new Tyrosinase inhibitor [16].

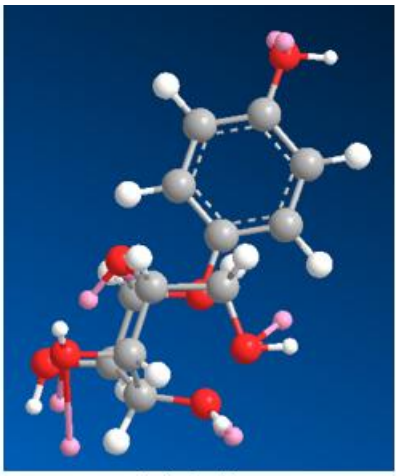


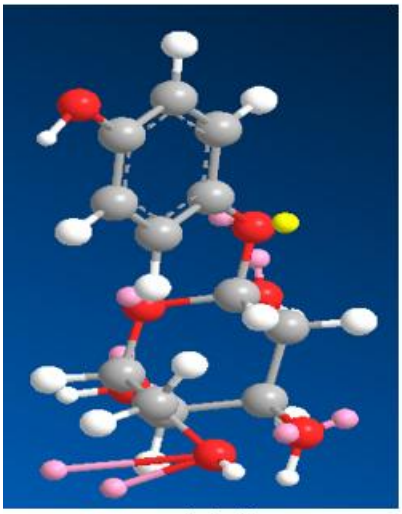

**Structures of competitive inhibitors indicating structural similarity with Tyrosine**



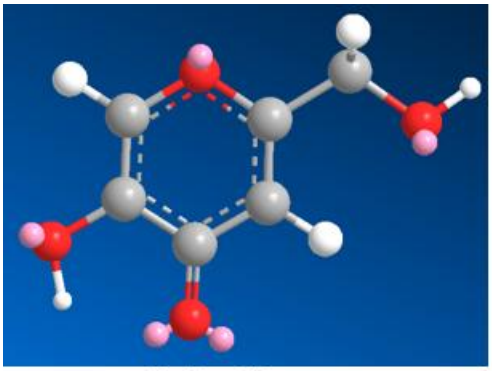

Hydroquinone 4% [17] has long been a well-established topical first line treatment when used alone or in combination with tretinoin or tropical steroids, also known as 'triple cream'. However, due to the concern about its side effect and a possible risk of cancer from its metabolites, HQ has been discontinued in many countries and replaced by potentially safer alternatives [19-20]. Arbutin which is glycosylated hydroquinone, has been proven to be an alternative to HQ. Slow hydrolysis of Arbutin to HQ by skin microflora Staphylococcus epidermidis and staphylococcus aureus have been reported [21]. Compared to arbutin, the hydrolyzed hydroquinone exhibits stronger tyrosinase inhibition and 1,1-diphenyl-2-picrylhydrazyl radical scavenging action. These results imply that the antioxidant action of hydroquinone may enhance the skin lightening effect of arbutin in the presence of normal skin microflora.


Hydroquinone

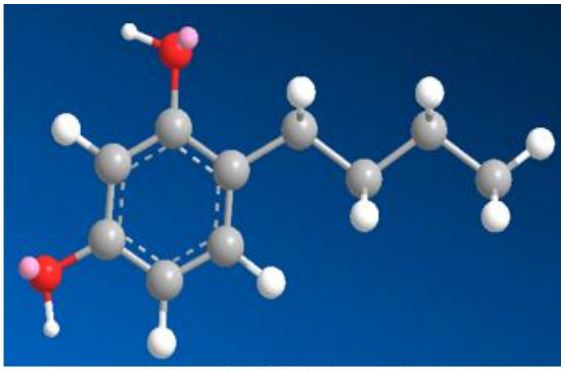

β-Arbutin


α- Arbutin

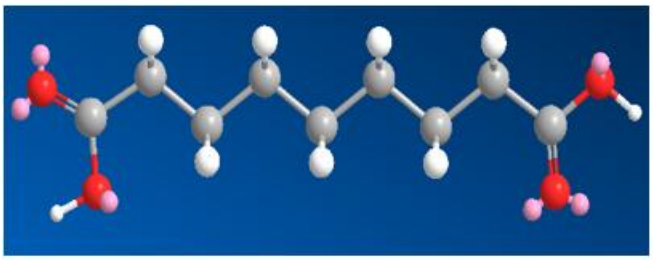

Deoxyarbutin



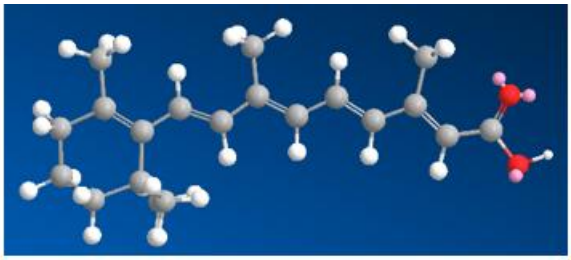
Kojic acid



4-n-Butylresorcinol



Azelaic acid



Tretinoin

**Scheme II:** Geometry optimized important inhibitors of tyrosinase

| Chemical | Mode of inhibition | Concentrations found in different cosmetical available in the market. |
|---|---|---|
| Hydroquinone | Competitive inhibition by inhibiting sulfhydryl group in Tyrosinase | 4% [22] |
| Arbutin | Reduces Tyrosinase activity | Up to 3 % [23-24] |
| Kojic acid | Inhibition of Tyrosinase Kinase production | 1-4% [25-26] |
| Tranexamic acid | Inhibits melanocytes down regulates mast cells, Inhibits plasmin | 3% [27] |
| Tretinoin | Inhibition of transcription of DNA to m-RNA thereby stopping production of Tyrosinase (before melanin synthesis) | 0.01-0.1%<br>Mostly recommended by dermatologist. |
| Azelaic acid | Reversible inhibition of Tyrosinase | 1-10 % [28] |
| Ascorbic acid (Vitamin C) | Acts reducing agent; causes reduction of o-dopaquinone to dihydroxyphenyl alanine (DOPA) | Not more than 20% [29] most of the products available in market have 10%. |
| Retinol | Inhibition of transcription of DNA to m-RNA thereby stopping production of Tyrosinase (before melanin synthesis); enhances Epidermal Cell turnover thereby reducing the duration of contact between keratinocytes and melanocytes | 0.25-1% [30] |
| n-Butyl resorcinol | Inhibitor of TRP-1 | 0.3% [31-32] |

Mann *et al* [33] recently examined how humans and mushroom tyrosine are inhibition by HQ, Arbutin and Kojic acid. In their study they reported that Arbutin and Hydroquinone inhibit human tyrosinase weakly as compared to Kojic acid. Thiamidol however showed strong inhibition for human tyrosinase as compare to Mushroom inhibitor. Among the different forms of Arbutin, deoxyarbutin have been found to have better inhibition properties as compared to α- and β-arbutin. Seemal R Desai [34] reported that no single therapy is a complete solution for hyperpigmentation. First line of approach is topical application of the combination of three (hydroquinone, topical retinoids and topical steroids). Topicals like arbutin, Kojic acid, azelaic acid, arbutin etc. Some of combinations which are currently available in the market are Arbutin + hyaluronic acid, Arbutin + Niacinamide, Kojic acid +arbutin+ niacinamide, Tranexamic acid + Niacinamide + hyaluronic acid. All the combinations show depigmentation if applied for a period for 4-8 weeks.

## 4. Conclusions

Tropical therapies/ treatments that use a multitherapy approach can help people with hyperpigmentation. Compounds like hydroquinone and arbutin, Kojic acid, n-butyl resorcinol, tretinoin, Azelaic acid, Tranexamic acid, Ascorbic acid, Retinols which have shown potential tyrosinase inhibition, and have now been used in cosmetic products. Undoubtedly, cosmeceuticals are effective in treating various skin problems because of their key ingredients. They are easily accessible and less expensive than prescription products. But most of them are not regulated and many of the constituents lack clinical data addressing their safety and efficacy. So before beginning a dermatologist's consultation is essential, as many intrinsic factors of the individual like gender, age, metabolism, genetics, lifestyle play role.

**Conflict of interest**: The author declares no conflict of interest.

**Funding**: No funding received for this research.

**Acknowledgement:** KA is thankful to Kirori Mal College, University of Delhi for institutional support.

## References

[1] Z. D. Draelos, D. B. Nelson. *In Vitro* and *In Vivo* Evaluation of an Emollient-Rich Moisturizer Developed to Address Three Critical Elements of Natural Moisturization. *J Cosmet Dermatol.* 24(4), e70085, 2025. doi: 10.1111/jocd.70085. PMID: 40176773; PMCID: PMC11966345.

[2] Z. D. Draelos, R. C. Higham, D. W. Osborne, M. S. Seal, P. Burnett, D. R. Berk. Assessment of the Vehicle for Roflumilast Cream Compared to a Ceramide-Containing Moisturizing Cream in Mild Eczema. *J Drugs Dermatol*. 23(10), 834-840, 2024. doi: 10.36849/JDD.2024.7958. PMID: 39361692.

[3] H. Baldwin, J. Del Rosso. Going Beyond Ceramides in Moisturizers: The Role of Natural Moisturizing Factors. *J Drugs Dermatol.*, 23(6), 466-471, 2024.doi: 10.36849/JDD.8358. PMID: 38834224.

[4] J. Piquero-Casals, D. Morgado-Carrasco, C. Granger, C. Trullàs, A. Jesús-Silva, J. Krutmann. Urea in Dermatology: A Review of its Emollient, Moisturizing, Keratolytic, Skin Barrier Enhancing and Antimicrobial Properties. *Dermatol Ther (Heidelb)*., 11(6), 1905-1915, 2021. doi: 10.1007/s13555-021-00611-y. Epub 2021 Oct 1. PMID: 34596890; PMCID: PMC8611129.

[5] S. C. Tang, J. H. Yang. Dual Effects of Alpha-Hydroxy Acids on the Skin. *Molecules*., 23(4), 863, 2018. doi: 10.3390/molecules23040863. PMID: 29642579; PMCID: PMC6017965.

[6] N. S. Sadick, M. P. Lupo, & Z. D. Draelos,(Eds.). *Cosmeceutical Science in Clinical Practice:* Second Edition (2nd ed.). CRC Press, 2023. https://doi.org/10.1201/9781315165905

[7] S. Nouveau, D. Agrawal, M. Kohli, F. Bernerd, N. Misra, C. S. Nayak. Skin Hyperpigmentation in Indian Population: Insights and Best Practice. *Indian J Dermatol*., 61(5), 487-95, 2016. doi: 10.4103/0019-5154.190103. PMID: 27688436; PMCID: PMC5029232.

[8] A. S Patil, A. S. Patil, P. Ugare, E. Jain, & R. S. Masareddy. Advancements in hyperpigmentation management: exploring conventional methods, phytoconstituents, novel approaches, and instrumental techniques. *Journal of Cosmetic and Laser Therapy*, *27*(1–2), 1–16, 2025. https://doi.org/10.1080/14764172.2025.2455157

[9] T. S. Chang An updated review of tyrosinase inhibitors. *Int J Mol Sci*.10(6), 2440-2475, 2009. doi: 10.3390/ijms10062440. PMID: 19582213; PMCID: PMC2705500.

[10] (a) S. Ullah, S. Son, H. Y. Yun, D. H. Kim, P. Chun, H. R. Moon. Tyrosinase inhibitors: a patent review. Expert Opin Ther Pat., 26(3), 347-62, 2011-2015, 2016. doi: 10.1517/13543776.2016.1146253. PMID: 26815044. (b) J. Leyden, W. Wallo. The mechanism of action and clinical benefits of soy for the treatment of hyperpigmentation. *Int J Dermatol*. Apr. 50(4), 470-477, 2011. doi: 10.1111/j.1365-4632.2010.04765.x. Epub 2011 Feb 20. PMID: 21332714

[11] Merima, Ibišević &, Nermina & Hadžigrahić, & Pilipović, Saša & Softic, Adaleta & Smajlović, Aida & Srabovic, Nahida & Husejnagic, Darja & Ademovic, Zahida & Karic, Enida & Kolarević, Lamija & Akeljić, Dženeta & Sljivic Husejnovic, Maida & Makić, Halid & Dedić, Samira. Tyrosinase inhibition, antioxidativeand antimicrobial activity of activesubstances and creams used in thetreatment of hyperpigmentation (kojicacid, niacinamide and grapevineextract). *Technologica acta.* 17. 1-6, 2024. 10.51558/2232-7568.2024.17.2.1.

[12] S. Zolghadri, A.Bahrami, H. Khan, M. T., J. Munoz-Munoz, F. Garcia-Molina, F. Garcia-Canovas, & A. A. Saboury, A -comprehensive review on tyrosinase inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *34*(1), 279–309, 2019. https://doi.org/10.1080/14756366.2018.154577

[13] Y. Matoba, & T. Kumagai, A. Yamamoto, H. Yoshitsu, & M. Sugiyama. Crystallographic Evidence That the Dinuclear Copper Center of Tyrosinase Is Flexible during Catalysis. *The Journal of biological chemistry*. 281, 8981-90. 2006. 10.1074/jbc.M509785200.

[14] A. Bijelic, M. Pretzler, C. Molitor, F. Zekiri, A. Rompel. The Structure of a Plant Tyrosinase from Walnut Leaves Reveals the Importance of "Substrate-Guiding Residues" for Enzymatic Specificity. *Angewandte Chemie* (International ed. in English). 54, 14677-680, 2015. 10.1002/anie.201506994.

[15] K. Sardana, S. Ghunawat. Rationale of using hypopigmenting drugs and their clinical application in melasma. *Expert review of clinical pharmacology*, *8*(1), 123-134, 2015. https://doi.org/10.1586/17512433.2015.977255

[16] A. Wilczek, Y. Mishima. Inhibitory effects of melanin monomers, dihydroxyindole-2-carboxylic acid (DHICA) and dihydroxyindole (DHI) on mammalian tyrosinase, with a special reference to the role of DHICA/DHI ratio in melanogenesis. *Pigment Cell Res.,* 8(2), 105-12, 1995. doi: 10.1111/j.1600-0749.1995.tb00649.x. PMID: 7659677.

[17] A. Palumbo, M. d'Ischia, G. Misuraca, G. Prota. Mechanism of inhibition of melanogenesis by hydroquinone. *Biochim Biophys Acta.* 1073(1), 85-90, 1991. doi: 10.1016/0304-4165(91)90186-k. PMID: 1899343.

[18] D. H. Seo, J. H. Jung, J. E. Lee, E. J. Jeon, W . Kim, C. S. Park. Biotechnological production of arbutins (α- and β-arbutins), skin-lightening agents, and their derivatives. *Appl Microbiol Biotechnol*. 95(6), 1417-25, 2012. doi: 10.1007/s00253-012-4297-4. Epub 2012 Jul 29. PMID: 22843425.

[19] W. G. Philipp-Dormston. Melasma: A Step-by-Step Approach Towards a Multimodal Combination Therapy. *Clinical, Cosmetic and Investigational Dermatology*, *17*, 1203–1216, 2024. https://doi.org/10.2147/CCID.S372456

[20] Y. Wang, R. Jiang, B. Xiong, J. Zhu, J. Sang, H. Li, C. Chen, Z. Xu, W. Zhang, Y. Chen, F. Yao, Feng & H. Sun. Clinical Investigation of Tyrosinase Inhibitors: Past, Present, and Future. *Drug Development Research.* JUNE, 86. 2025. 10.1002/ddr.70113.

[21] S. H. Bang, S. J. Han, D.H. Kim. Hydrolysis of arbutin to hydroquinone by human skin bacteria and its effect

on antioxidant activity. *J Cosmet Dermatol*. 7(3):189-93, 2008. doi: 10.1111/j.1473-2165.2008.00387.x. PMID: 18789053.

[22] R. L. Michael, C. A. Stratford, P. Ramsden, A. Riley, The influence of hydroquinone on tyrosinase kinetics, *Bioorganic & Medicinal Chemistry*, 20 (14), 4364-4370, 2012, https://doi.org/10.1016/j.bmc.2012.05.041.

[23] J. A. García, J. Teruel, J. Berná, J. Rodríguez-López, J. Tudela, G. Canovas. Action of tyrosinase on alpha and beta-arbutin: A kinetic study. PLOS ONE. 12(5), 2017. 10.1371/journal.pone.0177330

[24] Y. C. Boo. Arbutin as a Skin Depigmenting Agent with Antimelanogenic and Antioxidant Properties. *Antioxidants* (Basel).10(7), 1129, 2021. doi: 10.3390/antiox10071129. PMID: 34356362; PMCID: PMC8301119.

[25] M. Eslmifar, K. Khezri, M. Saeedi. Kojic acid applications in cosmetic and pharmaceutical preparations. *Biomedicine & Pharmacotherapy*. 110. 582-593, 2019. 10.1016/j.biopha.2018.12.006.

[26] J. Zilles, F. dos Santos, I. Kulkamp-Guerreiro, R. Contri. Biological activities and safety data of kojic acid and its derivatives: A review. *Experimental Dermatology*. 31, 1500-1521, 2022. 10.1111/exd.14662.

[27] P. Verma, K. S. Yadav. Novel formulations for topical delivery of tranexamic acid: assessing the need of epidermal targeting for hyperpigmentation disorders. *Expert Opinion on Drug Delivery*, *20*(6), 773–783, 2023. https://doi.org/10.1080/17425247.2023.2206645

[28] M. A. Pathak, E. R. Ciganek, M. Wick, A. J. Sober, W. A. Farinelli, T. B. Fitzpatrick. An evaluation of the effectiveness of azelaic acid as a depigmenting and chemotherapeutic agent. *J Invest Dermatol*. 85(3), 222-228, 1985. doi: 10.1111/1523-1747.ep12276684. PMID: 4031538.

[29] I. Lavilla, V. Romero, P. Costas, C. Bendicho. Kinetic spectrophotometric assay for the determination of vitamin C in cosmetics following ultrasound-assisted emulsification. *Analytical Methods*. 15, 951-958, 2023. 10.1039/D2AY01795D.

[30] Z. T. Rakuša, P. Škufca, A. Kristl, R. Roškar. Retinoid stability and degradation kinetics in commercial cosmetic products. *J Cosmet Dermatol.* 20(7), 2350-2358, 2021. doi: 10.1111/jocd.13852. Epub 2020 Dec 2. PMID: 33206444.

[31] N. T. Mohan, A. Gowda, A. Jaiswal, B. C. Kumar, P. Shilpashree, B. Gangaboraiah, M. Shamanna. Assessment of efficacy, safety, and tolerability of 4-n-butylresorcinol 0.3% cream: an Indian multicentric study on melasma. *Clinical, Cosmetic and Investigational Dermatology.* 9. 21-27, 2016. 10.2147/CCID.S89451.

[32] J. A. García, J. Teruel, V. Ortiz-Ruiz, J. Berná, J. Tudela, G. Canovas. 4- n -butylresorcinol, a depigmenting agent used in cosmetics, reacts with tyrosinase: *BR in the Cosmetics Industry*. 2016, IUBMB Life. 68. 10.1002/iub.1528.

[33] T. Mann, W. Gerwat, J. Batzer, K. Eggers, C. Scherner, H. Wenck, F. Stäb, V. J. Hearing, K. H. Röhm, L. Kolbe. Inhibition of Human Tyrosinase Requires Molecular Motifs Distinctively Different from Mushroom Tyrosinase. *J Invest Dermatol*. 138(7), 1601-1608, 2018. doi: 10.1016/j.jid.2018.01.019. Epub 2018 Feb 7. PMID: 29427586.

[34] S. R. Desai. Hyperpigmentation therapy: a review. *J Clin Aesthet Dermatol*. 7(8), 13-7, 2014. PMID: 25161755; PMCID: PMC4142815.

## Author Profile

**Dr. Kiran Arora** received her B. Sc, M.Sc, M. Phil, and PH. d degree from University of Delhi. Her specialization is Organic Synthesis. She has an experience of 18 years in teaching UG students in University of Delhi. Currently, she is teaching at Kirori Mal College for past 17 years. Apart from the core and advanced organic chemistry, she is also teaching chemistry of cosmetics and hygiene products to UG students as a skill enhancement course which motivated author to write this paper.