International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

A Review On: Various Inhibitors and Drugs Used In Skin Whitening Agents

Shreya Sharma*[1], Sangeeta Dahibhate*[2], Dr. Pratima Shinde*[3]

*[1] M.Pharm, Department of Pharmaceutics,Siddhant College ofPharmacy,Sudumbare,Pune, Maharashtra,India
*[2] M.Pharm,Department of Pharmaceutics,Siddhant College of Pharmacy,Sudumbare,Pune,Maharashtra,India
*[3]Assistant Professor,Department/HOD of Pharmaceutics,Siddhant College of Pharmacy,Sudumbare,Pune,Maharashtra,India.

Date Of Submission: 01-06-2021 Date Of Acceptance: 14-06-2021

ABSTRACT-The production of melanin takes place by the process of melanogenesis. Melanin is responsible for pigmentation of skin, eye and hair. Whitening agents are used for cosmetic purposes and useful to treat various disorders such as hyperpigmentation, melanoma, etc.The enzyme involved for the catalytic activity in the process of melanogenesis is tyrosinase. Thus, till date numerous tyrosinase inhibitors have been developed on the recent years many skin whitening agents act as competitive inhibitors of tyrosinase. Some agents inhibit maturation of tyrosinase. In this review we focus/discuss/present the overview the process of melanogenesis and the drugs involved in inhibition of tyrosinase catalytic activity, various skin disorder.

KEY WORDS-Tyrosinase inhibitors, melanogenesis, skin whitening agents.

INTRODUCTION-

Skin color is influenced by a number of intrinsic factors, including skin types and genetic factors and extrinsic factors including sunlight exposure and environment pollution. The recent research by cosmetic companies and research institutions has been focusing on development of novel whitening agents that selectively suppress the activity of tyrosinase (TYR) to reduce hyperpigmentation and avoiding cytotoxicity to normal healthymelanocytes.It is estimated approximately 15% of the world population invest in skin whitening agents with Asia is being dominated. Global industry analysts (GIA) have predicted that the universal market for skin lighteners will reach $23 billion by 2020, driven by new markets in Asia, particularly India, Japan and China. Melanin is produced from epidermis melanocytes in an appropriate ratio 1:36 with basal keratinocytes.Under normal physiological conditions, pigmentation has a beneficial effect on the photo-protection of human skin against harmful UV injury and plays an important evolutionary role in camouflage and animal mimicry. However, an excessive production of melanin causes dermatological problems such as freckles, solar lentigo (age spots) and melasma. In the Western culture it is still considered desirable to obtain a (bronze) tan. Despite warningsabout the consequences of excessive sun or UV exposure, the artificial tanning business has expanded strongly in the last decades. In the Eastern world, however, a centuries long tradition exists whereby a light complexion is regarded as equivalent to youth and beauty. Development ofpreparations for bleaching hyperpigmented lesions or to safely achieve overall whitening is one of the challenges for cosmetic industry. In recent years, the interest in skin whitening has growntremendously.

Human skin contains specialized cells, called melanocytes, which are located at the base of the epidermis. These cells are programmed to manufacture a brown pigment, called melanin, in response to exposure of skin to sunlight. Since melanin acts as a sunscreen, the production of this pigment by melanocytes is a defense response of the skin to the damaging and potential skin cancer causing rays of the sun. In addition to UV radiation, other factors can stimulate melanocytes to make melanin. Hormones, such as those in birth control pills can cause melanocyte “activation”, and exposure of the skin to any event that causes inflammation, such as acne, dermatitis, exposure to chemicals, etc., can also result in increased melanin production by melanocytes.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

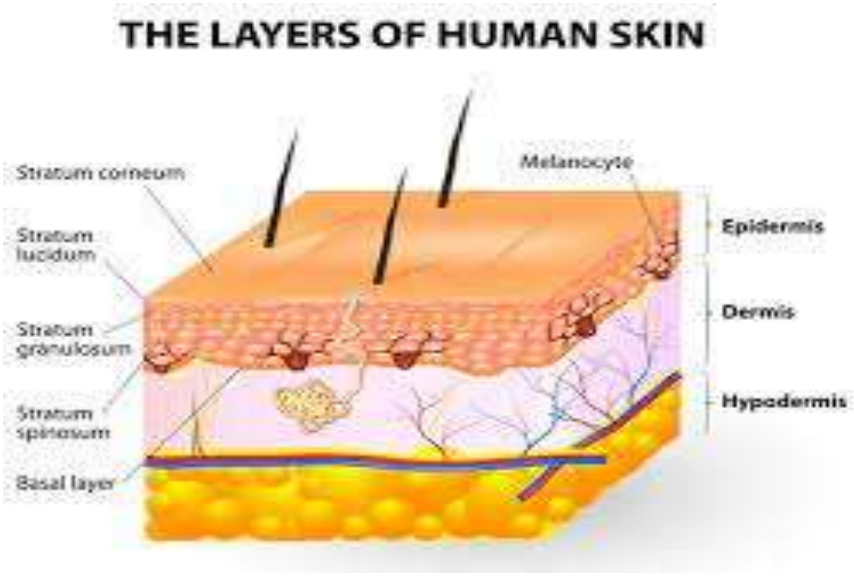


FIG.LAYERS OF SKIN

MELANOGENESIS-

Melanin is mainly produced by melanocytes that are localized in the epidermis, the outermost layer of the skin; it is also this layer that determines skin colour in humans. Melanin is primarily synthesized in melanosomes, which function as specialized organelles in melanocytes. Melanogenesis and chemical reactions inside the melanosomes, resulting in the production of two types of melanin: Eumelanin and pheomelanin. Eumelanin is an insoluble polymer that is dark brown-black in colour, whereas pheomelanin is a soluble polymer light red-yellow in colour that also contain sulphur. Both eumelanin and pheomelanin are formed by the conjugation of cysteine or glutathione. To gain an understanding of the mechanism of whitening agents, a summary of the signalling pathways associated with skin melanogenesis. The pigmentation process starts with the oxidation of L-tyrosine to L-dopaquinone (DQ) in the presence of the rate-limiting enzyme TYR. Following DQ formation, the resulting quinone undergoes intramolecular cyclization and oxidation, where it serves as a substrate for the synthesis of eumelanin and pheomelanin. During the process of melanogenesis, hydroxylation of L-tyrosine to form L-3,4-dihydroxyphenylalanine (L-DOPA) is the rate-limiting step of the whole process, which is catalysed by TYR.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

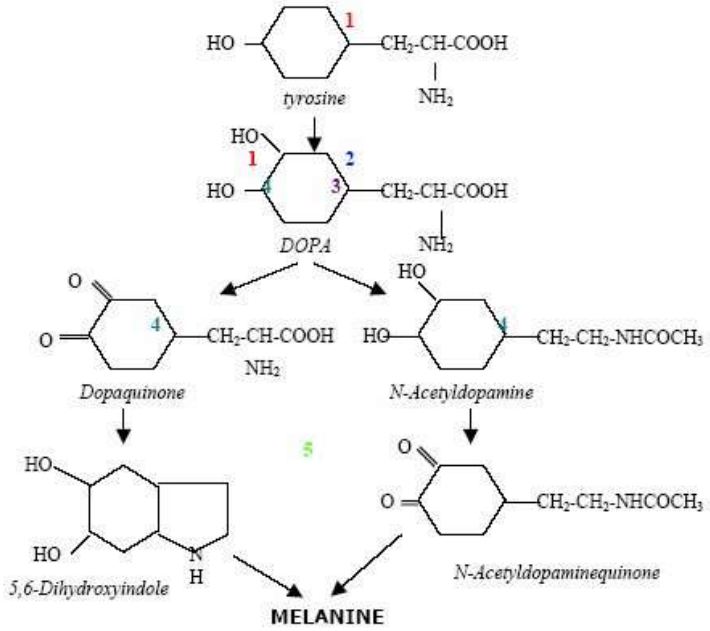


FIG.SYNTHESIS OF MELANINE

TARGETING TYROKINASE AS KEY ENZYME-

HQ is potentially mutagenic to mammalian cells and linked to a number of adverse reactions including contact dermatitis, irritation, transient erythema, burning, prickling sensation, leukoderma, chestnut spots on the nails, hypochromia. Arbutin, a prodrug of hydroquinone, is a natural product and reduces or inhibits melanin synthesis by inhibiting tyrosinase. However, natural forms of arbutin are chemically unstable and can release hydroquinone which is catabolized to benzene metabolites with the potential toxicity for bone marrow. Kojic acid use in cosmetics has been limited, due to its carcinogenicity and its instability during storage. L-Ascorbic acid is sensitive to heat and degrades easily. Ellagic acid is insoluble and thus poorly bioavailable, and for the tranexamic acid the melanogenic pathway remains undetermined. Thus, it is in great need of developing new tyrosinase inhibitors with drug-like properties.

Resveratrol analogue

Resveratrol (3,5,40-trihydroxy-trans-stilbene, 9) a widely distributed stilbene in nature such as in grapes, exhibited the inhibitory activity against mushroom tyrosinase through the mechanism of Kcat (suicide substrate) type inhibition. In vitro analysis in a-MSH-stimulated B16 murine melanoma cells, resveratrol inhibited the cellular melanin production via suppression of melanogenesis- related proteins such as tyrosinase, TRP-1, TRP-2 and microphthalmia-associated transcription factor (MITF) expression without any cytotoxicity up to 200 lM. The inhibitory effects ofresveratrol have been confirmed in an in vivo model using UV irradiated brownish guinea pigs. In this study, treatment of resveratrol with UVB-irradiated dorsal skin of guinea pigs visually decreased the hyperpigmentation. In an effort to improve the activity of resveratrol, demonstrated a study with a series of resveratrol analogue.

One of the most obvious cellular targets for depigmenting agents is the enzyme tyrosinase. The scientific literature on tyrosinase inhibition

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

shows that a large majority of the work has been conducted since 2000 and has mostly been devoted to the search for new depigmenting agents. Notably, many of these studies deal with tyrosinase inhibitors from natural sources and are mostly of Asian origin. However, early pioneering work in the field has been performed much earlier using 4-hydroxyanisole. This compound could serve as an alternative substrate for tyrosinase causing depigmentation both in vivo and in vitro. Since this and various other substituted phenolic compound can generate potentially toxic quinone products they were used in various studies aimed at the induction of toxicity mediated by tyrosinase in melanoma cells. Considerable interest in tyrosinase inhibitors exists also in the food industry because the activity of this enzyme is responsible for the browning of fruit and vegetables. Cysteine or ascorbic acid can be used to prevent the enzymatic browning of fruit and vegetables by binding the o-dopaquinone intermediates. More recently also 4-hexylresorcinol has been utilized for this purpose. Since safety considerations are very strict in food industry, the search for new, natural tyrosinase inhibitors without negative side effects is of utmost importance in this field of research. Work on synthetic and natural tyrosinase inhibitors has been recently reviewed in several papers. The tyrosinase inhibitors can be classified as competitive, uncompetitive, mixed type and non-competitive inhibitors. The nature of tyrosinase inhibition can be disclosed by measuring enzyme inhibition kinetics using Lineweaver-Burk plots with varying concentrations of L-DOPA as the substrate. This can be seen on example of polyphenol extracts from acerola (West Indian cherry) or a chalcone derivative isolated from Morus nigra (black mulberry) which has been described in recent work of Hanamura et al. and Zhang et al. Knowledge of the type of inhibition may be important in order to achieve better skin lightening effects since combined treatments may result in synergistic effects. This has been shown in case of the competitive tyrosinase inhibitor, arbutin and the non-competitive inhibitor, aloesin.

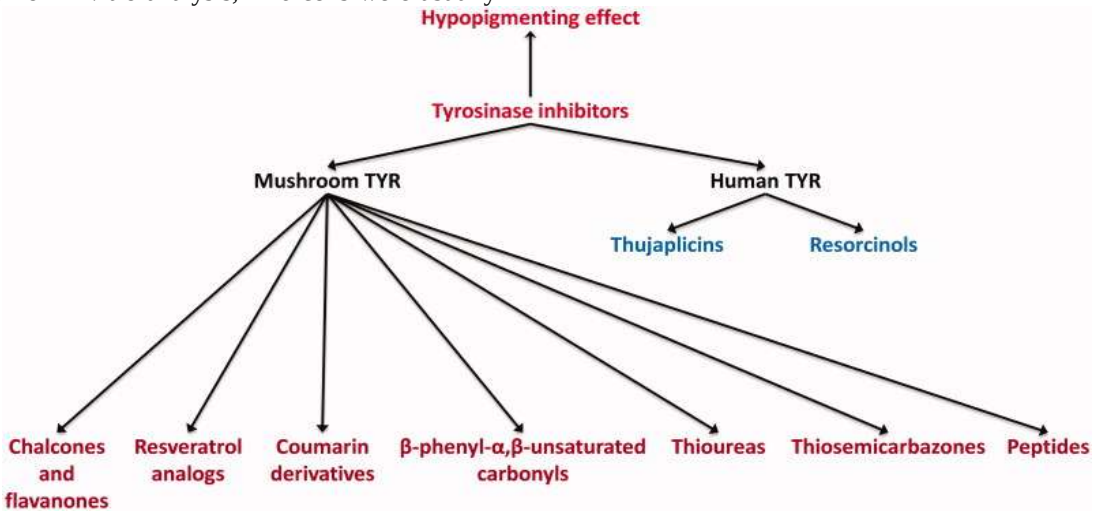
A 2009 paper by Chang states that a large majority of tyrosinase inhibitors show reversibleinhibition. In irreversible inhibition, covalent binding with the enzyme may cause its inactivation by altering the active site of the enzyme and/or by conformational changes to the protein molecule. Irreversible inhibition may also occur via the so-called suicide inhibition mechanism as described in the model by Land et al. Also, two 8-hydroxy isoflavones isolated from soy germ koji showed suicide inhibition of tyrosinase and have been tested with promising results in an in vivo assay with 60 volunteers. In we summarize the large number of studies using tyrosinase inhibitors from natural sources that have appeared, mostly in the last decade. In many of the investigations, the active ingredients from extracts of various species have been isolated and identified. In case the mode of tyrosinase inhibition was established, a comparison with IC50 values of well-known inhibitors suchas kojic acid and arbutin was often made. In some of the studies specific side groups (withsubstitutions to C4, C5 or C8 position) of resorcinol's isolated from the breadfruit (Artocarpus incisus) or from a 'bitter root' (Sophora flavescens) proved of great importance to their inhibitory potential. In some cases, modifications to the natural compounds were made, e.g., the De-glycosylation of stilbene compounds by cellulase treatment of the Veratrum patulum extract resulted in improved tyrosinase inhibition. Thus, exact knowledge on enzyme inhibition mechanisms is helpful for designing new whitening products based on targeting the key enzyme of melanogenesis, tyrosinase. Although tyrosinase plays a major role in melanin synthesis, one should realize that the regulation of skin pigmentation exists at various levels and therefore, different modes of interference are possible. There are indications that combined approaches could be more successful than targeting tyrosinase only.

Mushroom tyrosinase inhibitors

Tyrosinase from the mushroom Agaricus bisporus is frequently used as an enzymatic in vitro model for developing the skin whitening substances targeting human tyrosinase. Because of the commercial availability of mushroom tyrosinase (mTAR), most of the research has been studied with this enzyme. For screening of the compounds, the popular whitening agents, such as kojic acid, arbutin or hydroquinone, were used as a positive control. As a result, in recent years, numerous mushroom tyrosinase inhibitors from natural and synthetic sources have been identified. The inhibitory strength was expressed as IC50 value, which is theconcentration of the inhibitor needed to inhibit half of theenzyme activity in the tested condition. The Ki value is the reflectiveof ligand-binding affinity to the enzyme. The lower Ki valuemeans higher binding affinity, whereas higher Ki value means lower binding affinity. The Ki value for non-competitive inhibitors is essentially

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

the same numerical value as the IC50 of the inhibitors, whereas for competitive inhibitors, the Ki is about one-half that of the numerical values of IC50. For in vitro analysis, B16 cells were usually used because they are relatively easy to culture in vitro and shares the melanogenesis mechanisms of normal human melanocytes.



Induction of Pigmentation

For the development of effective skin whitening, we also need to understand processes that regulate the induction of pigmentation. Constitutive pigmentation is reflected by the phenotypes of the different skin types with varying pigmentation based on their genetic diversity. The facultative pigmentation acquired on top of the constitutive level can be obtained via different stimuli of which ultraviolet radiation (UVR) is well known as provoking the "tanning response". Various pathways can be induced by the signalling through basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), stem cell factor (SCF), endothelin-1 (ET-1), adrenocorticotropic hormone and α- melanocyte stimulating hormone (ACTH and α-MSH) via their respective receptors present on melanocytes and thus stimulating their pigment production. These signalling pathways could also serve as a means of specific targeting the melanogenic pathway.

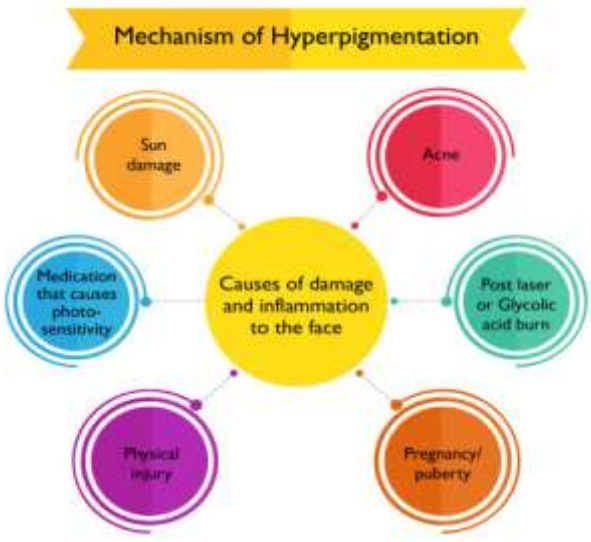
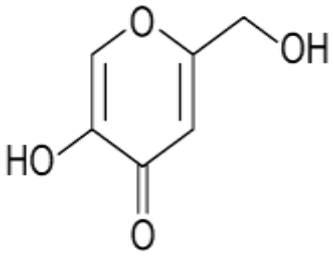


FIG.MECHANISM OF HYPERPIGMENTATION

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

DRUGS USED IN DEPIGMENTATION PROCESS-
1.KOJIC ACID



STRUCTURE-KOJIC ACID

The KA (the name 'kojic acid' was derived from "Koji") is a chemicalproduct that is obtained from various types of fungi such as A. flavus, A.oryzae, A. tamarii, and A. parasiticus . It is also produced fromthe fermentation of some Asian foods (e.g. soy sauce and rice wine),which acts as a primer for fungus or inoculum [38–44]. kojic Acid wasfirst marketed in 1955. The Charles Pfizer and Company, USA, was thefirst company to try to build this product. In recent years, kojic acidproducingcompanies include two in China and three companies inJapan, Switzerland, and the USA. Rapid growth of industries and discoveryof the potential uses of kojic acid and its derivatives, generatedgreat demands for this product. KA is classified in the group oforganic acids, which is obtained from different types of fungi duringaerobic fermentation process. Its chemical structure is identified as 5-hydroxy-2-hydroxymethyl-γ-pyron. Some of these species are capable of producing KA in large amounts, but genetic modifications could alter their ability togreater performance. As mentioned earlier, KA as a skinwhitening, skin lightener or depigmenting agent is used in cosmeticformulations. It is naturally produced by various species of Penicilliumand Acetobacter and various species of acetic acid bacilli. Several methods are suggested for the analysis of KA in variousindustries, including voltammetry, spectrophotometry, column chromatographywith ultraviolet detection, thin-layer chromatography, gaschromatography with or without flame ionization, mass spectrometrydetection, bio gel P-2 column chromatography, and high-performanceliquid chromatography with photodiode-array or ultravioletdetection.

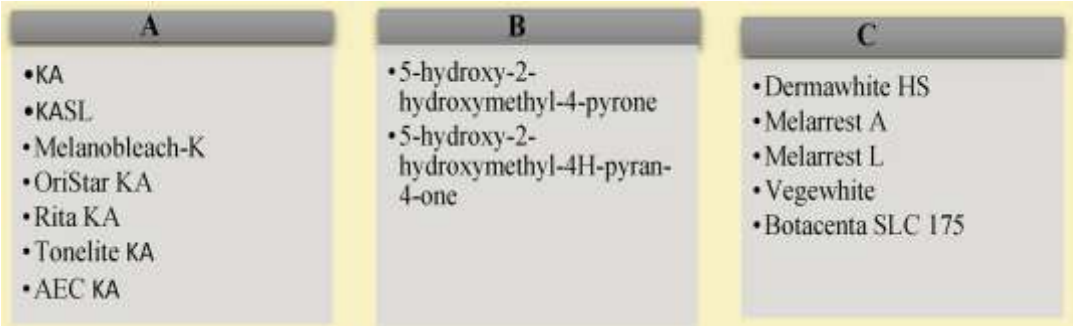


FIG.SCHEMATIC DIAGRAM OF TRADE NAME,TECHNICAL NAME OF KOJIC ACID

Transdermal penetration, depigmentation and development ofmethods

The topical absorption of KA according to pharmacokinetic absorptionstudies in rats and human skin, is estimated to be0.03–0.06 mg/kg/day. The genotoxic risk of KA as a skin lighteningagent for humans is less. The in vitro percutaneous absorption values ofKA in human skin resulted in 17%, and the maximum potential humansystemic exposure dose (SED) would be 1.7 mg or 0.028 mg/kg/day fora 60 kg adult human. This SED range is based on the application area ofhands and face.The results of an oral/topical pharmacokinetic study in rats showed18% of systemic exposure after topicalapplication. Pharmacokineticstudies in rats after oral and subcutaneous administration to rats,showed that KA was rapidly absorbed and metabolized. The

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

percutaneousabsorption of KA in human skin was investigated in vitro andrecovered 14C-equivalents (%) were determined by liquid scintillationcounting in the skin excess (%75.8 ± 9.3), stratum corneum(%3.7 ± 2.2), epidermisdermis (%9.2 ± 4.3) and the receptorfluid (7.8 ± 6.8). KA showed a significant tendency to penetrate intothe dermis and epidermis (penetration rate of 16.98 ± 10.28%, correspondingto 3.58 ± 2.38 14C-mgeq/cm2 of treated skin area).Percutaneous absorption of KA in six healthy postmenopausalJapanese women were measured before and after applying a creamcontaining 1% KA. All the concentrations in plasma were only slightlyabove the quantitation limit of 1 ng/ml. So, it was proved that KA hadnot the potential role for transdermal penetration into the blood.

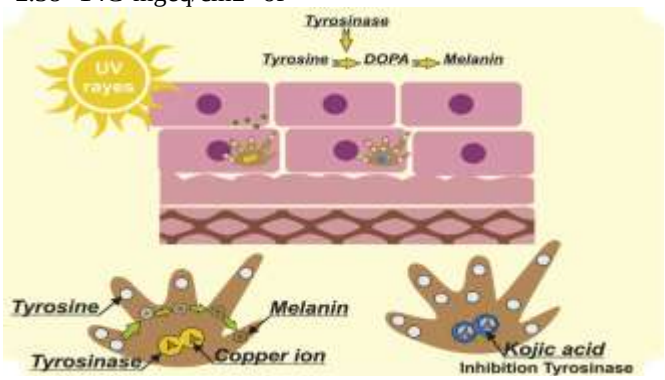


FIG-TYROSINASE INHIBITORY MECHANISM OF KA IN MELANIN BIOSYNTHESIS FOR CREATING MELANIN BY KA.

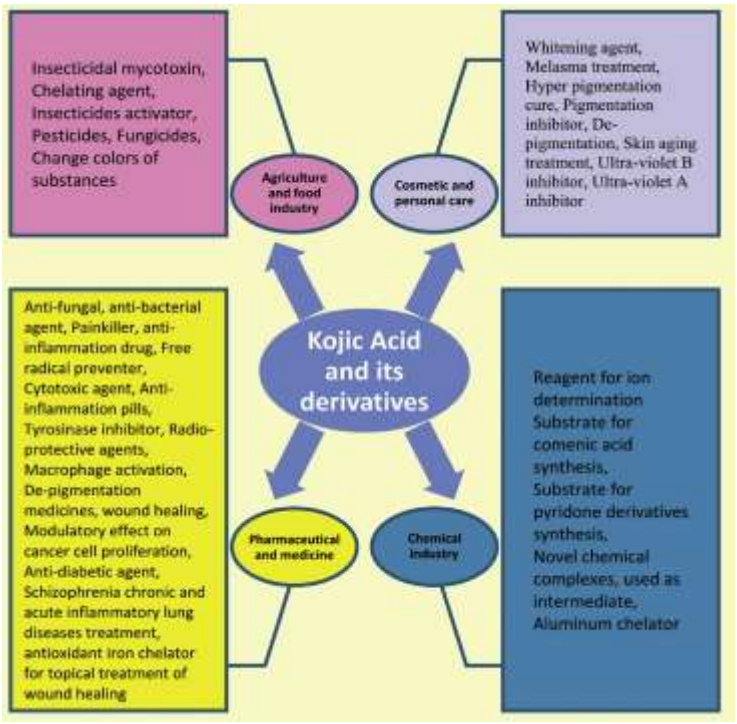


FIG-. KEY FUNCTION OF KA AND ITS DERIVATIVES IN DIFFERENT INDUSTRIES.

Characteristics and applications of KA in cosmetic andpharmaceutical preparations
The most important applications of KA are as follows:
a-Bleaching properties and skin protection in contrast to ultravioletlight in cosmetic products
b-Dental care products

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

In some studies, melanogenic inhibitory properties of KA have beenproven in vitro. Due to the carcinogenicity of HQ and its prohibition inAsia, the FDA has introduced KA as an alternative for HQ. Recently,chelates of KA and manganese and zinc metals have been introduced asprotective agents against gamma and radio rays. KA and its derivatives have become increasingly important due tovarious biological activities, including antimicrobial and antiviral, antitumor, antidiabetic, anticancer, anti-Speck, anti-parasitic, and pesticidal and insecticidal activities. In addition, KA and its derivatives are used as anti-oxidant,anti-proliferative, anti-inflammatory, radio protective and skinlighteningagent in drug and cosmetic products, due to their tyrosinaseinhibitory activity. Furthermore, KA could be developedas a chemo sensitizer to enhance efficacy of commercial antifungaldrugs or fungicides.Potential application of KA and its derivatives has been studied inveterinary medicine, cosmetic and chemical industry

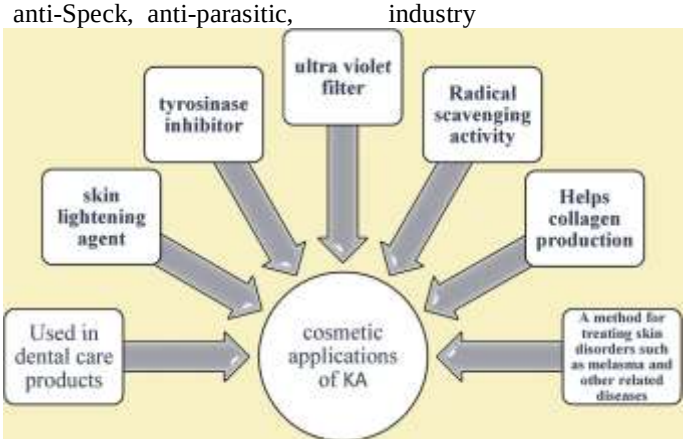
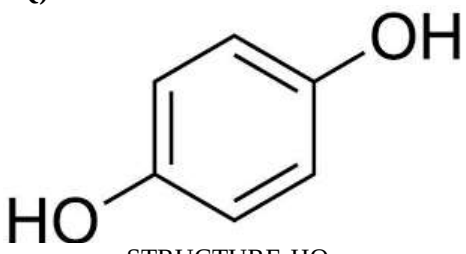


FIG-APPLICATIONS OF KOJIC ACID

2.1,4-DIHYDROXYBENZENE (HQ)

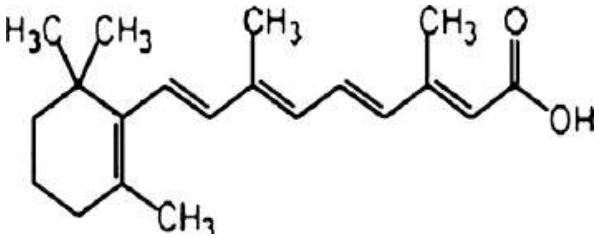


STRUCTURE-HQ

Most pharmacological depigmenting agents target the activity oftyrosinase, a key enzyme in melanin synthesis. Tyrosinase is acopper-containing transmembrane glycoprotein that is the rate Limitingenzyme in melanogenesis.HQ, a powerful tyrosinase inhibitor,is the most extensively investigatedantimelanogenicagent.HQ competes with the tyrosinase substrate (i.e., tyrosine)and prevents its enzymatic oxidation to dihydroxyphenylalanine. Inaddition, oxidative products of HQ cause oxidative damage tomembrane lipids and proteins, including tyrosinase.In a randomized,double-blind, placebo-controlled trial, Ennes et alreportedthat 38% of patients treated with 4% HQ achieved clinicalclearance of melasma in 12 weeks, compared with only 8% of patientsin the control group. In another randomized,double-blind trial, Haddad et alcompared the efficacy of 4% topicalHQ with a skin-whitening complex consisting of Arctostaphylos uvaursi,biofermented Aspergillus, grapefruit extract, and rice extract in30 patients with melasma. HQ showed a 77% improvement, whereas the skin-whitening complex showed a 67% improvement.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

3.TRETIONIN



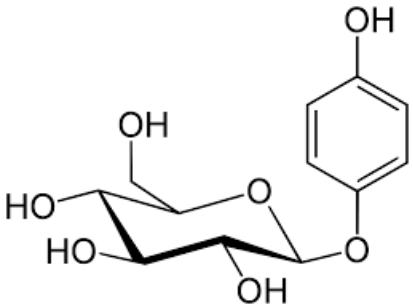
STRUCTURE-TRETINOIN

Tretinoin is another topical pharmacological agent that acts byinhibiting the activity of tyrosinase. This topical retinoid was firstused in combination with HQ to enhance its penetration; however,it was later recognized that retinoid alone has an effect onpigmentation by inhibiting the activities of tyrosinase and dopachrome conversion factor. Concentrations ranging from0.025% to 0.1% have been used to treat pigmentation disorders and skin aging. In 1993, a randomized controlled trial evaluating theefficacy of topical 0.1% tretinoin was conducted in patients withmelasma by Griffiths et al After 40 weeks of usingtretinoin, 68% of the patients were rated as "much improved" or"improved", whereas only 5% of the vehicle group showed"improvement". However, the rate of adverse reaction was alsohigh in the study groups. Moderate cutaneous adverse effects (erythemaand irritation) occurred in 88% of patients in the tretinoingroup and in 29% of the vehicle group. In another study performedby Kimbrough-Green et al, tretinoin also exhibited good clinicalefficacy with a high rate of adverse events. Moreover, areview article by Kang et alreported that topical retinoids wereeffective for the treatment of pigmentary disorders, either asmonotherapy or in combination with other topical agents.

Triple-combination cream

Triple-combination cream (TCC), which contains 4% HQ, 0.05%tretinoin, and 0.01% fluocinolone acetonide, is the most effectivetopical treatment for melasma reported to date. TCC is the only HQ Containingdrug approved by the United States Food and DrugAdministration for the treatment of melasma.As mentionedearlier, HQ and tretinoin show depigmenting effects by inhibiting the activity of tyrosinase. Fluocinolone acetonide is a corticosteroidthat reduces levels of cytokines, including endothelin-1 and granulocytemacrophagecolony-stimulating factor, which mediateUV-induced pigmentation. Apart from their individual depigmentingeffects, each ingredient of the TCC can help in reducing thepotential side effects of the other ingredients. Steroids reduce theirritation caused by HQ, and tretinoin ameliorates corticosteroidinducedepidermal thinning.

4.ARBUTIN



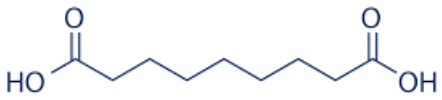
STRUCTURE-ARBUTIN

Arbutin, derived from the bearberry plant, is a naturally occurringHQ beta-D-glucopyranoside. It is commonly used in the productionof cosmetic agents and is known to exhibit depigmenting activity atnontoxic concentrations.Arbutin has been demonstrated tosuppress tyrosinase activity without affecting its messenger RNAexpression, and to inhibit 5,6-dihydroxyindole-2-carboxylic acid(DHICA) polymerase activity.In a randomized, open-label

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

studyconducted by Ertam et al,melanin level was significantlydecreased in 10 melasma patients treated with 1% arbutin for 6months.

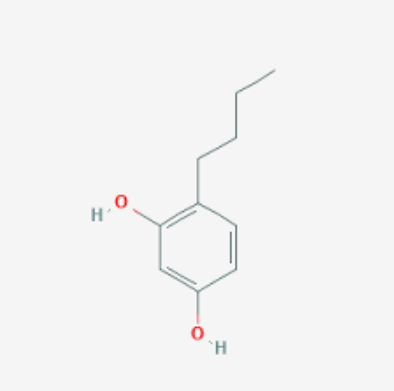
5.AZELIC ACID.



STRUCTURE -AZELAIC ACID

Azelaic acid is a naturally derived dicarboxylic acid present inMalassezia furfur. It inhibits tyrosinase activity, leading to thehypopigmented macules commonly observed in tinea versicolor.Bali-na and Graupecompared the efficacy of 20% azelaic acid andHQ in the treatment of melasma. In that 24-week trial, 64.8% ofpatients treated with azelaic acid exhibited "good" or "excellent"results, whereas 72.5% of patients treated with 4% HQ also reportedthe same results. Thus, it was concluded that there was no significantdifference in efficacy between these two treatments, and severeside effects (e.g., allergic sensitization or exogenousochronosis) were not observed with azelaic acid.

6.4-N-BUTYLRESORCINOL



STRUCTURE-4-N-BUTYLRESORCINOL

4-n-Butylresorcinol also directly inhibits the activities of tyrosinaseand tyrosinase-related protein-1 (TRP-1).We havedemonstrated the efficacy of this compound in several previousclinical trials.In a randomized controlled split-face trial, 0.1% 4-n-butylresorcinol cream showed rapid efficacy with excellenttolerability in patients with melasma.In another randomized,double-blind, vehicle-controlled, split-face study,liposome-encapsulated 4-n-butylresorcinol had significantlyreduced the melanin index after 8 weeks of application, withoutany occurrence of adverse events.

New approaches to developing depigmenting agents

The data described herein indicate that HQ is not a safe tyrosinaseinhibitor and that it is necessary to develop novel topical agents forthe treatment of pigmentary disorders. 4-n-Butylresorcinol may beused to produce a safe cosmetic agent, with the clinical efficacyrequired of a pharmacological agent. Furthermore, a multitargetapproach is necessary because the combined use of two agentswith different mechanisms of action can produce more powerful,additive effects. For example, 4-n-butylresorcinol acts mainly byinhibition of

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 851-862 www.ijprajournal.com ISSN: 2249-7781

tyrosinase activity and has no effect on MITF. However,when combined with hinokitiol, an additive effect is producedwhich reduces MITF expression.The combination of two agentswith different mechanisms may therefore be another useful strategyfor increasing the efficacy of these agents.

ACKNOWLEDGEMENT:

We would like to show my appreciation towards our supervisor Dr. Pratima Shinde, Assistant Professor, HOD, Department of Pharmaceutics, Siddhant College of Pharmacy, Sudumbare, Pune for her Support, guidance and encouragement.

CONCLUSION-

Whitening agents are largely represented in global landscape. The need for and fair skin is highly capitalized by both the cosmetic and dermatogistologic industries. Tyrosinase has become important targets for the development of hypo-pigmenting agents and thus tyrosinase is mostly studiedtarget for inhibiting the melanogenesis. Many drugs such as HQ, arbutin, kojic acid, etc. are used as tyrosinase inhibitors but they also show many side effects as discussed in review. Thus, there is great need for development of novel drugs with no side effects.

The review also focuses on recent studies on skin whitening agents such as chalcones, coumarin derivatives, thiourea, etc. repurposing of existing drugs has become one of the important approaches in drug discovery program of development potent melanogenesis inhibitor.

In conclusion there is great need for development of novel drugs as skin whitening agents. Therefore, more clinical studies are needed for designing and developing new products.

REFERNCES-

[1]. J.D. Bos, M.M. Meinardi, The 500 Dalton rule for the skin penetration of chemicalcompounds and drugs, Exp. Dermatol.: Viewpoint 9 (3) (2000) 165–169.

[2]. M. Saeedi, An Overview of Cosmetics and Toiletries, Shelfin Inc, 2013.

[3]. S.A. Nasrollahi, et al., Cell-penetrating peptides as a novel transdermal drug deliverysystem, Chem. Biol. Drug Des. 80 (5) (2012) 639–646.

[4]. N. Ookubo, et al., The transdermal inhibition of melanogenesis by a cell-membranepermeable peptide delivery system based on poly-arginine, Biomaterials 35(15) (2014) 4508–4516.

[5]. K. Khezri, M. Saeedi, S.M. Dizaj, Application of nanoparticles in percutaneousdelivery of active ingredients in cosmetic preparations, Biomed. Pharmacother106 (2018) 1499–1505.

[6]. Gupta AK, Gover MD, Nouri K, Taylor S. The treatment of melasma: a review ofclinical trials. J Am Acad Dermatol 2006; 55:1048e65.

[7]. Amer M, Metwalli M. Topical hydroquinone in the treatment of some hyperpigmentarydisorders. Int J Dermatol 1998; 37:449e50.

[8]. Tan SK, Sim CS, Goh CL. Hydroquinone-induced exogenous ochronosis in Chinesedtwocase reports and a review. Int J Dermatol 2008;47:639e40.

[9]. Haddad AL, Matos LF, Brunstein F, Ferreira LM, Silva A, Costa Jr D. A clinical,prospective, randomized, double-blind trial comparing skin whitening complexwith hydroquinone vs. placebo in the treatment of melasma. Int J Dermatol2003;42:153e6.

[10]. Park K-C, Huh SY, Choi HR, Kim D-S. Biology of melanogenesis and the searchfor hypopigmenting agents. Dermatol Sin 2010;28:53e8.

[11]. Briganti S, Camera E, Picardo M. Chemical and instrumental approaches to treathyperpigmentation. Pigment Cell Res 2003;16:101e10.

[12]. Cooksey, C.J.; Garratt, P.J.; Land, E.J.; Pavel, S.; Ramsden, C.A.; Riley, P.A.; Smit, N.P.Evidence of the indirect formation of the catecholic intermediate substrate responsible for theautoactivation kinetics of tyrosinase. J. Biol. Chem. **1997**, 272, 26226–26235.

[13]. Riley, P.A. Hydroxyanisole depigmentation: In-vitro studies. J. Pathol. **1969**, 97, 193–206.

[14]. Riley, P.A. Hydroxyanisole depigmentation: In-vivo studies. J. Pathol. **1969**, 97, 185–191.

[15]. Naish-Byfield, S.; Cooksey, C.J.; Latter, A.M.; Johnson, C.I.; Riley, P.A. In vitro assessment ofthe structure-activity relationship of tyrosinase-dependent cytotoxicity of a series of substitutedphenols. Melanoma. Res. **1991**, 1, 273–287.

[16]. Smit, N.P.; Peters, K.; Menko, W.; Westerhof, W.; Pavel, S.; Riley, P.A. Cytotoxicity of aselected series of substituted phenols towards cultured melanoma cells. Melanoma Res. **1992**, 2,295–304.
[17]. Available from: http://www.sironabiochem.com/products/skinlightening/
[18]. Francisco S, Stefania B, Mauro P, et al. Hypo pigmenting agents: an updated review on biological, chemical and clinicalaspects. Pigment Cell Res 2006;19:550–7.
[19]. Tsatmali M, Ancans J, Thody AJ. Melanocyte function andits control by melanocortin peptides. J Histochem Cytochem 2002;50:125–33.
[20]. Costin GE, Hearing VJ. Human skin pigmentation: melanocytesmodulate skin color in response to stress. FASEB J2007;21:976–94.Villarama CD, Maibach HI. Glutathione as a depigmentingagent: An overview. Int J Cosmet Sci 2005;27:147-53.
[21]. Hospers GA, Eisenhauer EA, de Vries EG. The sulfhydrylcontaining compounds WR-2721 and glutathione as radio-andchemoprotective agents. A review, indications for use andprospects. Br J Cancer 1999;80:629-38.
[22]. Arjinpathana N, Asawanonda P. Glutathione as an oral whiteningagent: A randomized, double-blind, placebo-controlled study.J Dermatolog Treat 2012;23:97-102.
[23]. Witschi A, Reddy S, Stofer B, Lauterburg BH. The systemicavailability of oral glutathione. Eur J Clin Pharmacol1992;43:667-9.
[24]. Hong SY, Gil HW, Yang JO, Lee EY, Kim HK, Kim SH, et al.Pharmacokinetics of glutathione and its metabolites in normalsubjects. J Korean Med Sci 2005;20:721-6.
[25]. Scarpa, A.; Guerci, A. Depigmenting procedures and drugs employed by melanoderm populations.J. Ethnopharmacol. **1987**, 19, 17–66.
[26]. Kamagaju, L.; Bizuru, E.; Minani, V.; Morandini, R.; Stévigny, C.; Ghanem, G.; Duez, P. An ethnobotanicalsurvey of medicinal plants used in Rwanda for voluntary depigmentation. J. Ethnopharmacol. **2013**,150, 708–717.
[27]. Fiori, F.; Andrisano, V. LC–MS method for the simultaneous determination of six glucocorticoids in pharmaceutical formulations and counterfeit cosmetic products. J. Pharm. Biomed. Anal. **2014**, 91, 185–192.
[28]. Perry, A.; Petit, A.; Bagot, M.; Villa, A.; Bellaiche, M.; Bourrat, E. Intoxication au mercure par procuration chez un enfant: Une nouvelle complication de la depigmentation volontaire. Arch. Pédiatr. **2014**, 21, 22–24. (In French)
[29]. Sène, D.; Huong-Boutin, D.L.T.; Thiollet, M.; Barete, S.; Cacoub, P.; Piette, J.C. Insuffisance surrénalienne haute symptomatique compliquant l'usage de dermocorticoïdes pour depigmentation volontaire.
[30]. Pillaiyar T, Manickam M and Namasivayam V: Skin whitening agents: Medicinal chemistry perspective of tyrosinase inhibitors. J Enzyme Inhib Med Chem 32: 403-425, 2017.
[31]. Videira IF, Moura DF and Magina S: Mechanisms regulating melanogenesis. An Bras Dermatol 88: 76-83, 2013.
[32]. D'Mello SA, Finlay GJ, Baguley BC and Askarian-Amiri ME: Signaling pathways in melanogenesis. Int J Mol Sci 17: pii: E1144, 2016.
[33]. Gillbro JM and Olsson MJ: The melanogenesis and mechanisms of skin-lightening agents--existing and new approaches. Int J Cosmet Sci 33: 210-221, 2011.
[34]. Desmedt B, Courselle P, De Beer JO, Rogiers V, Grosber M, Deconinck E and De Paepe K: Overview of skin whitening agents with an insight into the illegal cosmetic market in Europe. J Eur Acad Dermatol Venereol 30: 943-950, 2016.
[35]. Available from: http://cosmetics.specialchem.com/news/industry-news/skin-lightening-products-market-to-reach-usd 23-bn-by-2020-global-industry-analysts (Published on 2015-02-16)