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EXPLORING MELANOGENESIS IN ZEBRAFISH MODEL: INSIGHTS INTO DEPIGMENTATION MECHANISMS AND TREATMENT STRATEGIES

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ABSTRACT: Melanin synthesis and the function of zebrafish as a model organism in the study of depigmentation are thoroughly explored in the review article on melanogenesis and zebrafish. Melanogenesis, the process by which melanin is produced, depends on melanocytes, which are found in the basal layer of the epidermis. Pigmentation levels are controlled by a number of intrinsic (released by keratinocytes and fibroblasts, endocrine, inflammatory, and neurological cells) and extrinsic (drugs and UVR) regulatory mechanisms. Tyrosinase and other substrates, as well as l-tyrosine and L-dopa, are involved in the process of melanogenesis. Because of their genetic similarity to human pigmentation, zebrafish provide important insights into the processes involved in melanogenesis, the development of skin structure, and pigment cell systems. Along with discussing the causes of skin pigmentation, the mechanisms and signaling pathways that activate melanogenesis are also covered in the article. Treatment options for hyperpigmentation disorders include topical creams, oral medicines, chemical peels, and laser therapy. Because zebrafish pigment cells are produced from neural crest stem cells and resemble human melanocytes, they are an excellent model to investigate the processes involved in pigment synthesis and skin pigmentation.
Key words: Depigementation, Melanocyte, Melanogenesis, Pigment, Skin structure, Zebrafish

I. INTRODUCTION

The skin is an essential organ in human body which shields the skin from harmful substances and its is the source of different cells like keratinocytes and melanocytes which are found in the basal layer of epidermis (Boer M, *et.al*. 2016]. In the basal layer of epidermis, the melanocyte containing melanosomes which is an unique organelle whose primary function is the synthesis of melanin during a physiological process known as melanogenesis. A number of regulatory factors can alter essential pigmentation, which is a reflection of the amount of melanin that is genetically determined. These can be extrinsic (drugs and UVR) or intrinsic (released by keratinocytes and fibroblasts, endocrine, inflammatory, and neurological cells) (Cichorek M.*et.al.*,2013).

Melanogenesis is a multi-stage, intricate process that is mediated by a variety of enzymes. The metalloenzyme tyrosinase, which contains copper and aids in the synthesis of melanin in melanosomes, is a crucial enzyme in the process of melanogenesis. Tyrosine undergoes several metabolic processes that lead to the production of melanin with the aid of tyrosinase(Sanchez-Ferrer A *et.al.*, 1995 and Van Holde KE *et.al.*, 2001). 4,5 l-tyrosine and l-3,4-dihydroxyphenylalanine (L-dopa) are the important substrates involved in melanin biosynthesis (Solminski A, Constantino R., 1991a,b).

1.1 ZEBRAFISH:

In the 1970s, developmental researchers discovered that zebrafish could be a valuable resource due to their rapidly organogenesis and translucent embryos. Thousands of mutations were created in zebrafish throughout the 1990s, some of which mimicked human diseases, making them the first vertebrate large-scale mutagenesis screen. Because of their genetic resemblance to human pigmentation, zebrafish are gaining popularity as a lower vertebrate

model in the research of depigmentation. Due to their numerous traits that make them attractive for drug development—high fecundity, transparent embryos (Westerfield, M. 2000), real-time imaging (Eisen, J.S. 1996 and Fishman, M.C.1999), genetic similarities, conserved pathways, and the ability to study and treat illnesses- zebrafish are the most important research tool of the modern era.

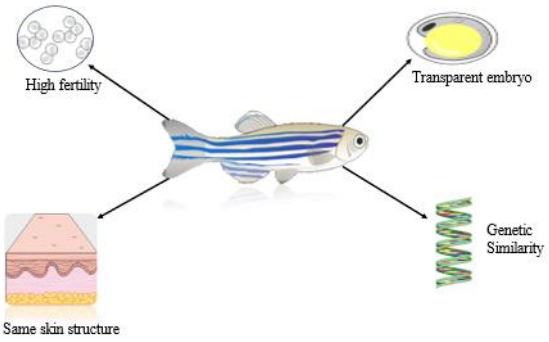

Figure 1 : Zebrafish advantages as a research model

1.2 ZEBRAFISH MODEL IN MELANOGENSIS:

The skin of zebrafish is composed of a multilayer epidermis and a collagenous stroma that is rich in fibroblastic cells and distinct keratinocytes. Furthermore, a vital characteristic of zebrafish skin is the existence of a pigment cell system (Cline A et.al.,2016 and Naomi R et.al., 2021). Zebrafish epidermis, dermis, and hypodermis are very comparable to human skin. Both the keratinized outer layer of human skin and mammalian appendages like as hair follicles and sebaceous glands are absent from it. The zebrafish is also a highly sought-after model for dermatological investigations since it develops parts of its dermis and epidermis as early as 1 day post-fertilization (dpf) and its skin structure fully develops 6 dpf. Nevertheless, the examination of that non-mammalian vertebrate model is an essential part of research concerning skin (Russo I. et.al.,2022). It has long been known that human participant clinical trials and preclinical research using in vivo models, such mice and guinea pigs, are trustworthy ways to assess the efficacy of various depigmenting therapies (Lin et.al., 2011, Mustafa et.al., 2014, Rizza et.al., 2012, Senthil Kumar et.al., 2013, Lee, B et.al., 2016, Tobiishi et.al., 2005). These models have many benefits, but they also have many downsides, particularly when it comes to morality, animal welfare, and ethical endpoints at facilities that conduct animal testing. All *in vivo* model research must adhere to ethical committee criteria, which include the complete application of the "3 Rs" (Replacement, Refinement, and Reduction). Zebrafish have been suggested as a possible depigmenting model based on these ideas. The medical and cosmetic industries are using this lower vertebrate more and more frequently (Kulkeaw, K *et.al.*, 2011, Singh A.P et.al., 2013, Choi et.al., 2007, Jin et.al., 1999).

The use of the zebrafish model in the research of pigment diseases is growing due to its conserved melanogenesis pathway and the ability to observe melanin production in melanophores as early as 1 dpf. Zebrafish pigment cells are derived from neural crest stem cells. Melanophores are what they produce. The appearance of melanocytes and melanophores is similar. Melanophores are located in the epidermis and hypodermis and do not transmit melanin, whereas melanocytes stay in the epidermis and transfer melanin to keratinocytes. However, the biology of melanophores and melanocytes is comparable. The model organism has many conserved genes that are similar to those in the human body and control melanocyte function and pigment synthesis, such as MITF, TYR, and TYRP1. Moreover, it has been found that the signaling pathways that control MITF activity in human and zebrafish pigment cells include MC1R, WNT, c-KIT, and ETBR (Neuffer S.J, Cooper C.D. 2022).

II. MECHANISM OF MELANOGENSIS:

Melanocytes are cells that produce pigment and are found in the iris of the eye, hair follicles, and the epidermis, the outermost layer of the skin. Melanin, which is what gives humans their color, is made by these cells. One important substance that protects human skin from UV rays is melanin. Sunlight-induced UV radiation causes the production of reactive oxygen species and reactive nitrogen species, which can cause inflammation, collagen deterioration, and DNA-damaged epidermal hyperplasia, among other cutaneous problems. In addition to causing excessive melanin synthesis, UV radiation exposure to the skin activates tyrosinase, a crucial enzyme in the process of melanogenesis that also damages DNA, induces inflammation, and causes various skin conditions (Solano.F et.al., 2006, Gillbro, J.M et.al., 2011, Simon, J.D et.al., 2009, D'Lschia, M et.al., 2013, Haq, R et.al., 2013).

First, the amino acid L-tyrosine initiates the melanogenesis process. Tyrosinase, an enzyme that is thought to be essential to the process, hydroxylates tyrosine to form L-dopa. L-dopa is subsequently oxidized to produce dopaquinone, an unstable step in the melanogenesis process. Dopachrome is oxidized by TRP-2 to 5,6-dihydroxyindole-2-carboxylic acid (DHICA), and TRP-1 facilitates the oxidation process that transforms DHICA into carboxylated indole-quinone (Barber JI et.al.,1984, Kobayashi T et.al., 1994). Dopaquinone combines with thiol compounds to form pheomelanin when they are present (Lee SY et.al., 2016). Conversely, in the absence of thiol compounds, dopaquinone undergoes many enzymatic processes to generate eumelanin (Burchill SA et.al., 1986). The fate of the human skin color phenotype is principally determined by the ratio and concentration of pheomelanin and eumelanin (Ito S et.al., 2003).

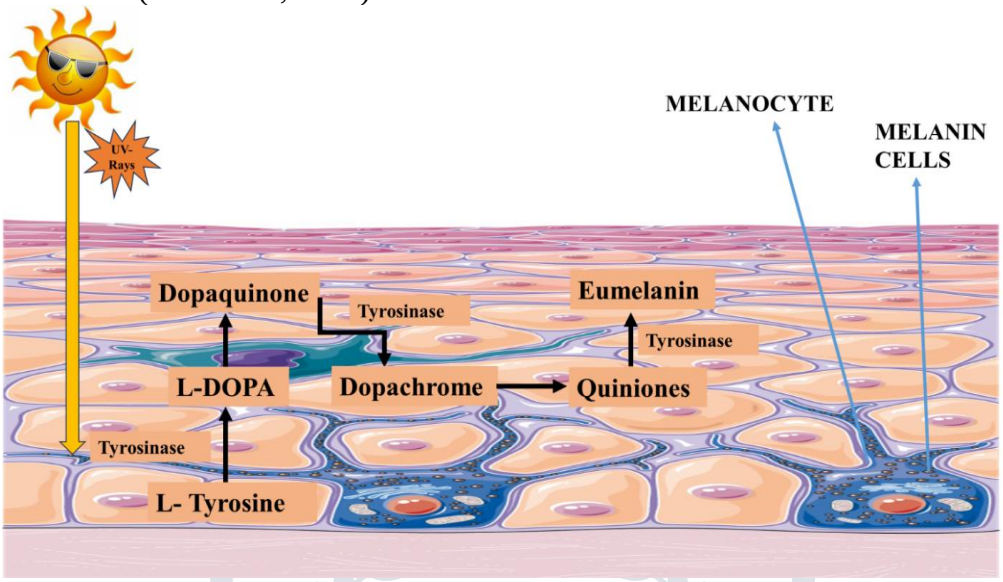

figure 02: mechanism of melanogenesis in melanocyte

III. SIGNALING PATHWAYS ACTIVATING MELANOGENISIS:

During physiological responses, the synthesis of melanin is dependent on several key enzymes and signaling pathways, including α-melanocyte-stimulating hormone (α-MSH), c-Kit, adrenergic receptors, melanocortin 1 receptor (MC1R), and Wnt receptors that interact with Wnt hormones, adrenaline, noradrenaline, and stem cell factor (SCF) (Cao, H. et.al., 2014, Huang, H.C et.al., 2013, Kim, K.N et.al., 2013, Su, T.R et.al., 2013). Following the activation of the c-Kit receptor by SCF, MAP (mitogen-activated protein) kinase and MITF are also activated. The binding of cAMP, which in turn encourages the activation of CREB and PKA, is triggered by the binding of adrenaline and noradrenaline to adrenergic receptors. In the end, this route results in MITF activation. MC1R receptors interact with cAMP via the same adrenergic receptor pathway that activates them in response to ACTH and α-MSH. Nitrogen oxygen (NO) radicals activate guanylate cyclase via a separate pathway, which in turn activates cGMP and MITF. Wnt receptor suppression of phosphorylation in GSK3β increases β-catenin and promotes phosphorylation, which accelerates anti-melanogenesis; specifically, wnt receptor activation increases β-catenin and the LEF/TCA complex, and activates MITF (Chung K.W et.al., 2013, Kim S.S et.al., 2013, Kim A et.al., 2008, Singh, S.K et.al., 2005). Tyrosinase, TRP-1 (DCT), TRP-2 (also called DOPA chrome tautomerase; DCT), and PKC-β are all expressed more in the process described above when MITF is active. As a result, melanin is generated. Conversely, dephosphorylation of MITF activates MITF, whilst phosphorylation of MEK/ERK and P13K/AKT in the extracellular signaling pathway downregulates MITF and has anti-melanogenesis effects.

table 1: various activation pathway of melanogenesis and its function

Component	Activation Pathway	Function
Stimulants		
α-MSH	Activation of MC1R → cAMP → MITF	Stimulates melanin synthesis
c- kit	Activation by SCF→ MAP kinase → MITF	Leads to MITF activation
Adrenergic receptors	Binding of adrenaline/noradrenaline → cAMP→ MITF	Triggers MITF activation through cAMP pathway

MC1R	Activation by ACTH/ α-MSH → cAMP→ MITF	Stimulates melanin synthesis through cAMP pathway
Wnt receptors	Activation→ β-catenin→ LEF/TCA complex→ MITF	Leads to MITF activation
ACTIVATION PATHWAYS		
SCF	Activates c-kit	Starts MAP kinase pathway which leads to activation of MITF
Adrenaline/noradrenaline	Binds to adrenergic receptors	Triggers cAMP production leading to MIFT activation
NO radicals	Activates guanylate cyclase	Induces cGMP production leading to MITF activation
MITF ACTIVATION		
MITF	Activated by MAP kinase, cAMP, cGMP,	Transcription factor regulating melanin synthesis
Tyrosinase	More expressed when MITF is active	Enzyme catalysing melanin synthesis
TRP-1(DCT)		Involved in melanin synthesis
TRP-2 (DCT)		
PKC-β		
REGULATION OF MITF		
Phosphorylation of MEK/ERK	Downregulation MITF	Inhibits melanin synthesis
Phosphorylation of P13K/AKT		
Dephosphorylation of MITF	Stimulates MITF	Promotes melanin

IV. CAUSES OF MELANOGENSIS:

a. Genetics: It turns revealed that skin tone is influenced by 125 genes. Genes and hormones govern the synthesis of melanin. By controlling their usage of medication and cosmetics, sun exposure, and other circumstances, an individual can control the amount of pheomelanin or eumelanin produced by their skin. These elements could cause the skin's tone to shift over time (Del Bino S et.al., 2018). Thus, one of the most frequent reasons of skin color is genetics. Genetics may make it possible to predict a person's melanocyte count. The skin cells known as melanocytes are in charge of making melanin. When tanning and hyperpigmentation occur, melanin-containing organelles called melanosomes must be transported and expanded; when hypopigmentation occurs, they contract (Suherlan S et.al., 2021). The pigment that gives skin its color, melanin, is more likely to be present in larger concentrations in those with darker skin tones. For instance, melanin levels are often higher in people with darker skin tones than in people with lighter skin tones (Jablonski N.G. 2021, Ainger S.A et.al., 2017, Feng Y et.al., 2021).

b. Sun exposure: Sun exposure is a major contributor to skin pigmentation. The body releases more melanin to shield itself from the sun's UV rays. This could enhance skin pigmentation in order to shield the skin from the sun's rays. These phases make up the formation mechanism.

Phase 1: UV radiation produces free radicals.

Phase 2 : UV light and free radicals are the biological agents that impact melanocytes

Phase 3: The enzymatic agent tyrosinase processes the amino acid tyrosine into the reddish-brown pigments known as melanin.

Phase 4: Biological compounds stimulate the pigment-producing enzyme Tyrosinase more than other substances.

Phase 5: The skin exfoliates and sheds melanin. Melanin is released as granules by nearby keratinocytes to give the skin its color (Solano F. 2020, Feng Y et.al., 2021, Kita R et.al., 2016).

c. Medication: It is possible for certain medications to lighten skin pigmentation. A particular category of drugs that can enhance the production of melanin, the pigment that darkens skin, is antibiotics. Concurrent use of some medications, such as birth control pills, may further exacerbate skin pigmentation. To find out if any medications could alter their skin tone, a patient should speak with their doctor (Armenta A.M et.al., 2019 and Adigun C.G. 2016).

V. TREATMENTS:

a. Topical creams: Skin hyperpigmentation at a particular place can be treated or managed with a range of topical dosage formulations, such as creams and gels. Applying hydroquinone topically has been a treatment for hyperpigmentation since the 1960s. It functions by inhibiting tyrosinase, which stops the synthesis of melanin. The items with strengths up to 4% are now on the market (Haddad, A. L et.al., 2003). Another medication that has a lot less melanotoxic effects is arbutin, a hydroquinone derivative. Its depigmenting effect is caused by suppression of tyrosinase and inhibition of melanosome development. Arbutin has a dose-dependent anti-tyrosinase effect, although utilizing higher doses must be done so cautiously as it can cause paradoxical hyperpigmentation (Piamphongsant, T. 1998). The crystalline alpha hydroxy acid known as glycolic acid is white and derived from sugarcane (Van Scott, E. J et.al., 1996). The effects of varying concentrations of glycolic acid. It induces keratinocytes to desquamate at lower dosages and promotes epidermolysis at higher ones (Fischer, T. C et.al., 2010). For hyperpigmentation problems, kojic acid is often used due to its several actions, one of which is tyrosinase suppression. Tyrosinase's ability to function as a catecholase is principally inhibited by it. based on an alternative study. The depigmenting and anti-melanogenesis effects of the drug are caused by the formation of interleukin-6 protein by kojic acid in keratinocytes (Cabanes, J et.al., 1994). Still, multiple studies have demonstrated that contact dermatitis is a common side effect of kojic acid therapy (Nakagawa, M et.al., 1995).

b. Oral treatments: Tranexamic acid is one of the oral drugs used as a second-line treatment for hyperpigmentation. Studies on guinea pig skin showed that it inhibits UV-induced plasmin activity, which reduces the activity of the tyrosinase enzyme. Prostaglandins and arachidonic acid levels consequently decline, which in turn has an impact on the tyrosinase enzyme (Cho, H. H et.al., 2013, Kato, H et.al., 2011). Melatonin is a free radical scavenger and antioxidant that is released by the pineal gland. It also inhibits the α MSH receptor and activates several antioxidant enzymes, such as glutathione peroxidase. When topical melatonin was applied alone, in conjunction with oral melatonin and 4% hydroquinone, or both, a study revealed that all melasma patients had much less pigmentation. It also led to a decrease in oxidative stress as evidenced by a rise in glutathione and a decrease in malondialdehyde (Hamadi, Salim A *et al.*, 2009).

c. Chemical Peels: For many hyperpigmentation problems, chemical peels are a frequent treatment. Chemical peels work by desquamating the outermost superficial layers of the stratum corneum. 14% resorcinol, 14% lactic acid, and 14% salicylic acid are present in Jessner's solution, an alcohol-based chemical peel. With good safety and performance, it has been used widely for a number of years as a medium depth chemical peel, de-keratinizing agent, and even penetration booster. Investigated studies showed the effects of Jessner's solution chemical peel on sixty Asian melasma patients in a randomized experiment. After 12 weeks of treatment, the melasma Area Severity Index (MASI) scores significantly decreased from the baseline 6.5+/-3.84 to 2.9+/-3.03 (Ejaz, A et.al., 2008). Because Tretinoin peels can produce similar outcomes to topical Tretinoin in terms of therapy and histology, but in a shorter amount of time—2.5 weeks as opposed to 4-6 months—they have been studied (Cuce, L. C et.al., 2001). A study found that increasing the concentration of Tretinoin peel from 1% to 10% decreased the length of skin contact from 4–8 hours to just 1 hour, all while maintaining the same efficacy (Ghersetich, I., Troiano, M., Brazzini, B., *et al*., 2010). Peels containing glycolic acid have also been demonstrated to be effective in treating hyperpigmentation disorders like as melasma and post-inflammatory hyperpigmentation. Peels can be used to treat a number of hyperpigmentation problems, although there is often worry due to their high concentration and potential side effects (Fischer, T. C., Perosino, E., Poli, F., *et al*., 2010).

d. Laser therpay: The process of Laser Therapy Light Amplification by Stimulated Emission of Radiation (Lasers) produces coherent light that is monochromatic and intense. Treatment options for skin conditions have evolved since the introduction of laser therapy, especially for hyperpigmentation. Despite the fact that opinions on laser therapy's efficacy and safety are still being debated, many individuals with hyperpigmentation problems have shown improvement. Intense pulsed light, or IPL, has shown promising improvements in the treatment of hyperpigmentation. This procedure makes use of a xenon-chloride lamp that emits light throughout a wide spectrum. Because characteristics like wavelength and fluence may be changed, it is commonly used for melanocytic lesions, vascular lesions, hair removal, and melasma (Sarkar, R., Garg, V., Arya, L., & Arora, P. 2012). Lowering the risk of post-inflammatory hyperpigmentation, the erbium:YAG laser's wavelength of 2940 nm allows for less thermal harm during skin ablation(Manaloto, R. M. P., & Alster, T. 1999).

5.1 NOVEL THERAPIES:

a. Nanostructured Lipid Carriers (NLC) and Solid Lipid Nanoparticles (SLN): Lipid carriers with nanostructure (NLC) and solid lipid nanoparticles (SLN) SLN and NLC are being studied as appealing candidates for topical distribution because they moisturize the stratum corneum and enhance drug penetration when they form an occlusive layer on the skin's surface. Enhanced stability, high drug loading, and

bioavailability are only a few of their many advantages. As a result, many anti-hyperpigmentation drugs have been created as lipid nanocarriers, including tyrosinase inhibitors. hydroquinone SLNs gel showed better drug-localization and skin targeting due to a larger hydroquinone deposition in the skin epidermis (46.5 ± 2.6%) than the hydroquinone gel (Ghanbarzadeh, S., Hariri, R., Kouhsoltani, M., *et al.*, 2015) . Kojic acid It has been demonstrated that SLNs have enhanced tyrosinase inhibitory action and controlled release in contrast to conventional kojic acid (Khezri, K., Saeedi, M., *et al.*, 2020). To lighten skin tone, curcumin, a well-known phytoconstituent, was combined to solid lipid nanoparticles (CUR SLNs). Studies on drug deposition also showed that after 24 hours, the CUR-SLN gel maintained more medication in the skin (82.32 ± 0.39%) than the traditional CUR gel (28 ± 0.24%). It is safe to apply the CUR-SLN gel topically as it passed skin irritation testing without producing erythema or irritation (Shrotriya, S., Ranpise, N., *et al.*, 2018). With such encouraging outcomes, SLN and NLC may be studied further and used to treat.

b. Phytochemicals: Phytochemicals, which are natural compounds extracted or produced from plants, have been used as a treatment for skin hyperpigmentation due to their ability to reduce melanogenesis through a variety of mechanisms. Aloe vera is known to contain the glycoprotein aloesin, which has been shown to have dose-dependent anti-tyrosinase activity. It keeps L-DOPA from oxidizing, and it has shown a greater affinity than kojic acid, arbutin, and other similar compounds. Its hydrophilicity and high molecular weight, however, have hampered its penetration of the stratum corneum, indicating the need for more effective novel delivery techniques (Choi, S., Park, Y. I., Lee, *et al.*, 2002). It has been demonstrated that the polyphenol ellagic acid reduces tyrosinase and melanogenesis. Ellagic acid was discovered in a study with thirty female melasma patients to significantly reduce the development of melanin (Ertam, I., Mutlu, B., *et al.*, 2008). Comparably, two flavonoids, resveratrol and silymarin, exhibit anti-inflammatory and photoprotective properties through a number of mechanisms, such as the suppression of UV-induced oxidative stress, DNA damage, and apoptosis (Choo, S.-J., *et al.*, 2009 and Kasai, K., *et.al.*,2006). Therefore, more studies on phytochemicals may be required to see how well they complement existing treatments to manage hyperpigmentation. It's also important to keep in mind that natural materials might occasionally include corticosteroids, which can taint them and increase the risk of allergic and phototoxic reactions.

c. Fractional Photothermolysis: This is a more modern form of laser therapy that preserves much of the skin's surface while producing multiple tiny thermal injury zones that act as a healing reservoir. The pigmentation in the basal layer is found in the microscopic epidermal necrotic debris (MENDs), which is extruded from the thermal damage zones (also referred to as microthermal treatment zones, or MTZ). The migration of MENDs is then aided by the keratinocytes around the wound's perimeter (Katz, T. M., Glaich, A. S., Goldberg, L. H., *et al.*, 2010). A randomized research found that 5% trichloroacetic acid was not as effective as fractional photothermolysis in improving MASI scores in patients with melasma. Almost one-third of the patients had recovered from post-inflammatory hyperpigmentation by the time the treatment was completed (Hong, S. P., *et al.*, 2012). In another study, ten female patients with melasma received four to six sessions separated by one to two weeks using fractional photothermolysis. According to the results, only thirty percent of the patients had less than 25% improvement, while sixty percent of them had a 75–100% lightening of their initial pigmentation (Rokhsar, C. K., & Fitzpatrick, R. E. 2005).

table 02 : different bioactive componds and its *invitro* and *invivo* studies

S. No	Bioactive compound	Melanin production	*In-vitro* studies	Results	*In-vivo* studies	Results	Ref
1.	Coumarin	Decreases	Mouse B16 melanoma cells	The treatment of a-MSH-stimulated B16 cells with each of phenyl-coumarins has decreased both melanin content and tyrosinase activity	Zebrafish	The treatment of phenyl coumarins in zebrafish larvae showed depigmentation and less toxicity than kojic acid and hydroquionone	Veselinović JB et.al., 2017
2.	Fisetin	Decreases	B16F10 Cells	Fisetin significantly increased intracellular and extracellular melanin production in B16F10 melanoma cells regardless of the presence or absence of α-melanocyte stimulating hormone (α-MSH).	Zebrafish	Pigmentation of zebrafish larvae by fisetin treatment decreased with no alteration in heartrates	Molagoda, Neelaka et.al., 2020
3.	Gallic acid	Decreases	B16 F10 Melanoma cells	Gallic acid treatment significantly and dose-dependently inhibited the cellular melanin content in melanoma cells	Zebrafish B6 Mice	Zebrafish: The body pigmentation in the zebrafish was remarkably decreased when 24 h post-fertilized embryos were exposed to GA for 36 h. B6 mice: After applying GA on ear skin of B6 mice, a substantial decrease in hyperpigmentation was observed after 4 weeks of GA treatment.	Kumar KJ et.al., 2013
4.	Seasamol	Decreases	Melanin cells	The present results indicate that sesamol inhibits melanin synthesis in melanoma cells by regulating cAMP, p38 MAP kinase and JNK MAP kinase signalling to suppress MITF, as well as inducing destruction of Tyr via proteasomal and lysosomal degradation	Zebrafish	Treatment of zebrafish embryos with sesamol for 72 h at concentrations up to 50 μM significantly inhibited skin melanin formation in developed larvae	Seunghwa Baek et.al., 2015

5.	Kaempferol	Increases	B16F10 Cells	B16F10 cells, it had markedly increased melanin level.	Zebrafish	In zebrafish, it has shown a positive response on melanogenesis.	Huihao Tang, *et.al.*, 2021
6.	Myricetin	Decreases	Anti-tyrosinase assay	Mearnsetin > myricetin > gallic acid.	Zebrafish	*In-vivo* assay revealed that myricetin showed anti melanogenic activity	Huang CY et.al., 2021
7.	DeoxyArbutin	Decreases	Mushroom tyrosinase Melanoma cells	DeoxyArbutin was effective in inhibiting tyrosinase activity. Arbutin<HQ<dA	Guinea pigs and in humans	3% 12 weeks 34 Caucasian 16 ethnic	Boissy RE et.al., 2005
8.	Hesperidin	Decreases	B16F10 Cells	Hesperidin, stimulated Erk1/2 phosphorylati-on which subsequently degraded MITF which resulted in suppression of melanogenic enzymes and melanin synthesis.			Lee HJ et.al., 2015
9.	Apigenin	Increased	B16F1 melanoma cells	Apigenin promotes melano-genesis by activating the p38 MAPK pathway			Yan Ye et.al., 2011
10.	Ascorbic acid	Increases	B16F10 melanoma cells	Ascorbic acid at 100 l M increased significantly melanin content and proliferation in B16F10 melanoma cells			Lee SA et.al., 2011

VI. Inhibition of Melanogenesis through Tyrosinase Inhibition:

Every component in the anti-melanogenesis mixture works by inhibiting various pathways. There are five techniques used. The inhibition of tyrosinase mRNA transcription, aberrant tyrosinase maturation, inhibition of tyrosinase catalytic activity, acceleration of tyrosinase degradation, and indirect regulation are the mechanisms that indirectly control tyrosinase activity (Ando, H.; Kondoh, H et.al., 2007). Tyrosinase has been the most widely used target for medications intended to lessen hyperpigmentation thus far (Solano.F et.al., 2006, Gillbro, J.M et.al., 2011, Simon, J.D et.al., 2009, D'Lschia, M et.al., 2013, Haq, R et.al., 2013). The regulation of tyrosinase activity provides the opportunity to regulate pigmentation in a number of ways. Numerous activities, such as mRNA transcription, glycosylation-mediated maturation, trafficking to melanosomes, and alteration of catalytic activity and/or stability, are impacted by tyrosinase regulation. Tyrosinase inhibitor-containing foods include mulberries, papaya, liquorice root, arbutin, glutathione, vitamin A (retinol), vitamin B3 (niacinamide), vitamin C, and kojic acid. The two that are still often utilized among them are arbutin and kojic acid because of their proven track records as effective whitening agents. Several synthetic and natural sources of tyrosinase inhibitors are known to exist (Takekoshi, S et.al., 2014 and Xie, L.P et.al., 2003).

VII. FUTURE SCOPE OF MELANOGENSIS IN ZEBRAFISH:

By using the zebrafish model to study the effects of various etiologies and therapies on individuals, researchers may be able to offer patients personalized therapy alternatives. Researchers studying pigmentation disorders now have greater resources at their disposal thanks to recent advancements in gene editing technology. Future research endeavors may employ gene editing methodologies to induce gene mutations in zebrafish models that mimic human pigmentation disorders, and subsequently examine the impact of these mutations on the disease's progression. Potential therapeutic targets can also be screened and assessed using the zebrafish model. The identification and confirmation of novel pharmacological targets should be the focus of future research in order to offer new options for the treatment of coloring disorders. Additional investigation into the extent of melanogenesis in zebrafish could focus on the genetic basis of pigment pattern creation, the role of microRNAs in regulating melanogenesis pathways, and the connections between melanocytes and other skin cell types. Moreover, new avenues for understanding the molecular mechanisms underlying zebrafish pigmentation may be opened by advances in imaging techniques such as live imaging of pigment cells in embryos and the development of high-throughput screening methods for identifying melanogenesis modulators. These areas have great potential for advancing our knowledge of melanogenesis and its implications for both basic research and potential therapeutic applications. As a result of scientific advancements and growing comprehension of zebrafish, researchers may now investigate disease pathophysiology and develop new treatments by utilizing zebrafish as a model organism to create animal models of skin pigmentation abnormalities. Future research should continue to explore the genesis of pigmentation disorders in detail, develop more effective treatments, and look into new therapeutic targets using technologies like gene editing and drug screening. These programs will benefit patients' quality of life and result in new discoveries about the treatment of hyperpigmentation disorders.

VIII. CONCLUSION:

A comprehensive overview of melanin formation and the significance of using zebrafish as a model organism for research on depigmentation. Melanocytes, which are found in the epidermis' basal layer, play a crucial role in the melanogenesis process, which produces melanin. In the process of melanogenesis the enzyme tyrosinase play an pivotal role. The study explores further into the processes and signaling routes that trigger melanogenesis, illuminating important enzymes and pathways such α-MSH, c-Kit, adrenergic receptors, MC1R, and Wnt receptors. A detailed discussion is held regarding the many factors that influence melanogenesis, including heredity, sun exposure, drug side effects, and available treatments including as chemical peels, oral pills, and topical creams. Zebrafish are an excellent source of information about melanogenesis pathways, skin structure development, and pigment cell systems because of their genetic resemblance to human pigmentation and their favorable study qualities. Current medical and cosmetic research relies heavily on the zebrafish model because of its conserved pathways, similar genetic makeup, and skin texture. In conclusion, the use of zebrafish models in research projects has potential to advance dermatology and solve the complexity of pigmentation problems highlighting its potential to further these fields.

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CONFLICT OF INTEREST

Authors does not have conflict of interest in the publication of this manuscript

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