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Natural Innovations in Hyperpigmentation Treatment: The Potential of Egg Shell Membrane and Quercetin

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Abstract
Hyperpigmentation (HP) is a prevalent skin condition characterized by the excessive production of melanin, leading to darker patches on the skin. Various factors, including sun exposure, hormonal changes, inflammation, and skin trauma, contribute to HP. The global HP treatment market was valued at $4.6 billion in 2022 and is expected to grow at a compound annual growth rate (CAGR) of 7.6% due to increasing demand for effective treatments. Current treatments for HP, including hydroquinone, arbutin, cysteamine, and kojic acid, primarily inhibit tyrosinase activity but often lead to adverse effects such as skin dryness, irritation, and peeling, which can reduce patient compliance. Therefore, there is a need for safer, more effective treatments. This review explores the potential of Egg Shell Membrane (ESM) as a natural therapy for HP. ESM, rich in collagen and hyaluronic acid (HA), has shown promise in enhancing skin hydration, boosting collagen production, and improving skin texture, making it a compelling candidate for HP treatment. Additionally, the polyphenol quercetin, known for its antioxidant and anti-inflammatory properties, may further enhance ESM's efficacy by inhibiting tyrosinase activity and reducing melanin production. While ESM and quercetin offer promising avenues for HP treatment, further research is needed to fully understand their mechanisms and optimize their use. This review also discusses the mixed results from studies on quercetin's effects on melanin formation and examines the toxicity and efficacy of quercetin across various experimental conditions.

Keywords
Hyperpigmentation, Egg Shell Membrane, Hyaluronic acid, Quercetin, Melanogenesis, Tyrosinase

INTRODUCTION

Hyperpigmentation (HP) is a frequent skin disorder in which melanin is produced in excess which causes some regions of the skin to become darker than the surrounding skin (Dharman & Sridhar, 2020). Factors such as sun exposure, hormone fluctuations, inflammation, and skin traumas, might contribute for the development of HP. Types of hyperpigmentation include melasma, freckles, sun induced pigmentation, and Post Inflammatory Hyperpigmentation (PIH), while Indians are more vulnerable to Chloasma or Melasma & PIH (Kutlubay et al., 2019). HP disorders were valued 4.6 billion USD in 2022 all over the world and is expected to have a compound annual growth rate (CAGR) of 7.6% (Research, 2023). Increasing demand in HP is believed to increase the market size. Coming to Melanocytes present in the different layers of

skin create and produces melanin more frequently as the skin ages and results in darkening of the skin. Hence, conditions causing skin HP are due to changes in melanocyte production or melanin dispersion (Jablonski & Chaplin, 2017; S. C. Taylor, 2002). The mechanism under melanin condition is due to hydroxylation of L-phenylalanine to L-tyrosine. L-tyrosine is hydroxylated by tyrosinase to produce 3,4-L-dihydroxyphenylalanine (L-DOPA), which is then oxidized to produce dopaquinone. This initiates the formation of melanin. A crucial component of melanogenesis is microphthalmia-associated transcription factor (MITF) which increases the production of tyrosinase and other associated proteins such as tyrosinase-related protein 1 (TRP1), and tyrosinase-related protein 2 (TRP2) (Dynoodt, 2013; Robertson, 2012). A wide variety of depigmenting agents and treatments are primarily used topically for hyperpigmentation conditions, differing in their mechanisms of action, efficacy, and safety profiles. Among the most common agents are those that inhibit the tyrosinase activity of cultured human melanocytes, including hydroquinone, arbutin, cysteamine, and kojic acid (KA). Other notable agents include tranexamic acid (TXA), which is antifibrinolytic; azelaic acid (AzA), which is anti-inflammatory; and niacinamide, which regulates NF-κB-mediated transcription of signaling molecules (Bazylevich et al., 2024)but all these treatments are certainly having some adverse effects like Skin dryness, irritation, skin peeling and also HP which might cause patients to become less compliant and satisfied (Davis & Callender, 2010; Nautiyal & Wairkar, 2021). Consequently, there is a critical need to design and develop formulation that effectively serve for HP.

We present here the use of Egg Shell Membrane (ESM) as a possible therapy for HP. The ESM, according to its natural composition, is a very interesting product to use as a natural source of collagen, hyaluronic acid (HA) as a crucial component (Ruff et al., 2009; J. Yoo, 2022). Several studies have demonstrated the effectiveness of these components in treatment of HP. In cosmetology, HA acts as a humectant, attracting and binding water to form a hydrogel that replenishes skin moisture and prevents water evaporation through the epidermis, thereby enhancing skin hydration. Combining HA with other active ingredients offers clear advantages over using HA alone. For instance, the combination of HA with arbutin or succinic acid is a well-established treatment for skin HP (Bazylevich et al., 2024; Liu et al., 2021). As well many of the most effective HP treatments focus on boosting collagen production. Collagen, the body's most abundant and powerful protein, plays a crucial role in wound healing and maintaining healthy skin and joints. Rich in the "anti-aging amino acid" glycine, collagen enhances skin hydration, repairs damaged, hyperpigmented skin, reduces fine lines and wrinkles, and improves skin texture. However, collagen production decreases with age, and free radicals can degrade the existing collagen in our bodies. Supplementation can help counteract these effects, reversing signs of aging and managing hyperpigmentation. Marine collagen, one of the most bioavailable sources, can be added to your morning coffee or breakfast to help repair skin and minimize hyperpigmentation while you go about your day (Amandean, n.d.).

Further in this regard we believe that quercetin will be beneficial if used as a combination of drug with ESM. Quercetin, a naturally occurring polyphenol found in many fruits, vegetables, and grains, is being explored for its potential in treating hyperpigmentation. Known for its powerful antioxidant and anti-inflammatory properties, quercetin has gained attention in dermatology and cosmetology for its possible role in reducing melanin production (Anand David et al., 2016; Zaid & Al Ramahi, 2019). It is believed to exert its ant melanogenic effects by inhibiting tyrosinase, an enzyme crucial for melanin synthesis. By downregulating tyrosinase activity, quercetin may reduce the production of melanin in the skin, potentially lightening hyperpigmented areas (Antão et al., 2021; Mohiuddin, n.d.) Figure 1. However, its effects are controversial, with in vitro studies, cell line experiments, and human trials yielding mixed results. Specifically, it remains uncertain whether quercetin increases or decreases melanin formation. This review also examines the toxicity and efficacy data of quercetin and its derivatives across various experimental conditions, including different cell lines, concentration ranges, and other parameters.

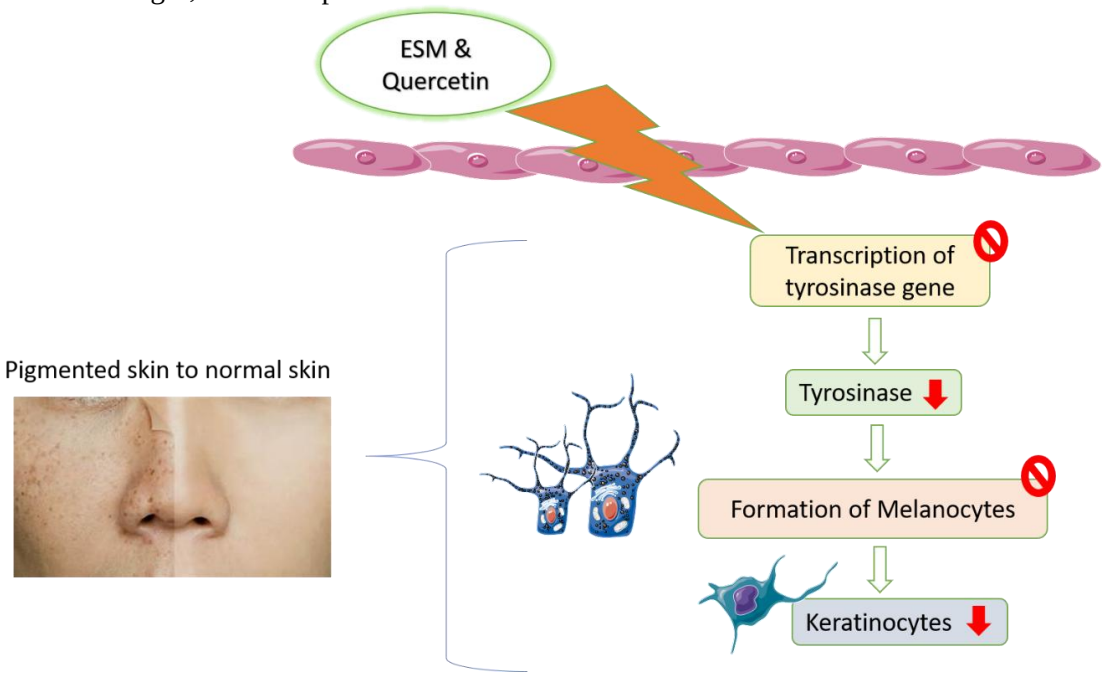

Fig. 1 Potential targeting agents for control of hyperpigmentation via tyrosinase inhibition

REGULATION OF MELANOGENESIS

Alterations in human skin are closely related to the type, amount, stage, and distribution of melanin. Skin color is determined by the epidermis, the outermost layer, where pigment-producing cells called melanocytes reside (Jy & De, 2007). These cells produce melanin, which plays a crucial role in protecting the skin from the harmful effects of UV radiation. Upon exposure to UV radiation, melanogenesis is upregulated through the activation of tyrosinase, a key enzyme in melanin production. This leads to an increase in melanin synthesis and can also result in DNA damage, inflammation, and other skin injuries (F et al., 2006; Jm & Mj, 2011). Melanocytes, derived from fibroblasts in the dermis and keratinocytes in the basal and suprabasal layers of the epidermis, transfer melanin pigments into the basal layers of the epidermis. UV radiation induces photo-oxidative stress, generating reactive oxygen and nitrogen species, which can cause cutaneous abnormalities such as DNA-damaged epidermal hyperplasia, collagen breakdown, and inflammation. Melanin pigments are naturally produced by the skin for photoprotection (Jy & De, 2007; d'Ischia M et al., 2013). Several factors, including stem cell factor (SCF), adrenaline, noradrenaline, β-melanocyte-stimulating hormone (β-MSH), and Wnt hormones, are involved in physiological responses and interact with receptors such as c-Kit, adrenergic receptors, melanocortin 1 receptor (MC1R), and Wnt receptors. For instance, MC1R signaling regulates cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA), promotes cAMP-response element-binding protein (CREB), and ultimately upregulates microphthalmia-associated transcription factor (MITF) in the nucleus. Upregulated MITF activates tyrosinase-related protein 1 (TRP1) in the Golgi apparatus, leading to the biochemical synthesis of melanin (Jy & De, 2007; d'Ischia M et al., 2013). The synthesis of melanin results in the production of blackish-brown eumelanin and yellowish-red pheomelanin, which are transported to melanosomes. Melanosomes undergo four maturation stages and reaction processes. In the presence of glutathione or cysteine, DOPAquinone is converted to cysteinylDOPA or glutathionylDOPA, forming pheomelanin. For eumelanin synthesis, DOPAquinone is converted to L-3,4-dihydroxyphenylalanine (L-DOPA) or leukodopachrome in the absence of glutathione or cysteine (An et al., 2009; Hc et al., 2013; Kn et al., 2013).

BIOCHEMICAL PATHWAYS OF MELANIN PRODUCTION

Understanding the signaling pathway of melanogenesis involves considering four pivotal receptors. Firstly, the c-Kit receptor is activated by stem cell factor (SCF), initiating MAP (mitogen-activated protein) kinase activation and subsequent stimulation of microphthalmia-associated transcription factor (MITF). Secondly, adrenergic receptors bind molecules such as adrenaline and noradrenaline, triggering cAMP binding, followed by the activation of CREB and protein kinase A (PKA)(Kw et al., 2013). Thirdly, MC1R receptors respond to adrenocorticotropic hormone (ACTH) and β-melanocyte-stimulating hormone (β-MSH), engaging in a pathway similar to adrenergic receptors involving cAMP. Additionally, a distinct pathway involves nitric oxide (NO) radicals activating guanylate cyclase, leading to cGMP production and subsequent MITF activation (Ss et al., 2013). Notably, the Wnt receptor pathway influences melanogenesis by activating GSK3β, which initiates phosphorylation and supports processes counteracting melanogenesis. Inhibiting GSK3β phosphorylation enhances β-catenin levels and facilitates the formation of the LEF/TCA complex, which further stimulates MITF (K. A. et al., 2008). Activated MITF orchestrates the expression of tyrosinase, tyrosinase-related protein 1 (TRP-1 or DCT), tyrosinase-related protein 2 (TRP-2, also known as DOPA chrome tautomerase), and protein kinase C-β (PKC-β), culminating in melanin production. Conversely, in the extracellular signaling process, phosphorylation of MEK/ERK and PI3K/AKT pathways acts to diminish MITF activity, thereby exerting anti-melanogenic effects. Conversely, dephosphorylation processes serve to activate MITF, promoting melanogenesis (Sk et al., 2005).

INHIBITING TYROSINASE FOR INHIBITING MELANIN PRODUCTION

The inhibition of melanogenesis by targeting tyrosinase is a significant area of study in dermatology and cosmetics. Tyrosinase is a key enzyme involved in the production of melanin, the pigment responsible for skin coloration and protection against UV radiation. Inhibition of tyrosinase activity can lead to decreased melanin synthesis, which is beneficial for conditions like hyperpigmentation (A. H et al., 2007). Various compounds and agents are known to inhibit tyrosinase, including Hyaluronic acid. These substances work by interfering with different stages of the melanin synthesis pathway, such as the conversion of tyrosine to L-DOPA and the oxidation of L-DOPA to dopaquinone. By blocking these enzymatic processes, they reduce the amount of melanin produced by melanocytes in the skin (F et al., 2006; Jm & Mj, 2011; T. S et al., 2014). The effectiveness of tyrosinase inhibitors varies based on factors such as their concentration in formulations, skin penetration ability, and safety profile. While these inhibitors are widely used in skincare products aimed at treating hyperpigmentation, their long-term effects and potential side effects, such as skin irritation or sensitization, are carefully studied and monitored. Therefore, targeting tyrosinase inhibition is a promising approach for managing melanogenesis-related skin conditions. Continued research into novel inhibitors and their mechanisms will further enhance our ability to develop effective treatments for hyperpigmentation and related disorders (Jd et al., 2009; Lp et al., 2003; d'Ischia M et al., 2013).

ESM

Annually, approximately 65.5 million metric tons of eggshells are produced worldwide, and this figure is expected to reach around 90 million tons by 2030 (Jr et al., 2015). According to the Environmental Protection Agency, eggshell waste

ranks as the 15th largest food industry pollutant. Almost all eggshells are discarded as waste and end up in landfills with little or no pre-treatment ("Synthesis of Dimethyl Carbonate over Waste Eggshell Catalyst," 2012), contributing to pollution through odor production from microbial activities. Utilizing eggshells can significantly reduce environmental impact by diverting this waste from landfills (M. S et al., 2020). ESM is a natural biomaterial found between the eggshell and egg white, known for its rich composition of proteins, peptides, and other bioactive compounds (Shi et al., 2021). Recently, ESM has gained attention in the skincare industry for its potential benefits in enhancing skin health and appearance. It is an organic substance known to enhance cellular activity and collagen production. Additionally, ESM helps prevent skin aging and mitigates damage caused by UV light and inflammation. Composed of insoluble protein keratin—found in feathers, hair, horns, scales, and nails—ESM exhibits high resistance to physical, chemical, and biological reactions ("Feeding the Skin," 2020). Due to its properties, ESM is recommended for use in formulations for moisturizers, wound recovery, skin growth, and anti-wrinkle agents. Collagen, another key component, has been shown to improve the water content of the stratum corneum, normalize trans epidermal water loss (TEWL) in UVB-irradiated mice, and increase both the water content of the stratum corneum and skin viscoelasticity in humans. In a previous study, we demonstrated that whole eggshell membrane hydrolysates (ESMH) possess a skin whitening effect, attributed to their tyrosinase inhibiting and L-DOPA oxidizing activities (J. H. Yoo et al., 2015). ESM does contain hyaluronic acid, among other bioactive compounds. Hyaluronic acid is a naturally occurring polysaccharide found in connective tissues, skin, and cartilage, known for its ability to retain water and provide hydration to the skin. Several studies and reviews confirm the presence of hyaluronic acid in eggshell membrane (*Extraction and Characterization of Hyaluronic Acid and Collagen from Eggshell Membrane Waste*, n.d.; "The Isolation and Characterisation of Hyaluronic Acid in Egg Shell," 1976; Khanmohammadi et al., 2014; Leong et al., 2023)

HYALURONIC ACID FOR HP

HA, a glycosaminoglycan is widely distributed throughout connective, epithelial, and neural tissues. It is a major component of the skin and plays a crucial role in tissue repair (V et al., 2010). HA offers several advantages: it can loosen corneocyte packing through its hydrophobic patch domain, helping to overcome SC barriers (Ja et al., 2012; Mb & Sa, 2005). Additionally, HA can actively adhere to melanocytes via cell surface HA receptors like CD44, facilitating targeted delivery to melanocytes (A. T et al., 2001). Furthermore, HA chains can form viscous nanogels by interacting electrostatically with phospholipid molecules in the TA-LP, which minimizes epidermal diffusion by limiting TA-LP penetrability (Y et al., 2020). Limited published data describe the safety and effectiveness of HA fillers in skin of color. Grimes and Few reported a 6% incidence of post-inflammatory hyperpigmentation at the injection site, which resolved with the use of topical steroids and 4% hydroquinone. Odunze et al. found no transient or permanent adverse outcomes in subjects with Fitzpatrick skin phototypes IV–VI using HA fillers. Taylor and Burgess observed pigmentation changes in 15% of patients, which resolved within 12 weeks (Grimes et al., 2009; O. M et al., 2007; S. Taylor & Burgess, 2007). Using meticulous techniques to minimize blood accumulation is essential for reducing complications when using HA fillers in darker skin types. Current studies show that patients with Fitzpatrick skin phototypes IV–VI can be effectively and safely treated for facial wrinkles and folds with HA fillers, delaying the need for surgery and reducing the risk of scarring. While some studies indicate that all HA fillers can be safely and effectively used in individuals with darker skin, the duration of wrinkle correction depends on the fillers' physical properties. Juvéderm fillers, with higher concentrations of HA and crosslinked HA, are expected to last longer in vivo compared to Hylaform and Captique fillers. In practice, Hylaform and Hylaform Plus last 3–4 months, Captique lasts 3–6 months, while Juvéderm fillers last from 9 months to a year or more (T. A & Gh, 2008; Cp, 2007; Ls et al., 2007; Ma et al., 2008). Tyrosine inhibitors play an important role as skin-lightening agents (S. A et al., 2004), while HA synthesis regulates skin hydration and the formation of wrinkles (E et al., 2012). HA, a non-sulfated glycosaminoglycan (GAG), is composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine. Additionally, HA regulates tissue repair, enhances the immune system response by activating inflammatory cells, and responds to fibroblast injury (Bai et al., 2012; Ph et al., 1986).

ANTI-MELANOGENESIS EFFECTS OF QUERCETIN

Quercetin is a versatile compound known for its significant biological activities. As a potent tyrosinase inhibitor, it impedes melanogenesis in mouse B16 melanoma cells and exhibits strong antioxidant and anticancer properties (T. S et al., 2013; Yj, 2012). Interestingly, quercetin has a contrasting role in human melanoma cells, where it acts as a melanogenesis accelerator (N. H et al., 2004; R et al., 2004; F. T & M, 2009). Studies have shown that it can decrease intracellular tyrosinase activity and inhibit mushroom tyrosinase in cell-free systems. Additionally, quercetin inhibits melanin production in B16 melanoma cells in a dose-dependent manner. Despite these inhibitory effects, some research reports that quercetin can stimulate cellular melanogenesis (F. T & M, 2009). Nagata et al. (2004) found that quercetin enhances melanogenesis by increasing both the activity and synthesis of tyrosinase in human melanoma cells and normal human melanocytes (N. H et al., 2004). Moreover, quercetin and its derivatives can stimulate melanogenesis even in the absence of -MSH in B16 murine melanoma cells ("The Leaf Extract of Mallotus Japonicus and Its Major Active Constituent, Rutin, Suppressed on Melanin Production in Murine B16F1 Melanoma," 2015). These opposing effects have sparked considerable debate, especially regarding the potential application of quercetin in cosmetics for tyrosinase enzyme activity inhibition. Structurally, quercetin belongs to the flavonoid family, featuring a heterocyclic pyrone ring connected to phenolic moieties on both sides. It often exists as rutin (quercetin-3-rutinoside), a glycoside form with a

disaccharide attached to the quercetin unit (C et al., 2001; Y. K et al., 2013, 2014; Sm et al., 2008). As a therapeutic agent, quercetin's roles are diverse, including anti-allergic, anti-inflammatory, anti-melanogenesis, and anti-carcinogenic effects. These activities suggest that quercetin acts as a free radical scavenger, targeting superoxide anions and lipid peroxyl species (Yh et al., 2012; Ym et al., 2011). Yamauchi et al. (2013 & 2014) reported that certain synthesized quercetin glycosides exhibit anti-melanogenesis effects with minimal cell toxicity. Specifically, these effective glycosides include those with the structures: R1 = cellobiose, R3 = OH, R5 = cellobiose; R1 = OH, R3 = cellobiose, R5 = cellobiose; and R1 = glucose, R3 = OH, R5 = glucose. Conversely, other quercetin glycosides either do not show anti-melanogenesis effects, or they accelerate melanogenesis, exhibit cell toxicity, or combine these drawbacks. As a result, quercetin glycosides are generally not suitable for use as whitening agents (Y. K et al., 2013, 2014).

Nagata et al. found that in cell systems, quercetin enhances tyrosinase activity without affecting mRNA expression, leading to the overexpression of the tyrosinase protein at concentrations of 1–20 µM. In contrast, in a cell-free system, tyrosinase activity is inhibited at concentrations of 10–100 µM. Interestingly, within cell systems, tyrosinase activity increases at 5–10 µM but is inhibited at 20–50 µM. The expression patterns of tyrosinase, TRP-1, and TRP-2 proteins vary with different quercetin concentrations. Specifically, at 10 and 20 µM, tyrosinase is overexpressed, but at 50 µM, its expression is slightly reduced. TRP-1 expression decreases gradually at 10, 20, and 50 µM, while TRP-2 is expressed at 5 and 10 µM and decreases gradually at 20 and 50 µM (N. H et al., 2004; Ym et al., 2011). Takekoshi et al. (2013) reported an increase in melanin content at quercetin concentrations greater than 50 µM. Tyrosinase and TRP-2 are overexpressed at quercetin concentrations of 5–160 µM, but there is no effect on TRP-1 expression at 50–160 µM. Additionally, the same group demonstrated that at 10 µM quercetin, melanin content increases, and tyrosinase is overexpressed after three days (T. S et al., 2013, 2014). For quercetin in Capparis spinosa L. extract, melanin content increases at concentrations of 50–500 µM, with tyrosinase expressed at 300 µM after 24 hours (M. K et al., 2009). Masuda et al. (2012) demonstrated that melanin content rises at 12.5–50 µM but decreases at 100 and 200 µM. In cell systems, tyrosinase activity is enhanced at 200 µM quercetin. With P-38 MAPK overexpressed, MITF is reduced, and ERK1/2 is overexpressed. However, the activation of MITF leads to low tyrosinase expression at the protein level at quercetin concentrations of 5 and 200 µM (M. M et al., 2012). Quercetin extracted from rosehip (Rosa canina L.) decreases melanin content at 20 µM and inhibits tyrosinase activity in both cell and cell-free systems at 10–40 µM, resulting in low tyrosinase expression at the protein level (F. T & M, 2009). An et al. (2008) tested quercetin derivatives with taxifolin and luteolin as additives, finding that melanin content decreases at 200 µM. In the presence of these additives in a cell system, tyrosinase activity is inhibited, yet tyrosinase is overexpressed at a quercetin concentration of 200 µM (Sm et al., 2008; "The Leaf Extract of Mallotus Japonicus and Its Major Active Constituent, Rutin, Suppressed on Melanin Production in Murine B16F1 Melanoma," 2015). Synthesized quercetin is associated with decreased melanin content at concentrations of 6.25–100 µM, linked to low expression of tyrosinase, TRP-1, TRP-2, and p38 MAPK, and a lack of stimulation of MITF and phosphorylated-p38 (p-p38) MAPK. Most quercetin derivatives lead to increased melanin content. However, quercetin-galactose-rhamnose-xylose and quercetin-glucose-rhamnose result in decreased melanin content at 72 µM after 72 hours, with downregulated mRNA expression levels of tyrosinase, TRP-1, TRP-2, MITF, and MC1R, resulting in low tyrosinase protein expression (Y. K et al., 2014). Arung et al. (2011) found that quercetin glucoside (from Allium cepa) decreases melanin content at concentrations of 1–100 µM ("Anti-Melanogenesis Properties of Quercetin- and Its Derivative-Rich Extract from Allium Cepa," 2011).

Quercetin's antioxidant activity is particularly significant for its anti-melanogenesis effects. It functions as an antioxidative agent by inactivating the tyrosinase enzyme, which directly ties its antioxidant properties to the prevention of melanogenesis. This relationship stems from quercetin's ability to scavenge free radicals, protecting against oxidative stress. The antioxidant properties of polyphenols, including quercetin, are essential for their anti-melanogenesis effects. As a result, extensive research has focused on quercetin's antioxidative capabilities to understand its role in inhibiting melanogenesis.

CHALLENGES AND FUTURE DIRECTIONS

As Tyrosinase inhibitors plays a diverse role in reducing skin HP especially in combination this strategy would be the good approach. So, Combination of ESM and Quercetin both show diverse activity on HP but it may be challenging in collection and extraction of ESM. Individuals from different genetic backgrounds and ethnicities can respond differently to HP treatments. So, certain treatments may be more effective or in individuals skin tones. But, getting regulatory approval for new treatments involves extensive testing and can be time-consuming and costly. Continuous monitoring for adverse effects is essential, especially for new treatments incorporating novel ingredients like ESM and quercetin. The biochemical pathways involved in melanin production are complex, and our understanding of how various treatments interact with these pathways is incomplete. Mixed results from studies on quercetin's role in melanogenesis highlight the need for more in-depth research to clarify its effects. Furthermore, the market for HP treatments is highly competitive, with many established products and new entrants. Developing a distinctive and effective product that stands out is challenging. Ensuring that new treatments are affordable and accessible to a broad audience is crucial for widespread adoption. Based on numerous in vitro studies and relatively few in vivo studies, quercetin and its derivatives show promise as anti-melanogenesis agents, but more confirmatory studies are necessary. Notably, pure quercetin, at concentrations above 50 µM, results in decreased melanin content, while at 10–20 µM, the melanin content increases in a concentration-dependent manner.

CONCLUSION

HP remains a prevalent and challenging skin condition that significantly impacts individuals' quality of life. While current treatments are effective, they often cause adverse side effects like skin dryness, irritation, and peeling, leading to reduced patient compliance. This highlights the need for safer and more natural alternatives. ESM, rich in collagen and HA, presents a promising natural option for treating HP by improving skin hydration, texture, and collagen production. Additionally, quercetin, a naturally occurring polyphenol with strong antioxidant and anti-inflammatory properties, has shown potential in treating HP by inhibiting tyrosinase activity and reducing melanin production. The combination of ESM and quercetin could offer a synergistic approach, addressing both the symptoms and underlying causes of HP more effectively. However, despite the potential benefits of ESM and quercetin, further research is needed to fully understand their mechanisms, optimize their formulations, and confirm their efficacy and safety in clinical settings. By exploring these natural alternatives, we may develop more effective, patient-friendly solutions for managing hyperpigmentation and improving skin health.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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AUTHOR CONTRIBUTIONS

Ashwin Ravichandran and R. Aishwarya Reddy has conceptualized and written original draft. Dr. R. Sureshkumar has supervised, and proof read the manuscript. M. Sai Varshini has contributed in writing original draft.

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