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Review Article

Melanogenic Imbalance in Freckles: Advances in Herbal and Conventional Pigmentary Modulation Therapeutics

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ABSTRACT

Freckles are benign, pigmented macules commonly seen in people with pale skin and high UV exposure. They result from an excess of melanin, which is produced by both genetic and environmental factors. Key enzymes, including tyrosinase and related proteins, are involved in dysregulated melanogenesis, leading to lesions known as ephelides and solar lentigines. Freckles are an important cosmetic problem, and treatment is sought even when they do not result in any medical issues. Common treatments include topical depigmenting agents such as vitamin C, tretinoin, hydroquinone, and kojic acid, and other physical modalities, which include chemical peels, laser therapy, and cryotherapy. Many successful treatments also have negative side effects including irritation, post-inflammatory hyperpigmentation, increased photosensitivity, and expense. Thus plant-based and herbal alternatives are preferred because of their safety, efficacy and sustainability. Botanicals that show strong anti-melanogenic effects have antioxidant activity, the ability to inhibit tyrosinase, or decreased melanin production by blocking mechanisms related to melanogenic signalling pathways. Examples include *Curcuma longa, Carica papaya, Morus alba, Glycyrrhiza glabra*, and *Camellia sinensis*. Preliminary *in vitro*, and *in vivo* animal models such as zebrafish and murine studies in the experimental group show depigmenting activity of compounds such as glabridin, curcumin, aloesin, and neocnidilide. Clinical studies proved that herbal therapies can be efficacious in the treatment of hyperpigmentation with minimal side effects. In summary, there is a need for unified evidence of herbal medicines for freckles through clinical trials as well as formulation of better dosage form.

Keywords: Freckle, Melanin, Antioxidants, Herbal remedies, Curcumin, Glabridin.

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INTRODUCTION

Freckles are small, flat, brownish patches on skin that range in size from 1 to 2 mm; people with fair skin are most likely to have more.[1] They result from the deposition of the melanin pigment by melanocyte cells, which is often influenced by UV light exposure and genetics.[2] It often occurs in childhood and can persist until about 20 years old.[1,2] Mostly face and arms are more prone owing to sun exposed area. Freckles are innocuous; however, they may indicate skin cancer risk from UV exposure. Types include post-inflammatory hyperpigmentation freckles, ephelides, solar lentigines, and hereditary.[3] People with light eyes, red, pale skin, and blond hair are more prone to emerge. Solar lentigines known as liver spots, sun spots, or age spots are more permanent, usually appear as flat dark patch on skin compared to ephelides. UV exposed vandalization could be the inception.[4,5]

Originating from American culture as little pigmentation spot, freckles was first used in the early 19th century with unique skin characteristics.[6] In the mid-century, following the tanned, often with freckles, and natural beauty movement that perceptions began to change. By 2000, freckles were allowed more cultural acceptance by fashion industry and media outlets. Scientists now think freckles can distinguished from moles, due to genetic variations in the MC1R gene.[7]

Chemical methods of bleaching, hydroquinone, phenolic compounds, and mercury salts, were the most common treatment in the early 1900s. These chemical methods provide effectiveness with side effects including allergic reaction, irritation, and toxicity.[8] Physical techniques like cryotherapy, chemical peels, dermabrasion and lasers, to remove freckles has grown popularly. Even though they are expensive, they produce quick result however, if applied to darker skin may cause post-inflammatory hyperpigmentation or other negative effects.[9,10]

Natural extracts containing phytochemical substances like phenols, flavonoids, and antioxidants have gained popularity due to the interest in plant-derived treatments for hyperpigmentation disorders like freckling. Several research studies have already

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been showed anti-inflammatory, melanin reduction and tyrosinase-inhibitory effects. The demand for sustainable skin systems is greater due to the growth of herbal cosmetics, which is driven by the need for non-toxic and skin friendly goods. According to recent studies, various medicinal plants have effectively controlled melanogenesis pathways, decreased oxidative stress and enhance skin tone.[11,12]

MELANOGENESIS

Melanogenesis, the process by which melanocytes synthesize melanin, is controlled by important enzymes such as Tyrosinase and Tyrosinase-Related Proteins (TRP-1 and TRP-2). The process inside melanosomes is initiated by UV light activating tyrosinase, a copper-dependent enzyme necessary for the initial phases of melanin formation.[13,14] From L-phenylalanine, L-tyrosine is transformed into L-DOPA and subsequently L-dopaquinone. The pathway then splits off to produce either pheomelanin (a reddish-yellow pigment) or eumelanin (a black-brown pigment). Eumelanin formation involves DCT (TRP-2), while pheomelanin synthesis requires cysteine. Catalase and glutathione peroxidase are examples of antioxidant enzymes that manage the balance between the two types of melanin, which is impacted by the redox state, particularly Glutathione (GSH) levels.[15]

CONVENTIONAL APPROACHES FOR THE TREATMENT OF FRECKLES

Conventional treatment refers to recognized routine medical procedure widely accepted and practised by healthcare professionals. These treatments are typically based on scientific research and clinical recommendations and may involve the use of medications, surgical procedures, physical therapy, or other established medical interventions.

Medical Treatment

Medical treatment primarily involves the use of topical agents that help lighten hyperpigmentation by inhibiting melanin production or promoting skin cell turnover.[12]

- Hydroquinone.
- Retinoids (e.g., Tretinoin).
- Azelaic Acid.
- Kojic Acid.
- Vitamin C (Ascorbic acid).

Surgical Treatment

Surgical treatment generally considered medical and cosmetic therapies and reserved for people seeking faster or more definitive cosmetic results.

Laser Treatment

A laser light when focused on the freckles, extra melanin in the skin absorbs the heat and gets destroyed, thereby reducing the spots. There are two types of laser treatments: Ablative and Non-ablative. Ablative lasers treatment particularly use heat for the treatment of skin spot whereas non-ablative lasers help stimulate collagen remodeling in the skin without harming the healthy skin.[46]

Chemical Peels

In chemical peeling, application of acid solutions on the skin to chemically exfoliate it and stimulate new skin cell growth. Product containing alpha-hydroxy acid like glycolic and lactic acid; beta-hydroxy acid like salicylic acid; or trichloroacetic acid help to fade freckles. An acid, when applied on the spots, helps peel off the pigmented layers of the skin and reveals a refreshing, new clear skin from underneath.[47]

Cryotherapy

Cryotherapy may be used due to its availability, however there is a risk of pigment alteration and scarring. Superficial chemical peels such as alpha and beta hydroxy acids, Jessner's, modified Jessner's, resorcinol and tricholoracetic acid peels (10-15%) are all used for removal of stratum corneum and therefore can even out pigmentation discolorations.[48]

Physical Modalities

Intense pulsed light

Skin spots can be treated using intense pulsed light and has minimal post-inflammatory hyperpigmentation, but demonstrates less efficacy than the Q-switched alexandrite and the short pulsed NdYag.[49]

Shortcoming of Allopathic Treatment

Skin Irritation and Side Effects

- Symptoms include dryness, peeling, redness, burning, or allergic reactions.
- Laser therapy and chemical peels can make sensitivity and discomfort worse.

Risk of Pigment Changes

- Cryotherapy, lasers, and peels results in Post-Inflammatory Hyperpigmentation (PIH).
- Prolonged use of some agents (e.g., hydroquinone) may cause exogenous ochronosis.

HERBAL PLANTS WITH ANTI-MELANOGENIC ACTIVITY

Table 1: List of Herbal plants with Anti-melanogenic activity.[45]

Sl. No.	Plant Name	Part Used	Active Compounds	Mechanism of action	References
1.	Aloe vera	Leaf gel	Aloesin, aloin, aglycone of aloenin, isoaloeresin D	Inhibits tyrosinase; aloesin reduces pigmentation by 34%.	[16]
2.	Amla (*Emblica officinalis*)	Fruit	Vitamin C, E, tannins, flavonolglycosides, mucic acid	Inhibits Trp-1 and MITF expression; modulates melanin pathway.	[17]
3.	Cutch tree (*Acacia catechu*)	Bark	Catechin	Strong tyrosinase inhibition.	[18]
4.	Green tea (*Camellia sinensis*)	Leaves	EGCG, EGC, ECG, GCG, gallic acid	EGCG inhibits melanin synthesis and tyrosinase at protein and mRNA levels.	[19]
5.	Indian Sarsaparilla (*Hemidesmus indicus*)	Root	vanillin, lupeol, hemidesminine	Inhibits L-DOPA to dopachrome conversion; antioxidant action.	[20]
6.	Jamaica Cherry (*Muntingia calabura*)	Leaf, flower, fruit	1-Deoxy-D-mannitol, flavonoids	Inhibits melanogenesis and tyrosinase; antioxidant activity.	[21]
7.	Licorice (*Glycyrrhiza glabra*)	Root	Glabridin, liquiritin, isoliquiritin, glycyrrhizin	Inhibits tyrosinase; prevents L-DOPA oxidation; glabridin shows highest inhibition.	[22]
8.	Lotus (*Nelumbo nucifera*)	Seed, leaf	Nuciferine, saponins, phenols	Antioxidant; skin whitening; protects against UVB.	[23]
9.	Neem (*Azadirachta indica*)	Oil/seeds	Azadirachtin, nimbin, nimbandiol	Tyrosinase inhibitor; antioxidant and antibacterial activity.	[24]
10.	Papaya (*Carica papaya*)	Fruit pulp, seeds	Papain, chymopapain A & B, flavonoids, vitamin C	High antioxidant activity (87%); reduces melanin through phenolic content.	[25]
11.	Saffron (*Crocus sativus*)	Stigma	Picrocrocin, crocin, isorhamnetin-3,49-diglucoside	Skin whitening agent; antioxidant; inhibits melanin formation.	[26]
12.	Sandalwood (*Santalum album*)	Oil	α-Santalol	Potent tyrosinase inhibitor; anti-aging and antioxidant properties.	[27]
13.	Turmeric (*Curcuma longa*)	Rhizome	Curcumin, demethylcurcumin, bisdemethylcurcumin	Inhibits tyrosinase and MITF/ TRP-1 expression; antioxidant and anti-inflammatory.	[28]
14.	*Vitex negundo*	Stem, poultice and leaf	Negundin A	Inhibit tyrosinase enzyme; used for ephelides and melasma treatment.	[29]
15.	White mulberry (*Morus alba*)	Root, and leaves	Mulberroside A, oxyresveratrol, and flavonoids	Inhibits the activity of monophenolase and tyrosinase; antioxidant.	[30]
16.	*Citrus aurantium*	Fruit	Vitamin C, hesperidin	tyrosinase inhibition, and antioxidant action.	[31]
17.	*Coffea arabica*	Seed	Caffeine, chlorogenic acids	Antioxidant, and reduce the pigmentation.	[32]
18.	*Larix sibirica*	Wood	Taxifolin	Control of melanin.	[33]

Sl. No.	Plant Name	Part Used	Active Compounds	Mechanism of action	References
19.	*Lepidium sativum*	Sprout	Sulforaphane	Inhibit the production of melanin and the inhibition of tyrosinase.	[34]
20.	*Mangifera indica*	Fruit	Mangiferin, phenolics	Reduction of melanin.	[35]
21.	*Pancratium maritimum*	Bulb	Narciclasine, lycorine	Reduce synthesis and melanin transfer.	[36]
22.	*Pinus densiflora*	Pollen	Flavonoids and amino acids	Supressing melanin which helps in skin nourishment.	[37]
23.	*Pisum sativum*	Seed	Peptides and Pisumin	Reduction in melanin	[38]
24.	*Swertia angustifolia*	Root	Xanthones	Decrease pigmentation and melanin production.	[39]
25.	*Sophora flavescens*	Root	Matrine, oxymatrine	Antioxidant and anti-melanin.	[40]
26.	*Rheum rhaponticum*	Root	Stilbenes	prevents the synthesis of melanin.	[41]
27.	*Derris membranacea*	Root extract	Flavonoids	inhibits melanogenesis and decreases pigmentation.	[42]
28.	*Actinidia chinensis*	Fruit	Vitamin C and actinidin	Melanin suppression and antioxidants.	[43]
29.	*Arctostaphylos uva-ursi*	Leaf	Arbutin	Tyrosinase inhibition, melanin synthesis blocker.	[44]
30.	*Bellis perennis*	Flower	Polyphenols, saponins	Down regulation of melanin production.	[45]

High Cost and Accessibility

- Advanced treatments like laser therapy, IPL, and chemical peels are expensive and not always covered by insurance.
- May require multiple sessions, increasing the financial burden.

Slow Onset of Results

- Topical treatments may take weeks to months to show improvement.
- Not ideal for patients seeking fast or immediate results.

Increased Photosensitivity

- Many treatments make the skin more sensitive to UV rays, increasing the risk of further damage if proper sun protection is not practised.[50,51]

ASSESSMENT OF DEPIGMENTING EFFICACY *IN VITRO* AND *IN VIVO*

Several *in vitro* and *in vivo* investigations have been carried out to look at how natural constituents, which are strong tyrosinase inhibitors, decrease melanogenesis. According to a recent study by Hseu *et al.*, the ubiquinone molecule Coenzyme CoQ10 (CoQ10) could limit p53/POMC, α-MSH synthesis, and ROS creation in UVA-irradiated keratinocyte HaCaT cells, thereby inhibiting tyrosinase activity and melanin production. By inhibiting the cAMP-mediated CREB protein signalling cascades, CoQ10 suppressed the formation of MITF and decreased the formation of melanin in α-MSH-stimulated murine B16-F10 cells. These results proved that CoQ10 is a viable depigmenting or skin-whitening agent that may find topical usage in cosmetics.[52]

Recently, there has been a prevalence of interest in the anti-melanogenic effect of rhizoma of the Chinese medicinal herb *Ligustrum sinense*. Twenty-four chemicals' constituents were extracted and identified from the ethyl acetate fraction of methanolic extracts of *L. sinense*.[53] Using murine melanoma B16-F10 cells, anti-melanogenesis experiment was performed of the pure isolates from *L. sinense*. According to findings, the chemical isolate 3-[3-(4-hydroxy-3-methoxyphenyl) allyl] ferulic acid and (3S,3aR)-neocnidilide showed anti-melanogenesis effect without causing cytotoxicity, with IC_{50} values of 78.9 and 31.1 μM, respectively. Using zebrafish embryos, research has been carried out and proved that (3S,3aR)-neocnidilide had considerable anti-pigmentation activity on zebrafish embryos at 10-20 μM, in contrast to arbutin (20 μM). Research had showed that (3S,3aR)-neocnidilide is a strong natural anti-melanogenic and noncytotoxic substance that has potential use as a skin-whitening agent in cosmetic applications.[52]

Using *in vivo* pigmented guinea pig model, Boissy *et al.'s* showed that the tyrosinase inhibitor, Deoxyadenosine (dA), could

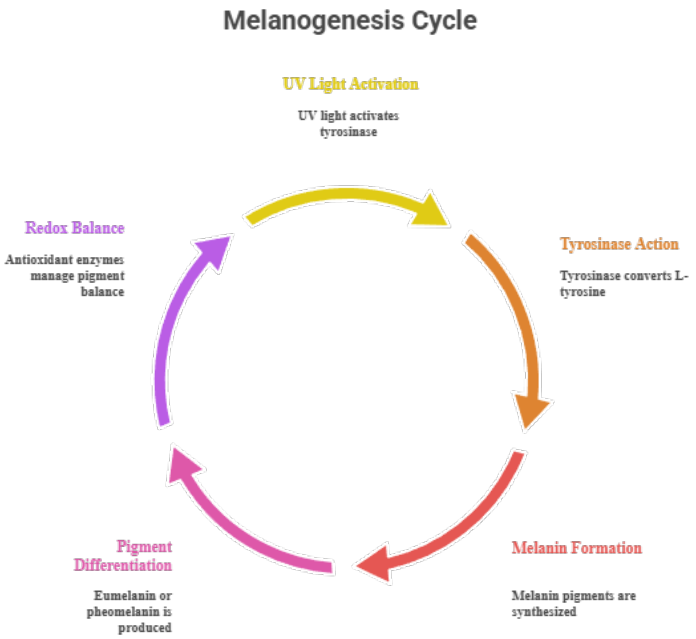

Figure 1: Melanin synthesis cycle.[15]

Figure 2: Management of Freckles.[48,49]

produce a quick and long-lasting skin lightening effect that can be reversible. On the other hand, arbutin and kojic acid does not lighten the skin, whereas HQ showed temporary skin-lightening effect. Additionally, clinical experiment results confirmed that dA is a tyrosinase inhibitor, along with significant decrease with overall skin pigmentation and improvement in solar lentigines in the populations of people with light or dark skin, respectively.[54]

POTENTIAL THERAPEUTIC EFFECTS: CLINICAL-BASED EVIDENCE

Literature of clinical trial enlighten about evidence-based clinical studies involving a range of natural and synthetic compounds, including green tea, ascorbic acid, ellagic acid, aloesin, licorice extracts, lignin peroxidase, kojic acid, niacinamide.[55] Natural ingredients from naturally occurring sources have demonstrated potential therapeutic effects and might give researchers and clinicians a better understanding of clinical practice in the future, in contrast to some synthetic chemicals like HQ and tretinoin.[56] The summary of clinical trials in Table 2.[45]

FUNCTIONAL MECHANISM

Curcumin

Curcumin has been studied for the expression of melanogenesis-related proteins (Microphthalmia Associated Transcription Factor (MITF), tyrosinase, cellular tyrosinase activity, Tyrosinase-Related Protein 1 and 2 (TRP-1, TRP-2), and activation of Extracellular Signal-regulated Kinase (ERK), melanogenesis-regulating signals including Phosphatidylinositol 3-Kinase (PI3K)/Akt/ Glycogen Synthase Kinase 3 (GSK 3β) and p38 MAPK in human melanocytes. Tyrosinase activity and

Table 2: Summary of clinical trials for synthetic and natural compounds.[55,56]

Chemicals	Type	Study Intervention/Year	Condition	Comparison	Status
Salicylic acid and Hydroquinone (HQ)	Synthetic	Double Blind Randomized Clinical Trial (14 weeks), 2008.	Melasma	20-30% Salicylic peels of acid mixed with 4% Hydroquinone cream Vs 4% HQ (topical).	Completed Phase 4
Tri-Luma Cream	Synthetic	Randomized controlled split- face clinical trial (10 weeks), 2008.	Melasma	Sequential Treatment with Intense pulsed light- infused with Tri-Luma cream Vs a mild inactive control cream (Cetaphil) with Intense pulsed light.	Terminated
Arbutin, Triamcinolone and Tretinoin	Natural (arbutin) and synthetic	Randomized Double Blind Clinical Trial, 2008.	Melasma	Tretinoin+ arbutin+ triamcinolone) Vs Triluma (hydroquinone + fluocinolone + tretinoin).	Suspended
Hydroquinone (HQ)	Synthetic	Randomized Controlled Split-face Clinical Trial (8 weeks), 2014.	Facial Melasma	4% HQ (topical) Vs placebo (topical).	Completed Phase 3
Lytera 2.0 and Hydroquinone (HQ)	Synthetic	Randomized Controlled Split-face Clinical Trial (12 weeks), 2017.	Facial Melasma	Lytera 2.0 Vs 4% HQ (topical).	Completed
Glutathione	Synthetic	Randomized Double Blind Clinical Trial (12 weeks), 2019.	Spot UV, spot polarization, and skin tone	Oral glutathione capsules (500 mg) Vs. Oral placebo tablet.	Completed Phase 1
Tranexamic	Synthetic	Three-arm Randomized Double-blinded Clinical Trial (12 weeks), 2019.	Melasma	Oral and 5% Tranexamic (topical) Acid in monotherapy Vs 4% HQ (topical).	On-going
Azelaic acid (AZA)	Natural	Randomized controlled, open-label trial, 2011.	Melasma	20% AzA Vs. 4% HQ (topical).	Completed
Aloesin	Natural	Controlled clinical Trial, 2002.	UVR-induced hyperpigmentation	Aloesin Vs. Arbutin Vs. Aloesin/Arbutin.	Completed

Chemicals	Type	Study Intervention/Year	Condition	Comparison	Status
Mulberry	Natural	Randomized controlled, Clinical Trial, 2011.	Melasma	75% mulberry Extract Vs. placebo.	Completed
Licorice Extracts	Natural	Split-face 17 controlled clinic trial, 2000.	Melasma	None	Completed
	Natural	Controlled clinical trial, 2013.	UVR-induced hyperpigmentation	None	Completed
	Natural	Randomized controlled clinical trial, 2016.	Melasma	4% liquiritin Vs. 2% liquiritin and HQ.	Completed
Kojic acid (KA)	Natural	Controlled study with a Prospective design.	Melasma	0.75% KA with 2.5% Vitamin C Vs. 4% Hydroquinone.	Completed
	Natural	Randomized controlled clinical trial, 2010.	Facial dyschromia	Compound (KA, glycolic acid) Vs. 4% Hydroquinone.	Completed
Niacinamide	Natural	Randomized controlled clinical trial, 2014.	Irregular facial hyperpigmentation	Cream containing 2% tranexamic acid combined with 2% niacinamide versus vehicle control.	Completed
	Natural	Open-label controlled trial, 2016.	Post-inflammatory hyperpigmentation	None	Completed
Ellagic acid	Natural	Randomized controlled clinical trial, 2008.	Melasma	1% arbutin Vs. synthetic 1% ellagic acid against synthetic 1% ellagic acid with natural ellagic acid found in plant extracts.	Completed
Arbutin	Natural	Randomized controlled clinical trial, 2008.	Melasma	1% arbutin Vs. Plant extracts with 1% ellagic acid.	Completed
Green Tea	Natural	Randomized controlled clinical trial, 2009.	Melasma	Green tea extract of 2% Vs. placebo control.	Completed
Turmeric	Natural	Randomized controlled clinical trial, 2010.	Facial hyperpigmentation	Turmeric extract cream formulation Vs. unknown control.	Completed
Soy	Natural	Controlled clinical trial, 2001.	Melasma	None	Completed
Ascorbic acid	Natural	Single group efficacy trial, 2013.	Severe melisma	Topical AA with trichloroacetic acid peel.	Completed
	Natural	Controlled clinical trial, 2007.	Bilateral epidermal melisma	Combined trichloroacetic acid peel and ascorbic acid Vs. trichloroacetic acid peel.	Completed
	Natural	Randomized controlled clinical trial/ split-face, 2003.	Melasma	Vitamin C Vs. distilled water.	Completed

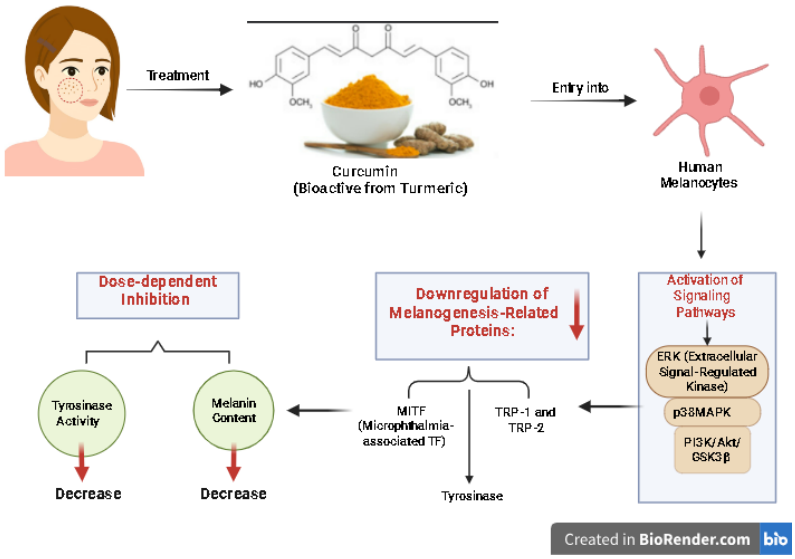

Figure 3: Curcumin in melanocytes molecular mechanism.[57]

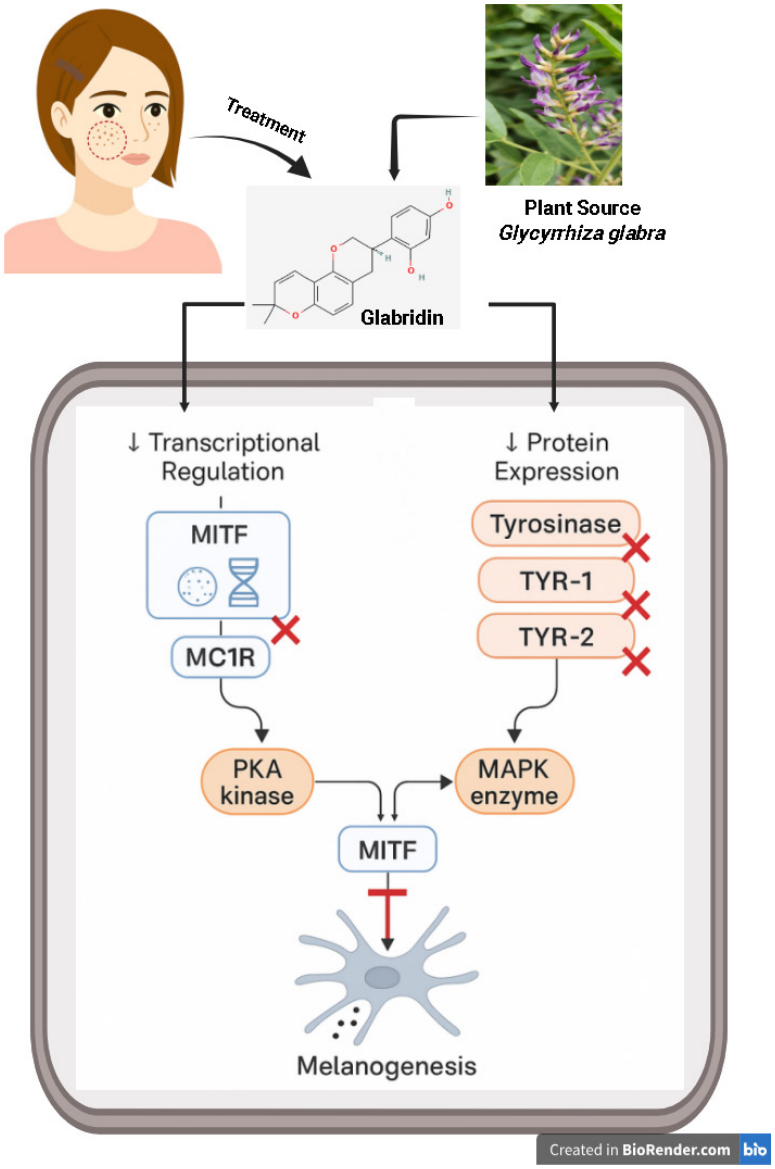

Figure 4: Glabridin in melanocytes molecular mechanism.[58]

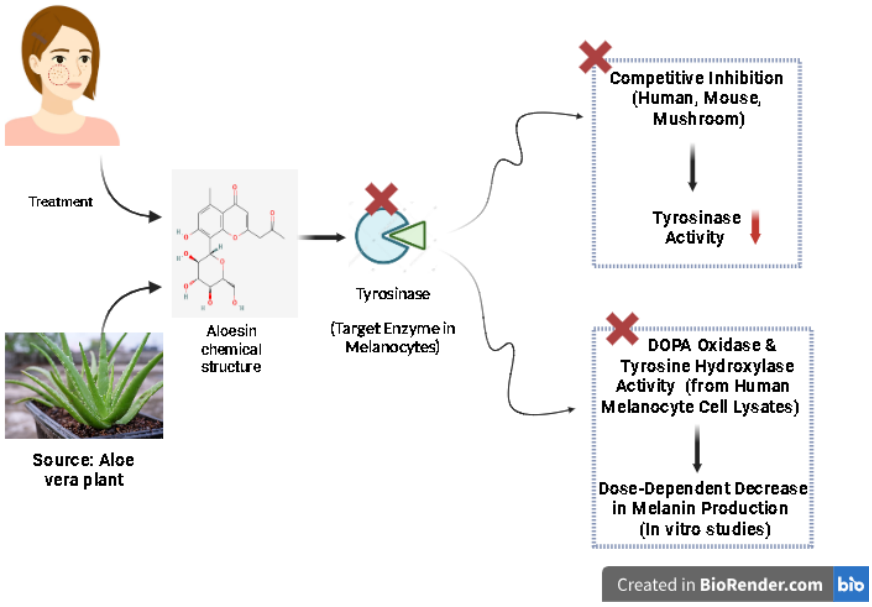

Figure 5: Aloesin in melanocytes molecular mechanism.[59]

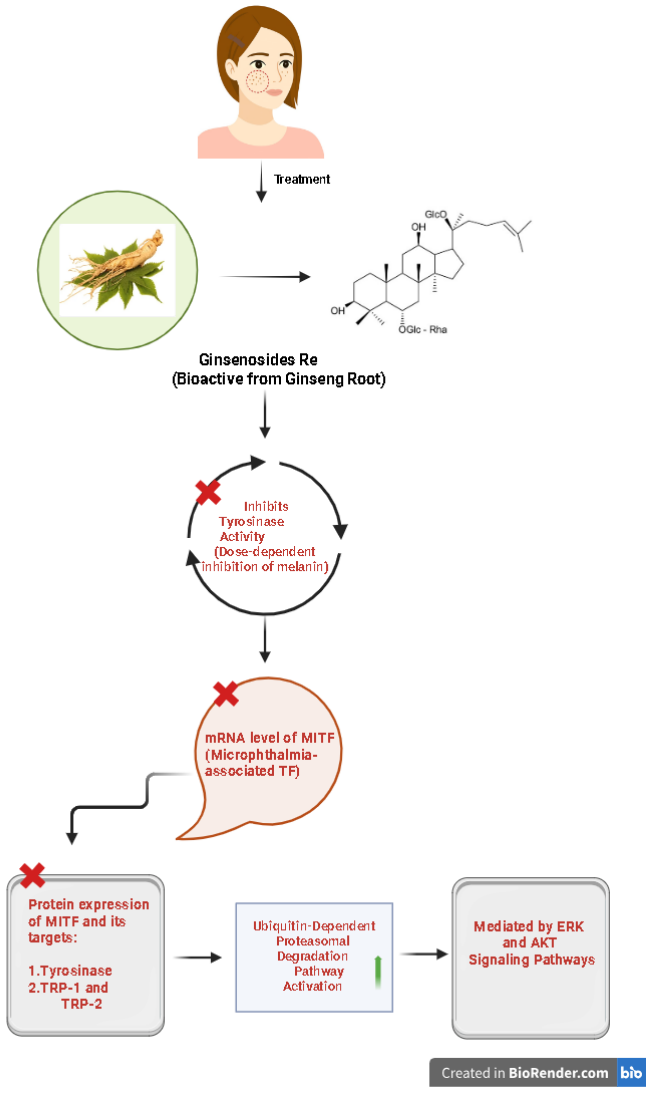

Figure 6: Ginsenosides in melanocytes molecular mechanism.[60]

melanin content, as well as the expression of melanogenesis-related proteins in human melanocytes, were inhibited by curcumin in a dose dependent manner. PI3K/Akt/ GSK 3β, ERK and p38 MAPK were activated by curcumin. According to the study, curcumin inhibited melanogenesis in human melanocytes through the activation of ERK, p38 MAPK or Akt/GSK signalling pathways.[57]

Glabridin

Glabridin in cultured B16 murine melanoma cells revealed the suppression of melanogenesis by downregulating transcriptional and protein expression of melanogenesis-related factors including Microphthalmia-Associated Transcription Factor (MITF), Melanocyte Stimulating Hormone Receptor (MC1R), Tyrosinase, Tyrosinase Related Protein-1 (TYR-1) and Tyrosinase Related Protein-2 (TYR-2). The suppression of melanogenesis by glabridin involves both PKA/MITF and MAPK/MITF signalling pathways.[58]

Aloesin

Aloesin, a compound isolated from the aloe plant, regulate melanogenesis via inhibition of tyrosinase. Enzyme kinetics studies using normal human melanocyte cell-based and cell lysates melanin production indicated that aloesin is a competitive tyrosinase inhibitor, alongside, supress 3,4-Dihydroxyphenylalanine (DOPA) oxidase activities of tyrosinase and tyrosine hydroxylase from normal human melanocyte cell lysates in a dose dependent manner.[59]

Ginsenosides

Ginsenosides effectively inhibit melanin synthesis in dose-dependent manner by suppressing the tyrosinase activity, an enzyme involved in melanin production. Moreover, ginsenosides reduced the mRNA level of Microphthalmia-Associated Transcription Factor (MITF), a key regulator of melanoma growth and melanin synthesis. In addition, ginsenosides decreased the protein expression of MIFT and its target genes including tyrosinase, tyrosinase related protein-1 and tyrosinase related protein-2, through a ubiquitin-dependent proteasomal degradation process, mediated by the ERK and AKT signalling pathways.[60]

CONCLUSION

Freckles, while benign in nature, are often regarded as a cosmetic issue, especially among those with pale skin and heightened exposure to ultraviolet radiation. Both genetic predisposition and environmental stressors contribute to its development by increasing melanin synthesis. Although they are effective to reduce hyperpigmentation, conventional therapeutic modalities like hydroquinone, retinoids, chemical peels, and laser interventions are often linked to side effects like dermal irritation, post-inflammatory hyperpigmentation, increased photosensitivity, and significant financial burden. This has led to a discernible shift in emphasis toward researching safe, sustainable methods of skin depigmentation through natural, plant-based substitutes. Through mechanisms like tyrosinase inhibition, antioxidant activity, and modulation of melanogenic signalling pathways, a wide range of botanicals, including *Glycyrrhiza glabra, Carica papaya, Morus alba, Camellia sinensis,* and *Curcuma longa*, have shown notable anti-melanogenic properties. The effectiveness of bioactive phytoconstituents such as glabridin, curcumin, and neocnidilide has been confirmed by *in vivo* and *in vitro* studies, including melanocyte and zebrafish models. Some of these phytoconstituents have depigmenting effects that are on par with or better than those of synthetic agents, but they do not cause cytotoxicity. The clinical feasibility of these natural agents in lowering hyperpigmentation and improving skin tone is further supported by studies assessing substances including aloesin, arbutin, kojic acid, and CoQ10. These outcomes support a paradigm shift toward integrative dermatological approaches, thus, scientifically supported herbal remedies supplement or even replace traditional therapies to provide a comprehensive, effective, and patient-centered approach for the management of freckle.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TRP: Tyrosinase-Related Proteins; **GSH:** Glutathione levels; **PIH:** Post inflammatory hyperpigmentation; **DA:** Deoxyadenosine; **HQ:** Hydroquinone; **KA:** kojic acid; **MITF:** Microphthalmia-Associated Transcription Factor; **MC1R:** Melanocyte Stimulating Hormone Receptor; **TYR 1:** Tyrosinase Related Protein-1; **TYR 2:** Tyrosinase Related Protein-2; **DOPA:** 3,4-Dihydroxyphenylalanine.

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