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A Review Article On Management Of Hyperpigmentation By Various Treatments

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Abstract

Hyperpigmentation of the skin is a dermatological disorder that causes the skin to become darker or discoloured. Treatments for hyperpigmentation problems frequently have low patient compliance and take a very long time to show benefits. First line treatment for hyperpigmentation is topical formulation, oral treatments. The second line treatment is chemical peel which is more invasive procedure and the third line treatment is laser treatments that are all part of the conventional treatment for hyperpigmentation. These treatments have drawbacks and side effects such erythema,redness,irritation, skin peeling, and dryness, and they take a long time to start showing results. These drawbacks of the traditional therapies allowed for more investigation into more recent approaches to hyperpigmentation management. Novel formulations including liposomes, phytochemicals, and nano/micro emulsion microneedling are a few of these treatments. Better results with fewer adverse effects and more therapeutic efficacy are being shown by a natural chemical.This review aims to several hyperpigmentation problems and their processes, as well as the latest and innovative treatment approaches for managing hyperpigmentation.

Keywords - Hyperpigmentation ,topical ,chemical peel ,laser treatment, novel therapy.

1.Introduction

A common dermatological disorder known as hyperpigmentation causes the skin to become darker overall. Numerous internal and environmental variables, such as hormone fluctuations, inflammation, trauma, acne, eczema, certain medications, UV exposure, etc., can cause these color changes in the skin. [1] The biological mechanisms involving the synthesis of melanin, the skin pigment, by melanocytes in the different layers of skin control skin pigmentation and coloration. Skin hyperpigmentation disease is thus caused by changes in melanocyte production or melanin dispersion.[2] Despite being a typical cosmetic concern for various skin types, middle-aged women and people with skin types III–VI are more likely to have hyperpigmentation.[3]

Nearly 50% of participants reported having skin discolouration and uneven skin tone, which are prevalent skin issues among African Americans. [4] People with deeper skin tones from Yemen and those with lighter skin tones from Lebanon and Syria are the main Arab Americans who report having PIH. [5] Melasma and hyperpigmentation were found to be 7.5% and 6.0%, respectively, in a different study that included 3,000 Latinos.[4] In Asia, PIH is more common in Malays and Indians than in lighter-skinned Chinese people. According to a research done in the Netherlands, 83.3% of people had solar lentigines on their back and 51.4%

on their face.[6]In a similar vein, pigmentary disorders other than vitiligo, the seventh most prevalent dermatosis, are reported by Caucasian patients. [7]

2.Types of hyperpigmentation

1. Melasma
2. solar lentigo[sunspots]
3. post inflammatory hyperpigmentation

2.1 Melasma

The term "melasma" describes a skin disorder known as acquired hypermelanosis, in which sun-exposed areas of the skin develop uneven patches of light to dark brown or gray-brown lesions .[8] It is primarily seen in women and typically affects the face and neck areas.[9]Asymmetrical, uneven, brown-colored, reticulated macules on sun-exposed skin, particularly the face, are the hallmark of melasma, an acquired hypermelanosis. Nonetheless, it has been suggested that melasma formation is influenced by a predisposed genetic background, female hormone stimulation, and prolonged ultraviolet (UV) exposure .[10] It is also shown that melanogenesis, which is mediated by H2 receptors through protein kinase A activation, is stimulated by the histamine released by mast cells in response to UV irradiation. It has been suggested that sebocytes play a role in the onset of melasma. The part sebocytes play in the pathophysiology of melasma requires more research .[11]

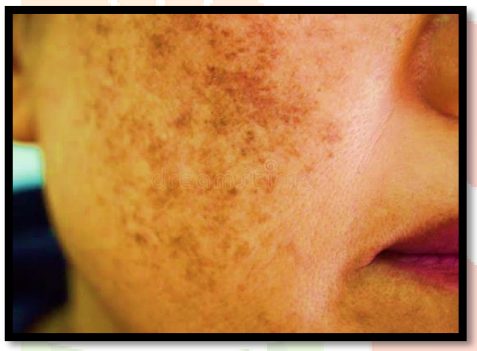

Figure 1 – Melasma[12]

2.2 Solar lentigens[sunspot]

Solar lentigines, sometimes known as "Age spots" or "Sunspots," is a disease in which regions of darkened macular lesions result in hyperpigmentation .[13]Darkened, reddish to light brown spots that usually appear on the face, neck, and arms are a common symptom of Ephelides, also known as freckles. They are more common in people with lighter or fairer skin and grow during the childhood stage .[14]The skin's dark patches are signs of ageing. Areas of skin that are frequently exposed to sunlight, such as face and the backs of the hands, are where they grow the most .[15]

Figure 2 – Sunspot[16]

2.3Post inflammatory hyperpigmentation[PIH]

Pih is another hypermelanosis skin disorder where dark patches appear after skin inflammation or damage.[5]All skin types can develop acquired hypermelanosis following inflammation or damage to the skin. It can be brought on by illnesses such dermatophytosis, allergic reactions, mosquito bites, psoriasis, medication-induced hypersensitivity reactions, irritating injuries, and cosmetic operations. However, it is frequently caused by impetigo, atopical dermatitis, and acne vulgaris. In fact, PIH is more prevalent in darkskinned individuals than acne. Melanin overproduction or uneven pigment dispersion following inflammation are the causes of PIH. Melanocyte activity may increase as a result of reactive oxygen species and inflammatory mediator stimulation. Whereas dermal PIH often has a grey to black coloring, epidermal PIH has a light to dark brown coloration.[10]

Figure 3 – Post inflammatory hyperpigmentation[17]

3.Pathophysiology of hyperpigmentation

Neural crest cells are used to form melanocytes, which give skin its tegument color. These cells, which are found in the basal layer at the dermal and epidermal interface, produce melanosomes.[18] Skin pigments like melanin are produced and stored in melanosomes, which are intracellular organelles that resemble lysosomes. Skin gets its color from the distribution of these pigments to nearby keratinocytes.The Raper Mason pathway, which uses a variety of spontaneous enzymatic processes to create melanin, is triggered by the amino acid L-tyrosine, which serves as the precursor for melanin formation. Black-brown Eumelanin and/or yellow-red Pheomelanin are produced via the melanogenesis process, which takes place inside a melanosome. L-dopachrome raises tyrosinase activity, while L-tyrosine stimulates the development of melanosomes. Thus, maintaining the homeostasis of the melanogenic system depends heavily on controlling the amounts of L-tyrosine and L-DOPA.As the rate-limiting enzyme of the melanin production pathway, tyrosinase is a glycoprotein (60–70 kDa) that includes copper. As such, it is thought to be a possible target for a number of medicinal treatments. The microphthalmia transcription factor (MITF) is a master transcription factor that controls the tyrosinase, TYRP-1, and TYRP-2 enzymes involved in melanogenesis. The epidermis and dermis contain the adrenocorticotropic hormone (ACTH) and α-melanocyte-stimulating hormone (α-MSH), which are important modulators of the melanogenesis pathway.[19]

During the keratinocyte development process, melanosomes degrade in different ways in different skin types. They either create melanin dust, as in lighter skin types, or they reach the outermost epidermal layers intact, as in darker skin. These intricate processes are therefore responsible for the wide range of skin tones and complexions that people exhibit.[20] Many hyperpigmentation diseases can be caused by a variety of intrinsic or extrinsic causes that interfere with the normal melanogenesis process. Alpha-MSH precursors, pro-opiomelanocortin (POMC) peptides, can be enhanced and regulated by signals and factors such UV, cAMP, and IL1.[18] Melanosomes are dispersed to the upper epidermis and adjacent keratinocytes for DNA photoprotection upon UV exposure. In order to stop cell proliferation with unrepaired DNA damage, it triggers the death of melanin-containing keratinocytes in the upper epidermis. Keratinocytes also contribute

to UV-induced hyperpigmentation by releasing a number of growth factors, including alpha-MSH and endothelin-1 (ET-1).[21]

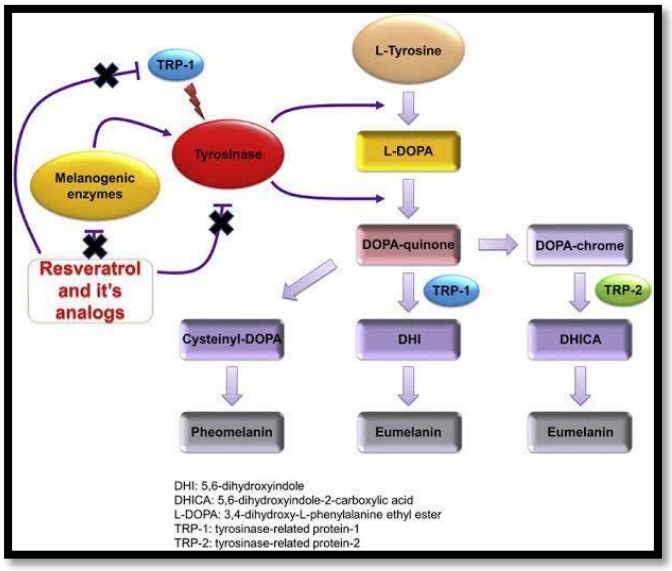

Figure 4 - Melanogenesis pathway[22]

Signals from fibroblasts, endothelial cells, keratinocytes, several hormones, inflammatory cells, and the nervous system are among the intrinsic components that contribute to hyperpigmentation. These cells have the ability to emit NO (nitric oxide) and ET-1, which enhance melanogenesis.[19] Tyrosinase activity is known to be enhanced by arachidonate-related chemical mediators, including PGs (PGE2, PGF2a), leukotrienes (LTC4, LTD4), and thromboxanes, which are released in greater amounts during inflammation. The synthesis of adenyl cyclase and cAMP has also been linked to muscarinic, alpha, and beta estrogen receptors. Thus, hyperpigmentation conditions like melasma and areolar hyperpigmentation may be exacerbated by the increased estrogen levels during pregnancy.[21]

The different pigmentation disorders can have different histopathologies for hyperpigmentation. Retinal ridge flattening and epidermal thinning are two histological characteristics of melasma. Here, there is a slight perivascular lymphohistiocytic infiltration and an increase in melanin content in the epidermis and dermis. A greater number of dermal melanophages, their melanin deposition, and bigger melanocytes with noticeable dendrites are all suggested by immunohistochemistry analysis. Studies using electron microscopy revealed that melanocytes and keratinocytes have more melanosomes. The lymphocytes surrounding blood vessels in the dermal papilla and dermal melanophages exhibit elevated epidermal melanin content in PIH. The significance of skin inflammation is highlighted by the elevated expression of many markers, including [CD]-68, c-kit, and MMP-2, which are also associated with perivascular lymphocytic infiltration, perifollicular, and dermal fibrosis. There are two distinct histological types of PIH: dermal and epidermal. While the latter is marked by increased pigment deposition in the dermis despite increasing melanogenic activity in the epidermis, the former is defined by increased melanogenesis and melanin deposition in the epidermis.[23]

4.Causes of hyperpigmentation

4.1Genetics

Surprisingly, skin tone can be influenced by 125 genes. As shown, hormones and genes control the synthesis of melanin. By choosing, for example, how much sun exposure they receive or how much medication and cosmetics they use, a person can affect the function and longevity of their skin as well as the amount of

pheomelanin or eumelanin they produce. Over time, these factors may change the skin tone.[15]Genetics is therefore one of the most common causes of skin color. The number of melanocytes that each person will have may be predicted by genetics. Skin cells called melanocytes are responsible for producing melanin. However, melanosomes—the organelles that carry melanin—must be transported and increased during tanning and hyperpigmentation, but they shrink during hypopigmentation.[24]People with darker skin tones are more likely to have higher quantities of melanin, the pigment that gives skin its color. For instance, melanin levels are usually higher in people with darker skin tones than in people with lighter skin tones.[25]

4.2 Sun exposure

Skin pigmentation is frequently caused by sun exposure. To protect itself from the sun's UV radiation, the body makes more melanin. Protecting the skin from the sun's rays may increase its pigmentation, illustrating how long-term exposure to UV light causes pigmentation to develop. The formation mechanism consists of five stages that is, free radicals are created by UV light, UV light and free radicals trigger biological agents that affect melanocytes, the cells that produce pigment, tyrosinase is an enzyme that converts the amino acid tyrosine into red or brown melanin pigments, enzyme Tyrosinase, which produces color, is activated by biological molecules, skin's natural exfoliation process causes skin cells to migrate to the outer layers and shed, resulting in the loss of melanin. The skin gets its color from the granules of melanin that are given by surrounding keratinocytes.[25]

4.3 Medication

Additionally, a number of drugs may lighten the pigmentation of the skin. Antibiotics, one type of medications, can increase the synthesis of melanin, which will lighten the color of the skin. Additionally, skin pigmentation may worsen when taking certain medications together, such as birth control pills. To find out if their medication may affect their skin tone, a patient should consult their physician.[26]

5.Reason of increase melanin

A number of factors can lead to an increase in melanin production:

1. Sun Exposure: The sun's ultraviolet (UV) rays activate melanocytes, which are the cells that produce melanin, causing tanning as a defense mechanism.[27]
2. Hormonal Changes: Conditions like melisma can arise from increased melanin production caused by hormones, especially during puberty or pregnancy (e.g., increased estrogen).[28]
3. Genetics: Skin color and vulnerability to specific situations are influenced by an individual's genetic propensity to create more melanin.[29]

6.Treatments for hyperpigmentation

Various cell receptor antagonists, melanocyte stimulation inhibitors, tyrosinase enzyme inhibitors, melanosome transfer inhibitors, and degraders of melanin produced in keratinocytes, as shown in Figure, are possible targets for the depigmenting and hyperpigmentation control drugs. Tyrosinase, the most significant rate-limiting enzyme of the melanogenesis pathway, is inhibited as part of the extensively used strategy.

6.1Topical treatments

Table 1 – List of topical agents for hyperpigmentation along with mechanism of action and advantages.

Topical agents	Mechanism of action	Advantages	References
Hydroquinone	Inhibit tyrosinase to interfere with melanin synthesis.	Gold standard for hyperpigmentation treatment.	[30]
Arbutin	Inhibits tyrosinase and melanosome maturation.	Derivative of hydroquinone with lesser melanotoxic effects.	[31]
Glycolic acid	Desquamation of keratinocytes (low concentration);Epidermolysis (high concentration).	Effective exfoliant and aids in hyperpigmentation treatments.	[32]
Kojic acid	Inhibits tyrosinase (blocks catecholase activity); Induces interleukin-6 formation in keratinocytes.	Various mechanism for depigmentation.	[33]
Retinoids	Inhibit melanogenesis (MSH or L-tyrosine); Influence cell proliferation, differentiation, and inflammation.	Effective against photoaging and PIH; third generation retinoids are safer.	[34]
Tretinoin	Reduces melanin synthesis; Effective against hyperpigmentation.	Improve skin texture and tone.	[35]
Azelaic acid	Inhibits tyrosinase; Anti-proliferative effect on melanogenesis.	Does not affect normal melanocytes or cause ochronosis.	[36]

6.2Oral treatments

Table 2 – List of oral drugs for hyperpigmentation along with mechanism of action and advantages.

Drugs	Mechanism of action	Advantages	References
Tranexamic acid	Inhibits plasminogen activation, reducing melanin production.	Effective for melasma; usually well-tolerated; rare side effects include nausea and risk of thrombosis.	[37]
Glutathione	Antioxidant that reduces melanin production.	Mixed evidence for effectiveness; available as supplements; may improve skin tone in some patients.	[38]
Polypodium leucotomos extract	Antioxidant and anti-inflammatory effects on skin.	Often used for photoprotection; may help with hyperpigmentation caused by sun exposure.	[39]
Vitamin B3	Reduces melanin transfer to keratinocytes.	Help lighten skin when combined with other treatments; well-tolerated.	[40]
Cysteamine	Inhibits melanin synthesis.	Oral use less common; primarily used topically for hyperpigmentation.	[41]
Zinc supplements	Anti-inflammatory reduce melanogenesis.	Often used to support other	[42]

		hyperpigmentation treatments.	

6.3 Chemical peels

Chemical peels are effective for hyperpigmentation, second only to topical treatments. They work by exfoliating the top layers of the skin and enhancing topical agent penetration.

Jessner's Solution: Contains salicylic acid, lactic acid, and resorcinol (14% each). Proven effective in melasma, reducing MASI scores significantly.[43]

Tretinoin Peels:Provide results in 2.5 weeks, with concentrations from 1%-10% showing efficacy.[44]

Salicylic Acid (20%-30%): Shows mixed results, comparable to Jessner's but less effective in some hyperpigmentation cases.[45]

Lactic Acid: Safe for dark skin, reducing MASI scores by 56% in melasma.[46]

Trichloroacetic Acid (TCA): Effective but risks post-inflammatory hyperpigmentation, especially in darker skin .[47]

6.4Laser treatments[48]

Laser treatment is a widely used and effective method for addressing hyperpigmentation, including conditions such as melasma, sunspots, post-inflammatory hyperpigmentation, and freckles. Here's an overview:

Types of Lasers for Hyperpigmentation

1.Fractional Lasers (e.g., Fraxel):Targets deeper layers of the skin to stimulate collagen production and renewal.Commonly used for deeper pigmentation issues and scars.

2.Q-switched Lasers (e.g., Nd:YAG):Effective for superficial pigmentation, such as sunspots and freckles.Delivers energy in short pulses to break up melanin deposits.

3.Picosecond Lasers:Provides shorter bursts of laser energy compared to Q-switched lasers, leading to fewer side effects.Suitable for treating stubborn pigmentation with minimal downtime.

4.IPL (Intense Pulsed Light):Not a laser but uses broad-spectrum light to target pigment.Best for lighter skin tones and milder hyperpigmentation.

Benefits

-Non-invasive with minimal downtime.

-Stimulates collagen production and improves skin texture.

-Customizable based on skin type and pigmentation depth.

Risks and Considerations

-Potential side effects include redness, swelling, temporary darkening (post-inflammatory hyperpigmentation), and, rarely, scarring.

-Not always suitable for darker skin tones due to increased risk of post-inflammatory hyperpigmentation.

-Multiple sessions are often required for optimal results.

Preparation and Aftercare

-Pre-Treatment: Avoid sun exposure, retinoids, and exfoliants for at least a week before the procedure.

-Post-Treatment: Use sunscreen (SPF 30 or higher), avoid direct sun exposure, and follow a gentle skincare routine.

- **Side effects**

Here are potential side effects of all treatments;[49]

1]Topical Treatments: Dryness, peeling, redness, and increased susceptibility to sunlight; mild irritation, redness, and potential allergic responses; and skin irritation, redness, and, with extended use, ochronosis (a bluish-black discoloration).

2] Chemical Peels: Dryness, peeling, and redness of the superficial peels.
Medium/Deep Peels: Redness, crusting, swelling, and a protracted healing time. potential infection or scarring.

3]Laser Treatments: Temporary discomfort, redness, and swelling. Risk factors include discomfort, swelling, crusting, scarring, and either hyperpigmentation or hypopigmentation.

4]Oral Treatments: Headache, uncommon blood clotting problems, and digestive problems.

7.Novel therapies for hyperpigmentation

7.1 Novel formulation

A)Liposomes

Liposomes are tiny, spherical vesicles composed of a bilayer of cholesterol and phospholipids that can contain both hydrophilic and hydrophobic drugs. They may readily integrate with the cell membrane and change the fluidity of the membrane to improve stratum corneum penetration and efficiently administer the medication. In an in vitro investigation, arbutin liposomes showed slower skin penetration and more skin deposition than arbutin solution, which ultimately leads to decreased systemic absorption of the medication. Patients with melasma had their liposomal serum containing retinol, 4-n-butylresorcinol, and azelaic acid examined. Following treatment, the melasma severity scale (MSS) decreased from "moderate" to "milds," and the MASI score increased from 41.7% to 85%.[50]Although they only have a single lipid monolayer, nanosomes and liposomes are remarkably similar. The safety and effectiveness of topical vitamin C nanosomes using iontophoresis were assessed in a single-blind clinical investigation, which also compared them to 70% glycollic acid peei for melasma patients. Photographs and a baseline comparison were used to assess the results, and it was discovered that the nanosome improved hyperpigmentation more effectively than glycollic acid peel. Additionally, vitamin C nanosomes experienced fewer and more temporary side effects, including skin dryness, burning, and irritation.[51]

B)Nano/Micro emulsion

The two immiscible phases of nanoemulsions and microemulsions are an oil phase combined with an aqueous phase with the aid of surfactants. These carriers' size, ability to improve the solubility of both hydrophilic and lipophilic medicines, and other characteristics make them promising vehicles for topical medication administration and cosmetics. The effects of hydroquinone microemulsion on hyperpigmentation and melasma were investigated. Compared to 30% release from hydroquinone cream, 87.405% hydroquinone was released from the microemulsion after 24 hours in vitro. Histopathology demonstrated that this microemulsion did not cause any skin irritation or disturbance of the epidermal layers.When formed into nanemulsion (KMO), kojic monooleate, a tyrosinase inhibitor, showed a 54.76% survival rate of 3T3 cells.[52] Similarly, tyrosinase inhibition and increased drug retention were investigated in azelaic acid and hyaluronic acid nanoemulsion. The formulation considerably decreased tyrosinase activity and had high skin penetration in vitro, according to the in vitro mushroom tyrosinase inhibition experiment. Therefore, the use of nanoemulsions and microemulsions to treat hyperpigmentation and melasma may be investigated.[53]

7.2Microneedling

In order to trigger a wound-healing response, microneedling involves rolling a tool studded with microneedles over the skin to pierce the epidermis and reach the upper dermis (0.5 mm). In order to treat hyperpigmentation problems, it was investigated as a way to improve trans-epidermal administration of several medicines. Rucinol and sophora-alpha serum were assessed in a clinical investigation both with and without microneedling. When compared to the serum alone, the microneedle combination group's MASI score significantly decreased.[54]Similar outcomes were reported when a triple combination cream comprising 0.05% tretinoin, 4% hydroquinone, and 1% fluocinolone acetonize was used in conjunction with microneedling. Treatment with microneedling and tranexamic acid microinjections improved melasma patients' hyperpigmentation more than the control group in a randomised research.[55] The effectiveness of microneedling therapy for acne pigmentation scars was evaluated in 39 dark-skinned patients. When evaluated two and four weeks following microneedling treatment, the results demonstrated a significant improvement above baseline scores. Therefore, in order to treat hyperpigmentation disorders, microneedling may be investigated as a potential and successful supplemental therapy for deeper and more consistent penetration of the depigmenting chemicals.[56]

7.3Phytochemicals

Phytochemicals natural compounds collected or synthesized from plants have been used to treat skin hyperpigmentation. A glycoprotein called aloesin, which is isolated from aloe vera, has been shown to exhibit dose-dependent anti-tyrosinase activity. It has demonstrated more affinity than kojic acid, arbutin, and other substances and functions by preventing L-DOPA oxidation. However, because of its large molecular weight and hydrophilicity, it has poor penetration into the stratum corneum, indicating the need for more effective innovative delivery strategies.[57] Extracted from fern species, Polypodium leucotomos has anti-inflammatory, antioxidant, and photoprotective properties. Oral Polypodium leucotomos reduced the cutaneous pigmentation response in patients who had previously been exposed to PUVA, according to a clinical investigation.[58]

Another study examined how oral polypodium leucotomos extracts, administered at a daily dose of 480 mg for 28 days, affected the pigmentation caused by visible light in 22 patients with Fitzpatrick skin types IV–VI. Following the injection of Polypodium leucotomos extract, the spectroscopic analysis indicated a significant reduction in delayed tanning and permanent pigment darkening. The immunohistochemistry results also showed a decrease in indicators for cellular damage.[59]Similarly, the flavonoids resveratrol and silymarin demonstrate photoprotective qualities via a number of pathways, including anti-inflammatory, DNA damage, apoptosis, and inhibition of UV-induced oxidative stress.[60]Therefore, more research on phytochemicals may examine how well they work in conjunction with conventional treatments to effectively treat

hyperpigmentation. It is also crucial to remember that natural substances are occasionally tainted with corticosteroids and frequently carry a number of dangers for allergic and phototoxic reactions.

8.Natural treatment for hyperpigmentation

In addition to photosafety, a number of drugs and therapies can be used to safely and effectively cure darker skin hyperpigmentation, albeit they may cause side effects. Therefore, the best option for treating skin hyperpigmentation is to use herbs and phytoconstituents. The following lists a few herbs along with how they work to treat skin hyperpigmentation.

➢ Tyrosinase inhibitory effect

The copper-containing enzyme tyrosinase is glycosylated, has multiple uses, and is only present in melanocytes.[61]I-tyrosine is catalyzed to become I-DOPA, which is then transformed into dopaquinone and dopachrome.[62] Melanin is created when dopachrome polymerizes. Tyrosinase enzyme inhibition reduces the synthesis of melanin, which aids in the removal of skin hyperpigmentation. Tyrosinase activity is inhibited by extracts of herbal medications such as licorice, aloe vera, and many more.

➢ Aloe [63]

Synonyms: Aloe barbadensis, Ghrita Kumari (Ayurvedic name)Aloe gel, Kumari
Chemical Constituents: Polysaccharides: Acemannan, glucomannan, Vitamins: Vitamin A, C, E, B12 , Minerals: Zinc, magnesium, calcium, selenium, Enzymes: Amylase, lipase, and carboxypeptidase, Phenolic Compounds: Aloin, emodin, barbaloin.
Biological Source: Aloe vera is derived from the leaves of Aloe barbadensis Miller, a species of the family Asphodelaceae (Liliaceae).

Uses for Hyperpigmentation:
1. Skin Lightening: Aloe vera contains aloesin, which inhibits tyrosinase activity, an enzyme responsible for melanin synthesis, reducing hyperpigmentation.
2. Anti-inflammatory Effects: Reduces skin irritation, aiding in conditions that exacerbate pigmentation.
3. Antioxidant Properties: Protects the skin from oxidative stress, which can lead to hyperpigmentation.
4. Moisturization: Helps improve skin texture ↓ and hydration, µ.. noting even skin tone.

Figure 5 – Aloe vera[64]

➢ Curcuma longa[65]

Synonyms: Diferuloylmethane,Turmeric yellow, Curcuma longa extract, Natural curcuminoid
Chemical Constituents : Curcumin, Demethoxycurcumin, Bisdemethoxycurcumin.

Biological Source: Curcumin is derived from the dried rhizomes of Curcuma longa.
Plant Family: Zingiberaceae.

Uses for Hyperpigmentation:

1. Anti-inflammatory properties:Curcumin inhibits pro-inflammatory cytokines like TNF-a and IL-6, reducing skin inflammation that exacerbates pigmentation.
2. Antioxidant activity:Neutralizes free radicals and oxidative stress, which contribute to melanocyte activation.
3. Tyrosinase inhibition:Curcumin suppresses the enzyme tyrosinase, reducing melanin synthesis in hyperpigmented areas.
4. Skin-lightening effects:Curcumin regulates melanin production through interference with melanogenesis signaling pathways.
5. Wound-healing properties:Its ability to heal damaged skin may improve pigmentation irregularities.

Formulations: Curcumin is used in creams,serums, or oral supplements, often combined with other compounds like niacinamide for enhanced efficacy.

Limitations: Curcumin's low bioavailability can limit its effectiveness. However, formulations with piperine or nanoparticles enhance absorption.

Figure 6- Curcumin[66]

➢ Glycyrrhiza glabra[liquorice][67]

Scientific Name: Glycyrrhiza glabra
Common Names: Licorice, Liquorice root, Sweetwood, Yashtimadhu (Sanskrit), Mulhatti (Hindi).

Chemical constitutents:1.Triterpenoids:
Glycyrrhizin (glycyrrhizic acid): A sweet compound and the primary bioactive component.
Glycyrrhetic acid (aglycone form of glycyrrhizin).

2. Flavonoids:Liquiritin**,**Isoliquiritin**,**Glabridin (potent skin-lightening agent).
3. Chalcones:Licochalcone A, B, C, and D.
4. Polysaccharides, Coumarins, and Saponins

Biological source: Obtained from the dried roots and stolons of Glycyrrhiza glabra L. (family Fabaceae).
Native to the Mediterranean region, Central Asia, and parts of India.

Uses for Hyperpigmentation:

1. Glabridin:Inhibits tyrosinase activity, which reduces melanin synthesis.
Demonstrated antioxidant and anti- inflammatory properties, preventing UV- induced hyperpigmentation.
2. Liquiritin:Reduces melanin accumulation in the skin, prom geven tone and brightness.
3. Licochalcone A:Acts as an anti-inflammatory agent, protecting skin cells from oxidative stress and reducing redness.
4. Glycyrrhizin:Hydrates and soothes the skin, often used alongside active depigmenting agents.

Figure 7 – Glycyrrhiza glabra[68]

➢ Green tea extract[69]

Synonyms:Camellia sinensis extract, Epigallocatechin gallate (EGCG) extract, Tea polyphenols extract, Thea sinensis extract.

Chemical Constituents: Green tea extract is rich in bioactive compounds, primarily polyphenols. The key chemical constituents include:

1. Catechins:Epigallocatechin gallate (EGCG) (most active component), Epigallocatechin (EGC), Epicatechin gallate (ECG), Epicatechin (EC).
2. Flavonoids:Kaempferol, Quercetin
3. Alkaloids:Caffeine, Theobromine, Theophylline
4. Other Components:Amino acids (e.g., L-theanine), Vitamins (C, E, B2),Minerals (potassium, manganese)

Biological Source: Botanical Name: Camellia sinensis (L.) Kuntze
Family: Theaceae

Uses in Hyperpigmentation:

Green tea extract is used in hyperpigmentation treatment due to its ability to regulate melanin production and protect against oxidative stress.

1. Inhibition of Tyrosinase Activity:EGCG reduces melanin synthesis by inhibiting tyrosinase, the enzyme responsible for melanin production.
2. Antioxidant Properties:Catechins in green tea neutralize free radicals, reducing oxidative stress that can trigger hyperpigmentation.
3. Anti-inflammatory Effects:EGCG reduces inflammation, which can exacerbate pigmentation issues.

Figure 8 – Green tea extract[70]

➢ Papaya[71]

Synonyms:Carica papaya (scientific name), Pawpaw (common name in some regions), Melon pear (in some countries)

Chemical Constituents: Papaya contains several bioactive compounds with medicinal properties. The key

chemical constituents include:

1. Papain: A proteolytic enzyme that aids in the breakdown of proteins and is widely used in cosmetics.
2. Chymopapain: ther enzyme similar to papain, also involved in protein breakdown.
3. . Carotenoids: Such as beta-carotene, which is a precursor of vitamin A, and lycopene, which has antioxidant properties.
4. Flavonoids: These compounds have antioxidant effects and help reduce oxidative stress.
5. Vitamin C: An antioxidant that helps in collagen synthesis and skin brightening.
6. Alpha-hydroxy acids (AHAs): Known for their exfoliating profes, AHAs can help with skin renewal and hyperpigmentation treatments.

Biological Source:

Plant Name: Carica papaya

Family: Caricaceae

Origin: Native to the tropical Americas, now widely cultivated in tropical and subtropical regions.

Uses for Hyperpigmentation:

Papaya has been traditionally used in various skin-care treatments due to its exfoliating, moisturizing, and healing properties. The enzymes and AHAs sent in papaya can help treat hyperpigmentation through the following mechanisms,

1. Exfoliation: The AHAs in papaya exfoliate the skin, removing dead skin cells and revealing a brighter, even-toned complexion.
2. Reduction of Melanin Production: Papaya is known to help reduce melanin formation in the skin, which can lighten dark spots and hyperpigmentation.
3. Collagen Boosting: The vitamin C in papaya stimulates collagen production, improving skin texture and reducing the appearance of dark spots.
4. Gentle Skin Brightening: The fruit's enzymes and antioxidants help fade blemishes, freckles, and age spots, making the skin appear more even-toned.

Figure 9 – Papaya[72]

- **Neem**[73]

Synonyms: Indian Lilac**,**Margosa Tree**,**Nim

Chemical Constituents: Neem contains a diverse range of bioactive compounds, including:

Limonoids (e.g., Azadirachtin, Nimbin, Nimbidin, Salannin)

Flavonoids (e.g., Quercetin, Kaempferol) Essential oils (e.g., Nimbidin and terpenes)

Biological Source: Neem is obtained from the tree Azadirachta indica, belonging to the family Meliaceae.

Parts Used: Leaves, bark, seeds, fruits, and oil.

Uses for Hyperpigmentation: Neem has several properties beneficial for skin health, including:

1.Anti-inflammatory: Reduces redness and irritation caused by hyperpigmentation.

2.Antioxidant: Protects skin from oxidative damage, promoting an even skin tone.

3.Antibacterial and Antifungal: Helps in treating acne and infections, which can worsen hyperpigmentation.
4.Melanin Regulation: Flavonoids and limonoids in neem may help reduce excess melanin production.
5.Skin Rejuvenation: Neem's bioactive compounds promote the healing of damaged skin cells.

Application:

1.Neem oil or paste can be applied directly to the affected areas.
2.Neem extracts are incorporated into creams, lotions, and face masks for reducing dark spots and uneven pigmentation.

Figure 10 – Neem[74]

➢ Saffron[75]

Synonyms: Crocus sativus,Kesar,Zaffran.
Chemical Constituents:Carotenoids:Crocin (responsible for its color),Crocetin,Picrocrocin (responsible for the bitter taste),Volatile Oils:Safranal (responsible for the aroma),Flavonoids:Kaempferol,Quercetin.
Other Components:Proteins, sugars, minerals, and vitamins (especially riboflavin).
Biological Source: Saffron consists of the dried stigmas of Crocus sativus, a plant belonging to the family Iridaceae.
Uses of Saffron for Hyperpigmentation: Saffron is widely used in traditional and modern dermatology for its skin-lightening and anti-hyperpigmentation properties. The mechanisms include:
1.Inhibition of Tyrosinase Activity:Crocin reduces melanin synthesis by inhibiting tyrosinase, a key enzyme in melanin production.
2.Antioxidant Properties:Crocin and safranal reduce oxidative stress, which can exacerbate pigmentation.
3.Anti-inflammatory Effects:Reduces inflammation associated with hyperpigmented skin conditions like melasma.
4.UV Protection:Protects the skin from UV-induced pigmentation due to its photoprotective properties.
General Uses of Saffron:Skin brightening, treatment for acne scars, and anti-aging.
Medicinal Uses: Antioxidant, anti-inflammatory, antidepressant, and neuroprotective properties.
Culinary Uses:As a natural colorant and flavor enhancer.For hyperpigmentation, saffron can be applied topically in formulations like creams or masks combined with other ingredients like honey or milk, or taken orally as supplements or in food.

Figure 11 - Saffron[76]

Conclusion

There are numerous ways to cure hyperpigmentation, a common skin problem. Usually the initial line of treatment, topical medications can irritate the skin, especially when used in greater concentrations. The second line is chemical peels, which are effective but can be more costly and cause dry skin. The effectiveness of oral treatments varies. Although they are regarded as a third-line alternative, laser therapies have a higher risk of adverse effects despite their potential for effectiveness. In general, long-term usage of current medicines frequently raises safety concerns. To better control hyperpigmentation while reducing side effects, a number of innovative formulations are now being researched. Natural remedies have also showed potential, yielding positive outcomes with negligible adverse effects.

Future scope

The future of treating hyperpigmentation is changing because to developments in technology, individualized medicine, and dermatological research. The following are some crucial areas for improvement:

Specific Treatments: The development of medications that target particular melanogenesis pathways, such as the suppression of tyrosinase, an enzyme essential to the synthesis of melanin, is the main focus of research. For instance, the effectiveness of novel formulations and medications like tranexamic acid is being investigated. Combination Therapies: To improve outcomes and address several reasons causing hyperpigmentation, future treatments may increasingly combine topical medicines, oral drugs, and procedural techniques.[77] Biologics: Research into biologic substances that can alter skin reactions and target the inflammatory processes that lead to pigmentation.[78] Light and Laser Therapies: It is anticipated that further developments in laser technology and light therapies will enhance the effectiveness of hyperpigmentation treatments. In order to maximize outcomes and reduce skin harm, newer laser systems are being developed.[79]

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