Review

A Comprehensive Review on Skin Pigmentation-Types, Causes, and Treatment

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Review

A Comprehensive Review on Skin Pigmentation-Types, Causes, and Treatment

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Abstract: Humans have extremely variable skin pigmentation and melanin production influenced by genetics, UV exposure, and some medications. A significant number of skin illnesses that result in pigmentary abnormalities have an impact on patients' physical appearance as well as their psychological and social well-being. Skin pigmentation can be divided into two basic categories: hyperpigmentation, where pigment appears to overflow, and hypopigmentation, where pigment is reduced. Albinism, melasma, vitiligo, Addison's disease, and post-inflammatory hyperpigmentation, which can be brought on by eczema, acne vulgaris, and drug interactions, are the most common skin pigmentation disorders in clinical practice. Anti-inflammatory medications, antioxidants, and medications that inhibit tyrosine, which prevents the production of melanin, are all possible treatments for pigmentation problems. Skin pigmentation can be treated orally and topically with medications, herbal remedies, and cosmetic products, but a doctor should always be consulted before beginning any new medicine or treatment plan. This review article explores the numerous types of pigmentation problems, their causes, and treatments, as well as the 25 plants, four marine species, and 17 topical and oral medications now on the market that have been clinically tested to treat skin diseases.

Keywords: skin pigmentation; melanin; Tyrosinase inhibitors; hypopigmentation; hyperpigmentation; vitiligo; skin-lightening; depigmentation

1. Introduction

Skin pigmentation, which refers to how much melanin the body generates, determines the color of the skin. The two main types of melanin, eumelanin, and pheomelanin, are produced by melanocytes in the epidermal layer of the skin. Pheomelanin causes lighter skin tones, while eumelanin is responsible for darker skin tones. [1,2]

The skin is protected from sunburn by the dark brown pigment eumelanin (compound 1 in Figure 1), which absorbs UV rays from the sun. Darker skin tones are related to higher levels of eumelanin, while lighter skin tones are associated with lower levels. The capacity of eumelanin to prevent skin cancer is one of its additional benefits. Studies have shown that those with higher levels of eumelanin had a lower chance of developing skin cancer than people with lower levels. By absorbing solar heat and maintaining the body cool, eumelanin also helps to regulate body temperature. [3,4]

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Pheomelanin, the pigment, is a lighter yellow-red tint (compound 2 in Figure 1). Because pheomelanin does not absorb UV rays as effectively as eumelanin, those with higher levels have lighter skin tones and are more prone to skin damage and sunburns. Pheomelanin does, however, have certain benefits. It helps to control body temperature and can keep the body cool in hot conditions by reflecting heat away from the body. Pheomelanin can also help prevent melanoma and other types of skin cancer. [5,6]

On chromosome 16, gene locus q24.3, the gene regulates the quantity of melanin produced for the melanocortin G-protein coupled receptor 1 (MC1R). The MC1R gene controls skin and hair color, modulates tanning (sensitivity to light exposure and sunburn), and increases melanoma risk. [7,8]

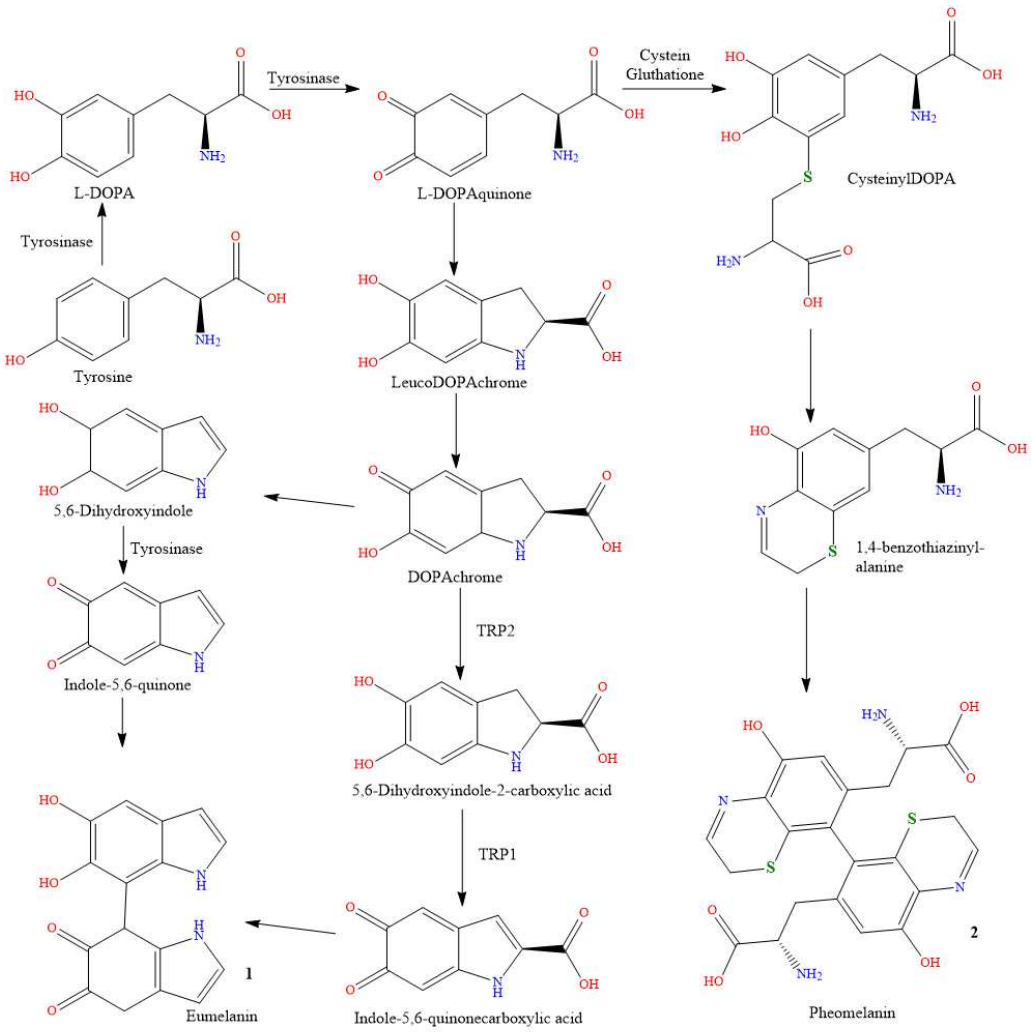

Figure 1. Schematic representation for melanin synthesis pathway.

The rates of melanin synthesis vary across members of the same family and between racial groups (Figure 1). This variation (MSH) is caused by genetics, sun exposure, and certain hormones that stimulate melanocytes, such as adrenocorticotropic hormone (ACTH), lipotropin, and melanocyte-stimulating hormone. Using more melatonin results in a dirty, grayish-brown skin tone. [8–10]

2. Causes of Skin Pigmentation

Skin pigmentation is a common condition that can be triggered by various factors. The three leading causes of skin pigmentation are genetics, sun exposure, and particular medications. Understanding the fundamental causes of skin pigmentation will help us understand how to treat and prevent it. [2]

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2.1. Genetics

Surprisingly, 125 genes can affect skin color. Genes and hormones control the melanin manufacturing process seen in Figure 1's flowchart. The skin cells' capacity to function and live and how much pheomelanin or eumelanin they generate are under a person's control. As time passes, these factors may cause changes in skin tone [1]. Genetics is thus one of the most common causes of skin pigmentation. How many melanocytes the person has can be predetermined by genetics. It is produced by melanocytes, which are skin cells that produce melanin. However, melanosomes (the organelles that contain melanin) must be transferred and increased during hyperpigmentation and tanning, but melanosomes decrease during hypopigmentation [11]. People with darker skin tones are likelier to have higher quantities of melanin, the pigment that gives skin its color... For instance, people with darker skin tones often have more melanin than those with lighter skin tones. [12–14]

2.2. Sun Exposure

Sun exposure is another common factor in skin pigmentation. When exposed to UV rays from the sun, the body produces more melanin to protect itself. This can make the skin more pigmented to defend against the sun's rays. Figure 2 illustrates how those with lighter skin tones are more likely to experience enhanced skin pigmentation after prolonged sun exposure [4,14,15].

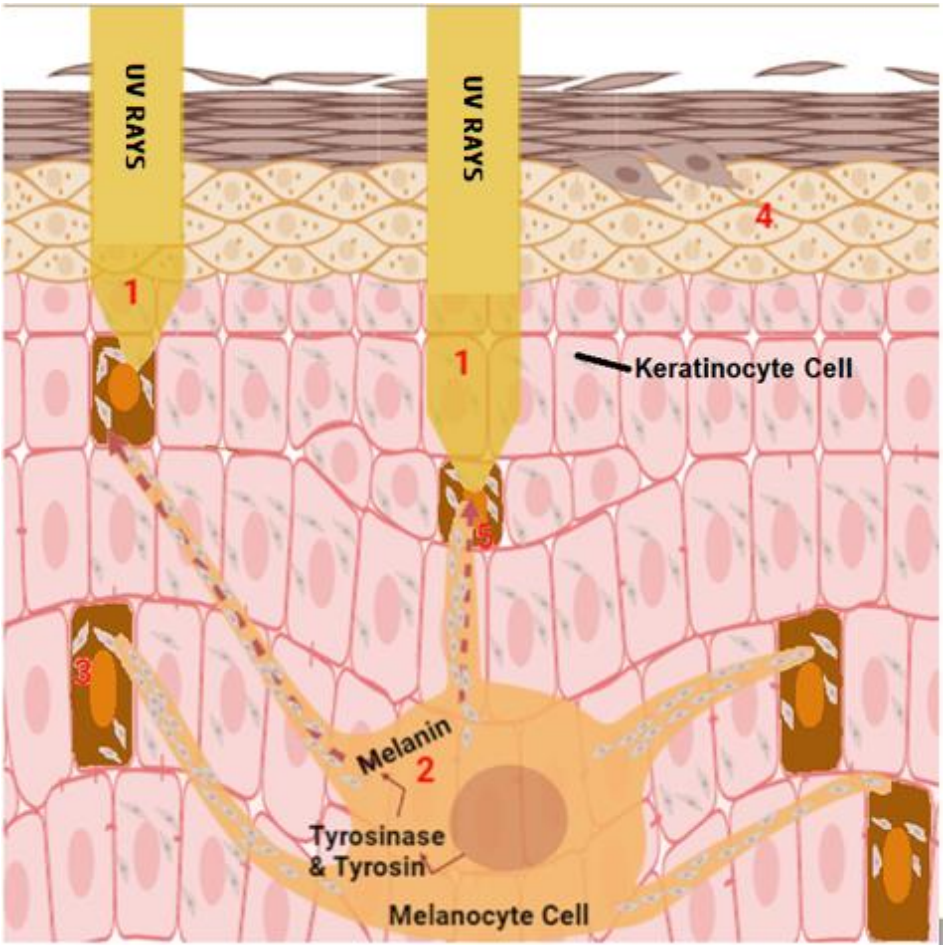

Figure 2. (1) Ultraviolet radiation produces free radicals. (2) Free radicals and UV light both operate as biological triggers for the melanocytes, the pigment-producing cells. (3) The tyrosinase enzyme, which creates colors, is influenced by biological circumstances to manufacture more of them. (4) Tyrosine, an amino acid, is transformed into melanin pigments, which can be either red or brown in color, by the enzyme tyrosinase. (5) Melanin is transferred from melanocytes into the surrounding keratinocytes as granules to give the skin its color.

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2.3. Medications

Several medications may also lighten the skin's pigment. One class of drugs, antibiotics, can boost melanin synthesis, increasing skin color. When certain medications, such as birth control pills, are taken together, skin pigmentation may also intensify. A person taking medicine should speak with his doctor to find out if the medication could impact the color of his skin. [7,16,17]

3. Types of pigmentation disorders

While ill, a person's skin tone may alter, becoming lighter (hypopigmentation), as seen in Figure 3A,B, or darker (hyperpigmentation), as seen in Figure 3C,D. Melanin, the pigment that regulates skin color, is produced less frequently by the body, which results in hypopigmentation. Hyperpigmentation, on the other hand, is an increase in melanin synthesis. [4,5,18]

3.1. Causes of hypopigmentation

Prior skin trauma, including skin sores like blisters, infections, burns, exposure to chemicals, and other wounds, is the most common cause of low melanin content. (hypopigmentation). After healing injuries, the skin is paler than the surrounding skin surfaces. [19] Other genetic diseases can result in hypopigmentation in different parts of the skin. As seen in Figure 3, hereditary disorders such as albinism, melasma, fungal infections, pityriasis versicolor, pityriasis alba, and vitiligo can result in hypopigmentation as the mechanism in Figure 4. At birth, albinism is caused by a genetic abnormality called low melanin concentration. The prevalent physical traits of albinos include a white complexion, dark blue eyes, and white hair. [20,21] The genetic melasma condition can cause brown or blue-gray spots to develop on a person's arms or face. Hormones, sun exposure, or contraceptive medication may bring it on. [22,23]

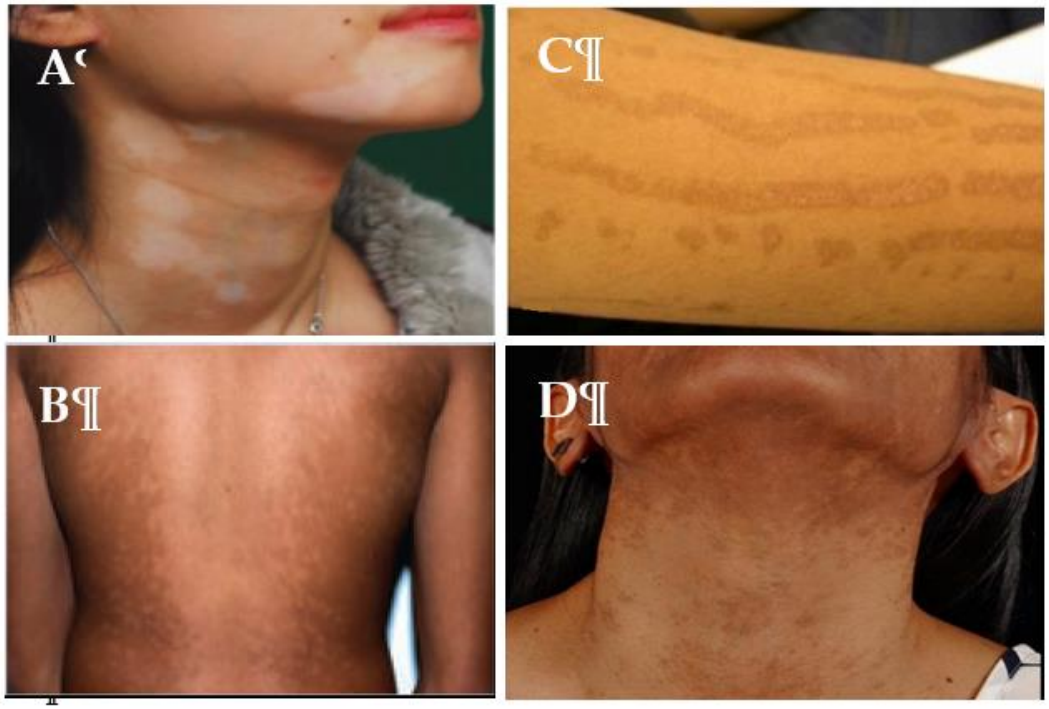

Figure 3. hypopigmentation (**A**) [22], (**B**) [23] and hyperpigmentation (**C**,**D**) [24] cases. Figure 3A: Reproduced with permission from Joo-Heung Lee, Cho-Rok Kim, Dong-Youn Lee, Photodermatology, Photoimmunology & Photomedicine; published by John Wiley and Sons, 2011. Figure 3B: Reproduced with permission from Jeremy P Hill, Jonathan M Batchelor, The BMJ; published by BMJ Publishing Group Ltd, 2017. Figure 3C,D: Reproduced with permission from Narumol Silpa-archa, Indermeet Kohli, Suteeraporn Chaowattanapanit, Henry W. Lim, Iltefat Hamzavi, Journal of the American Academy of Dermatology; published by Elsevier, 2017.

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Despite the fact that the Malassezia genus is responsible for the widespread fungal infection known as tinea versicolor, also known as pityriasis versicolor, it is possible for fungi to infect humans and change the color of their skin. Small regions of discoloration are brought on by malassezia's alteration of the skin's normal melanin pigmentation. The patches on the shoulders and buttocks may be lighter or darker than the overall healthy skin tone. [25] Pityriasis alba is a skin condition that typically affects adolescents and teenagers and is characterized by oval or circular hypopigmented lesions with soft scales. Lesions on the face, upper body, and arms, which are more noticeable in those with darker skin tones, may be modestly erythematous before becoming hypopigmented. [26]

Another common hypopigmented skin disorder is depigmentation, which occurs when the skin completely loses pigment and turns white. It is exemplified by the autoimmune disease vitiligo, which is characterized by melanocyte loss, a common cause of depigmentation, and macules of a white chalky substance on the skin. Smooth, white patches develop on the skin as a result of vitiligo, as seen in cases in Figure 5A,B. Vitiligo is frequently written off as a minor issue. [27,28]

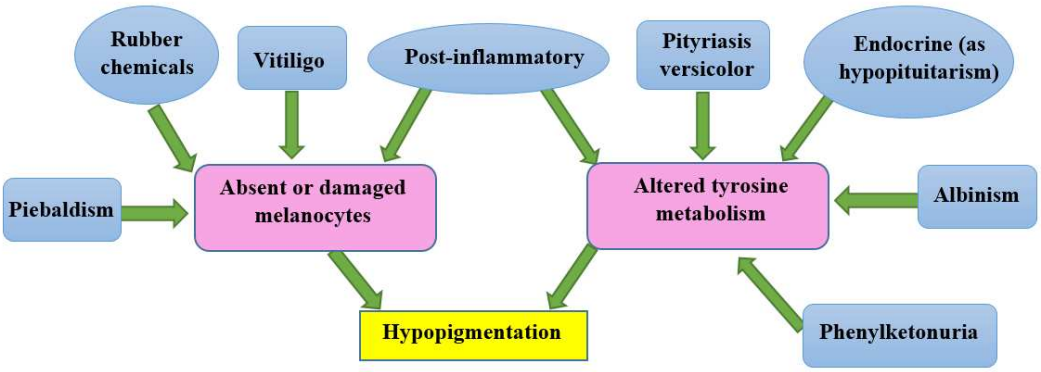

Figure 4. The mechanisms involved in some types of hypopigmentation.

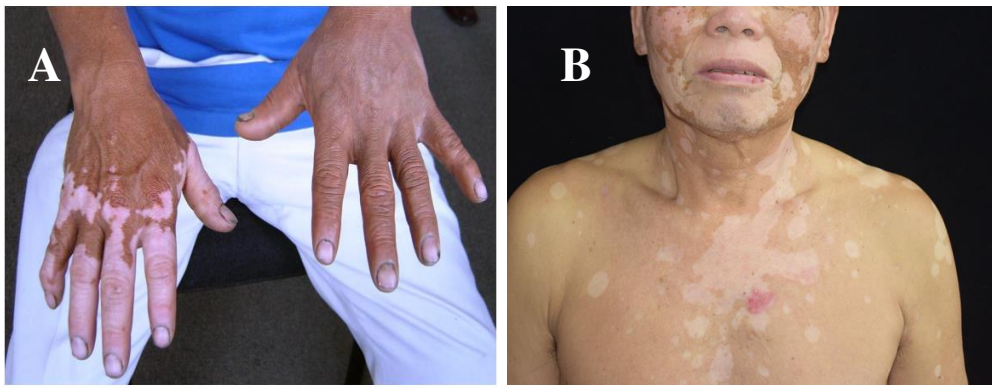

Figure 5. Depigmentation cases [27,28]. Figure 5A: Reproduced with permission from Louise McMichael, the BMJ; published by BMJ Publishing Group Ltd, 2012. Figure 5B: Reproduced with permission from Jing Jing, Xiao-Yong Man, the BMJ; published by BMJ Publishing Group Ltd, 2021.

3.2. Causes of hyperpigmentation

Hyperpigmentation results from an increase in melanin production. The main causes of a rise in melanin production, such as examples C and D in Figure 3 are sun exposure, dermatological illnesses, hormones, aging, hereditary factors, skin injuries or inflammation, and acne [24].

Sun exposure is the only known cause of this pigmentation condition because it predominantly stimulates melanin synthesis. Melanin protects the skin from UV radiation, acting as a natural sunscreen. Hyperpigmentation, however, could result from extensive sun exposure. Figure 2 previously showed that early exposure to the sun could worsen dark spots by mimicking melasma, age spots, and post-inflammatory spots. [24] Two examples of hyperpigmentation brought on by hormonal factors are chloasma and melasma. It has been discovered that the female sex hormones

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estrogen and progesterone boost melanin synthesis when the body is exposed to sunlight, resulting in this condition, which is prevalent in women. A negative side effect of hormone replacement treatment is hyperpigmentation. [29] Melanocyte numbers decline with age, but those still around grow and specialize. These physiological changes show how aging spots in adults over 40 become more apparent. [30] Genetics has an impact on pigmentation. The development of melanocyte function, which influences skin color, requires specific genes. [31] It appears after skin inflammation or damage, as indicated by the name post-inflammatory hyperpigmentation. Some of these are Burns, wounds, psoriasis or atopic dermatitis, chemical exposure, and acne. The skin looks darker and discolored once the wound has healed. [28] The deep skin layer dermis can get infected by papules, pustules, and acne. Unusual dark patches appear when sick skin areas produce more melanin than usual. Similarly, the true causes of the hyperpigmentation problem are infections of the fatty glands and hair follicles. Typically, minor acne won't lead to hyperpigmentation. Acne pimples that have been squeezed, squashed, or punctured will likewise discolor and hyperpigmented. [32]. The following causes of hyperpigmentation: pregnancy-related birthmarks, age spots, acne scars, and several drugs, including antibiotics, birth control pills, antimalarials, and tricyclic antidepressants. Dark skin patches and impaired adrenal gland function are symptoms of Addison's disease, an uncommon ailment. Hyperpigmentation can occasionally happen as a result of laser or light therapy. [33]

4. Drugs for Treatment of Skin Pigmentation

Despite being well-recognized for many years, drugs for skin pigmentation have only recently become more widely available. Topical creams and oral pills are the primary medications for skin pigmentation. It would be best to balance the advantages and disadvantages of both medicines to choose which is most beneficial. [33,34]

4.1. Oral Medications

Oral medicine is a potential substitute for treating skin ailments and modifying skin tone. Such drugs are beneficial because they are more potent than topical creams and do not have to be applied or disposed of as frequently as topical creams. However, there are certain drawbacks to taking oral medications. They can be expensive and cause more significant side effects than topical therapies. [35]

Compound 3 in Figure 6 is tranexamic acid (Traxamac® 250 mg), one of several coagulation modifiers. In addition to eczema, melasma, other associated ailments, toxic reactions, urticaria, and its effects on erythema, itching, swelling, and other recognized symptoms, it has also been used to treat various illnesses. A plasmin inhibitor called tranexamic acid prevents the plasminogen activator from converting plasminogen to plasmin by reversibly shutting off lysine binding sites on plasminogen molecules. This reduces atypical fibrinolysis and prevents blood loss. According to recent studies, tranexamic acid helps tyrosinase untangle tangles. It might avoid and stop hyperpigmentation by reducing melanin production. It is a widely used pharmaceutical technique that is easily accessible and effective against pigment spots. Although it inhibits the effects of tyrosinase and changes the relationship between keratinocytes and melanocytes, it decreases dermal vascularity and lessens melanin production. [36–40]

Using tranexamic acid orally in a dosage of 250 mg twice daily for six months on 75 patients, clinical and photographic evaluation reveals an initial decline in melasma after the first month for 82.4% of patients and 94.6% in the second month. The development of pigmentation has been used to measure the treatment's success (excellent if >90%, good if >60%, fair if >30%, and poor if 30%). After six months, the overall development rate is 95.9%, with 10.8% being excellent, 54% being good, and 31.1% being fair. which is evidence that oral tranexamic acid is a safe and effective melasma treatment. [41,42]

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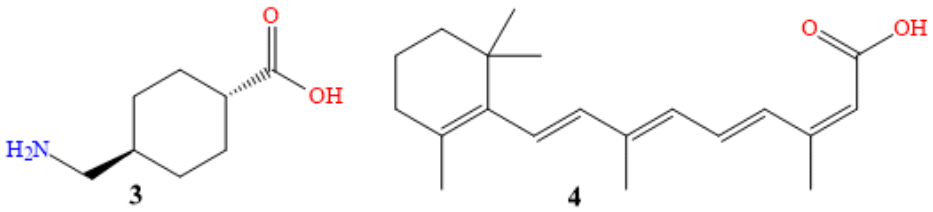

Figure 6. Chemical structures of tranexamic acid (**3**), and isotretinoin (**4**).

Mexameter® was utilized to evaluate the suggest lesional melanin index (MI) ranks and the erythema index (EI) scores for 25 patients who received 1,500 mg twice daily for two months. Both of these scores fell off dramatically. Histological examination confirmed significant decreases in mast cell counts, vessels, and epidermal pigmentation. Here is an illustration of how oral tranexamic acid reversed melasma-related dermal changes, including increased vascularity, decreased mast cell populations, and decreased melasma-related epidermal pigmentation. [43,44]

In a 25-woman research, certain sides of the face received twice-daily applications of 5% topical tranexamic acid for 12 weeks as a melasma treatment. Mexameter and Melasma Area and Severity Index (MASI) results revealed a notable drop in MI and MASI scores. Additionally, for 12 weeks, 23 melasma patients applied a 2% tranexamic acid emulsion twice daily to their whole faces. With a rise in the lightness values and a decrease in the erythema values, the mMASI and chromameter results showed a significant improvement in the fourth and eighth weeks. [45–47]

Isotretinoin is the 13-cis retinoic acid derivative of vitamin A (Isotane® 20 mg, molecule 4 in Figure 6). [48–50]. In treating acne vulgaris, oral isotretinoin exerts its effects by reducing sebaceous gland activity, Propionibacterium acnes development, and inflammation. This facilitates pore cleaning and inhibits the growth of new zits. [51–53]

The administration of 20 mg of Accutane (isotretinoin) orally was randomly assigned to sixty patients (aged 35 to 65); 42 of the women and 18 of the males. It was administered three times a week for no more than two months, and tracking continued for months after the study was over. The 60 patients reported reductions in their wrinkles, pore thickness, and pore size. They noticed that the skin became significantly smoother and lighter in color. Both the elasticity and tone of the skin improved. Additionally, they noticed a decrease in pigmented lesions and hyperpigmentation. [54,55]

The severity of acne was assessed by MASI for 30 individuals of either sex who were receiving 20 mg of isotretinoin as a monotherapy and were between the ages of 18 and 25. A reduction of roughly 73.4% was seen in patients who took 20 mg of oral isotretinoin for 16 weeks. [56,57]

4.2. Topical Creams

Topical creams are the most common type of drug used to treat skin pigmentation. They are applied directly to the affected area and can lighten or darken the skin. The main advantage of topical creams is that they may be used at home and don't require a trip to the doctor. Additionally, they are typically less expensive than oral medications. Topical cream application, however, comes with several drawbacks. They can be messy and time-consuming to apply, and they might only sometimes be as effective as oral medications. [58,59]

Topical steroids are the most often recommended drug in dermatology. It is prescribed for various conditions, including eczema, psoriasis, atopic dermatitis, lichen simplex chronicus, intertrigo, and psoriasis, due to its immunosuppressive, anti-mitogenic, and anti-inflammatory characteristics. The dosage varies from one to three times per day. Betamethasone 0.05% (Betnovate-N®, chemical 5 in Figure 7) and clobetasol 0.05% (Dermovate®, compound 6 in Figure 7) are examples of topical steroids. NF-Kappa B inhibitors betamethasone and clobetasol are glucocorticoids that prevent neutrophil apoptosis and demarginating. Betamethasone and clobetasol are phospholipase A2 inhibitors, which also reduce the production of arachidonic acid derivatives. Additionally, glucocorticoids encourage the anti-inflammatory gene interleukin-10. [60–62]. a

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common ingredient in cream or ointment treatments. Numerous local and systemic adverse effects of topical steroids have been attributed to their continuous use. [63–65]

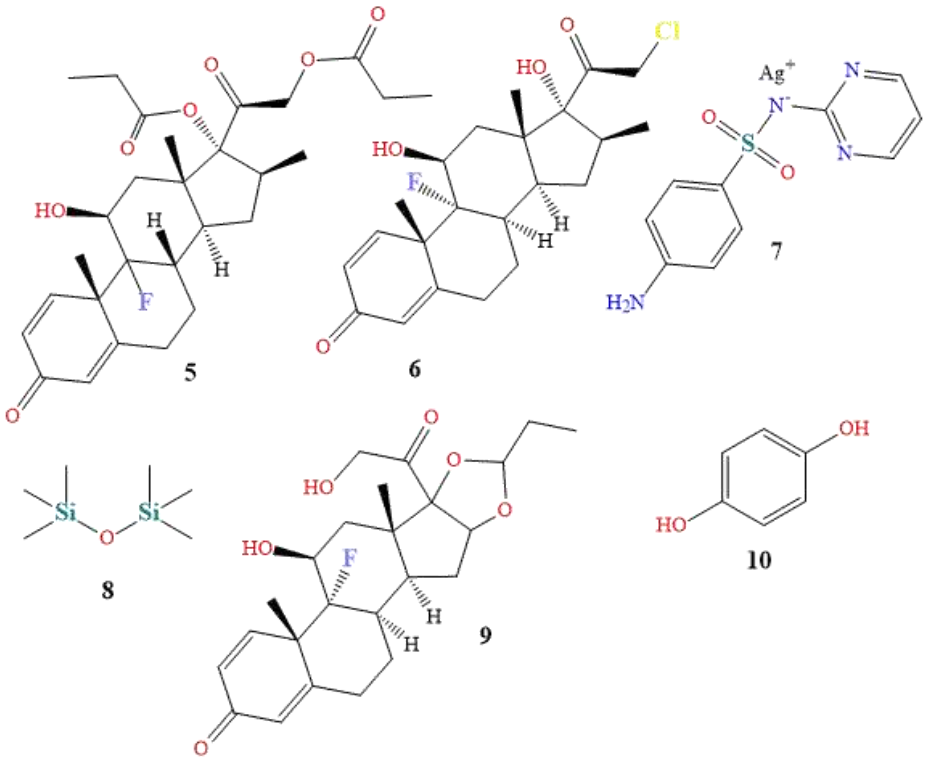

Figure 7. Chemical structures of betamethasone (5), clobetasol (6), silver sulfadiazine (7), dimethicone (8), triamcinolone (9), and hydroquinone (10).

15 vitiligo patients of both sexes (F: M 1.14: 1) utilized betamethasone cream 0.05% twice daily throughout three-month research. Based on the patients' degrees of minimal pigmentation/no reaction, moderate, noticeable pigmentation, and outstanding pigmentation, the improvements of the patients were rated as (25%), (25-50%), (50-75%), and (> 75%), respectively. Compared to 40.0% of patients with limited pigmentation or no reaction, 46.7% and 13.3% showed a moderate or severe pigmentation response after therapy. [66,67]

Seven hundred thirty-one patients with moderate to severe plaque psoriasis with 3% to 20% body surface area participated in the 4-week Clobetasol Spray trial, which used two doses of clobetasol propionate spray 0.05% twice daily as treatment. The change in target plaque severity was the primary outcome measure. According to the major outcome measures scale, 80.0% of the patients in the therapy group were clear or nearly unambiguous and had a decrease in severity from the beginning. [68,69]

A topical anti-infective cream, silver sulfadiazine (Silvadene®, chemical 7 in Figure 7) is primarily used to prevent and cure burn injuries. Silver sulfadiazine solution with 1% API dissolves in water. Proteins become denaturized and enzyme activity is reduced by silver ions. Additionally, silver ions bind to proteins and surface membranes, leading to membrane proton leakage and cell death. Sulfadiazine competitively inhibits PABA, a naturally occurring bacterial substance that acts as a substrate for the dihydropteroate synthase enzyme. These organisms must carry out the blocked process to produce folic acid [70]. Silver sulfadiazine exhibits broad-spectrum action against both gram-positive and gram-negative pathogens. It has been demonstrated that it promotes wound and injury repair and has anti-infective qualities. [71,72]. Twenty-seven individuals with 2° burn injuries were randomly assigned to receive silver sulfadiazine throughout a 4-week study. After four weeks of treatment, the healing condition of 2° deep dermal burn wounds were determined to be (0–25%), (26–50%), (51–75%), and (76–100%), respectively, as poor healing, moderate healing, fast healing, and excellent healing. While 8 and 13 patients had a mild and quick recovery, six patients with 2° deep

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dermal burn lesions had poor healing. [73] Mixtures of creams, shampoos, powders, mouthwash, and gels contain both an anti-infective and a steroid component to treat skin or scalp infections. [74] Triamcinolone and dimethicone are ingredients in the drug (TriHeal80®; see components 8 and 9 in Figure 7). Topical corticosteroids produce similar antipruritic, anti-inflammatory, and vasoconstrictive effects. [75].

Triamcinolone is a phospholipase A2 inhibitor that acts on cell membranes to prevent the lysosomal membranes of leukocytes from rupturing. This prevents the production of arachidonic acid, which in turn lowers lipoxygenase and cyclooxygenase while inhibiting the production of prostaglandins and leukotrienes [76,77]. Dimethicone, a silicone oil, exhibits viscoelastic qualities. It has moisturizing properties, is utilized as a surfactant, antifoaming agent, and lubricant to cure skin irritation. To reduce the rate of water evaporation, dimethicone is used topically [78,79]. When used four times per day for two months and monitored for another two months, triamcinolone 0.1% mouthwash successfully treated oral lichen planus in 20 patients. All effectiveness endpoints assessed using the visual analog scale, the verbal health impact profile score, and the objective clinical score all revealed a significant improvement in the patients. [80–82]

Under the brand name Tri-Luma®, a triple combination cream is sold that includes the active components tretinoin, hydroquinone, and fluocinolone in concentrations of 0.01%, 4%, and 0.05%. [83]. Hydroquinone is the most often used skin-lightening or depigmenting substance (compound 10 in Figure 7). It treats dyschromic skin diseases such as melasma, chloasma, freckles, and post-inflammatory hyperpigmentation by suppressing melanin production. It stops tyrosinase from converting L-3,4-dihydroxyphenylalanine into melanin due to its structural similarity to a specific analog of melanin. [83,85] Fluocinolone (molecule 11 in Figure 8) treats symptoms, including itchiness, swelling, and redness caused by skin problems. [86,87] Retinol (compound 12 in Figure 8) cures skin aging. It was shown that it might be beneficial for concerns related to skin aging. The most remarkable feature is that treatment results manifest eight to twelve months after using the tretinoin 0.1% cream preparation. The most frequent side effects of tretinoin include very small skin irritability and a transient, mild, and clinically uncomfortable burning sensation. [85,88,89]. Sixty patients with moderate (grade 2) or severe (grade 3) melasma received treatment for eight weeks with the triple combination cream. At weeks 4, 6, and 8, the triple combination cream significantly improved the overall results, with an improvement rate of 73% (44/60). The percentage of participants who thought the triple combination cream was "excellent" as a treatment was 50%, while the most often mentioned adverse effects were erythema, burning, and desquamation. [90].

Additionally, a 12-week open-label trial was created to gauge the effectiveness and safety of applying topical retinol 0.15% twice daily. At the fourth, eighth, and twelve weeks, it was found that 39%, 77%, and 77% of patients, respectively, had significant improvement. When using topical retinol, dryness, erythema, peeling, stinging, and burning were some side effects that were tolerated.[91].

Dermatitis, eczema, rashes, and allergies are just a few of the skin conditions that TriDerm® is used to treat. The swelling, redness, and itching that are brought on by these various disorders are reduced by triamcinolone. It includes corticosteroids that range in strength from mild to potent. The mechanism of action of TriDerm is composed of betamethasone, clotrimazole, and gentamicin (compounds 13 and 14 in Figure 8), which results in the antipruritic, anti-inflammatory, and vasoconstrictive effects of betamethasone, as well as the broad-spectrum bactericidal antibiotic effect of gentamicin and the broad-spectrum antifungal effect of clotrimazole. The contents of the cell leak out when clotrimazole reacts with the fungal cell membrane. Gentamicin is an effective topical skin therapy for bacterial infections. [91–95]. The study included 68 patients with itchy dermatoses, including atopic dermatitis, contact dermatitis, and true eczema. 33 of the patients received a twice-daily application of a topical cream containing betamethasone, clotrimazole, and gentamicin on the affected body parts. The effectiveness of the therapy was assessed after 7, 14, and 28 days. On the seventh day of treatment, there is a reduction in the inflammatory process and subjective symptoms. Five of the 33 patients saw a scientific recovery on the fourteenth day of getting treatment. After 28 days of therapy, the patient had fully recovered medically. [96]

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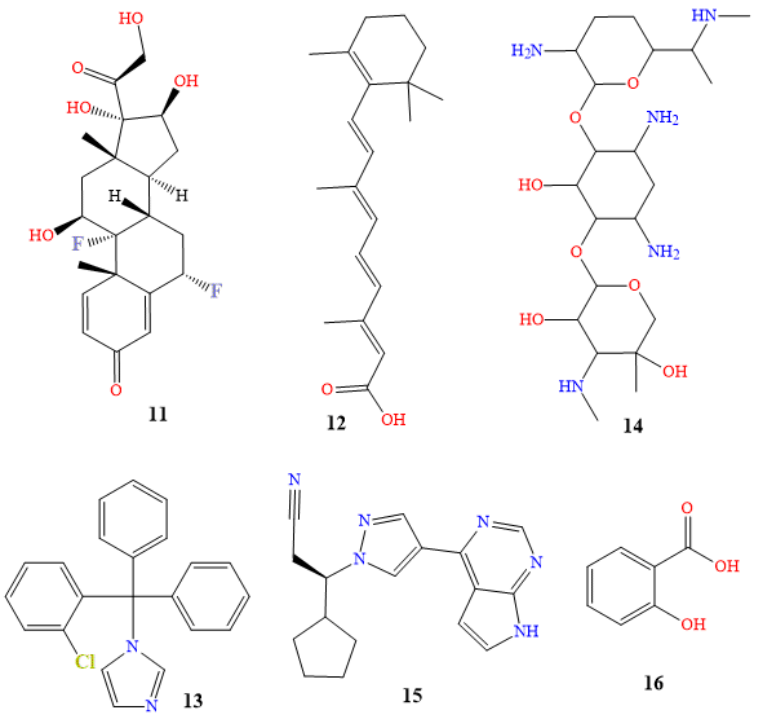

Figure 8. Chemical structures of fluocinolone (11), tretinoin (12), clotrimazole (13), gentamicin (14), ruxolitinib (15) and salicylic acid (16).

The main component of the topical anti-cancer drug Opzelura® is ruxolitinib (compound 15 in Figure 8). A class of drugs known as Janus kinase inhibitors, which includes roxolitinib, has an effect on the immune system. JAK inhibitors may reduce the immune system's ability to fight off infections. [97–100]. JAKs serve a variety of purposes. JAK1 and JAK3 increase lymphocyte existence and differentiation, whilst JAK2 increases the signal transduction of thrombopoietin and erythropoietin. JAKs are located in the cytoplasmic region of cytokine and growth factor receptors. JAKs are also activated and undergo cross- and tyrosine phosphorylation. Ruxolitinib has a low affinity for JAK3 but is a solid and selective inhibitor of JAK2 and JAK1. Ruxolitinib reduces plasma levels of pro-inflammatory cytokines and inhibits myeloproliferative by downregulating the JAK-STAT pathway [101,102]. The randomized controlled trials recommended using ruxolitinib 1.5% cream for treating vitiligo twice daily in various patients. It was shown to demonstrate clinically excellent repigmentation of all body areas, including the acral region, after 24 weeks, with continued improvement through week 52. It was well tolerated in patients with long-standing high contamination. [103,104].

Salicylic acid (Salvax®, compound 16 in Figure 8), podophyllum resin (Podocon-25®, compound 17 in Figure 9), and podofilox (Condylox®, compound 18 in Figure 9) are a few examples of topical keratolytic that are administered topically to the skin to soften keratin. It facilitates the peeling of skin cells. It supports the skin's capacity to retain moisture and aids in the treatment of dry skin conditions. generally used to treat skin diseases such as psoriasis, acne, warts, keratoses, and acne. [105,106]. More topical brand names for reducing skin pigmentation are included in Table 1.

Because of its keratolytic qualities, salicylic acid, a lipophilic B-hydroxy acid, is frequently used in cosmetic product formulations as a skin scaler for lightening. Arachidonic acid is reduced from converted to prostaglandins and thromboxanes by COX-1 and COX-2 inhibitors. Salicylic acid also has anti-inflammatory and antibacterial effects. [107,108]. Twenty Latin American women over the age of 18 with moderate to severe bilateral melasma participated in a small, potential randomized controlled trial to compare the efficacy of salicylic acid 20%–30% scaler every two weeks followed by up to eight weeks in combination with hydroquinone 4% twice daily for 14 weeks, versus hydroquinone 4% alone. A narrowband reflectance spectrophotometer (Mexameter MX-16) was used to quantify the degree of pigmentation on the affected and unaffected skin on each face. The Melasma

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Place and Severity Index (MASI) was used to assess the severity of the melasma. 33% of that 44% were regarded as having mild development and slight improvement, with 44% showing more significant progress on the peeled aspect. One patient (6%) was noted to have only slightly more growth on the unpeeled side. The peeled side had advanced more than the unpeeled side, according to 83% of the nonblinded patients (four somewhat, seven moderately, and four significantly). One patient (6%) thought the unpeeled aspect was more advanced, whereas twelve percent (12%) believed there was no difference.

Table 1. Topical brands drug for the treatment of skin pigmentation.

Class	Generic name	Brand names ®	Dosage form
Topical steroids	Betamethasone	Etnovate, Diprolene, Luxiq, Beta-Val, Diprolene AF	Cream, gel, ointment, lotion
	Clobetasol	Dermovate, Clobex, Olux, Olux-E, Temovate, Clobevate, Clodan, Cormax, Cormax Scalp, Embeline, Embeline E, Impeklo, Tovet	Solution, spray, ointment, gel, foam, lotion, cream, shampoo
	Triamcinolone acetonide	DermasilkRx SDS Pak, Dermasorb TA , DermaWerx SDS Pak, Kenalog , Oralone , Trianex , Triderm	Cream, ointment
Topical anti-infectives	Silver topical	SilvaSorb, Aceso Ag, Solox	Cream, gel, foam
Topical steroids with anti-infectives	Dimethicone and triamcinolone topical	Yaliira Pak, Ellzia Pak, TriaDime-80, TriHeal-80	Creams, shampoos, powders, gels
Topical depigmenting agents	Fluocinolone, hydroquinone and tretinoin topical	Tri-Luma, Triderma	Cream
	Hydroquinone topical	Melquin HP, Alera, EpiQuin Micro, Esoterica, Hydro-Q, Melamin, Melpaque HP, Nuquin HP, AMBI Fade, Blanche, Esoterica Nighttime, Glytone, Lustra-Ultra, Melamin-C, NeoStrata HQ Skin Lightening, Olivia Quido, Fade cream, Remergent HQ	Cream
Topical keratolytics	Salicylic acid topical	Bensal HP, KeralytGel, Salex, Acnex, Aliclen, DHS Salicylic Acid 3%, Durasal, Keralyt Shampoo, Stri-Dex, Akurza, DermalZone, Dr Scholl's, Fostex, Freezeone, Rayasal, Salvax, Stridex,	Liquid, soap, cream, lotion, foam
	Podophyllum resin topical	Podocon-25, Podofin, Pododerm	Topical solution
	Podofilox topical	Condylox	Topical gel, topical solution

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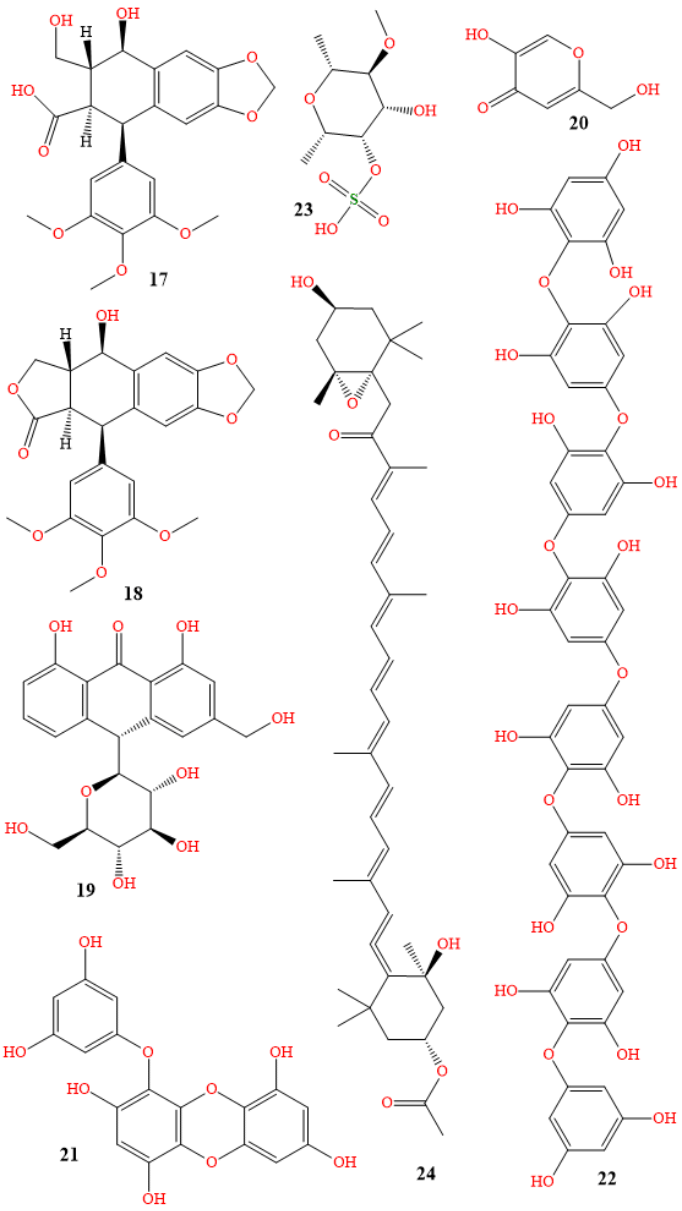

Figure 9. Structures of podophyllum resin (17), podofilox (18), aloin (19), kojic acid (20) phlorotannins (21), octaphlorethol A (22), fucoidan (23), and fucoxanthin (24).

5. Natural hyperpigmentation treatment

Despite the wide range of therapies available, a growing number of people are choosing plants and natural items as alternatives. Plant-based and natural remedies have been used for treating skin issues for ages, and they are gaining popularity as a secure and efficient method to treat skin hyperpigmentation. [111–115].

Vitamins A, B, C, and E can all be used to address skin pigmentation problems and are necessary for healthy skin. Each vitamin, which can be obtained in foods or supplements, has specific advantages. [116,117]

Niacin, Pantothenic acid, and biotin are the B vitamins most frequently found in skincare products. Niacin, also known as niacinamide, is a vitamin that is used in face creams and masks to minimize the appearance of enlarged pores, fine lines, and dullness. Pantothenic acid is also applied to dry, flaky skin as a moisturizer. Numerous hair, nail, and skin care products include biotin [118,119]. Ascorbic acid (vitamin C), an antioxidant, inhibits tyrosinase by binding to copper and suppressing the oxidative polymerization of melanin precursors, which prevents melanin synthesis in the melanogenesis pathway [120,121]. A statistically significant decrease from baseline to Week 16

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was observed in a trial on 39 patients using 25% L-ascorbic acid dissolved in Nmethyl-2-pyrrolidone and dimethyl isosorbide, as indicated by MASI values and mexameter data. [122,123]. A particular kind of vitamin E is alpha-tocopheryl acetate. When fat is subjected to oxidation and during the spread of free radical reactions, vitamin E, a powerful chain-breaking antioxidant, prevents the synthesis of reactive oxygen species molecules. [124–126]

Artocarpus lakoocha and *Glycyrrhiza glabra* extracts have been reported to exhibit tyrosinase inhibitory effects and melanin pigment reduction. For the treatment of hyperpigmentation, the combination of 9:1 Artocarpus lakoocha and Glycyrrhiza glabra decreased melanin pigment by up to 53% in B16 cells by lowering the production of tyrosinase (TYR), microphthalmia-associated transcription factor (MITF), and tyrosinase-related protein-2 (TRP-2). [127–129]

Antioxidants and fatty acids included in oils like rosehip, jojoba, and argan oil aid in reducing inflammation and brightening the skin. Natural oils can also shield the skin from the effects of the environment, preventing further discoloration. Aloe vera also includes aloin (compound 19 in Figure 9), which has been demonstrated to lighten skin and function well as a nontoxic hyperpigmentation therapy. Sharique described aloe vera as a natural depigmenting ingredient. [130–132]

When used as an emollient, jojoba oil exhibits first-rate lubricity without having an oily or greasy texture in single-segment and emulsion structures. It can also contribute to the skin's effective water regulation during transpiration, reducing evaporation without obstructing the passage of gases or water vapor [133–136]. According to a study, jojoba oil (or its ozonized or hydrogenated derivatives) has emollient properties. The study discovered that a significant increase in skin surface flexibility developed within 5 minutes and persisted for hours, suggesting a potential application in solutions for dry skin [137]. Jojoba liquid wax was found to be just as effective at treating diaper rash as triamcinolone acetonide, nystatin, neomycin, and gramicidin. Jojoba oil is also an anti-inflammatory. Due to the absence of systemic adverse effects, jojoba had the benefit of being safer [138]. Additionally, it has anti-acne and anti-psoriasis qualities, which allow the dissolution of sebum deposits through the hair follicles due to its capacity to infiltrate the follicles, eliminate the comedones, and clear the skin [139].

In a research, ten women used argan oil as a bandage on their skin for 28 days. None of the women experienced itching or noticed any skin irritation or redness, demonstrating the oil's efficacy in reducing the amount of pigmentation. These women did observe a minor decrease in melanin content in the vicinity of the bandage, though, which lends credence to the idea that the oil lessens pigmentation. [140–142]. Licorice root extract, turmeric extract, and green tea extract are other herbal extracts high in antioxidants that help to reduce inflammation and brighten the skin.

Since ancient times, licorice root extract has been utilized for its medical benefits, particularly for skin care. It has glycyrrhizin, which has been shown to have antioxidant and anti-inflammatory properties. [143]. Given that it is thought to help enhance skin look and treat some skin disorders, these qualities make it a popular ingredient in skin care products [144]. Several research have been done to determine whether licorice root extract is effective for treating skin conditions. According to a study, licorice root extract is useful for reducing hyperpigmentation and lightening the skin [145]. Atopic dermatitis symptoms may be lessened by licorice root extract, according to a different study [146]. James M. Spencer also demonstrated in his research that licorice root extract was efficient in lessening the severity of rosacea, melasma, and acne [147]. Additionally, licorice root extract reduced the appearance of black spots and redness, as was discovered in a 2019 study by Maria Yusuf Dhariwala. [148]

Since ancient times, turmeric extract has been valued for its therapeutic benefits. It has a yellow tint and various health advantages due to the presence of the active component curcumin. when it comes to pigmentation and skin conditions. Strong anti-inflammatory qualities found in curcumin can help lessen skin inflammation brought on by a variety of skin conditions, including psoriasis and eczema [149–152]. Antioxidants included in turmeric extract reduce oxidative damage that can cause skin aging and pigmentation disorders like melasma by neutralizing free radicals [153]. Curcumin also has skin-lightening qualities. By preventing the formation of the melanin-producing enzyme tyrosinase, it can lessen hyperpigmentation and make the skin lighter. [154] Curcuminoids, which are found in turmeric, have exfoliating qualities that aid to gently remove dead skin cells and

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encourage skin regeneration, minimizing the appearance of hyperpigmentation and dark patches [155]. Using turmeric extract to treat skin issues was the subject of a 2018 study by Alexandra R. Vaughn. In psoriasis, eczema, and acne patients, the study found that turmeric extract was beneficial in lowering skin inflammation and enhancing skin health [156]. A topical cream with turmeric extract proved successful in lowering the severity of acne in patients after four weeks of treatment, according to a 2018 study by Penelope J. Kallis.[157]

Another organic component that has been investigated for its therapeutic advantages for the skin is green tea extract. It has a lot of polyphenols and antioxidants, as well as anti-inflammatory and skin-protective qualities [158–160]. Green tea extract works in a variety of ways to treat pigmentation issues and skin problems. Catechins and epigallocatechin gallate (EGCG), two antioxidants found in green tea, work to combat free radicals that can damage skin and speed up the aging process [161]. Green tea extract also has strong anti-inflammatory qualities that can help lessen skin irritation brought on by a variety of skin diseases such acne, eczema, and rosacea [162]. EGCG in green tea extract can help inhibit tyrosinase activity, reducing the production of melanin and thus lightening the skin [163]. Furthermore, green tea extract has been shown to offer some protection against UV radiation, which can cause skin damage and contribute to pigmentation disorders [164]. A clinical study has been conducted for 11 patients on the use of green tea extract for treating acne; this study found that green tea extract was effective in reducing the number of acne lesions and improving overall skin health [165]. Another published in 2017 found that green tea extract effectively reduced the appearance of fine lines and wrinkles in the skin [166].

Kojic acid (Enshine® cream 2%, compound 20 in Figure 9) has been found to be effective in treating various skin disorders and pigmentation issues due to its mechanism of action. It works by inhibiting the activity of tyrosine, which reduces the production of melanin, which can help to fade dark spots and hyperpigmentation [167–169]. In addition to its tyrosinase-inhibiting properties, kojic acid has antioxidant and anti-inflammatory properties; these can be particularly beneficial for individuals with acne, rosacea, and other inflammatory skin conditions [170–173]. One study published in 2016 by Peter J. Gust evaluated the efficacy of a cream containing 2% kojic acid, 10% glycolic acid, and 2% hydroquinone for treating melasma. The study involved 40 participants who applied the cream twice daily for 12 weeks. The results showed a significant reduction in the severity of melasma in the treated group compared to the control group, with no reported adverse effects [174]. In another study, Tamara Searle investigated using a cream containing 2% kojic acid, 1% arbutin, and 5% vitamin C to treat age spots. The study involved 60 participants who applied the cream twice daily for 12 weeks. The results showed a significant reduction in the number and severity of age spots in the treated group compared to the control group, with no reported adverse effects [175]. Several herbs and naturally occurring substances commonly used in skincare products for their ability to lighten skin and reduce hyperpigmentation are listed in Table 2.

Phlorotannins (compound 21 in Figure 9) from the brown algae (brown seaweed) play a crucial role in the reduction of hyperpigmented effects and the prevention of premature skin aging. They protect the skin from the sun's infrared and blue rays.

Moreover, it encourages the production of cellular energy, increasing the skin's oxygenation. This process enhances cell innovation and decreases pigmentation and the skin's general look. Their antioxidant activity stops the deterioration of the collagen that firms the skin [176–178]. Clinical trials and meta-analyses have investigated the effects of phlorotannins on skin disorders and pigmentation. A randomized, double-blind, placebo-controlled study published in 2022 found that a phlorotannin-rich Ecklonia cava (Phaeophyceae) extract improved skin hydration, elasticity, and wrinkle formation in women with dry skin. Another randomized, double-blind, placebo-controlled study found that a phlorotannin-rich extract of Ascophyllum nodosum reduced facial pigmentation and improved skin elasticity in women with age spots. [179,180]

Marine-derived chemicals from *Undaria pinnatifida, Octopus vulgaris,* and *Sargassum polycystum*, have all been investigated for their ability to enhance skin pigmentation and have antioxidant, anti-inflammatory, and immunomodulatory properties. These compounds include octaphlorethol A, fucoidan, and fucoxanthin (compounds 22-24 in Figure 9) [181–186]. Several studies have

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investigated the effects of octaphlorethol A on skin disorders and pigmentation. A study found that octaphlorethol A inhibited melanin production and reduced skin pigmentation in human melanoma cells. Another study found that octaphlorethol A reduced inflammation and improved skin barrier function in mice with atopic dermatitis. [187,188]. In addition, a randomized, double-blind, placebo-controlled study found that a cream containing fucoidan and marine collagen improved skin hydration, elasticity, and wrinkle formation in women with dry skin [189]. In addition, a randomized, double-blind, placebo-controlled study found that a cream containing fucoidan and marine collagen improved skin hydration, elasticity, and wrinkle formation in women with dry skin [190]. A survey of 11 randomized controlled trials found that the carotenoid pigment, fucoxanthin, supplementation was associated with a significant reduction in the severity of melasma. However, the authors noted that the quality of the inclusive studies was generally low, and more research is needed to confirm these findings [191–193].

Table 2. Plants discovered to treat hyperpigmentation in the past ten years.

Name of plant	Family	Growth place	Active compounds
Angelica sinensis [194]	Apiaceae	East Asia	4-ethylresorcinol, 4-ethylphenol, 1-tetradecalnol
Artocarpus [195]	Moraceae	Southeast Asia	Artocarpin, cudraflavone C, artocarpanone
Callicarpa longissima [196]	Lamiaceae	Southeast Asia	Carnosol
Crataegus azarolus [197]	Rosaceae	European	Ursolic acid, hyperoside, virtexin-2″-O-rhamnoside
Cyperus rotundus [198]	Cyperaceae	Africa, France, Austria, southern Asia	Valencene, camphene, carryophyllene oxide
Juniperus chinensis [199]	Cupressaceae	China, Myanmar, Russian, Korea	Widdrol
Morus nigra [200]	Moraceae	Iberian Peninsula	Isoquercitrin, rutin, chlorogenic acid
Oryza sativa [201]	Poaceae	China	p-coumaric, ferulic
Passiflora edulis [202]	Passifloraceae	Brazil, Paraguay, Argentina	Piceatannol, resveratrol, quercetin
Salvia officinalis [203]	Lamiaceae	Mediterranean region	7a-methoxyrosmanol, isorosmanol
Sesamum indicum [204]	Pedaliaceae	Africa, India	Sesamol
Punica granatum [205]	Lythraceae	Mediterranean	Punicalgin
Litchi chinensis [206]	Sapindaceae	China, India, Bangladesh, Vietnam, Thailand, Malaysia, Indonesia, Pakistan, Cambodia, Bangladesh, Himalayas	Rosmarinc acid, gallic acid

6. Conclusion

Skin pigmentation refers to the color of an individual's skin, which is determined by the amount of melanin in the skin produced by melanocytes. Eumelanin and pheomelanin are the two primary forms of melanin. Dark skin tones are caused by eumelanin, which protects against skin cancer and sun damage. While pheomelanin produces lighter skin tones, which can control body temperature and offers protection from skin cancer. Some causes of skin pigmentation include genetics, sun exposure, hormonal changes, skin trauma, and certain medications. In addition, some skin pigmentation disorders, such as melasma, albinism, and vitiligo, which caused by genetic mutations.

There are two primary types of skin pigmentation; hyperpigmentation occurs when there is an overproduction of melanin, leading to areas of darker skin. This can be caused by sun exposure, hormonal changes, and certain medications. Or hypopigmentation occurs when there is a loss of melanin, leading to lighter skin areas. This can be caused by genetic conditions, skin trauma, and certain medications.

Clinical trials and meta-analysis show that oral medication by tranexamic acid and isotretinoin tablets could treat various skin illnesses, including eczema, melasma, and other related conditions. In addition, clinical trials indicate that the topical forms of betamethasone, clobetasol, silver sulfadiazine, triamcinolone, dimethicone, fluocinolone, hydroquinone, clotrimazole, ruxolitinib, salicylic acid, and tretinoin are effective in treating skin disorders. Furthermore, Natural extracts like rosehip, jojoba, argan oil, Aloe vera, Licorice root, curcumin, green tea, Kojic acid, phlorotannin,s and vitamins A, B, C, and E have potent anti-inflammatory properties that can help reduce inflammation in the skin caused by various skin conditions such as acne, eczema, and rosacea, which can be classified as a treatment for hyperpigmentation along with octaphlorethol A, fucoidan, and fucoxanthin marine extracts.

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