Chapter

On the Intricacies of Facial Hyperpigmentation and the Use of Herbal Ingredients as a Boon for Its Treatment: Cosmeceutical Significance, Current Challenges and Future Perspectives

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Abstract

Facial hyperpigmentation is the term used to express areas on irregular pigmentation in the skin. It appears as darkened patches on the face that make the facial skin look uneven. Facial hyperpigmentation is not physically debilitating but has been associated with enhanced psychosocial complications including anger, depression and frustration. These psychosocial burdens, in turn, have inference on quality of life and self-esteem. So, the treatment of facial hyperpigmentation seems to be a growing concern to the dermatologists today and they have been practising several treatment modalities including chemical peeling, laser therapy, dermabrasion, etc. But, those are found to be associated with various after-effects. Hence, the use of plants and its products is highly recommended as they are reported with either none or fewer after-effects. The present chapter draws attention to the forms of facial hyperpigmentation with their aetiologies and available treatment options for them with associated side effects. Furthermore, we have discussed about the other side of treatment with herbal ingredients which are safe and have less or no side effects. This chapter will be of value to the dermatologists who are searching for naturally derived ingredients for treating facial hyperpigmentation, in line with consumer expectations and preferences.

Keywords: hyperpigmentation, psychosocial, treatment modalities, etiology, herbal ingredients, novel agents

1. Introduction

Melanin is the natural polymer pigment responsible for imparting color to the skin, hair, and eyes as well as provides the photoprotection of the skin against ultraviolet radiation. It is produced inside the specialized organelles, melanosomes of melanocytes through a complex process called melanogenesis. Although melanin protects the skin from UVB radiation damage, its overproduction leads to the problem of hyperpigmentation and its related disorders. Post-inflammatory disorders,

ephelides, solar lentigines, melasma, etc. are the common diseases of hyperpigmentation. Skin color imperfection due to hyperpigmentation spots on the face causes psychological problems in patients and takes them far from their social life. The public perceptions of tanned skin as being healthy and attractive merged with growing demand of treatment of facial hyperpigmentation provoke huge interest cosmeceutically as well as pharmaceutically [1–4].

Facial hyperpigmentation is a common and emergent concern to the dermatologists today. Treatment for facial hyperpigmentation seems to be difficult as there is no universally accepted treatment for it, and also the efficiency of known active agents is different. Majority of reports concerning the treatment of the disease consist of small series of patients. So, it becomes challenging to evaluate the efficacy of variety of therapy. Moreover, there are various options, but some of them come under growing scrutiny, emphasizing the research into pathogenesis and treatment. Sunscreen, chemical peeling, laser therapy, dermabrasion, topical treatment, cosmetic camouflages, etc. are the different treatment modalities used to treat facial hyperpigmentation. Though they are very effective and instant treatment for hyperpigmentation, its long-term exposure causes various side effects. Persistent erythema, swelling, pain, allergic reactions, herpes recurrence, acne, dyspigmentation, etc. are some of the various after effects associated with these treatment strategies [5–7].

In opposition to the state of affairs with these treatment options, we have the other side with herbal treatment which are nowadays attaining importance due to their low cost and ease of use and are believed to be free from risk of handling them as well as scarcely pollute the environment. Consequently, a dermatological formulation, including active ingredients of strictly natural origin, is designed by a variety of scientist to protect the skin from exogenous and endogenous harmful agents. There are many chemical reactions involving various enzymes that are engaged in melanogenesis. So, there is a wide range of targets or mechanisms against which to screen for skin pigmentation control agents. Active compounds isolated from different plants inhibit melanogenesis with no cytotoxicity by different mechanisms including inhibition of tyrosinase and other related protein expressions, inhibition of tyrosinase activity, inhibition of melanin dispersion and translocation, etc. [8–10].

Hence, the present chapter highlights the commonly occurring hyperpigmentary diseases of the face and their aetiologies. The available treatment options for hyperpigmentation along with the problems associated with them. As there is vast flora available on earth which has valuable medicinal properties, they are used for the treatment of many incurable diseases. Consequently, plants and its products are used for the treatment of hyperpigmentation through different mechanisms of action. Various studies on the use of plants for hyperpigmentation treatment have also been discussed in the present chapter.

2. Biosynthesis of melanin

Melanin is the end product of complex multistep transformation of amino acid, L-tyrosine. It is the polymorphous and multifunctional biopolymer represented by eumelanin (brown-black melanin), pheomelanin (brown-red melanin), and allomelanin (nitrogen-free melanin). This can be differentiated on the basis of chemical composition and monomer subunit structure of melanin. It has been found that there are four factors involved in melanin formation: (1) tyrosine as substrate, (2) tyrosinase with its coenzyme, (3) molecular oxygen, and (4) dihydroxyphenylalanine (DOPA). Tyrosine is converted into melanin by a series of enzymatic reaction [11–13].

Biosynthesis of melanin can be initiated from either the hydroxylation of L-phenylalanine to L-tyrosine or directly from L-tyrosine, which is then hydroxylated to L-dihydroxyphenylalanine (L-DOPA). In the next step, L-DOPA is oxidized to dopaquinone which is common to both eu- and pheomelanogenic pathways. Formation of eumelanin involves transformation of dopaquinone to leukodopachrome, followed by a series of oxidoreduction reactions. Dihydroxyindole (DHI) and DHI carboxylic acid (DHICA) are produced as intermediates, which undergo polymerization to form eumelanin. Pheomelanin synthesis also begins with dopaquinone; this is conjugated to cysteine or glutathione to yield cysteinyldopa and glutathionyldopa, for further transformation into pheomelanin. Mixed melanin contains both eu- and pheomelanin [12, 14–18].

3. Hyperpigmentary diseases of the face and their etiology

Melanocytes are responsible for the synthesis and distribution of melanin pigment, by the process of melanogenesis which involves different stages from embryonic development, melanin synthesis, to its transfer to neighboring keratinocytes. The importance of each of these stages and their mechanisms is evident in clinical defects in the form of hypopigmentation or hyperpigmentation. Exposure of the skin to UV radiation or other exo- and endogenous sources/allergen poses erythema, variation of vascular responses and immunosuppression, formation of inflammatory mediators, or overproduction of melanin which leads to pigmentary disorder, i.e. hyperpigmentation [19–21].

Facial hyperpigmentation is a common and growing concern to the dermatologists today. The difference in structure and function of the skin, as well as the influence of cultural practices, produces variable skin diseases of the face based on skin type. There are many skin conditions quite unique to person skin of color. Some of them are summarized here.

3.1 Postinflammatory hyperpigmentation

Postinflammatory hyperpigmentation (PIH) refers to the darkening of the skin that arises after cutaneous injury or inflammatory eruption. Hyperpigmentation results from the melanocyte's response to the cutaneous insult, which causes increased production of melanin. Acne lesions, scratches, insect bites, ingrown hairs, etc. are among such cutaneous insults. It has been found that patients of darker skin are more susceptible to this pigment alteration. Postinflammatory changes can occur both in the epidermis and dermis of the skin. In epidermal hyperpigmentation, there is an increase in melanin production and/or its transfer to keratinocytes. In dermal postinflammatory hyperpigmentation, a damaged basement membrane allows melanin to enter the dermis, which is then phagocytosed by dermal macrophages, called as melanophages. Macrophages may also migrate into the epidermis, phagocytose melanosomes, and then return to the dermis. Melanin within dermal melanophages may persist for years [22–25].

Physical examination of PIH includes small to large hyperpigmented macules and patches of variable size in any distribution. The time required for the normalization of dyspigmentation is unpredictable and depends on many factors including the patient's baseline skin tone, the type and intensity of the injury or inflammation, and the patient's sun exposure habits [22, 24].

3.2 Maturational dyschromia

It has been observed as darkening of facial skin tone, even outside of extensive sun exposure and sometimes termed as general uneven tone. Maturational dyschromia can be described as diffuse hyperpigmentation usually occurs on the lateral forehead and cheek bones. According to one of the survey-based studies, more than one third of black women have complaint of uneven skin tone. These alterations in skin tone are possibly due to chronic sun exposure over many years. Maturational dyschromia may be misdiagnosed as melasma, acanthosis nigricans, or postinflammatory hyperpigmentation [26].

3.3 Ephelides

Ephelides, or freckles, are caused by an increase in photoinduced melanogenesis and increase in transport of fully melanized melanosomes from melanocytes to keratinocytes. It occurs on sun-exposed area of the body, predominantly the face, dorsal side of hands, and trunk. They are 1–3 mm hyperpigmented macules that are round, oval, or irregular in shape. They might increase in number and distribution but can fade with aging. Ephelides are benign and there is no tendency of it to transform into malignant. Ephelides are benign and show no susceptibility for malignant transformation. Some ephelides represent as a subtype of solar lentigo [27, 28].

3.4 Lentigines

Lentigines are found more commonly in white subjects including African-Americans and American-Indians. Individuals of skin type I and III are more likely to develop solar lentigines. Solar lentigines result from a local propagation of basal melanocytes and a consequent increase in melanization, differing from freckles, which result from increased melanin production. Like ephelides, they also occur in sun-exposed areas, particularly the dorsal side of hands and forearms, face, upper back, and chest. Solar lentigines are 2–3 cm well circumscribed, round, oval, or irregularly shaped macules that differ in color from tan to dark brown [29, 30].

3.5 Melasma

Melasma is a common and well described form of hyperpigmentation that is seen most commonly on the face. It is a common disorder of hyperpigmentation affecting millions worldwide and at least 90% of those are females. It predominantly affects women with darker skin types, i.e. Fitzpatrick skin phototypes III and IV. It has also been referred to as chloasma or 'the mask of pregnancy' because the condition is often associated with pregnant women. There is recently no exact etiology, but multiple factors like ultraviolet radiation, hormonal alteration, genetic predisposition, and/or inflammation have all been involved. Physical examination of the disease includes light to dark-brown patches with irregular margins usually distributed symmetrically on the centrofacial, malar, and mandibular regions and can also be seen on the forearms [31].

On the basis of location of melanin, melasma can be differentiated into epidermal, dermal, mixed, and indeterminate types. In epidermal type, the pigment is brown, and borders are well defined, whereas in the dermal type pigment is gray brown, and borders are scantily defined. When there is melanin in both epidermis and dermis, mixed-type melasma occurs, and the term interdeterminate type may be used when it is not easy to classify even with the aid of Wood's light [32].

3.6 Lichen planus pigmentosus

Lichen planus pigmentosus is an unusual variant of lichen planus common in individual with skin types III and IV. It affects young to middle-aged adults generally those from India, Latin America, and the Middle East. Clinically, there are oval or irregular gray-brown to brown macules or patches with usually diffused and symmetrical pattern on sun-exposed areas, including the forehead, and neck, or intertriginous areas. Lesions are often symmetrical and can present in unilateral, linear fashion. The etiology for the disease is unknown, but immunological mechanisms associated with cellular immunity and exposure to ultraviolet light appear to be concerned [33, 34].

4. Treatment strategies for facial hyperpigmentation

Treatment for facial hyperpigmentation seems to be challenging as there is no universally accepted therapy for it, and also the efficacy of existing agents is different. Majority of reports regarding treatment consist of small series of patients, so it is difficult to evaluate the efficacy of a variety of therapies. Additionally, there are multiple options available, but some of them come under increasing scrutiny, underscoring the requirement of research into pathogenesis and treatment. On the whole, treatment includes removal of provoking factors, photoprotection, and active pigment reduction with either topical formulations or physical approaches [35, 36].

4.1 Sunscreen

Numerous evidence-based studies showed that light from both UV and visible spectrum can induce variation in pigmentation pattern of the skin. Both UVA and UVB cause increased melanin synthesis resulting in delayed tanning. Sun protection is found to be the most significant step which has to be taken to prevent and to cure hyperpigmentation. So, broad spectrum UVA and UVB protective sunscreen with SPF of at least 30 including a physical block (e.g. titanium dioxide and zinc oxide) should be recommended in order to protect the skin from hyperpigmentation [37, 38]. It has been observed that the use of broad spectrum sunscreen on the first day after skin resurfacing can decrease the incidence of postinflammatory hyperpigmentation after laser treatment [39].

4.2 Cosmetic camouflage

Cosmetic camouflage is the application of makeup including cream and powder to conceal color. Physical blocking opaque sunscreens also have camouflage facial hyperpigmentation and prevent photoinduced darkening. Many patients find that the use of makeup helps even out skin tone. Moreover cosmetic camouflage solves the psychological problems that a skin imperfection is sometimes able to irritate; it allows to rejuvenate its own beauty and to return to its own social life [40]. A single-centre clinical trial was conducted by Roberts et al. on females with mild to moderate facial hyperpigmentation to assess the efficacy of multifunctional facial primer. They found it very effective for immediate or long-term improvement of hyperpigmentation when used over a period of 12 weeks [41].

4.3 Chemical peel

Chemical peels can be used for the treatment of facial hyperpigmentation either alone or combined with other regimens. Most common chemicals used for peeling

are trichloroacetic acid, phenol, lactic, glycolic acid, retinoid, etc. In this technique, a chemical solution is applied to the skin which makes it exfoliate and ultimately peel off; it means it damages the skin in a controlled manner. Finally the newer skin appears with no hyperpigmentary spots. After chemical peel, the skin becomes more sensitive to sun, so the use of sunscreen is recommended. Generally, there are three types of chemical peels based on the depth of the skin they exfoliate: superficial peel, medium peel, and deep peel. In superficial peel, mild acids like alpha hydroxy acids are used to exfoliate the skin. It only penetrates the outermost layer of the skin. Trichloroacetic acid or glycolic acids are used in medium peel to remove damaged skin; they reach to the middle and outer layer of the skin. On the other hand, deep peels fully penetrate the middle layer of the skin. Medium-depth peel should be highly recommended and performed with caution, and deep peels are not at all recommended because of the high risk of permanent pigmentary changes. Although chemical peeling may help in improving facial hyperpigmentation, they can also cause irritation which leads to dyspigmentation [42].

4.4 Dermabrasion

Dermabrasion is the non-chemical superficial removal of the upper skin with abrasive tool. Patients with resistant melasma, especially with well-known dermal components that are hard to treat, have been successfully treated with dermabrasion. Methods with the use of 16-mm diameter coarse grit diamond fraise are considered successful. Ninety seven percent of patients were found to have improvement, and only around 1% was found to develop hypertrophic scars or permanent hypopigmentation [43]. In most of the other cases, mild to moderate improvement has been shown with dermabrasion. Histopathologically, decreased melanization and regular distribution of melanosomes were commonly observed in biopsy samples of patients treated with dermabrasion [44].

4.5 Laser therapy

Laser and light therapy is a promising and effective treatment for a variety of hyperpigmentation conditions. In particular, longer wavelength is the most widely used laser because it can penetrate deeper and can target dermal pigments. Lasers and light sources should only be used by the experienced physician, and it should only be attempted after other modalities have been proven to be unsuccessful for a particular disorder. This treatment strategy however is quite challenging because of the high risk of damage to surrounding tissues that can lead to long-lasting and delayed postinflammatory hyperpigmentation. So, proper patient counseling with regard to side effects, and expectations should always be done prior to any laser therapy [45, 46].

4.6 Topical treatment

The majority of topical agents used are those that disrupt the enzymatic processes of pigment production within melanocytes. Different agents like hydroquinone, kojic acid, arbutin, retinoids, etc. have been used either alone or in combination with varying degree of efficacies. Kligman formulation having combination of hydroquinone, tretinoin, and hydrocortisone has been used in many skin lightening creams. Modified combination of Kligman formulation has also been successfully tested by various scientists during their studies, and now they have been practised in various lightening creams. But continuous applications of these agents have been found to have certain side effects. Hydroquinone is the gold standard for the treatment of facial hyperpigmentation and has been used for many

years, but adverse reactions have been associated with hydroquinone, which include asymptomatic transient erythema, irritation, and exogenous ochronosis [47]. Kojic acid is a known sensitizer and can cause erythema and contact dermatitis. Similarly, arbutin at higher concentrations can cause paradoxical hyperpigmentation [48].

There are various national and international brands who are claiming that the skin will glow after a short period of time on topical application of their cream. They are claiming that their products are entirely safe as they are using herbal ingredients. But, it is not possible to make the skin glow and white in a short span of time without using harmful substances such as heavy metals. The Centre for Science and Environment (CSE) has reported that about half of the 73 national and international brands of popular cosmetics contain high levels of toxic heavy metals such as mercury, cadmium, etc. The CSE's Pollution Monitoring Lab had tested popular fairness creams and found 44% mercury in it. According to Sunita Narain, director general of CSE, 'Mercury is not supposed to be present in cosmetic products. Its mere presence in these products is completely illegal and unlawful [49]'.

5. Consequences of conventional treatment strategies

Although there are several modalities of treatment for facial hyperpigmentation available today including physical therapies or chemical agents, none of them are entirely satisfactory. Traditional topical agents like hydroquinone, kojic acid, arbutin, etc. are highly effective, but their long-term exposure causes several side effects. Persistent erythema, swelling, pain, allergic reactions, herpes recurrence, acne, dyspigmentation, etc. are some of the various after effects associated with treatment strategies like chemical peeling, dermabrasion, laser therapy, and cosmetic camouflage [50, 51].

There is a high risk of damage to the surrounding tissues when treated with laser therapy. During one of the clinical trials on woman patients, allergic reactions have been reported when treated with chemical peel using tretinoin. Patients exhibited itching, swelling, and erythema on their entire face [52]. Though the use of sunscreen with 50+ SPF may protect the skin from sun tan, its long-term use significantly decreases the cutaneous vitamin D production which is necessary for bone health and hence increases the risk of osteoporosis [53].

6. Natural herbal-based treatment for hyperpigmentation

Due to the consequences of conventional treatment modalities for skin hyperpigmentation, scientists and dermatologists are now looking for the treatment which will be safe and having very less or no side effects as well as do not contaminate the environment. Thus, the use of herbs and their ingredients for skin hyperpigmentation treatment is gaining interest as they are found to be safer, milder, and healthier than synthetic products. Dermatological formulation, including active compounds of strictly natural origin, is designed to protect the skin from hyperpigmentation. The aim of using natural ingredients is to reduce skin hyperpigmentation without causing undesirable hypopigmentation and irritation in the skin [10].

As there are many processes and enzymes involved in melanogenesis, there is a wide range of targets or mechanisms against which to screen for skin pigmentation control agents. Active compounds extracted from different plants inhibit melanogenesis without melanocyte toxicity by different mechanisms including inhibition of tyrosinase and other related protein expressions, inhibition of tyrosinase activity, inhibition of melanin dispersion, and translocation.

6.1 Inhibition of tyrosinase activity

As tyrosinase is the key enzyme of melanogenesis, inhibitors of this enzyme have caught the interest of dermatologists to prevent abnormal accumulation of melanin. There are various botanical agents that are acting through interfering in the pathway leading to melanin synthesis by inhibiting the activity of tyrosinase [54].

p-Coumaric acid extracted from the fresh leaves of *Panax ginseng* was used to inhibit the oxidation of L-tyrosine catalysed by mushroom tyrosinase [55]. Epicatechin gallate, gallocatechin gallate, and epigallocatechin gallate were the three major components isolated from green tea, and their efficacy of the inhibition of mushroom tyrosinase was assessed and found that green tea was the strongest inhibitor. Kinetic analysis revealed that these components inhibit tyrosinase via competitive inhibition [56]. Similarly, studies of Hridya et al. [57] and Hridya et al. [58] demonstrated that brazilein isolated from *Caesalpinia sappan* and santalin isolated from *Pterocarpus santalinus* have been found to reversibly inhibit tyrosinase in a mixed-type manner. Both the compounds inhibited tyrosinase activity dose dependently.

Recently, Kim et al. [59] have isolated five flavonoids, kushenol A, 8-prenylkaempferol, kushenol C, formononetin, and 8-prenylnaringenin, from *Sophora flavescens* to find out compounds with inhibitory activity towards tyrosinase. They have tested the ability of these flavonoids to block the conversion of L-tyrosine to L-DOPA by tyrosinase. Among the five compounds, kushenol A and 8-prenylkaempferol exhibited potent inhibitory activity which was further confirmed by molecular docking analysis.

6.2 Inhibition of tyrosinase and other related protein expressions

To develop treatment therapies for hyperpigmentation, many natural products have been tested which aimed at inhibiting production and expression of enzymes involved in rate-limiting steps of melanogenesis pathway including tyrosinase, tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (TRP-2).

Macelignan isolated from *Myristica fragrans* has shown inhibitory action on melanogenesis and significantly decreased the expression of tyrosinase, tyrosinase-related protein-1, and tyrosinase-related protein-2 expressions in melan-a murine melanocytes. Macelignan effectively inhibits melanin synthesis and thus could be used as a new skin whitening agent [60]. Panduratin A isolated from *Kaempferia pandurata* was also found to inhibit melanin biosynthesis. Through western blot analysis, panduratin A has shown decrease expression of tyrosinase, TRP-1, and TRP-2 proteins [61]. Similarly, curcumin suppressed the expression of melanogenesis-related protein expression such as tyrosinase, TRP-1, TRP-2, and MITF in alpha-melanocyte-stimulating hormone (MSH)-stimulated B16F10 cells [62].

Panax ginseng is a medicinal herb, which contains various ginsenoside with therapeutic effects. Lee et al. [63] isolated floralginsenoside (FGA), ginsenoside Rd. (GRd), and ginsenoside Re (GRe) from *Panax ginseng* berry. Among the three, floralginsenoside (FGA) was observed to impart more inhibitory effect on melanogenesis through decreased expression of microphthalmia-associated transcription factor in a dose-dependent manner. In addition to this, FGA also induced extracellular signal-regulated kinase phosphorylation level in melan-a cells. Peng et al. [64] evaluated the antimelanogenic and depigmenting activity of 10-hydroxy-2-decenoic acid (10-HDA) from royal jelly of *Apis mellifera*. They have reported that 10-hydroxy-2-decenoic acid (10-HDA) would reduce melanin biosynthesis through inhibiting the expression of tyrosinase, TRP-1, TRP-2, and MITF in B16F1 melanoma cells.

In a recent study, Ko et al. [65] investigated that n-hexane fraction of *Sageretia thea* downregulated melanogenesis through reduced expression of tyrosinase, TRP1, TRP2, and MITF. Bioactive compounds responsible for melanogenesis inhibition were identified through gas chromatography-mass spectrometry (GC-MS) analysis as methyl linoleate and methyl linolenate.

6.3 Inhibition of melanosome transfer to keratinocytes

Regulation of skin pigmentation depends on several processes. The transfer of melanosomes from melanocytes to keratinocytes is one of the major factors which play a crucial role in cutaneous pigmentation. Hence there are various treatment modalities developed to inhibit melanosome transfer in order to prevent hyperpigmentation.

Niacinamide, a derivative of vitamin B3, can be found in many foods including meat, milk, eggs, green vegetables, etc. Greatens et al. [66] found that niacinamide inhibits melanosome transfer to keratinocytes in cocultures of keratinocytes and melanocytes. They have assessed the effect of niacinamide on facial hyperpigmented spots through human clinical trials and observed the reduction of hyperpigmented lesion. Methylophiopogonanone B extracted from *Ophiopogon japonicus* also appeared to reduce melanosome transfer [67]. Similarly, centaureidin (5,7,3′-trihydroxy-3,6,4′-trimethoxyflavone) derived from *Achillea millefolium* also reduced melanosome transfer to keratinocytes. It was believed that centaureidin activates Rho which leads to melanocyte dendrite retraction without affecting melanogenic enzyme expression [68].

7. Conclusion

Hyperpigmentation is a common condition characterized by patches or spots on the skin. Pigment spots appear mainly on body parts that are exposed and hence are more commonly found on face. Facial hyperpigmentation is not only the problem concerned with pharmaceuticals and cosmeceutical sciences, but it is a problem that can pressurized the beauticians also to find out its treatment. Besides of being a disease, it is also associated with psychosocial complications. So, the appropriate treatment for hyperpigmentation is the need of the day. There are various treatment modalities available in medical sciences in order to treat hyperpigmentation, but many of them come under increasing scrutiny due to the side effects they impart on the patient skin. Herbal ingredients on the other hand are free from side effects and can hardly contaminate the environment. Hence, they are used for the treatment of facial hyperpigmentation. Many plants and their products have been used successfully to treat hyperpigmentation. But still, there are infinite numbers of plants which are yet to be characterized for their efficacy to treat hyperpigmentary problems of the face. Scientists all over the world would therefore try to evaluate more potent agents using various state-of the-art techniques that are highly effective and safe for the treatment of hyperpigmentation.

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Conflict of interest

The authors declare no conflict of interest.

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