

## Insights into the treatment strategies for hypopigmentation disorders by natural herbs: current updates and future prospects

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### Abstract

Skin pigmentation is a natural phenomenon that plays an important part in the appearance and biology of all animals, including humans. The process of melanogenesis, which results in the formation of the pigment melanin within melanocytes, determines skin colour. This process is controlled by both inherent and external factors. Tyrosinase catalyzes an essential step in melanogenesis; dysfunction of tyrosinase leads to reduce melanin synthesis which results in severe clinical and aesthetic problem of hypopigmentation disorders. Therefore, the key method in the management of aberrant skin pigmentation for both cosmetic and therapeutic purposes is the regulation of melanin synthesis. In order to regulate and control skin hypopigmentation, this review article discusses the treatment strategies from plant extracts and their active principles with stimulating effects on melanin synthesis and tyrosinase activity, as well as to elucidate scientifically validated plant extracts in order to naturally increase melanin synthesis and treat hypopigmentary disorders.

**Keywords:** Hypopigmentation; Melanogenesis; Melanocytes; Tyrosinase; Melanin synthesis

### 1. Introduction

Melanocytes are melanin-producing cells in the skin that are derived from the neural crest, which are an important component of human skin physiology [1]. The most recognized function of melanocytes is the production of melanin, which gives skin and hair colour and protects epidermal cells from UV-induced alterations in DNA structure [2,3]. Melanocytes are specialized dendritic cells that have the unique and fascinating property of synthesizing melanin, a complex pigment that imparts color to skin, hair, and eyes through a series of chemical and enzymatic reactions [4,5]. Melanin overproduction and underproduction are key research topics in cosmetology and dermatology, not only from the aesthetic perspective of achieving a flawless skin tone, but also from the clinical perspective of preventing and treating various skin disorders such as melasma, vitiligo, albinism, and etc. [6,7,8].

With regard to skin and its ailments, drug development in skin pharmacotherapy is a huge, ever-expanding subject, and therefore, researchers are developing novel, safe, and sensitive pharmaceutical products and drugs [1,9]. Melanocytes, or pigment-bearing cells, play a significant role and have become priorities for high-throughput screening programmes because they are thought to have clinical relevance to skin-related ailments. Many plant extracts and their active compounds have recently received a lot of attention for their skin-darkening effects on melanocytes [10-14]. In the cosmetic and medicinal treatment of abnormal skin pigmentation, regulating melanin production is an important technique. As a result, there is a substantial public health need for commercially suitable or enhanced preparations that can be safely applied to human and animal skin to counteract hypopigmentation's harmful effects [1,15,16].

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Although there are a variety of hypopigmentation treatment options available today, including physical therapy and pharmaceutical agents but none of them are completely effective. So, the present study will focus on using different plants extract/botanicals to naturally increase melanin synthesis in order to treat hypopigmentary disorders. As it became evident from the history of human civilization that human beings have relied on nature for the treatment of disease, as the use of plants or its extract forms the basis of ancient traditional medicines. The advantages of using natural flora as therapeutic agents in treating several ailments are their safety, better patients tolerance, and instead of being inexpensive, they are effective and easily available having a long history of uses. For these reasons, several plants have been investigated for the phytochemical they contained and their role in skin repigmentation. This review will highlight the synthesis, mechanisms of melanin repigmentation, and treatment strategies for hypopigmentation disorders by natural herbs. Thus, it is evident that plant extracts play an important role in the treatment of various hypopigmentary disorders, and this will give an experimental basis for the development of new pharmacotherapies for dermatological anomalies such as vitiligo therapy.

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## 2. Melanin Synthesis

Melanin is the polymeric brown or dark pigment in mammalian skin and hair and is synthesized in specialized cells referred to as melanocytes, which are present within the dermis and inside the matrix and outer root sheath of hair follicles. It performs an essential function in maintaining epidermal homeostasis [17-19]. Generally, two types of melanin pigment are found in mammals: insoluble black or brown eumelanin and soluble red or yellow pheomelanin, which decides the colour of hair, skin, or eyes [20]. Melanogenesis refers to the mechanism of synthesis of melanin, however, more generally, it involves the processes of melanosome production, transport of melanosome, conversion of melanosome to keratinocytes, and metabolism of melanin, since these processes are also essential for pigmentation of the skin and hair [21]. Melanin synthesis starts with the oxidation of L-Tyr or L-dihydroxyphenylalanine (DOPA) by tyrosinase (TYR), which is followed by the development of pheomelanin or eumelanin, depending on whether or not conjugation reactions with L-Cys or glutathione ( $\gamma$ -Glu-Cys-Gly) are included in the intermediate step [22-24]. Many essential enzymes involved in melanin synthesis, such as TYR, tyrosinase-related protein 1 (TYRP1), and dopachrome tautomerase (DCT) are induced by proopiomelanocortin (POMC)-derived peptide hormones such as  $\alpha$ -melanocyte stimulating hormone (MSH),  $\beta$ -MSH, and adrenocorticotrophic hormone (ACTH) [25-26]. Tyrosinase, a copper-dependent enzyme necessary for melanin synthesis, is an enzyme found in melanocytes. Since tyrosinase catalyses a critical phase in melanogenesis, its dysfunction causes a decrease in melanin production, resulting in significant clinical and aesthetic problems of hypopigmentation [27-29].

The biosynthetic pathway of melanin formation involves a number of steps in the enzymatic conversion of tyrosine to melanin via dihydroxyphenylalanine (DOPA). Biosynthesis of eumelanin and pheomelanin can be started via hydroxylation of phenylalanine to tyrosine or directly by tyrosine. Tyrosinase (TYR), EC (1.14.18.1), has been identified as a first-rate limiting and trifunctional enzyme in the melanogenesis cascade, where the amino acid L-tyrosine is the critical substrate for initiating this biosynthetic pathway with the formation of dopaquinone and the oxidation of DOPA back to dopaquinone (formed at the redox exchange between dopaquinone and cyclo dopa) [29-31]. Melanogenesis is thus regulated in melanocytes and melanoma cells by a cascade of enzymatic reactions coordinated at the intensity of tyrosinase. The enzyme converts tyrosine to dopaquinone, which is the rate-limiting stage in melanogenesis [32,33]. External use of natural products that act as UV absorbers, promoters of melanin synthesis, antioxidants, and anti-inflammatory agents can help skin's UV protection capability [34].

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## 3. Skin hypopigmentation

Hypopigmentation is the general term used for any type of decreased or absent skin pigmentation. It may be congenital or acquired, diffuse (generalized) or localised, and present alone or in combination with a number of congenital or acquired disorders. Despite the fact that it is a cosmetic condition, it can be psychologically damaging and stigmatising [35,36]. Hypopigmentary disorder of the skin is characterized by the reduction/complete loss of skin pigmentation. Mostly three possible theories have been proposed to understand the mechanism of hypopigmentation; the first one is associated with the genetic insult which results in loss of melanocytes during embryonic development (e.g., piebaldism), second by retardation/alteration in production and/or distribution of melanin (e.g., oculocutaneous albinism and tinea versicolor), and third one is by destruction of melanocytes (e.g., vitiligo) [37, 5].

Hypopigmentation disorders are generally categorized based on their age of onset, aetiologies, and extent of involvement. Vitiligo, albinism, pityriasis alba, Vogt-Koyanagi-Harada syndrome, idiopathic guttate hypomelanosis are the variable forms of hypopigmentation. Among all vitiligo which is also referred as leukoderma is the most idiopathic disease [1].

### 3.1. Albinism

Albinism is a skin pigmentation condition that affects people of all ethnicities and from all over the world. Albinism is a group of hereditary disorders of melanin synthesis marked by a lack of melanin pigment or a reduction in melanin pigment from birth. Albinism is characterized by a loss in the complex metabolic pathway that produces melanin from tyrosine [38]. Oculocutaneous albinism (OCA) is an autosomal recessive condition in which the biosynthesis of melanin in melanocytes is completely absent or severely reduced. Albinism is characterized by a normal number of melanocytes in the epidermis and follicles but a complete or partial lack of melanin pigment [39,40].

### 3.2. Vitiligo

Vitiligo is a hypopigmentary disorder of the skin in which cutaneous and ocular melanocytes are selectively destroyed that result in loss of pigmentation. It affects 1–2% of the population including both sexes and all races equally [41]. Multiple theories have been proposed, including genetic, neural, biochemical, viral, and autoimmune mechanisms. However, an autoimmune mechanism has been proposed as the most accepted cause of vitiligo. In previous studies, it has been demonstrated that most important feature in vitiligo is alternation of the melanocyte ratio at the dermal-epidermal junction. The long dendritic, melanin granules filled, dopa positive melanocytes were found to be prominent in the outer peripheries of vitiligo lesions [42].

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## 4. Conventional treatments available for hypopigmentation

The main objective of the treatment is to control the degeneration of melanocytes and stimulates its migration and distribution to surrounding cells. Conventional treatment for hypopigmentation such as topical treatment and physical or phototherapy remains the basis of modern treatment. Treatment of hypopigmentation involves the use of topical corticosteroids or tars (topical cream), light or laser treatment, or surgical skin grafting. Psoralen and ultraviolet (PUVA) is the most widely used method for its treatment and is recommended as the first-line therapeutic modality. Treatment strategies are broadly categorized into physical, pharmacological, and surgical.

### 4.1. Physical Treatment

Physical treatment includes utilization of light or radiation such as ultraviolet radiation of both UVA and UVB spectrum of different efficacies.

#### 4.1.1. Narrow Band UVB-NBUVB

Narrow band UV (NBUVB) of wavelength 311-313 nm can be given to the whole body of vitiligo patients using lamps. Previously, it was considered as a first-line option and an effective and safe treatment for hypopigmentation. But, longer exposure to UV radiation may cause skin ageing or skin cancer.

#### 4.1.2. PUVA Therapy

Oral PUVA therapy is considered as one of the most popular treatments introduced in 1968. It consists of UV radiation of wavelength 320-400 nm and the photosensitizing drugs usually psoralen in the form of 5- methoxypsoralen or 8-methoxypsoralen. The drug can be administered orally 2 hours before light treatment. More frequent side effects associated with these treatment modalities are cutaneous phototoxicities, photo ageing, nausea and the risk of skin cancer.

#### 4.1.3. Monochromatic Excimer Light

The combination of monochromatic excimer light with xenon chloride gas emits light with a wavelength of 308nm. There are two forms of producing this light; the excimer LASER that produces a coherent and monochromatic light and the excimer lamp that produces a non-directional and non-coherent light of 308nm. These treatment forms differ from NBUVB in their mode of application, as they may be applied in a more localized fashion in the lesions [43,44].

### 4.2. Pharmacological Treatment

#### 4.2.1. Topical Corticosteroid

The use of topical corticosteroids in vitiligo treatment is considered as a first-line treatment due to its cost-effectiveness and easy application [45]. The application of corticosteroid topically is appropriate for the treatment of localized vitiligo and hence used on small affected areas particularly elbow, knees, and face. A retrospective study showed that the

efficacy of class 3 corticosteroid is higher than that of class 4 corticosteroid. The incidence of atrophy was also observed with class 4 corticosteroid [46].

However, studies recommended the use of high-power corticosteroid but its use is limited to 2-3 months only. So, the use of low power corticosteroid is considered in order to minimize the adverse effects. It is also recommended that if there is no clinical response observed in the patient of localized vitiligo after topical corticosteroid application, its use should be discontinued [47].

#### 4.2.2. Immunomodulators

Topical immunomodulators are potent therapeutic agents that work via an immunological pathway. It can either suppress or enhance immune and inflammatory responses in the skin. Generally, tacrolimus and pimecrolimus are used as immunomodulators for the treatment of hypopigmented spots including that in vitiligo. The mechanism of action of these drugs involves calcineurin inhibition which results in down-regulation of T-cell reactivity and disturbance in the transcription of proinflammatory cytokine genes which are essential in the pathophysiology of the early immune response [48]. Similarly, prostaglandin E has an immunomodulatory effect on melanocytes and controls their proliferation. It has been used for the treatment of vitiligo and there was significant improvement in vitiligo conditions observed during treatment with the use of topical prostaglandin E [49].

### 4.3. Surgical Treatment

Vitiligo patients who failed to respond to classical therapies having stable vitiligo are treated with surgical therapy. These methods are generally used for the areas not easy to treat such as elbows, eyelids, knees, and lips. Tissue grafting and cell suspension grafting are the two broad techniques of surgical treatment which consist of the following types:

#### 4.3.1. Tissue Grafting

##### Punch Grafting

Punch grafting is performed by making multiple punches of different sizes on affected areas and then transplanting it with 1-2 mm thickness punch biopsies from the donor area. Better repigmentation with good cosmetic results was observed with punch grafting. Malakar and Dhar [50] observed 90-100% repigmentation rates in around 75% of patients treated with punch graft. The appearance of repigmentation after punch graft was reported as 29 days. The appearance was faster in mucosal followed by segmental, focal, and acrofacial; additionally, quicker in parasternal, infraclavicular areas and lips followed by other areas [51].

An autologous mini punch graft with motorized punches can also be used for stable vitiligo especially on larger areas including difficult sites in a single session which can be effective [52]. There are certain adverse effects found with larger grafts such as cobblestoning which has been corrected with electro fulguration. Studies also proved that punch graft combined with NBUV or topical corticosteroid gives much better results [53,54].

##### Suction Blister Epidermal Grafting

In this technique, dermo-epidermal separation from the donor site is done by applying constant suction in order to obtain a thin graft and the recipient area is prepared by laser therapy and dermabrasion. A retrospective study showed that more than 75% repigmentation has been achieved in 89% of patients under study [55]. This method offers good therapeutic results but is time-consuming. In a comparative evaluation of punch grafting, suction blister and split-thickness, workers reported that suction blister was more effective than the other two techniques for the removal of hypopigmented scars. It gives cosmetically better results in a shorter duration of time [56].

##### Split Thickness Grafting

Like suction blister grafting, this technique also involves the preparation of the recipient area by dermabrasion followed by a split-thickness graft of the donor area. To obtain a thin skin graft, a dermatome is needed and hence this procedure requires skill and an experienced person to handle dermatome. Sameem *et al.*, [57] have described split-thickness grafting as a promising treatment for recalcitrant vitiligo. Ultrathin split-thickness grafting followed by UVB therapy was also reported as an effective treatment option for stable vitiligo. Repigmentation appeared on the second week after ultrathin split grafting followed by UVB therapy and good to excellent results were seen in 90% of the patients [58]. Although it gives good results with 90-100% repigmentation rates as proved by Agrawal and Agrawal, [59] there are certain side effects associated with this technique like scarring at normally pigmented donor area and incompatibility of color at recipient area [60].

#### 4.3.2. Epidermal Cell Suspension Grafting

##### Cultured Epidermal Cell Suspension Grafting

This method is definitely beneficial as it increases the number of cells by using the tissue culture technique. Using less donor tissue, it can treat larger recipient areas. But this method is costly and require a sophisticated tissue culture laboratory, also the use of certain mitogens in the culture medium raised the question about safety [61]. Non-cultured method on the other hand is much better than cultured method as it is faster and gives better results [62].

##### Non-Cultured Epidermal Cell Suspension Grafting

In this method, the skin fragment is extracted as a biopsy from the donor area. The epidermis is separated from the dermis by treating the skin fragment with trypsin. After consequent steps, suspension of keratinocytes and melanocytes is obtained which is then transplanted to the recipient area. It offers good results with excellent color compatibility at the recipient site [63,64].

Although cellular methods have advantages in the surgical management of hypopigmented conditions, such as the requirement of small size donors and efficacy in large hypopigmented macules. But the treatment cost and requirement of special reagents are disadvantages. However, with continued refinement of this technique, they are bound to get extra popularity in the future [65].

## 5. Consequences of available treatments for hypopigmentation

Although there are several modalities of treatment for hypopigmentation available today including physical therapies or chemical agents, but none of them is entirely satisfactory. More frequent side effects associated with PUVA and laser treatments are cutaneous phototoxicities, photo ageing, nausea and the risk of skin cancer. Graft rejection is the major drawback of use of grafting technique for vitiligo patients. The incidence of atrophy was observed with class 4 corticosteroid while used for the treatment of hypopigmentation. Hence, the use of low power corticosteroid should be recommended. Though Q-switched laser induced pigmentation very quickly but various discomforts observed with it [66].

## 6. Natural herbal based treatment for hypopigmentation

Natural herbal extracts have strong phytochemical properties that are now being exploited all over the world, and there is a sudden increase in Ayurvedic or traditional uses of plant wealth in the treatment of diseases such as cancer, arthritis, sterility, psoriasis, and diabetes. Plant extracts have been used to treat hypopigmentation and vitiligo since time immemorial. Of late, we have found significant advancement in the field of research using natural products, demonstrating the growing interest of academic researchers and pharmaceutical companies in developing successful herbal agents and their formulations for the treatment of hypopigmentary disorders [67]. Below are the various plants and their constituents successfully validated for their repigmentation ability:

**Table 1** Summary of scientifically validated plant extracts which can be used as skin darkening agents and their possible mechanism of action

S.No.	Plant Name	Experimental Assay / Cell type/ Animal model	Target site/ Mode of action	References
1.	<i>Capparis spinosa</i> and <i>Erica multiflora</i>	B16 cells	Tyrosinase expression ↑ Melanin content ↑	[68]
2.	<i>Moricandia arvensis</i>	B16-F0 cells	Melanin, Tyrosinase activity	[69]
3.	<i>Cassia alata</i>	Melb-a melanoblast	Melanin, Tyrosinase activity, Dendritogenesis, Migration	[70]
4.	<i>Cassia occidentalis</i>	Melb-a melanoblast	Melanin, Tyrosinase activity, Dendritogenesis, Migration	[71]
5.	<i>Daphne gnidium</i>	B16-F0	Melanin, Tyrosinase activity	[72,73]
6.	<i>Polygonum multiflorum</i>	Human melanocytes	MITF, Melanocyte migration	[74]

7.	<i>Eclipta Prostrate</i>	Human melanocytes	Melanin, Tyrosinase activity, MITF, Melanocyte migration	[74]
8.	<i>Rehmannia Glutinosa</i>	Human melanocytes	Melanin, MITF	[74]
9.	<i>Pyrostegia venusta</i>	B16/F10 melanoma cells	Melanogenesis (low concentration) ↑	[75]
10.	<i>Vernonia anthelmintica</i>	B16-F10 cells and normal human primary melanocytes	p38-MAPK activation and MITF induction of tyrosinase	[76]
11.	<i>Kaliziri</i>	B16 melanoma cells	tyrosinase activity and melanin content	[77]
12.	<i>Melia azedarach</i>	B16/F10 melanoma cells	Melanin ↑ TRP1 expression ↑	[78]
13.	<i>Melissa officinalis</i>	human keratinocytes model	melanin production	[79]
14.	<i>Glycyrrhiza glabra</i>	B16 melanoma cells	TRP-2 ↑ Melanogenesis ↑ cAMP pathway ↑ AP-1 & CREB ↑	[80,81]
15.	<i>Vigna angularis (Adzuki beans)</i>	B16-BL6 melanoma cells and C3H/HeJ mice	<i>in vitro</i> and <i>in vivo</i>	[82]
16.	<i>Vitex agnus castus</i>	R6-NHEM-2	Melanin content ↑ Skin-tanning ↑	[83]
17.	<i>Citrus sinensis, C. reticulata, C. aurantium</i>	B16/F10 melanoma cells	MAPKs ↑ α-GSK ↑ CREB ↑	[84]
18.	<i>Nelumbo nucifera</i>	Flower essential oil	MITF-M ↑ TRP-2 ↑	[85]
19.	<i>Passiflora edulis, Passiflora incarnate and Peganum harmal</i>	B16/F10 melanoma cells	Activation of p38 MAPK pathways TYR ↑ TRP1 ↑ TRP2 ↑	[86]
20.	<i>Salvia miltiorrhiza</i>	B16/F10 melanoma cells	Tyrosinase ↑ Melanin content ↑	[87]
21.	<i>Salvia officinalis</i>	B16/F10 melanoma cells	Melanin ↑ and tyrosinase activity (low concentration)	[88]
22.	<i>Garcinia mangostana (Mangosteen)</i>	B16/F1 melanoma cells	Tyrosinase activity & expression ↑	[89]
23.	<i>Chlorophytum tuberosum and Chlorophytum borivilianum</i>	teleost fish, Channa punctatus	Melanin content ↑	[90]
24.	<i>O. javanica</i>	B16/F1 melanoma cells	Melanin content ↑ Tyrosinase expression ↑	[91]

			25.SOD-1, SOD-2, and GSH expression ↑	
25.	<i>Psoralea corylifolia</i>	<i>Fish scale Melanophores</i>	Melanin dispersal responses	[92]
26.	<i>Nigella sativa</i>	Melanophores of the wall lizard	Melanin dispersal responses	[93]
27.	<i>Fallopia multiflora</i>	B16 melanoma cells	Tyrosinase activity ↑	[94]
28	<i>Agaricus bisporus</i>	B16F10 melanocytes	Phosphorylation cAMP and CREB	[95]

This is not the end of the list as a large number of plant extracts (Table 2) have been scientifically validated using either *in-vitro* or *in-vivo* methods, from the past many years for the hunt of developing safe and novel skin darkening ingredients against hypopigmentation and much more are in a queue. To understand the action mechanisms of a variety of plants and their active ingredients on pigmentation of skin, our research group is actively working on it in our laboratory. The extracts of various plants including *Psoralea corylifolia*, *Piper nigrum*, *Chlorophytum borivilianum*, *Nigella sativa*, *Withania somnifera*, *Ficus carica* and *Berberis vulgaris* have been validated by us for their melanogenic activity via cholinergic and adrenergic receptors in different animal models such as fishes, reptiles, and amphibians. Nevertheless, the exact mechanism by which these plants induce melanogenesis was not fully understood and there is quite substantial scope for the expansion of therapeutic modalities to cure hypopigmentary disorders such as vitiligo.

## 7. Conclusion and Future Prospects

It is a well-known fact that melanin is very essential pigment found in melanocytes and provides a defensive mechanism against photo damage of skin cells, but uneven melanin production leads to undesirable conditions specified as hypopigmentation. Several treatment modalities including physical, chemical, and surgical have been used to overcome the problem of hypopigmentation. But many of them come under increasing scrutiny due to the side effects they imparts. Hence the use of herbal ingredients for the treatment is highly recommended. Keeping in view of the researches carried out on skin darkening efficacy of many plant extracts against hypopigmentation, there are several questions yet to be clear, regarding exact mechanism of action, efficacy in experimental models as many of the stimulators of melanin synthesis have been found to fail in the *in vivo* or clinical tests because either they are not able to penetrate the skin surface or if penetrate, they were ineffective as they loses their biological activity. Hence, novel drug delivery systems are highly recommended and accordingly, there is an urgent need for the implementation of new and potent alternative options to confirm the safety of therapeutic modalities for hypopigmentation disorders.

## Compliance with ethical standards

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All authors have declared there is no conflict of interest and all authors have carefully read the manuscript and approved for submission.

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