

Potential of Herbal Drugs in the Treatment of Vitiligo

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Abstract

Review Article

Vitiligo is an acquired cutaneous autoimmune disorder of pigmentation, with an incidence of 1% to 2% worldwide. There are many hypotheses for the pathogenesis of vitiligo. Recent data provide strong evidence supporting an autoimmune pathogenesis of vitiligo. The quality of life is majorly affected by symptoms of vitiligo. The immune system is targeted by medical treatments and tries to reverse the destruction. The goal is to restore the skin's color by restoring healthy melanocytes to the affected area. Topical therapy is employed as first-line treatment in localized vitiligo. Plants have been the basis of many traditional medicines throughout the world for thousands of years and continue to provide new remedies to mankind. T cells from vitiligo skin are highly reactive towards melanoma cells and serve as an effective source to treat melanoma and stays as a solution for vitiligo. There have been many treatments to cure vitiligo such as use of steroid creams, narrow band UVB (ultraviolet B), PUVA (psoralen and ultraviolet A light), various surgical techniques, vitamin D analogues and pseudocatalase. These treatments are subjected for undesired side effects whereas some herbal and natural treatments act against the immune system with no side effects. Thus, the recent resurgence of plant remedies resulted from several factors, such as effectiveness of plant medicines and lesser side effects as compared with modern medicines. This review presently gives a detailed investigation on various herbs and different treatments modalities that can be used for the treatment of vitiligo.

Key words: Vitiligo, skin, treatment, plants, pigmentation.

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INTRODUCTION

Vitiligo refers to an idiopathic, usually progressive condition of skin due to depigmentation [1, 2]. It is widely spread throughout the world irrespective of male/female, young and old, and all anatomical parts of the body. Although it is not a clinical or pathological condition, still a condition which the individuals segregated based on the appearance. A genetic predisposition is considered to be involved in the disease [1, 3]. Research says that the condition is mainly due to loss of melanin pigment in the skin [4]. It is also considered as a hypopigmentary disorder that affects at least 1% of the general population, causing important cosmetic and psychosocial problems. India has the largest population suffering from vitiligo (1.7%). The incidence rate of vitiligo was between 0.1% and 2%. The causes of vitiligo may be due to genetic, immunological, and neurological factors. Most of the cases of vitiligo are mainly due to genetics which is triggered by environmental factors. In this review, we attempt to consolidate all the factors which affect the condition and treatment methods and modern approaches for the same [5- 8].

Vitiligo is of several types that are as following

(a) **Segmental vitiligo** is less common, presents at an earlier age, is unilaterally distributed, and is less prone to relapse [9, 10].

(b) **Generalized vitiligo** is increasingly recognized to be an autoimmune disease [11–13], yet its initiation and the precise pathogenesis of melanocyte destruction remain to be elucidated. Among the processes implicated during this type are immune dysregulation, neurogenic factors, catecholamine-mediated cytotoxicity, and oxidative stress [14, 15]. Treatments available to induce repigmentation include topical steroids, calcineurin inhibitors, vitamin D analogs, phototherapy, laser therapy, and surgery; however, no topical products currently carry US FDA approval to increase the rate of repigmentation in vitiligo [16–18]. Accordingly, there is interest among patients and physicians in the use of complementary treatments, such as herbal and vitamin supplements [16]. The efficacy and safety of these products is much less well established than those of drugs that are subjected to a formal clinical, preclinical and clinical development

pathway and require the approval of the FDA for marketing clearance.

Factors causing vitiligo

Vitiligo or leucoderma is a disorder with full of complexity. The factors which cause this skin disorder are as following:

- The emergence of white patches can be brought on by a variety of impulsive causes.
- Vitiligo was first appeared following a stressful event, such as an accident, job loss, severe sunburn, or serious illness and death of a family member which has been reported by many peoples [19].
- The mechanism of vitiligo was lying on three theories *i.e.* one theory states that a chemical has been released by nerve endings in the skin that is toxic to the melanocytes. A second theory states that the melanocytes have the nature of self-destruction. The third theory states that this disease is a type of autoimmune disease which involves the immune system to target on the body's own cells and tissues.
- **Autoantibody responses** - The blood of patients with vitiligo contain antibodies to melanocytes. The comparison has been done between the antibodies that are related to the extent of the disease being detected in 50% of patients with minimal vitiligo and to the 93% of patients with greater depigmentation. Immunofluorescence has been detected that shows the binding of vitiligo patient IgG to cultured melanocytes increased with disease extent and activity. Auto antigens in some vitiligo appear to be expressed on cells other than melanocytes. The most valuable contribution was in identifying relevant target antigens made possible by some studies has been done on anti-melanocyte antibody reactivity [20].

Prevalence of vitiligo in children

Childhood vitiligo (CV), defined as vitiligo that begins before the age of 12 years, is common and may differ from post-CV in terms of epidemiology, clinical presentation, comorbidities, and treatment options. Several general population-based studies have assessed the prevalence of vitiligo in children and adolescents worldwide, and rates of 0-2.16% have been reported [21]. Most of these studies have used school children of different ages as their reference population. Large studies that encompassed preschool-aged children include a study [22] that showed a prevalence of 0.09% and 0.15% in children and adolescents aged 0–9 years and 10–20 years, respectively, and prevalence of 0.1% in children aged 0–9 years and 0.36% in children and adolescents aged 10–19 years were reported in Chinese study [23].

Disease onset before the age of 4 years is uncommon [24- 28]. Two studies from India [25, 26] and one from China [27] reported that the onset of vitiligo before the age of 4 years was shown in 17% of

children, 42–49% of children of age between 4 and 8 years, and 35–40% of children with vitiligo of age between 9 and 12 years. One recent study has been done showing the comparison between the clinical features of vitiligo starting before 3 years of age (early-onset vitiligo) and of the disease starting between 3 and 18 years of age (later-onset vitiligo) [29]. The results shown that 15% of patients included had early-onset disease and that these patients had higher percentages of body surface area (BSA) involvement and increased rates of disease progression. However, the two groups were similar in terms of repigmentation after treatment, vitiligo type, halo nevi, sex ratio, or personal and family history of autoimmune diseases.

No clear sex preference has been established for CV. Studies from India [25, 26], the US [30], Greece [24], France [31], and Brazil [28] reported predominance of female *i.e.* 57–66%. On the other hand, studies from Korea [32], China [27], Jordan [33], and the US [30] described equal numbers of patients for both sexes. Most studies report no difference in the female: male ratio between CV and PCV [24, 31, 32]; however, a female preponderance in CV, compared with PCV, has been reported [25]. The typical clinical presentation of CV consists of well circumscribed amelanotic (whitish) macules or patches, surrounded by normally pigmented skin. Lesions shown could be round, oval, or irregular in shape and vary in size from millimeters to several centimeters in diameter. Vitiligo patches has been appeared on any area of the body, but typical sites frequently affected include the face, dorsal surface of the hands and feet, fingers, elbows, knees, shins, axillae and anogenital region. The disease seems to have a predilection for locations that are normally hyperpigmented or subjected to repeated trauma, friction, or pressure [34]. In India, this type of trauma was observed in 11% [26] to 24% [25] of children with vitiligo characterized by the development of vitiligo lesions in sites of trauma commonly known as Koebner phenomenon.

Autoimmune comorbidities in vitiligo: general considerations

The autoimmune theory has been the most widely accepted theory for causation, especially for generalized vitiligo [35]. This theory suggests that melanocytes were destroyed by an autoimmune mechanism [36]. The high prevalence of autoantibodies against melanocytes in vitiligo patients and the frequent presence of concomitant autoimmune disorders in 10–15% of vitiligo patients compared to 1–2% of the general population were some of the most apparent correlations between vitiligo and autoimmunity [37, 38]. Infiltrating lymphocytes has been found at the margin of lesions in most vitiligo patients [39- 41]. In some cases, high frequencies of circulating melanocyte-specific cytotoxic T lymphocytes (CTL) have been found in vitiligo patients [40]. Interestingly, a study has been done comparing CTL responses to melanocyte

antigens in melanoma and vitiligo found a qualitative difference between the cytotoxic responses in the two conditions, as the melanocyte-specific T cells involved in vitiligo had higher affinity [41]. Further support for the autoimmune theory was increased prevalence of the same autoimmune disorders in unaffected first-degree relatives of vitiligo patients [35, 42, 43]. Furthermore, recent genome-wide association study has shown that generalized vitiligo involves genetic susceptibility loci shared with autoimmune diseases [43, 44]. In addition, vitiligo patients respond to some extent to immunosuppressive treatments [45] and finally, vitiligo involvement in the eyes and inner ear further support an autoimmune etiology [36]. Allelic association studies as well as genome-wide association studies has shown higher prevalence of concomitant autoimmune diseases in vitiligo patients [46].

The prevalence rates for comorbid autoimmune diseases have been seemed to be varying depending on the population studied. In several studies from North America, 19–30% of the patients had autoimmune diseases [43, 47, 48]. In India, a low prevalence of 2.94% was found [35] and in other Asian countries like Japan and Taiwan, rates were 20.3% and 14.4%, respectively [44, 49]. Studies from Europe reported autoimmune comorbidities in 15.4–41.5%, [50, 51] in Iran this number was 25.8%, [52] while a very high prevalence of 55% was found in Turkey. However, the authors of this study have attributed this high prevalence in part to high rates of consanguineous marriages in Turkey [53]. In a recent African study, comorbid diseases have been documented in 26% of the patients with vitiligo. However, autoimmune comorbidities constituted only 2.8% [54]. Both familial and sporadic vitiligo is associated with increased frequency of autoimmune diseases [55, 56]. Of the various autoimmune disorders, thyroid disease was the most common [44, 47, 48, 55, 56]. Other diseases include alopecia, pernicious anemia, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), diabetes mellitus, Addison's disease, inflammatory bowel disease (IBD), Sjogren syndrome, dermatomyositis, and scleroderma.

Convergence theory of vitiligo

To paint a full picture of vitiligo etiology, the individual puzzle pieces are currently merging, thus providing ample encouragement to revisit the convergence theory of vitiligo and understand how the expectations set forth in 1993 hold true in 2018. A re-appraisal of the convergence theory is presented here for the worldwide spread disease *i.e.* vitiligo:

A: Melanocyte loss

When the 'convergence theory' was published, the fate of melanocytes in vitiligo skin was still unclear, thus it has been now accepted that melanocytes were lost from depigmented lesions [57]. In vitiligo epidermis, melanocytes were readily quantified once

melanocyte-specific antibodies became available and overall paucity of melanocytes in depigmented skin has been confirmed by newer antibodies [58, 59]. These findings indicate that to replenish the melanocyte pool resources has been provided by vitiligo therapeutics. Investigations into melanocyte loss have been enabled by newer techniques for characterizing melanocyte populations via isolation of RNA using a rapid immunostaining protocol [60]. Also, surgical methods to restore melanocyte abundance have become clinically available with mixed results before melanocyte loss was established [61]. As several studies revealed the presence of some differentiated melanocytes in depigmented skin which clearly shows that the loss of melanocytes from vitiligo lesions has been no longer considered complete [62–64]. It has been unclear whether a small population of intralesional cells remains or these sparse melanocytes has returned to the epidermis after the original injury [65].

B: Environment

Approximately half of patients have reported that mechanical stress and associated koebnerization were some forms of stress that can induce vitiligo [66]. When reduced expression of E-cadherin equates to reduced cellular adherence, mechanical stress may cause the aforementioned melanocytorrhagy [67]. Additionally, the responses to questionnaires have cleared the role for psychological stress on vitiligo development and progression. Also, the occurrence of stressful life events preceding vitiligo development has been supported by significant insight gained from publications [68]. Alexithymia (the inability to identify and describe experienced emotions), insecure attachment and poor social support than controls have been exhibited more apparently by vitiligo patients [69]. Thus, patients increasingly vulnerable to stress and vitiligo development due to certain disease-associated personality traits. Though, there is little evidence to support that only vitiligo patients would be sensitive to bleaching treatment [70]. It has been more likely to damage the melanocytes of patient specifically give rise to cytotoxic immune responses which results in progressive depigmentation [71].

C: Intracellular metabolism

When vitiligo developing in response to topically applied chemicals, it was termed as 'chemical leukoderma' though its etiology is similar to other vitiligo cases [72, 73]. An autotoxicity has been caused due to toxic intermediates (including quinones) that form after melanocyte-specific enzymatic activity [74]. However, melanin synthesis has been taken place in both healthy and patient-derived melanocytes. The relative activity of enzymes protecting melanocytes from oxidative damage has been investigated to explain the selective development of progressive depigmentation in vitiligo-prone individuals.

D: Microbial symbiosis

Vitiligo being the skin disorder has been associated with infection for reasons other than a causative relationship. To stigmatize vitiligo patients, similarity in appearance to leprosy has been continued in the patients [75]. As infected Schwann cells may be a target for the same etiologic factors as melanocytes due to a largely shared differentiation pathway which has shown the possibility of existence of similarities in etiology [76].

Other findings has been suggested the role for infectious agents including responses to a vitiligo patient. The increased frequency of *H. pylori* infections and antibacterial serum titers among vitiligo patients has been significant, though no correlation to disease activity was reported [77]. HIV and vitiligo co-occurrence was reported, wherein vitiligo could surround the HIV-associated Kaposi sarcoma nodules [78].

E: Heredity

DNA sequence analysis could be helpful to understand the complex polygenic additive mode of inheritance of vitiligo [79]. Vitiligo causes may be due to cluster within families and populations, and with 20% of patients which has been reported in an affected first-degree relative, also parents are often concerned about the odds of an unborn child inheriting vitiligo for vitiligo prevalence [80]. This emphasizes the importance of defining sequence variants in development of disease. However, environmental parameters might influence disease on a greater scale. In its current phase, to better understand how both DNA sequence changes and differences in transcript abundance of downstream gene products command the functional differences, this topic may be beneficial from advances in computational systems biology and also in understanding the diseases [81].

Vitiligo and lifestyle modification

There is various location of vitiligo which provides the clues as to its triggers or causes. Skin lesions are frequently localized to the seborrheic area in stress-induced cases, the lesions are usually localized to sites of injury or pressure in traumatic type's case and depigmented lesions tend to occur in areas of a specific pre-existing dermatitis in dermatitis associated types. Doctors often has been advised the patients to alter modifiable living habits by assuming the predisposing and aggravating factors that may help in identify vitiligo etiology [82].

Food additives, antioxidants, vitamins

In the treatment of vitiligo, diet has not been considered very important. However, from a variety of sources, a healthy balanced diet with nutrients can be helpful in vitiligo. There are foods that are considered either beneficial for or detrimental in vitiligo, but they differ in foods opinion and they often lack medical evidence to substantiate their claims according to

complementary and alternative medicine (CAM) practitioners. Often, recommendations have been determined by a food's composition of vitamins, antioxidants and microelements. On the other hand, on the risk of allergic reactions and irritation, either of which could trigger or exacerbate vitiligo, the detrimental effects of foods or food additives were frequently based on.

Foods should be avoided

When a patient is suffering from vitiligo, certain foods were harmful to the body as insisted by some Ayurvedic specialists. This includes tamarind, tomatoes, sour or pickled food items, citrus fruits and juices, papayas, tinned foods or drinks, chocolate, grapes and cocoa products, coffee, pears, oily or spicy foods, dairy products, blueberries, eggs and fish [83]. Consumption of pork, chicken, and wheat has not been recommended by traditional Korean medicine specialists for patients with vitiligo. Also, sour foods, non-vegetarian foods, ascorbic acid and flavored drinks and foods with artificial colors may worsen the condition as suggested by homeopathic doctors.

One study has suggested that cashews, red chilies, cherries, raspberries, pistachios, oak, cassavas, areca nuts, cranberries, mangoes, blackberries, and tea contain naturally-occurring plant phenols and polyphenolic compounds, or tannins that could possibly aggravate vitiligo due to their phenolic structures [84].

One study has shown that Nickel has been found in foods such as cocoa and chocolate, crisps, wheat flour, instant tea (green or black) and roasted salted cashews. As, Nickel has been eliminated through sweat, but consumption of high concentrations of nickel can cause a cutaneous reaction. Therefore, Foods containing nickel should be avoided in the patient who was allergic to nickel, and suffered from vitiligo in the areas prone to sweating such as the shoulders, flanks, buttocks, and sacrum [85, 86].

However, most patients do not adhere to restrictions on these types of foods. Also, eating barbecued meats may increases the production of oxygen free radicals and carcinogens in the body as well as lowers levels of antioxidants. Therefore, patients need to be counseled on making a balance between these types of foods in their diets and maximizing antioxidant intake from vegetables and fruits. They should also cut back on junk foods and other instant foods and should go for are low in calories and have high nutritional value.

Some people have different opinions on whether these foods are actually harmful and he or she could easily become more stressed and lose the benefits of a balanced diet, if they has to avoid all of the foods listed above. So, the best way to combat this disease

was to increase the consumption of fruits and nuts in the daily routine diet.

The cutaneous reactions induced by foods was of major concern as patients and doctors should pay special attention to it. The foods listed above may cause irritation that leads to skin inflammation which further results in Type I anaphylactic hypersensitivity (atopic dermatitis or urticaria) and Type IV delayed hypersensitivity (allergic contact dermatitis) both of which has the capability to exacerbate vitiligo. However, doctors do not need to prohibit all patients from these foods as these adverse events were rarely occurred.

Furthermore, patients should follow the personnel hygiene routine *i.e.* rinse and wash their mouths (perioral and oral cavities) and hands after meals. Patients with celiac disease (wheat or gluten-sensitive enteropathy), should minimize their intake of wheat particularly those with associated dermatoses such as dermatitis herpetiformis or psoriasis as wheat or gluten can aggravate cases of vitiligo [87].

Certain customs can lead to skin inflammation and exacerbation of vitiligo because of the eating habits of specific ethnic groups. For example, Koreans may get affected by systemic contact dermatitis as they enjoy urushiol-containing foods for gastrointestinal relief and Korean chicken or duck soup made with *Rhus* plants which ultimately results in drastic condition [88]. Therefore, it has become necessary to perform further research studies in different regions of the world so that specific native foods that cause allergic or irritant reactions can be identified.

Food to be beneficial

To encourage in the treatment of vitiligo, eating a variety of fish, meats, vegetables, and fruits were found to be beneficial. However, doctors need to take this into consideration about the patients who were particular about the foods they eat. Also, meats or fish such as shark and tuna can be poisoned with dioxin, mercury, or heavy metals, which could be problematic.

Many studies have shown that reactive oxygen species are increased in the epidermis of active disease. Food can serve as antioxidants. It has been known that various reactive oxygen species were involved in the destruction of melanocytes in vitiligo. Inhibition in the progression of vitiligo and the administration of antioxidants to patients with vitiligo may be due to elimination of these reactive oxygen species as being hypothesized by Scientists. A study has shown the report on statistically significant better response in patients compared to phototherapy alone when the patients were administered with combination of phototherapy and antioxidants [89, 90, 91]. Recently, another study showed that significantly improvement in

the clinical effectiveness of phototherapy by oral supplementation with alpha-lipoic acid [92].

Effectiveness of antioxidants in vitiligo

High doses of antioxidants (as part of combination treatment with other vitiligo therapies) have decreased the risk of abrupt deterioration of vitiligo according to the clinical experiences of the authors. Thus, patients with vitiligo were advised to select foods rich in antioxidants. These antioxidant-rich foods include pomegranates, broccoli, ginger, beets, kale, red cabbage, peppers, spinach, pineapples, olives, black beans, tomatoes, red clover, strawberries, kiwi, blueberries, nuts (*e.g.*, walnuts, cashew nuts), grapes, oranges, lemons, sunflower seeds, black sesame, perilla seeds, *Agaricus bisporus* (common/crimini mushrooms), green tea, and coffee. Patients can use commercial nutritional supplements, if the aforementioned foods were not available. These include products containing genistein (black bean extract), omega-3 fatty acids, gamma linolenic acid, carotenoids, quercetin, vitamin C, green tea polyphenol, co-enzyme Q10, selenium, alpha-lipoic acid, , and vitamin E, and others.

Some believed in the advantages of vitamin C as an antioxidant outweighs the risk of hypopigmentation, and recommended that patients have to take vitamin C at a dosage of 0.5-2 grams daily. Although some specialists insist that vitamin C is harmful in vitiligo because of its skin whitening properties but it may be a myth.

For psoriasis and autoimmune diseases, omega-3 fatty acids were poly-unsaturated fatty acids (PUFAs) that are known to be beneficial. The beneficial effect in vitiligo was due to its anti-inflammatory, antioxidant, and antidepressant effects [93]. Gammalinolenic acid, another PUFA from evening primrose oil, were considered effective for atopic dermatitis [94]. More effective when vitiligo occurs with atopic dermatitis in flexural or periorbital areas, and other areas vulnerable to stimuli. Vitamins and minerals (microelements) were also important. Some studies have demonstrated that in unaffected individuals, the level of vitamin B12, folic acid, copper, and zinc in patients with vitiligo may be lower. Microelements such as selenium, copper, and zinc were essential in the diet or as supplements. Thus, it was preferable to take vitamin B12 along with folic acid due to the considerable synergistic effects of the pairing [95]. Also, it was recommended that patients obtain these nutrients from vegetables and fruits such as spinach, tomatoes, kiwi, *Agaricus bisporus*, or multivitamin supplements.

Processed Food additives

Various food additives including: dyes, color retention agents, fungicides, preservatives, sweeteners, thickeners, defoaming agents, emulsifiers, flavors, and

chemicals introduced at the agricultural or animal husbandry phases, among many other possible ingredients were added in the processed foods such as those found in cans or bottles, and preserved or tinned meats such as ham or sausage.

As the medical evidence for the harmful effects food additives is weak, while food additives were generally considered harmful in vitiligo. In patients with atopic dermatitis, intolerance reaction by acting on mast cells directly may occurred due to food additives like preservatives (sodium benzoate, potassium sorbate, sodium propionate), monosodium glutamate (MSG) or coloring agents (sodium nitrate and certain FD&C colors) [96]. Consuming food additives in large amounts may also increase the risk of a stress reaction which shows a harmful effect on vitiligo itself and accompanying skin diseases such as atopic dermatitis.

Medicinal plants for vitiligo

In controlling the activity of vitiligo and in inducing repigmentation of the white macules, many data has been reported to support the efficacy of the herbal compound, especially if administrated with other conventional therapies (e.g. corticosteroids, phototherapies) [97, 98].

Ginkgo biloba

The leaves and seeds of Ginkgo biloba (also known as “maidenhair tree”), had been largely used in medicine for a very long time and is one of the oldest trees on Earth. Recent studies have been done on Ginkgo extracts which shows that the drug was effective when administrated alone [99, 100]. Unfortunately, the results in term of repigmentation were not uniform. The following fact may be explained by different factors: the genetic differences of the analysed populations, the treatment duration, different type of Ginkgo biloba extracts and the number of administrated doses per day [100]. The drug was probably safe and well-tolerated at therapeutic dosages (normal value: 120 mg/day). Only mild disturbances *i.e.* restlessness and gastrointestinal disorders may result in daily dosage > 240 mg. Also, to avoid over-thinning of their blood and haemorrhaging, patients on anticoagulants should only take ginkgo under medical supervision for a correct prescription.

Khellin

The plant Amni visnaga has been used as herbal medicine for different purposes (e.g. kidney diseases, asthma and others), since ancient Egyptian times. Khellin was a naturally occurring furanochromone, derived from the plant Amni visnaga. Analogues of khellin, with safer profiles and better efficacy, have been developed and introduced in medicine in the last decades for the treatment of vitiligo, because of khellin drastic side effects, including liver dysfunction and allergic reactions,

where they provide good results in combination with UVA phototherapy. Khellin acts by stimulating melanocytes proliferation and melanogenesis as the exact mechanism of action was not much clear [101]. It may be administrated both systemically (oral administration) or topically and the association of oral khellin to UVA is better known as KUVA therapy [102]. The study has been done showing the oral intake of khellin gelatin capsules and, after about 2.5 hours, the patient was irradiated with UVA. The duration of the therapeutic session was repeated 2 - 3 times a week. The clinical results were quite safer and similar to PUVA therapy. Unlike psoralens effects, khellins have also shown less phototoxic, and DNA mutagenic effects but the long-term risk of carcinogenesis has to be determinate [103]. The topical application of khellin was same as that of topically applied PUVA, associated with UVA radiation (topical KUVA therapy) or natural UVR (sol - KUVA therapy). [104]. More recently, a study has been conducted showing that topical application of khellin 4% has been successfully used in association to monochromatic excimer light 308 nm [105]. Therefore, the clinical results regarding repigmentation rate and safe profile suggested that this combination may be useful for vitiligo treatment.

Psoralea corylifolia

Recently, the most popular treatment for vitiligo is Psoralen plus UVA (PUVA therapy) that has been considered to be the first vitiligo treatment for several decades. A Chinese herb *Psoralea cordyfolia* contains active constituent *i.e.* Psoralen is a photosensitising compound, derived from this plant. In association to UVA exposure for a long time, it has been used to treat vitiligo by combining topical or systemic psoralea seed extract. The mechanism of action of therapeutic protocols, such as the beneficial effects and the collaterals of the plants are well - known. Another study has been done suggesting the well - known and characterized treatment option was the topical PUVA, based on the topical application of psoralea extract or derived products, and in the successive exposure to a UVA source [106].

Green Tea Polyphenols

The leaves of green tea contain green tea polyphenols derived from the extracts, that has been used in medicine since ancient time. Because of their composition in Epigallocatechin-3-gallate (EGCG), they act as anti - inflammatory, anti - oxidant, and immunomodulatory agents [107]. Both systemically and topically, the drug can be administered [108]. Recent data suggest that by stopping the oxidative stress of the melanocyte-unit, green tea polyphenols may be useful for vitiligo treatment [109].

Curcumin

Golden spice turmeric belong to family zingiberaceare contains curcumin is a polyphenol derived from the rhizome (“*Curcuma longa*”).

Curcumin has been used for the treatment of different diseases because of its numerous properties (e.g. antioxidant, anti-proliferative, anti-inflammatory, antiviral, antibacterial and antifungal properties) [108]. Recently, for vitiligo treatments, tetrahydrocurcumin cream has been used in association with NB - UVB. The phototherapy has been performed twice a week for 12 weeks. Patients showed a slightly better repigmentation compared to the ones treated only with NB-UVB at the end of the therapeutic protocol [109]. Finally, as an adjuvant therapy in vitiligo patients, curcumin may be orally administered.

Pyrostegia venusta

Herb named as *Pyrostegia venusta* (also known as “cipó – de – são - joão”) belongs to family Bignoniaceae, has been studied. Mainly, distributed in

southern Brazil, where topical formulations were commonly used for the treatment of vitiligo. The herb seems to be effective for its antioxidant, anti-inflammatory and melanogenic properties. Even if its mechanisms of action were still under investigation [110].

Capsaicin

The plant chili peppers contain capsaicin as one of the active components of the genus *Capsicum*. The drug has been proposed as a therapeutic tool for vitiligo treatments due to its anti-inflammatory and antioxidant properties. An experimental study recently has been done confirming how the incubation of keratinocytes, taken by the perilesional skin of a vitiliginous patient, with capsaicin showing the effect by inhibiting the cellular damage by ROS [111].

Other medicinal plants for vitiligo treatment

S. No	Scientific Name	Ver. name	Family	Part Used	Mode of Use	References
1.	<i>Acacia chundra</i> (Roxb)	sundra	Mimosoideae	Bark, Leaf	Bark and leaf paste is applied on the spots	[112]
2.	<i>Andrographis paniculata</i> (butm.f.)	nelavemu	Acanthaceae	Whole plant	whole plant paste is applied	[114]
3.	<i>Aristolochia indica</i>	gadida gadapa	Malvaceae	Leaf	Leaf juice is applied over spots	[113]
4.	<i>Clitoria ternatea</i> L.	sankupulu	Fabaceae	Root	Root paste is applied on the patches	[114]
5.	<i>Cassia auriculata</i> L.	thangedu	Caeslpinaceae	Flower	Flower paste is applied on patches	[112]
6.	<i>Cassia tora</i> L.	pedda kasindha	Caeslpinaceae	Seed	Equal parts of Seeds of <i>Cassia tora</i> , seeds of <i>Psoralea corylifolia</i> and wood of <i>Melia azadiarachta</i> made into paste with rose water is applied.	[115]
7.	<i>Curcuma longa</i> L.	pasupu	Zingiberaceae	Rhizome	Take a tsp. of turmeric powder twice daily in the morning and evening with hot milk for six months. It is beneficial in leucoderma.	[113]
8.	<i>Holoptelea integrifolia</i> (rox)	Nemali nara	Ulmaceae	Bark, Leaf	Bark and leaf paste of plant are applied externally on the spots.	[114]
9.	<i>Indigofera tinctoria</i> L.	Kajhar	Fabaceae	Seed, Bark	Seed and bark paste is applied on spots	[112]
10.	<i>Ocimum sanctum</i> L.	tulasi	Lamiaceae	Stem, Root	Drinking an infusion made from the stem of the basil plant prevents leucoderma. Take a basil plant with its roots, wash it and clean it well, pound it and cook it slowly in half liter oil. When the water evaporates and only the oil is left mash and strain it to get the basil oil. Apply it on white spots.	[115]
11.	<i>Pandanus fascicularis</i> L.	Mugali chettu	Pandanaceae	Leaf	Leaf paste is applied on spots.	[115]
12.	<i>Pongamia pinnata</i> L.	Ganuga	Fabaceae	Leaf	Leaf juice is applied on the spots.	[113]

13.	<i>Psoralea corylifolia</i> (L.)	Vakuchi	Fabaceae	Seed	The parts of the plant used for topical application are the essential oil extracted from the seeds. As a diluted essential oils, when topically applied to white depigmented patches show tremendous effect.	[114]
14.	<i>Punica granatum</i> L.	Dannima	Punicaceae	Leaf	Put pomegranate leaves to dry in the shade, grind them into a fine powder, sieve it and take 8 gm. of it each in the morning and evening with fresh water.	[114]
15.	<i>Raphanus sativus</i>	mullangi	Brassicaceae	Seed	Radish seeds are also highly beneficial for treating this condition. Powder around 25 gm. of radish seeds and add them to red vinegar. Apply it regularly on the white patches to treat this disorder	[113]
16.	<i>Trichodesma zeylanicum</i> (Burm.f.)	Adavi nugu teega	Boraginaceae	Leaf	Leaves applied as pasted.	[115]
17.	<i>Vitex negundo</i> L.	Nalla Vavila	Vitaceae	Stem, Leaf	Stem and leaf juice is used.	[112]
18.	<i>Vigna radiate</i> L.	Pesalu	Fabceae	Seed	Black gram seed paste applied regularly for several months proves to be useful.	[115]
19.	<i>Vernonia anthelmintica</i> L.	sahadevi	Asteraceae	Seed	1. The powdered seeds of this herb taken with a decoction of <i>Emblie myrobalan</i> and catechu. (2) The powdered seeds taken alone (1 tsp.) (3)The powdered black seeds taken daily in the morning with pepper or sesame seeds in equal parts with warm water, just after perspiring. It is indicated that if one of the above methods is followed for one year, resolution of vitiligo will occur.	[115]
20.	<i>Withania somnifera</i> L.	Aswagandha	Solanaceae	Root, bark	The mixture of <i>Withania somnifera</i> root bark, bark of <i>Embelia ribes</i> (vaibidang), leaves of <i>Plumbago zeylanica</i> (chitrak), seeds of <i>Croton tiglium</i> (jamalgota), and fruit pulp of <i>Cassia fistula</i> (amaltas) with cow's urine are applied on white patches for 2-3 months.	[115]

CONCLUSION

Vitiligo is an autoimmune skin disease which targets pigmentary cells and constitutes a huge research innovation for those interested in melanocyte biology and pigmentation disorder. Topical steroids are probably first line therapy for most patients. A number of balancing treatments for vitiligo, specifically herbal

products and vitamin supplements, have been studied to supplement traditional treatment modalities and that seems to be encouraging. But now the time has come to offer patients hope for therapy by recognizing suitable antibody targets in vitiligo. T cells from vitiligo skin are highly responsive towards melanoma cells and serve as an active source to treat melanoma. This could also

provide a basis for the expansion of diagnostic tests. Markers for important T cell responses in patients with the disease could be served by Antigens recognized by vitiligo antibodies. While a number of studies have shown beneficial effects associated with the use of these alternative treatments, larger, well-controlled trials are justified to firmly establish the place of these agents in the therapeutic hierarchy. However, the use of these alternative treatments can be considered as a supplement to the treatment regimen of interested or treatment intractable patients as they appear to be relatively safe and may provide additional value in outcomes and patient satisfaction.

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