

ROLE OF HERBAL MEDICINES IN VITILIGO TREATMENT - CURRENT STATUS AND FUTURE PERSPECTIVES

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ABSTRACT

Vitiligo is a depigmentation disorder with complex causes. Nonetheless, recent progress has been made to unravel the pathophysiology of vitiligo. In this review, we provide an overview of the currently known herbal medicine for vitiligo treatment and also highlighted the herbs that have been used in clinical trials. In view of traditional uses, herbs such as *Ammi visnaga* L., *Angelica sinensis*, *Eclipta alba* L., *Ginkgo biloba*, *Picrorhiza kurroa* Royle Ex Benth, and *Psoralea corylifolia* L, have been highlighted. Enormous efforts in vitiligo drug discovery are currently needed. Interleukin-17 inhibition, tumor necrosis factor- α inhibition, heat shock protein-70i (HSP70i) inhibition, keratinocyte turnover modulators, and regulatory T cells (Tregs) modulators have been discussed as promising new targets for vitiligo drug development. Thus, we strongly believe that this review may be useful for rationalize new herbal drug for vitiligo treatment.

Keywords: Vitiligo, Melanocyte, *Ammi visnaga*, *Psoralea corylifolia*, Regulatory T cells (Tregs) modulators.

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INTRODUCTION

Vitiligo is a pigmentation disorder, in which pigmentation cells (melanocytes) of skin are destroyed, which results in smooth, white patches in the midst of normally pigmented skin. People with vitiligo may also associate with eye abnormalities and have a high incidence of diabetes mellitus, pernicious anemia, and thyroid disease [1].

History

The term vitiligo has been derived from the latin word “vitilus” meaning calf. The term was first coined by Celsus, Roman physician in the 1st Century A.D. [1]. According to him white patches of the disease resembled the white patches of a spotted calf. Vitiligo is an ancient disease mentioned in religious texts such as Holy Quran, Veda, and Bible. The disease is even documented as “Bai Dian Feng” in traditional Chinese medicine, “Shewetakusta” in Indian classic Atharva Veda, “Kilas” in Vinay Pitah (Buddhist sacred book) and “Bars,” and “Phulbehri” in Arabic and Punjabi language [2].

Prevalence

It affects approximately 1–2% of world’s population, but the prevalence has been reported as high as 4% among some South Asian, Mexican, and American populations. In hospital Kuala Lumpur, Malaysia during the period of 2003–2007, approximately 2.2% new cases have been reported for this disease within the same period [3].

Epidemiology

It affects individuals of all age, races, ethnicity, and skin types. In Malaysia, vitiligo has been reported among all ethnic races [4]. Dark skin persons (African and Asian) usually face more stigmatization, discrimination and more possibly psychosocial problems [5].

Types of vitiligo

In general, it is classified according to the distribution, pattern, and extent of depigmentation. According to Nordlund and Lerner [6], it has been classified into three types as i) localized, ii) generalized, and iii) universal vitiligo. Localized vitiligo is again sub-classified as focal and

segmental, whereas generalized vitiligo into acrofacial, vulgaris, and mixed subtypes [7].

Pigment biochemistry

Melanin is the major skin pigment, synthesized by specialized cells called melanocytes. Melanin is formed through series of oxidative reactions involving the amino acid tyrosine in the presence of tyrosinase (enzyme). Melanocytes synthesize the melanin within membrane-bound organelles called melanosomes, and later melanosomes are transferred through dendrites to surrounding keratinocytes. Each epidermal melanocyte secretes melanosomes to approximately 40 keratinocytes (1:40) in the neighborhood, and this entire unit is known as epidermal melanin unit. Thus, the type (eumelanin/pheomelanin) and amount of melanin synthesized by the melanocyte and its distribution in the surrounding keratinocytes determine the actual color of the healthy skin. Four major steps which are involved in melanogenesis process, they are (1) the development of melanocyte precursor cells (melanoblasts) and their migration from the neural crest to peripheral sites; (2) differentiation of melanoblasts into melanocytes; (3) survival and proliferation of melanocytes; and (4) formation of melanosomes and production of melanin [8]. All the four steps are important for normal melanin biosynthesis, any disturbance in the melanin pathway results in either hypopigmentation (example albinism and vitiligo) or hyperpigmentation of skin (for example, Addison’s disease and melasma).

Etiology of Vitiligo

Although vitiligo is extensively studied in the past five decades, its etiology is still unclear. 13 prevailing theories of vitiligo (as shown in the Fig. 1) have been reviewed by Speeckaert *et al.* [9]; however, none of these hypotheses explain the entire spectrum of the vitiligo disease.

Diagnosis of vitiligo

Wood’s light has been used to diagnose the vitiligo in the patients having skin type I and II [10].

TREATMENT OF VITILIGO

Many modalities have been used and continue to be used for the treatment (as shown in Fig. 2).

In spite of different treatment modalities, it is often troublesome and frustrating both for the patients as well as the physician [10]. To date, no Food and Drug Administration approved medical treatments for vitiligo was available [11]. In the present review, we highlight the role of herbal medicine in vitiligo treatment. In the treatment of vitiligo by oral use of *Psoralea corylifolia*/*Ammi majus* plant extracts particularly when combined with sun exposure, was known in ancient India, China, Egypt, and Japan [12]. El Mofty [13] was pioneer in Egypt for vitiligo treatment who used the crystallized active components of *A. majus* mainly 8-methoxypsoralen, both alone and in combination with exposure to sunlight. Later a number of natural psoralens were reported in certain plant families such as Umbelliferae (Parsley, Parsnip, and Celery), Rutaceae (Bergamot fruits, Gas plant, Cloves, and Citrus fruits), and Moraceae (Figs). 13 herbs (as shown in the Table 1) used in the treatment of vitiligo have phototoxic property, which have been used either alone or in combination with sunlight/ultraviolet light (UV).

In addition to these 21 terrestrial plants in Peninsular Malaysia have been reported for phototoxic activity [34]. Another 13 herbs used in the treatment of vitiligo have known to induce melanocyte proliferation, migration and, in turn, stimulant melanogenesis process (as shown in Table 1). In addition to these three herbs have been reported for melanogenic activity [35] two herbs, namely *P. corylifolia* L and *Tribulus terrestris* L reported to have both phototoxic and induce melanocyte proliferation/migration properties. Whereas three herbs such as

Cnidium officinale, *Eclipta alba* L, and *Eclipta prostrata* L reported to have both phototoxic and immunomodulatory properties. *Angelica sinensis*, only herb reported to have phototoxic, induce melanocyte proliferation/migration, and immunomodulatory properties (as shown in Table 1).

Apart from individual herbs, certain herbal products have been reported for vitiligo treatment includes

1. Anti-vitiligo™ - An herbal formulation from True Herbals, Lahore, Pakistan and the main herbal ingredients are *Berberis vulgaris* L., *Cocos nucifera* L., *Nigella sativa* L, and *P. corylifolia* L [1].
2. Callumae - a product, which contains three herbs such as *Ammi visnaga* L., *Ginkgo biloba*, and *P. kurroa* Royle Ex Benth [18].
3. Herbo-mineral capsule (ALG-06), which contains four herbs, namely *Azadirachta indica* A Juss, *P. corylifolia* L., *Punica granatum* L, and *Trigonella foenum-graecum* L [36].
4. Kakodumbaradi thaila - An herbal formulation which contains four herbs such as *Atylosia trinervia* (DC.) Gamble, *Eclipta prostrata* L., *Ficus hispida* Linn, and *Sesamum indicum* L [37].
5. Kalawalla® - An herbal formulation from American Lifestyle, New York, USA, and the main herbal ingredients are *Polypodium leucotomos*, which has been proven to have immune-modulatory activity [1].
6. Tolenorm™ - a product, which contains five herbs such as *Cocos nucifera* L., *Indigofera tinctoria* Linn, *Piper longum* Linn, *P. corylifolia* L, and *Wrightia tinctoria* R.Br [38]
7. Vitilo® lotion, which contains eight herbs such as *Acorus calamus* L., *A. indica* A Juss, *Curcuma amada* Roxb, *Curcuma longa* L., *Pongamia glabra* L., *P. corylifolia* L., *Pterocarpus santalinum* L, and *Rubia cordifolia* L [39].
8. Vitilax - An herbal formulation, which contains 10 herbs, namely *A. sinensis* Oliv, *Astragalus membranaceus* Fisch, *Atractylodes japonica* Koidz, *Cassia occidentalis* L., *Cnidium officinale*, *Curcuma longa* L., *Cuscuta japonica* Choisy, *Paeonia lactiflora* Pall, *Salvia miltiorrhiza*, and *Tribulus terrestris* L [18].

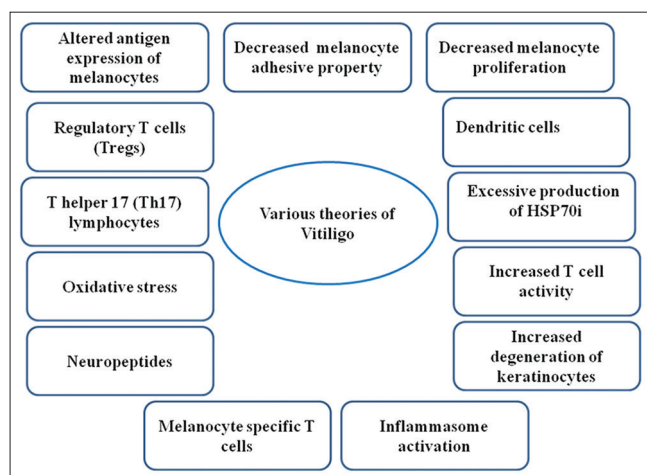


Fig. 1: Represents various theories of Vitiligo

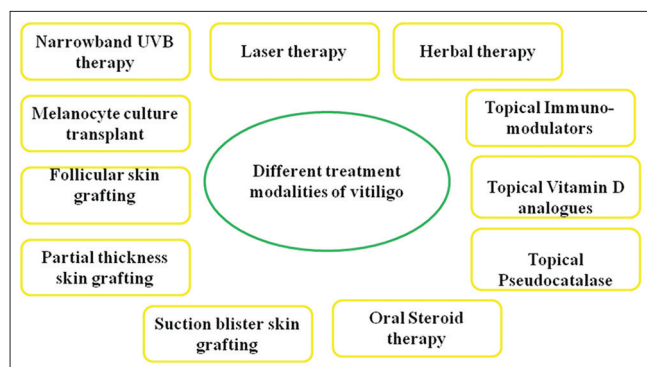


Fig. 2: Represents different treatment modalities of vitiligo

Six trials investigated the use of herbs in the treatment of vitiligo has been discussed by Szczurko and Boon [14]. Four of these clinical trials utilized plants (such as *P. kurroa*, *Ammi visnaga*, and two *P. leucotomos*) all were given orally in conjunction with (UVA or UVB) phototherapy; one clinical trial the use of oral *Ginkgo biloba* (40 mg) alone and another one trial also use the extract of *Cucumis melo* alone, without any conjunction phototherapy. In a nutshell, no converging results have been drawn for these clinical trials [14]. Apart from these trials, one more pilot trial has been carried using *Ginkgo biloba* (60 mg) alone [40]. Chakraborty *et al.* [41] reported that *A. indica* A Juss (leaf glycoprotein) inhibits regulatory T cells in cancer, which may also utilize for vitiligo treatment (as this one of an herbal ingredient of Herbo-mineral capsule [ALG-06]). Recently, Zhu *et al.* [42] reported epigallocatechin-3-gallate (EGCG) from green tea has a new therapeutic agent for vitiligo.

MISCELLANEOUS

Table 2 provides a comprehensive summary of the patents pertaining to vitiligo treatment using both natural and synthetic products.

Pandey [60] reported a novel ayurvedic formulation (containing of seven herbs such as *Aegle marmelos*, *A. indica*, *E. alba*, *Ficus religiosa*, *Ocimum tenuiflorum*, *Phyllanthus emblica*, and *P. corylifolia*) for the treatment of vitiligo. Recently, *Abrus precatorius* (seeds), *A. majus* (seeds), and *Pterocarpus marsupium* (heartwood) have been used for the treatment of vitiligo [61-63] Mosensons *et al.* [64] reported that mutant heat shock protein (HSPi_{Q435A}) as a potent agent for treating vitiligo.

FUTURE PERSPECTIVES

In recent years efforts to discover and develop new vitiligo drugs have gained much attention among the researchers, as result of

Table 1: Herbs used for Vitiligo treatment

S. no	A) Herbs having photosensitizing/phototoxic property	Reference
1.	<i>A. visnaga</i>	Szczurko and Boon [14]
2.	<i>A. lancea</i>	Wat <i>et al.</i> [15]
3.	<i>A. japonica</i>	Bark <i>et al.</i> [16]
4.	<i>C. tinctorius</i>	Wat <i>et al.</i> [15]
5.	<i>F. carica</i>	Bark <i>et al.</i> [16]
6.	<i>F. hispida</i>	Srivastava [17]
7.	<i>Hypericum sp.</i>	Yoon <i>et al.</i> [18]
8.	<i>P. kurroa</i>	Szczurko and Boon [14]
9.	<i>P. tenuifolia</i>	Yoon <i>et al.</i> [18]
10.	<i>P. leucotomos</i>	Szczurko and Boon [14]
11.	<i>R. crispus</i>	Yoon <i>et al.</i> [18]
12.	<i>S. anacardium</i>	Srivastava [17]
13.	<i>X. strumarium</i>	Bark <i>et al.</i> [16]
	B) Herbs having melanocyte proliferation/migration stimulation property	Reference
14.	<i>A. dahuricae</i>	Zhang <i>et al.</i> [19]
15.	<i>A. membranaceus</i>	Yoon <i>et al.</i> [18]
16.	<i>C. occidentalis</i>	Babitha <i>et al.</i> [20]
17.	<i>C. chinensis</i>	Li <i>et al.</i> [21]
18.	<i>F. carthami</i>	Zhang <i>et al.</i> [19]
19.	<i>L. bicolor</i>	Yoon <i>et al.</i> [18]
20.	<i>L. lucidum</i>	Yoon <i>et al.</i> [18]
21.	<i>M. scurfpea</i>	Mou <i>et al.</i> [22]
22.	<i>P. nigrum</i>	Lin <i>et al.</i> [23]
23.	<i>P. corylifolia</i>	Liet <i>et al.</i> [21]
24.	<i>R. schlippenbachii</i>	Yoon <i>et al.</i> [18]
25.	<i>S. miltiorrhiza</i>	Chiang <i>et al.</i> [24]
26.	<i>T. terrestris</i>	Li <i>et al.</i> [21]
	C) Herbs having immunomodulatory property	Reference
26.	<i>C. pilosula</i>	Zhuang <i>et al.</i> [25]
27.	<i>C. melo</i>	Dhasarathan <i>et al.</i> [26]
28.	<i>G. biloba</i>	Parsad <i>et al.</i> [27]
29.	<i>N. sativa</i>	Paarakh [28]
30.	<i>P. vulgaris</i>	Yoon <i>et al.</i> [18]
	D) Herbs having both phototoxic and melanocyte proliferation/migration stimulation properties	Reference
31.	<i>P. corylifolia</i>	Khushboo <i>et al.</i> [29] and Li <i>et al.</i> [21]
32.	<i>T. terrestris</i>	Yoon <i>et al.</i> [18] and Li <i>et al.</i> [21]
	E) Herbs having both phototoxic and immunomodulatory properties	Reference
33.	<i>C. officinale</i>	Bark <i>et al.</i> [16] and Joseph de la Cruz <i>et al.</i> [30]
34.	<i>E. alba</i>	Wat <i>et al.</i> [15] and Jayathirtha and Mishra [31]
35.	<i>E. prostrata</i>	Wat <i>et al.</i> [15] and Karthikumar <i>et al.</i> [32]
	F) Herbs having phototoxic, melanocyte proliferation/migration stimulation and immunomodulatory properties	Reference
36.	<i>A. sinensis</i>	Yoon <i>et al.</i> [18]; Deng & Yang [33] and Zhuang <i>et al.</i> [25]

A. visnaga: *Ammi visnaga*, *A. lancea*: *Atractylodes lancea*, *A. japonica*: *Atractylodes japonica*, *C. tinctorius*: *Carthamus tinctorius*, *F. carica*: *Ficus carica*, *F. hispida*: *Ficus hispida*, *P. kurroa*: *Picrorhiza kurroa*, *P. tenuifolia*: *Polygala tenuifolia*, *P. leucotomos*: *Polypodium leucotomos*, *R. crispus*: *Rumex crispus*, *S. anacardium*: *Semecarpus anacardium*, *X. strumarium*: *Xanthium strumarium*, *A. dahuricae*: *Angelica dahuricae*, *A. membranaceus*: *Astragalus membranaceus*, *C. occidentalis*: *Cassia occidentalis*, *C. chinensis*: *Cuscuta chinensis*, *F. carthami*: *Flos carthami*, *L. bicolor*: *Lespedeza bicolor*, *L. lucidum*: *Ligustrum lucidum*, *M. scurfpea*: *Malytea scurfpea*, *P. nigrum*: *Piper nigrum*, *P. corylifolia*: *Psoralea corylifolia*, *R. schlippenbachii*: *Rhododendron schlippenbachii*, *S. miltiorrhiza*: *Salvia miltiorrhiza*, *T. terrestris*: *Tribulus terrestris*, *C. pilosula*: *Codonopsis pilosula*, *C. melo*: *Cucumis melo*, *G. biloba*: *Ginkgo biloba*, *N. sativa*: *Nigella sativa*, *P. vulgaris*: *Prunella vulgaris*, *P. corylifolia*: *Psoralea corylifolia*, *T. terrestris*: *Tribulus terrestris*, *C. officinale*: *Cnidium officinale*, *E. alba*: *Eclipta alba*, *E. prostrate*: *Eclipta prostrate*, *A. sinensis*: *Angelica sinensis*

the recognition of the worldwide importance of fighting vitiligo disease. Moreover, world vitiligo day has been observed on June 25 every year as a way to create global awareness. There is a high need to have public-private collaboration and long-term action plan to discover, develop, and deliver new drugs for vitiligo treatment. Recent understanding the multifactorial, multistep etiology of vitiligo, has identified many potential targets for new drugs. New promising targets may include Interleukin-17 (IL-17) inhibition, tumor necrosis factor- α inhibition, heat shock protein-70i (HSP70i) inhibition, keratinocyte turnover modulators, and regulatory T cells (Tregs) modulators. Time is our tough judge, and really no one wants to lose the golden opportunity to develop

new, safe, affordable, and effective vitiligo drugs from a natural source.

AUTHOR'S CONTRIBUTIONS

RN (first author), who wrote the manuscript and submitted the same as part of PDF programme. Intan (research supervisor), who had added value to it. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

Table 2: Patents pertaining to Vitiligo treatment

S.no	Patent (Country)	Year	Important claim	Reference
1.	United States (US) patent	2014	Preventing or treating vitiligo using <i>Pueraria</i> genus plant extract or puerarin as an active agent.	Kim <i>et al.</i> [43]
2.	United States (US) patent	2013	Treating vitiligo using <i>Stachytarpheta</i> species plant extract or its active constituent/s or its derivatives.	Ferreira [44]
3.	European patent (EP)	2007	Treating vitiligo using <i>Pimenta racemosa</i> extract along with <i>Cucumis melo</i> , <i>Citrus aurantifolia</i> , coenzyme Q10, and pyridoxine chlorhydrate	Paleo and Rojas [45]
4.	European patent (EP)	2014	Treating vitiligo using <i>Vigna unguiculata</i> seed extract.	Msika <i>et al</i> [46]
5.	European patent (EP)	2010	Treating vitiligo using <i>Lycium barbarum</i> (wolfberry) extract	Vidal <i>et al.</i> [47]
6.	United States (US) patent	2014	Treating vitiligo using nerve growth factor (NGF) of human/murine/recombinant origin along with other ingredients.	Liotta [48]
7.	United States (US) patent	2015	Treating vitiligo using fluoxetine	Shang <i>et al.</i> [49]
8.	United States (US) patent	2015	Treating vitiligo using rapamycin along with other ingredients.	Bacus [50]
9.	United States (US) patent	2015	Treating vitiligo using pentapeptides (example: YSSWY/YRSRK).	Hantash and Ubeid [51]
10.	United States (US) patent	2015	Treating vitiligo using rapamycin along with other ingredients, especially forskolin/colforsin (cAMP activator agent).	Bacus and Moran [52]
11.	United States (US) patent	2015	Treating vitiligo using compounds I {N2-3-aminosulfonyl-4-methylphenyl-5-fluoro-N4-[4-(prop-2ynyloxy)phenyl]-2,4-pyrimidinediamine} and II {5-fluoro-N2-(4-methyl-3-propionylaminosulfonylphenyl)-N4-[prop-2-ynyloxy)phenyl]-2,4-pyrimidinediamine}	Magilavy [53]
12.	Worldwide (WO) patent	2015	Treating vitiligo using aromatic-cationic peptides, especially D-Arg-2', 6'-Dmt-Lys-Phe-NH2.	Wilson [54]
13.	Korean patent (KR)	2011	Treating vitiligo using <i>Cassia occidentalis</i> extract.	Kim <i>et al.</i> [55]
14.	Korean patent (KR)	2011	Treating vitiligo using <i>Cassia alata</i> extract.	Kim <i>et al</i> [56]
15.	Korean patent (KR)	2015	Treating vitiligo using liquiritigenin (active compound isolated from <i>Glycyrrhizae radix</i> extract).	Ku <i>et al.</i> [57]
16.	United States (US) patent	1997	Treating vitiligo using glycosphingolipids and endothelin-like peptide (human placenta extract).	Bhadra <i>et al</i> [58]
17.	Chinese patent (CN)	2016	Treating vitiligo using herbal composition comprises of <i>Syzygium cumini</i> , <i>Thermopsis barbata</i> , <i>Ajuga lupulina</i> , <i>Primula sikkimensis</i> , and <i>Corydalis hendersonii</i> extract	Shao Peicai [59]

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