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

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Received: 21 April 2018, Revised and Accepted: 21 May 2018

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-alpha 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.

INTRODUCTION
Vitiligo is a pigmentation disorder, in which pigmentation cells (melanocytes) of skin are destroyed, which results in 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 (Buddist 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 Nollund 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 were 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 Herbs, 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 B. kurroa Royle Ex Bent [18].
3. Herbo-mineral capsule (ALG-06), which contains four herbs, namely Asadichakra indica A Juss, P. corylifolia L., Punica granatum L., and Trigonella foenum-graecum L [36].
4. Kalodumbaradhi 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. Kalavalla™ - An herbal formulation from American Lifestyle, New York, USA, and the main herbal ingredients are Polygodium leucotomos, which has been proven to have immune-modulatory activity [1].
6. Tokenorm™ - 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 Acors 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 Oth, Astragalus membranaceus Fisch, Atractyloides japonica Koehn, Cassia occidentalis L., Cnidium officinale, Curcuma longa L., Cuscuta japonica Choisy, Paeonia lactiflora PALL, Salvia miltiorrhiza, and Tribulus terrestris L [18].

Six trials investigated the use of herbs in the treatment of vitiligo has been discussed by Szcurko 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]. Chakraborthy 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 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]. Chakraborthy 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 has been discussed by Szczurko and Boon [14]).

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.    | A. visnaga                                       | Szczurko and Boon [14] |
| 2.    | A. lancea                                        | Wat et al. [15] |
| 3.    | A. japonica                                      | Bark et al. [16] |
| 4.    | C. tinctorius                                    | Wat et al. [15] |
| 5.    | F. carica                                        | Bark et al. [16] |
| 6.    | F. hispida                                       | Srivastava [17] |
| 7.    | Hypericum sp.                                    | Yoon et al. [18] |
| 8.    | P. kurroa                                        | Szczurko and Boon [14] |
| 9.    | P. tenuifolia                                    | Yoon et al. [19] |
| 10.   | P. leucotomos                                    | Szczurko and Boon [14] |
| 11.   | R. crispus                                       | Yoon et al. [18] |
| 12.   | S. anacardium                                    | Srivastava [17] |
| 13.   | X. strumarium                                    | Bark et al. [16] |
| 14.   | A. membranaceus                                  | Reference |
| 15.   | A. membranaceus                                  | Zhang et al. [19] |
| 16.   | C. officinale                                    | Babitha et al. [20] |
| 17.   | F. chinensis                                     | Li et al. [21] |
| 18.   | F. carthami                                      | Zhang et al. [19] |
| 19.   | L. bicolor                                       | Yoon et al. [18] |
| 20.   | L. lucidum                                       | Yoonet al. [18] |
| 21.   | M. scurfpea                                      | Mou et al. [22] |
| 22.   | P. nigrum                                        | Lin et al. [23] |
| 23.   | P. corylifolia                                   | Liet al. [21] |
| 24.   | R. schlippenbachii                               | Yoon et al. [18] |
| 25.   | S. miltiorrhiza                                  | Chiang et al. [24] |
| 26.   | T. terrestris                                    | Li et al. [21] |
| 27.   | C. pilosula                                      | Zhang et al. [25] |
| 28.   | C. melo                                          | Dhasarathan et al. [26] |
| 29.   | G. biloba                                        | Parsad et al. [27] |
| 30.   | N. sativa                                        | Pararak [28] |
| 31.   | P. vulgaris                                      | Yoon et al. [18] |

B) Herbs having melanocyte proliferation/migration stimulation property

| S. no | C) Herbs having immunomodulatory property |
|-------|------------------------------------------|
| 32.   | P. corylifolia                           | Reference |
| 33.   | T. terrestris                            | Khushboo et al. [29] and Li et al. [21] |
| 34.   | E. alba                                  | Yoon et al. [18] and Li et al. [21] |
| 35.   | E. prostrata                             | Reference |
| 36.   | A. sinensis                              | Yoon et al. [18]; Deng & Yang[33] and Zhuang et al.[25] |

D) Herbs having both phototoxic and melanocyte proliferation/migration stimulation properties

| S. no | D) Herbs having both phototoxic and melanocyte proliferation/migration stimulation and immunomodulatory properties |
|-------|-----------------------------------------------------------------------------------------------------------------|
| 37.   | P. corylifolia                                                                                                  |
| 38.   | T. terrestris                                                                                                   |
| 39.   | C. officinale                                                                                                   |
| 40.   | E. prostrata                                                                                                    |
| 41.   | A. 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-alpha 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 program. 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.
A stimulatory effect of treating vitiligo using glycosphingolipids and endothelin-like peptide. Kim Treating vitiligo using rapamycin along with other ingredients. United States (US) European Treating vitiligo using fluoxetine. United States (US) Patent (Country) Reference. Treating vitiligo using compounds comprising of Msika et al. [46]. Treating vitiligo using nerve growth factor (NGF) of human/murine/recombinant origin along with other ingredients. Lioyta et al. [48]. Treating vitiligo using cyclin-dependent kinase inhibitors. Wang et al. [49]. Treating vitiligo using herbal composition comprises of Perry and Anderson [50]. 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 *Pueraria* genus plant extract or puerarin as an active agent. | Kim et al. [43] |
| 2.   | United States (US) patent | 2013 | Treating vitiligo using *Stachybotrys* species plant extract or its active constituent(s) or its derivatives. | Ferreira [44] |
| 3.   | European patent (EP) | 2007 | Treating vitiligo using Pinus radiata extract along with *Cucumis melo*, *Citrus aurantifolia*, coenzyme Q10, and pyridoxine chloride. | Paley and Rojas [45] |
| 4.   | European patent (EP) | 2014 | Treating vitiligo using *Vigna unguiculata* seed extract. | Msika et al. [46] |
| 5.   | European patent (EP) | 2010 | Treating vitiligo using *Lycium barbarum* (wolfberry) extract. | Vidal et al. [47] |
| 6.   | United States (US) patent | 2014 | Treating vitiligo using nerve growth factor (NGF) of human/murine/recombinant origin along with other ingredients. | Lioyta et al. [48] |
| 7.   | United States (US) patent | 2015 | Treating vitiligo using fusoxetine. | Shang et al. [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/coforsin (cAMP activator agent). | Bacus and Moran [52] |
| 11.  | United States (US) patent | 2015 | Treating vitiligo using compounds I (N-[2-3-aminosulfonyl-4-methylphenyl]-5-fluoro-N-[prop-2-ynlyoxy]phenyl)-2,4-pyrimidinediamine} and II (5-fluoro-N-[4-methyl-3-propionylaminosulfonylphenyl]-N-[prop-2-ynlyoxy]phenyl)-2,4-pyrimidinediamine} and forskolin/coforsin (cAMP activator agent). | Maglavy [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 *Cassia occidentalis* extract. | Kim et al. [55] |
| 14.  | Korean patent (KR) | 2011 | Treating vitiligo using *Cassia alata* extract. | Kim et al. [56] |
| 15.  | Korean patent (KR) | 2015 | Treating vitiligo using liquiritigenin (active compound isolated from *Glycyrrhiza radix* extract). | Ku et al. [57] |
| 16.  | United States (US) patent | 1997 | Treating vitiligo using glycosphingolipids and endothelin-like peptide (human placenta extract). | Bhadra et al. [58] |
| 17.  | Chinese patent (CN) | 2016 | Treating vitiligo using herbal composition comprises of *Syzygium cumini*, *Thermopsis barbata*, *Ayuga lupalina*, *Primula sikkimensis*, and *Corydalis hendersonii* extract. | Shao Peical [59] |

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