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REVEIW ARTICLE

A REVIEW ON LEUCODERMA AND REPORTED HERBS FOR ITS TREATMENT

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Received 24 March 2012; Revised 20 April 2012; Accepted 24 April 2012, Available online 15 May 2012

ABSTRACT:
Leucoderma is an acquired cutaneous disorder of pigmentation, with an incidence of 1% to 2% worldwide. There are many hypotheses for the pathogenesis of leucoderma. Recent data provide strong evidence supporting an autoimmune pathogenesis of leucoderma. Leucoderma can have major effect on quality of life. Topical therapy is employed as first-line treatment in localized leucoderma. Plants have been the basis of many traditional medicines throughout the world for thousands of years and continue to provide new remedies to mankind. The recent resurgence of plant remedies resulted from several factors, such as effectiveness of plant medicines and lesser side effects compared with modern medicines. Psoralen containing plants have been used for centuries in popular medicine to treat leucoderma. Further advancement in treatments using different derivatives of psoralen molecules may result in decrease possibility of long-term side effects such as cutaneous malignancies. In this review we wish to present a detailed investigation on various herbs that can be used for the treatment of leucoderma.
Keywords: Leucoderma, melanin, psoralen, herbs, furanocoumarins

INTRODUCTION:

Leucoderma is the most common chronic depigmentation disorder or hypopigmentation disorder affecting 1-2% of the world population[1]. It includes the loss of functioning melanocytes which causes the appearance of white patches on the skin[2]. These white patches tend to become progressive with time[3]. Any location on the body can be affected and the people with leucoderma have white patches in many areas of the body[4]. The disorder affects all the races and both the sexes equally; however, it is more noticeable in people with dark skin[5].

Although leucoderma is usually not harmful medically and causes no physically pain, its emotional and psychological effects can be devastating[6]. Infact, in India, those with the disease, especially women, are sometimes discriminated against in marriage. Developing leucoderma after marriage can be ground for divorce. Regardless of person's race and culture, white patches of leucoderma can affect emotional and psychological well-being and self-esteem. People with leucoderma can experience emotional stress, particularly if the condition develops on the visible areas of the body (such as face, hands, arms and feet) or on the genitals. Adolescents, who are particularly concerned about their appearance, can be devastated by widespread leucoderma. Some people who have leucoderma feel embarrassed, ashamed, depressed or worried about how others will react[7].

Leucoderma can be classified into two types[8,9]:

1).Bilateral (or Generalized):

Bilateral or Generalized Leucoderma can begin at any age and tends to progress intermittently over the life of the patient. It produces depigmentation which is remarkably symmytrical in distribution. A patch on the right side of the body is matched by a patch in a similar location on the left side of the body. The entire body can depigment although it rarely does so.

2).Unilateral (or Segmental):

Unilateral or Segmental Leucoderma commonly begins in childrens and young adults and progresses for a limited period, usually 1-2 years, and then remains static for the rest of the life of the individual. It affects just one side of the body contrast to Bilateral Leucoderma, the distribution is asymmetrical on the skin.

MELANIN PIGMENT:

Melanins are polymorphous and multifunctional biopolymers. It includes eumelanin, pheomelanin, neuromelanin and mixed melanin pigment (shown in figure 1)[10].

Intact mature melanosomes pass from basal melanocytes into keratinocytes and their lysosomal compartment to become melanin dust in the upper nonviable layers of the skin[11]. Melanin is synthesized by melanocytes within melanosomes that are transferred into the surrounding keratinocytes[12]. The keratinocytes transport the melanin and melanosomes from the basal layer of the epidermis to the stratum corneum where they are desquamated into the environment (as shown in figure. 2)[13].

 ISSN: 2250-1177 CODEN: JDDTAO

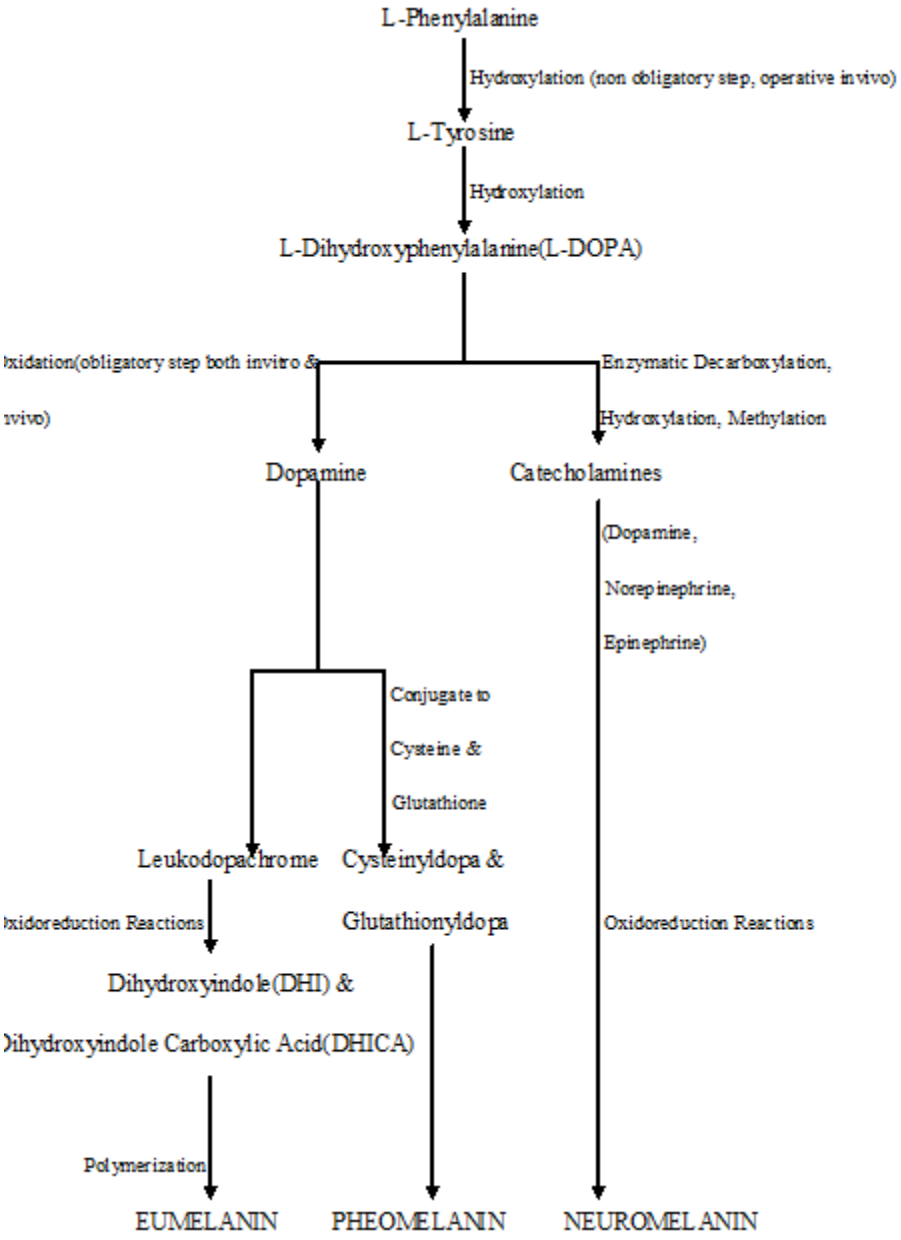

Figure 1: Biosynthesis of Melanin Pigment[10]

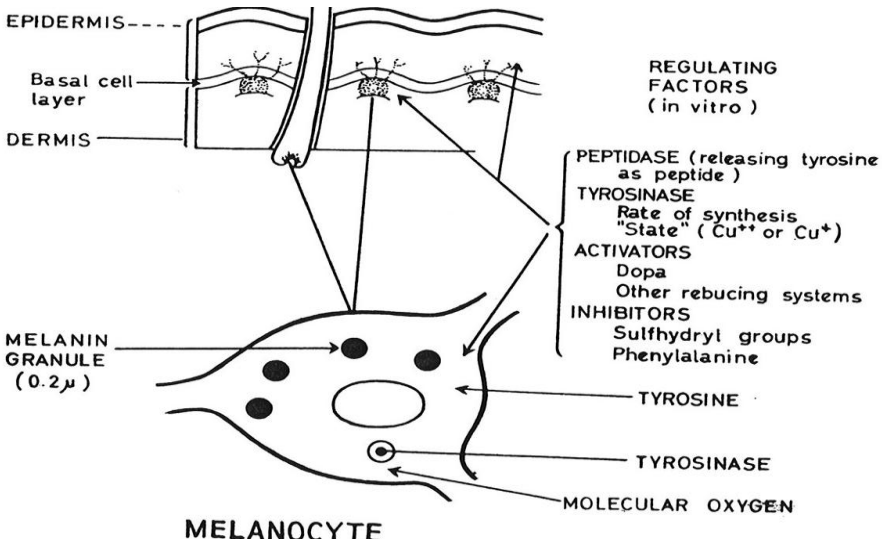

Figure 2: Factors Regulating Mammalian Melanogenesis[13]

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PATHOPHYSIOLOGY OF LEUCODERMA:

There are two basic mechanisms whereby the skin can become white[14]. Some disorders inhibit or retard the production of melanin formation and the skin develops hypopigmentation[15]. Such disorders include, among many others, oculocutaneous albinism, pityriasis alba, tinea vesicolor and nevus depigmentosus[16]. In these disorders, melanocytes are present in normal numbers in the epidermis but produce less than normal amounts of melanin. Typically the skin exhibits mild to marked hypopigmentation.

In contrast, other types of leucoderma are characterized by the absence of melanocytes and therefore, complete absence of melanin. Such disorders include piebaldism, the leucoderma of lupus erythematosus and other scarring disorders and vitiligo. These types of leucoderma typically are totally depigmented. Vitiligo and lupus cause a destruction of melanocytes during postnatal life. Piebaldism affects the migration of melanocytes during embryogenesis and the infant is born with depigmenattion of the hair and skin. The etiology of leucoderma is poorly understood. Various factors (stress, trauma, exposure to sunlight, infections, malignancies, neural abnormalities, melatonin, receptor dysfunction, impaired melanocyte migration, some drugs, endocrine disease and cytotoxic compounds) have been implicated in the development of leucoderma. Despite these various factors the exact cause of leucoderma remains unclear. Many theories[17] (biochemical theory, cytotoxic theory, oxidant-antioxidant theory, neural theory, viral theory, autoimmune theory, self destruct theory, growth factor theory and convergence theory) have been proposed to explain this disorder along with factors (as shown in table 1).

Table 1: Research Work on Leucoderma Skin

S.NO	STUDY ON VITILIGO SKIN SHOWS	REFERNCE
1	Decreased Level of VIT1 mRNA Elevated Level of MSH-6	18
2	Increased Area of Rough Endoplasmic Reticulum	19
3	Increased Level of T Cells Increased Level of Macrophages	20
4	Presence of High Frequency of Skin-homing Melanocyte-specific Cytotoxic T Lymphocytes(CTL's)	21
5	Increased Level of Th 17 Cells Increased Level of Activated Dendritic Cells	22

TREATMENT AVAILABLE FOR LEUCODERMA:

In general topical monotherapy is indicated for mild to moderate vitiligo[23,24]. Current treatment options for vitiligo include medical, surgical and additional treatments[25,26]. Medical treatment targets the immune system and helps to arrest the spread of depigmentation[27,28]. In cases of stable vitiligo, repigmentation can be achieved by dermatosurgical techniques and additional includes use of cosmetics[29,30]. Both surgical and medical treatment have their own limitations. Additional can only cover the patch and can be used along with surgical and medical treatments[31].

A).Medical Therapies

1).Topical Steroid Therapy: Topical steroids are useful for the treatment of localized leucoderma. Marked or almost complete repigmentation can be obtained with potent corticosteroids (betamethasone, valerate, triamcinolone) and very potent corticosteroids (clobetasol, fluticasone propionate).

2).Psoralen Photochemotherapy

a).Topical Psoralen Photochemotherapy: Topical PUVA (Psoralen Plus UltraViolet light A) includes lower cumulative UVA doses than oral PUVA and lack of ocular and systemic toxicity. Low concentrations of psoralens should be used. The patient should be exposed to UVA approximately 20 to 30 minutes after application of the topical preparation. Following treatment the area is washed, a broad-spectrum sunscreen is applied and excessive sun exposure is avoided for at least 24 hours.

b).Oral Psoralen Photochemotherapy: Oral PUVA involves the administration of psoralens orally followed by exposure to long-wavelength UVA irradiation.

3).Depigmentation: Depigmentation is a more drastic form of treatment, when leucoderma is extensive i.e. leucoderma universalis. Depigmentation involves fading the rest of the skin on the body to match the already white areas by using permanent melanocytotoxic agents such as Monobenzyl ester of hydroquinone cream (Benzoquin), 4-methoxyphenol (4-MP).

B).Surgical Therapies

1).Autologous Skin Grafts: In this technique grafts are implanted into perforations prepared at the recipient sites. Pigment spread leading to repigmentation can be stimulated by phototherapies.

2).Skin Grafts Using Blisters: In this technique blisters can be induced by different ways such as vacuum or liquid nitrogen. The mechanical split occurs at the dermoepidermal junction. The recipient site is prepared by dermabrasion. The graft is applied and secured on the recipient site.

3)Micropigmentation (Tattooing): In this technique permanent dermal micropigmentation is done by using a nonallergic iron oxide pigment to camouflage recalcitrant areas of leucoderma.

4).Autologous Melanocyte Transplant: In this technique noncultured keratinocyte-melanocyte suspensions obtained from a shave biopsy of the buttock or full-thickness biopsy

of the scalp and Melanocytes obtained from the hair follicles and interfollicular epidermis and keratinocytes are placed into a suspension for direct application to the recipient site without expansion in culture.

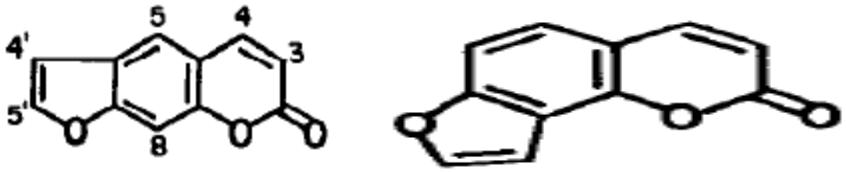
C).Additional Therapies

1).Sunscreen: Leucodermic skin is more susceptible to sunburn and long term photodamage. To prevent sun-induced darkening of the surrounding normal skin, broad spectrum high protection factor sunscreens (SPF_{15-30}) which provide protection from UVB and UVA light should be used.

2).Cosmetic: Camouflage is often used to cover affected areas. This may be practical for patients that have minimal disease or segmental disease.

NATURAL FURANOCOUMARINS AS TREATMENT FOR LEUCODERMA:

Psoralens belong to a group of heterocyclic compounds, the furanocoumarins, which are found in four or five major plant families. The umbelliferae and rutacae are the largest and most important of these; the leguminosae and moraceae include few but widely distributed species. Chemical structures of Psoralen and Isopsoralen are described (as shown in the figure. 3)[59]



Psoralen Isopsoralen

Figure 3: Chemical structures of Psoralen and Isopsoralen[59]

Many familiar edible plants as celery, figs, caraway, lemon, etc., contain psoralens. As such, psoralens are components, in normal diet, and they may even play a role in the physiology and biochemistry of normal human skin. It is of interest to mention that psoralens are found in many herbal remedies that have been employed for centuries[32,33]. Furanocoumarins are synthesized when the furan ring is built on a suitably substituted coumarin derivative. A furan ring can be condensed with a coumarin molecule in 12 different ways and each of the resulting compounds can become the parent of a family of psoralen-like derivatives. Only those with a linear tricyclic structure resembling that of psoralen are active, potent photosensitizers. Those with a non-linear structure (angular nodes) like that of iso-psoralen and iso-pseudo-psoralen are inactive[34,35]. The mechanism of repigmentation of leucoderma patches under psoralen therapy cannot be clearly defined in the light of the available knowledge of the cause of leucoderma. However, it may be justifiable to suggest that one or more of the following mechanisms may operate in the process of repigmentation of leucoderma[36,37]:

1). Through the increased tolerance to sun, and ultraviolet rays psoralens permit much longer solar or ultraviolet light irradiation and thus allow stronger stimulation to the melanocytes.

2). Dopa positive melanocytes have been claimed to be present in the so-called relative leucoderma. Repigmentation may occur in areas having melanocytes that still retain, although slightly, dopa positively but not in areas having no dopa positive melanocytes. Psoralens may bring about stimulation of these weak dopa positive melanocytes to be actively engaged in melanogenesis.

3). Psoralens may induce migration of active melanocytes from the surrounding normal epidermis or hair melanocytes, lead to colonization of the depigmented areas by the melanocytes of the pigmented hair bulb.

4). Psoralens may correct the ultrastructural abnormalities of the leucoderma melanocytes.

Table 2: Reported Herbs that are claimed to be used in the condition of Leucoderma

S.No	Biological Name of The Plant	Family	Common Name	Active Chemical Constituent	Ref
1	*Albizzia lebbek*	Black ebony	Fabaceae	Saponins, stigmastadienone	58
2	*Aloe barbadensis*	Aloes	Aloeaceae	Antraquinone glycosides	55
3	*Alstonia scholaris*	Indian devil tree	Apocyanaceae	Hallucinogenic indole alkaloids	55
4	*Althaea officinalis*	Marshmallow	Malvaceae	Altheacoumarin glycosides	42
5	*Ammi majus*	Ammi	Umbelliferae	Furanocoumarins	41,52
6	*Ammi visnaga*	Khella	Umbelliferae	Furanocoumarins	52
7	*Angelica sinensis*	Dong quai	Umbelliferae	Ferulic acid	57
8	*Apium graveolens*	Celery	Umbelliferae	Furanocoumarins	43
9	*Arisaema amurense*	Tian nan xing	Araceae	Diacylglycerlgalactoside	57
10	*Aristolochia bracteata*	Bracteated birthwort	Aristolochiaceae	Anthraquinones	56
11	*Astragalus membranaceus*	Astragalus	Fabaceae	Saponins, flavonoids	57
12	*Atractylodes japonica*	Japanese	Compositae	Patchoulene	57

		atractylodes			
13	*Azadirachta indica*	Neem	Meliaceae	Azadirachtinol, nimbosterol	51,52
14	*Bambusa arundinaceae*	Bamboo	Bambusaceae	Polyuronides, pentosans	53
15	*Bituminaria bituminosa*	Arabian pea	Fabaceae	Furanocoumarins	44
16	*Carthamus tinctorius*	Safflower	Compositae	Phenols, flavonoids	57
17	*Cassia angustifolia*	Senna leaf	Leguminosae	Anthraquinone glycosides	42
18	*Cassia occidentalis*	Coffee senna	Caesalpiniaceae	Anthraquinone glycosides	57
19	*Citrullus colocynthis*	Wild gourd	Cucurbitaceae	Saponins, phytosterol glycosides, alkaloids	58
20	*Citrus limonia*	Rangpur	Rutaceae	Furanocoumarins	43
21	*Cnidium officinale*	Chunkung	Umbelliferae	Butlyidenephthalide	57
22	*Codonopisis pilosula*	Dang shen	Campanulaceae	Hesperidin, alpha spinosterol, beta spinosterol	57
23	*Cuscuta chinensis*	Chinese dodder	Fabaceae	Quercetin, kaemferol, hyperoside	57
24	*Dalbergia sissoo*	Dalbergia	Fabaceae	Isoflavones, stigmasterols	53,58
25	*Daucus carota*	Wild carrot	Umbelliferae	Furanocoumarins	38
26	*Diplotaenia damavandica*	Kozal	Umbelliferae	Furanocoumarins	43
27	*Eclipta alba*	Bhringraj	Asteraceae	Steroids, flavonoids	43
28	*Elaeagnus bockii*	----------	Elaegnaceae	Furanocoumarins	43
29	*Ficus carica*	Common fig	Moraceae	Furanocoumarins	45
30	*Foeniculum vulgare*	Fennel	Umbelliferae	Furanocoumarins	39
31	*Gentiana scabra*	Chinese gentian	Gentianaceae	Xanthones, picroside	57
32	*Ginko biloba*	Gingko	Ginkgoaceae	Furanocoumarins	46,52
33	*Glycyrrhiza glabra*	Liquorice	Fabaceae	Glycyrrhitinic acid, flavonoids	42
34	*Helectoris isora*	Indian screw fruit	Sterculiaceae	Sitosterols, flavonoids	56
35	*Lawsonia inermis*	Henna	Lythraceae	Xanthones, glycosides	53
36	*Liquidambar formosana*	Formosan gum	Hamamelidaceae	Beta-sitasterol, oleanolic acid	56
37	*Lyceum Chinese*	Wolfberry	Solanaceae	Beta-sitosterol,ferulic acid	56
38	*Malva sylvastris*	Tall mallow	Malvaceae	Flavonoids, carotenoids, phenols	42
39	*Melia azadirach*	Kattu vembu	Meliaceae	Vanillic acid, melianol	55
40	*Milk thistle*	Marian thistle	Asteraceae	Flavanolignan, triterpene glycosides	52
41	*Mimosa pudica*	Lajwanti	Fabaceae	Alkaloids, tannins	53
42	*Murraya koenigii*	Curry leaf tree	Rutaceae	Terpines	53
43	*Nigella sativa*	Kalonji	Ranunculaceae	Glucoside melanthin metarbin	52
44	*Ocimum sanctum*	Tulsi	Lamiaceae	Eugenol, oleanolic acid	53
45	*Operculina turpenthum*	Trivruth	Convolvulaceae	Coumarin, beta sitosterol	42
46	*Paeonia lactiflora*	Garden peony	Ranunculaceae	Monoterpene glycoside, albiflorin	57
47	*Pastinaca sativa*	Parsnip	Umbelliferae	Furanocoumarins	43
48	*Petroselinum crispum*	Parsley	Umbelliferae	Furanocoumarins	41
49	*Picorrhiza kurroa*	Kutki	Scrophulariaceae	Picrosides	47,52, 57
50	*Plumbago indica*	Fire plant	Plumbaginaceae	Plumbagin, vanillic acid, beta sitosterol	50
51	*Polygala tenuifolia*	Chinese senega	Polygalaceae	Presengenin, xanthones	57
52	*Polypodium leucotomos*	Golden polypody	Polypodiaceae	Furanocoumarins	48
53	*Prunella vulgaris*	Selfheal	Lamiaceae	Phenols, tannins, saponins	57
54	*Prunus persica*	Peach	Rosaceae	Glycerides, sterols	57
55	*Psoralea corylifolia*	Babchi	Fabaceae	Furanocoumarins	40
56	*Ruta graveolens*	Herb of grace	Rutaceae	Furanocoumarins	49
57	*Semecarpus anacardium*	Bhilwa	Anacardiaceae	Sterols, flavonoids, glycosides	50,52
58	*Solanum nigrum*	European black nightshade	Solanaceae	Phenols, anthocyanidins	57
59	*Swertia chirata*	Indian gentian	Gentianaceae	Xanthones, oleanolic acid	57
60	*Tecomella undulata*	Roheda	Bignoniaceae	Stigmasterol	54

 ISSN: 2250-1177 CODEN: JDDTAO

CONCLUSION:

Furanocoumarins are biologically active natural compounds found mainly in plants belonging to the Umbelliferae, Rutaceae, Apiaceae, Asteraceae, Fabaceae, Oleaceae, Moraceae, Thymeleaceae Families. Furanocoumarins forms monofunctional adducts which would less likely promote cutaneous malignancies as compared to bifunctional adduct. The application of psoralens and different derivatives of psoralens with potentially fewer acute side effects has been one of the most recent advancements in the treatment of leucoderma. Psoralen containing plants have been used for centuries in popular medicine to treat leucoderma, a skin disease characterized by lack of pigmentation. Further advancement in treatments using different derivatives of psoralen molecules should strive to decrease the possibility of long term side effects such as cutaneous malignancies.

ACKNOWLEGDEMENTS:

Authors wish to acknowledge Drug Information Centre of CT Institute of Pharmaceutical Sciences, Shahpur Campus, Jalandhar, Punjab, India, for providing literature facilities during the preparation of this review article.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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 ISSN: 2250-1177 CODEN: JDDTAO