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Review Article

Unconventional Treatments for Vitiligo: Are They (Un) Satisfactory?

Serena Gianfaldoni[1*], Georgi Tchernev[2,3], Jacopo Lotti[4], Uwe Wollina[5], Francesca Satolli[6], Miriam Rovesti[6], Katlein França[7], Torello Lotti[1]

[1]University G. Marconi of Rome, Dermatology and Venereology, Rome 00192, Italy; [2]Department of Dermatology, Venereology and Dermatologic Surgery, Medical Institute of Ministry of Interior (MVR-Sofia), General Skobelev 79, 1606 Sofia, Bulgaria; [3]Onkoderma - Policlinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606, Sofia, Bulgaria; [4]University G. Marconi of Rome, Dept. of Nuclear, Subnuclear and Radiation Physics, Via Plinio 44, Rome 00193, Italy; [5]Städtisches Klinikum Dresden, Department of Dermatology and Allergology, 01067 Dresden, Germany; [6]Department of Dermatology, University of Parma, Via Gramsci 14, Parma, Parma 43126, Italy; [7]University of Miami School of Medicine, 1400 NW 10th Avenue, Miami, Florida 33136-1015, United States;

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***Correspondence:** Serena Gianfaldoni. University G. Marconi of Rome, Dermatology and Venereology, Rome 00192. E-mail: serena.gianfaldoni@gmail.com

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Abstract

The authors show a brief overview of the vitiligo's unconventional therapies. A part for well-documented effectiveness of L-phenylalanine, PGE2 and antioxidant agents in the treatment of vitiligo, for the other therapeutical approaches more investigations are needed.

Introduction

Despite the numerous therapies of proven efficacy available for vitiligo treatment, in the last decades new unconventional drugs had been introduced for the correction of cutaneous disease.

The authors show a brief overview of the vitiligo's unconventional therapies.

Alpha Lipoic Acid

Alpha lipoic acid is an organosulfur compound with important antioxidant properties. It is commonly found in many dietary products, such as tea, wine, beer, vegetable (e.g. broccoli, spinach), fruit and soy products [1]. Moreover, Alpha lipoic acid is found in yeast, kidney and liver. Recently, it is produced in laboratory for medical purpose. Alpha-lipoic acid is used for the treatment of different disorders, such as diabetes, HIV/AIDS, cancer, liver and eye diseases, and others. It is generally administrated orally at various dosages, ranging from300 to 1,800 mg daily.

Due to its antioxidant properties, recently, alpha-lipoic acid has been proposed in the treatment of vitiligo, to prevent the destruction of melanocytes by

free radicals. It is generally used as adjuvant therapy in association to more conventional treatments (e.g. corticosteroids, phototherapy). Recent data underline its safe profile and effectiveness in terms of acceleration of cutaneous repigmentation in vitiligo patients [2][3).

Flavonoids

Flavonoids (also known as Bioflavonois) are polyphenolic compounds, with antioxidants, anti-inflammatory and anti-microbial properties. They are widely found in plants and in many dietary products (e.g. wine, beer, tea, onions, blueberries, bananas, all citrus fruits, dark chocolate and others). Because their antioxidant action, flavonoids have been proposed as supplements in the treatment of vitiligo patients [4].

A particular mention is due to quercetin, a member of flavonoids, which has been evaluated, both in vitro and in vivo, for the treatment of the pigmentary disease [1]. Different studies underline how quercetin is able to protect keratinocytes and melanocytes by the oxidative damage, suggesting its effectiveness as adjuvant oral therapy in vitiliginous patients [5][6). Moreover, it has been observed how the topical application of quercetin may prevent ultraviolet radiation cellular damage [7].

Fluorouracil

Fluorouracil (also known as 5-fluorouracil or 5-FU) is a pyrimidine analog of the antimetabolites family, used in oncology for about 40 years, because of its anticancer properties.

By some decades, it has been also used by dermatologist for the topical treatment of vitiligo [8]. The drug has been observed to be safe and effective in inducing repigmentation. Better results have been achieved in patients, who previously underwent to an epidermal abrasion (e.g. classical dermabrasion, cutaneous laser ablation), of skin lesions [9][10].

Recently, Capebetacina has been also proposed for vitiligo treatment.

Capecitabine is an oral prodrug of 5-FU, used in the treatment of metastatic colon and breast cancers. It has been observed how its use cause cutaneous hyperpigmentation [11][12]. At the moment, more studies have to be conducted to evaluate the potential use of the drug in the treatment of vitiligo.

Glutathione (GSH)

Glutathione is a well-known antioxidant able to protect cellular components by oxidative stress damage. Recently, some studies underline how its oral use as supplement may be useful in preventing cells photo- damage [13][14]. Unfortunately, more data are needed for its potential use in the treatment of vitiligo.

L-DOPA

L-DOPA is an amino acid, normally produced from the amino acid L-tyrosine by the enzyme tyrosine hydroxylase. It is the precursor of some neurotransmitters (dopamine, noradrenaline and adrenaline), and of the melanin.

In medicine, it is used in the clinical treatment of Parkinson's disease and dopamine-responsive dystonia.

In seventies, by the description of neuromelanin loss from the substantia nigra in Parkinson’s patients, some authors hypotezed its potential use in vitiligo treatment. Unfortunately, only few cases reported its efficacy in vitiligo. First was Grainger who described the beard repigmentation in a Parkinson patient treated with L-DOPA [15]. Successively, Goolamali repoted the repigmentation of vitiliginous patients treated with levoDOPA plus UV lights [16]. In the same period, Woolfson et al treated 16 patients, affected by vitiligo, with a topical preparation of L-DOPA 10% or 20% in a fatty alcohol/propylene glycol base. The results were unsatisfactory [17]. Since then, while no other studies confirmed the utility of the drug in therapy of the pigmentary disease, different studies underlined the role of L-DOPA in inducing vitiligo [18].

Levamisole

Levamisole is an antihelminthic agent, which has been observed to have important immunoregulatory properties [19]. For this property, the drug has been used in the treatment of vitiligo. Few studies demonstrated how Levamisole may be considered as a valid and therapeutic tool, able to arrest the course of the disease and to induce repigmentation [20]. Even if the drug may be uses alone, the association with conventional therapies (e.g. corticosteroids) seems to be more effective [21].

L-Phenylalanine

L-Phenylalanine is an essential α-amino acid, which is used to biochemically form proteins, coded for by DNA. L-Phenylalanine is the natural precursor for tyrosine, which is further converted into cathecholamines (dopamine, noradrenaline and adrenaline) or in the cutaneous pigment melanin. L-Phenylalanine may be introduced with dietary products (e.g. eggs, chicken, liver, beef, milk, cheese, soybeans) or nutritional supplements (e.g. aspartame), which are industrially produced by use of Escherichia coli, a bacterium able to produce large amount of phenylalanine and others amino acids [22]. The amino acid is usually safe, except for people affected by phenylketonuria, a rare genetic disorder charaterized by the inability to metabolize phenylalanine because of the lack of the enzime phenylalanine hydroxylase.

L-Phenylalanine is widely used in medicine for the treatment of different diseases (e.g. depression, attention deficit-hyperactivity disorder, Parkinson's disease, chronic pain, osteoarthritis, rheumatoid arthritis).

Because it is a precursor of melanin [23], dermatologists use the amino acids as a therapeutic tool for vitiligo treatments.

L-Phenylalanine may be administrated both orally (50 – 100 mg/kg of body weight) or topically, and provide better results if combined with UV exposure. The oral administration of phenylalanine (50 – 100 mg/kg of body weight) combined with UVA exposure (also known as PAUVA) is well-known therapy for vitiligo since long time. It is generally well-tolerate and provide quite good results in term of repigmentation rate [24]. Recently, a variant of the classic PAUVA has been experimented. It consists in the oral intake of khellin encapsulated in L-phenylalanin stabilized phosphatidylcholine liposomes, in combination with ultraviolet light therapy (both UVA and UVB). The treatment (also known as KPLUV) has been shown to be effective and safe for the treatment of vitiligo patients [25].

Different therapeutic options are based on the oral and topical application of L-Phenilalanin plus ultraviolet radiation, both natural (sol-therapy) or artificial (UVA or nb-UVB) [26]; and on the oral and topical L- phenylalanine, associated to local clobetasol propionate, and UVA/sunlight [27]. Both the protocols have provided good results in term of repigmentation.

On the other hand, there is the possibility to treat vitiliginous patches with topical L-phenylalanine (cream with L-Phenylalanine 10%), alone, or better, in association with phototherapy/target phototherapy [28]. Finally a mention is due to the introduction of an innovative combined treatment, which is based on the topical application of a cream composed by phenylalanine, cucumis melo extract, and acetyl cysteine, followed by the irradiation with target nb-UVB. The therapeutic protocol has been seen to be effective and safe for vitiligo treatment [29].

Melagenine

Melagenine is an alcohol extract of human placenta, which has been proposed for the topical treatment of vitiligo patients [30]. Even if the exact mechanism of action is still unclear, it seems to stimulate the melanoblast and melanocyte proliferation and the melanogenesis [31]. Classically, it is applied twice a day, alone or in association with ultraviolet radiation. Interestingly, a pilot study underlines the effectiveness of topical melagenine in combination with 20 minutes of infrared exposure twice daily, in the repigmentation of scalp vitiligo [32]. Recently a new formulation of melagenine (Melagenina plus) has been formulated; it consists in a alcohol human placental extract with calcium. The drug is applied once a day, and seems to be effective in stimulating the repigmentation [33]. No side effects had been described in the use of both Melagenine and Melagenine plus. Unfortunately, no recent data are available on the use of melagenine in vitiligo.

Metals

Zinc is a metal, which has many vital functions in human, such as regulation of RNA and DNA metabolism, signal transduction, gene expression, cofactor for enzymes and antioxidant defense system, and cellular apoptosis [34]. It can be assumed with animal-sourced food (e.g. meat, fish, shellfish, fowl, eggs, dairy), food plants (sesame, poppy, mustard, beans, nuts, grains, pumpkin seeds, sunflower seeds and others) and dietary supplements.

Recently, it has been proposed for vitiligo treatment, in association to conventional therapies, such as topical corticosteroid [35]. Unfortunately, the few data, which are today available, don’t support its efficacy in the treatment of the pigmentary disorder.

Minoxidil

Topical Minoxidil (2% or 5%) is a vasodilator drug, which is used topically to treat different forms of hair loss (e.g. male androgenetic alopecia, female

androgenetic alopecia, alopecia areata and other) [36]. Even if exact mechanism of action is not well understood, it seems possible that, by widening blood vessels, Minoxidil allows more oxygen and nutientes to the hair follicles.

About its potential use in vitiligo treatment, only the study of Srinivas et al. reports its efficacy. The authors described how the association of the daily use of topical 2% Minoxidil with alternate day PUVA, was able to induce local hyperthricosis and marker repigmentation in two vitiligo patients [37].

Unfortunately, no other studies about Minoxidil in vitiligo have been conduced and some clinical reports underline controversial results, such as the appearance of leucoderma after the use of the drug [38].

Minerals

Since the discovery of the role of oxidative stress in the pathogenesis of vitiligo, some minerals with proved antioxidative effects, such as Selenium and Manganese, have been proposed as adjuvant oral therapies for the treatment of the skin disease, in association to more conventional therapies (e.g. phototherapy). Unfortunately, today only few studies are available on their use, in terms of both dosage and efficacy [39][40][41].

Omega-3 polyunsatured fatty acids

Omega-3 fatty acids are polyunsaturated fatty acids, with antioxidant and anti-inflammatory properties.

In medicine, they are administrated for the treatment of different disorders, such as cardiovascular diseases, rheumatoid arthritis, atopic diseases, neurodegenerative disorders, cognitive problems, and others [42][43]. They can be assumed with different foods (e.g. fish, fish and krill oils, fruits) or as industrial supplements.

Recently, omega-3 fatty acids have been proposed for vitiligo treatment and to limit the side effects due to phototherapies [1]. Unfortunately, no data are available.

Prostaglandin E2 (PGE2)

Prostaglandin E2 is a member of prostaglandins, a group of hormone-like substances that participate in a wide range of body functions (e.g. uterine contraction, control of blood pressure, modulation of inflammation). In details, PGE2 is an immunomodulatory agent, capable to stimulate melanocytes [44].

In the last years, a topic gel composed by PGE2 has been introduced for the treatment of vitiliginous patients. The drug has been observed to be effective both used alone or in combination with topical corticosteroids or target nb-UVB phototherapy [45][46][47]. No relevant side effects have been described.

Pseudocatalase

In the last years, topical cream cointaning pseudocatalase has been proposed as a valid therapeuthic tool for vitiligo. The drug acts reducing the free radicals and improving the catalase action. Generally, it is applied twice a day. Better results seem to be achieved when pseudocatalase is associated to sol-therapy, UVA or nb-UVB [48][49]. Unfortunately, not all the research confirm this data: some studies underline how the use of pseucocatalase, used alone or associated to UVR, doesn't add any beneficial [50][51].

Resveratrol

Resveratrol is a natural phenol, with marked antioxidant and anti-inflammatory properties. It may be assumed with diet (e.g. wine, peanut, cocoa) or artificial supplements. Recent studies show how its suppletion may be useful in vitiligo treatment, also in association to the classical PUVA-therapy [52][52][53].

Soybeans

Soybeans (also known as soya beans) are a type of legume, particularly rich in flavonoids, which explain how they can be used in vitiliginous patients to halt the oxidative stress phenomenon [1].

Recently, researchers have isolated by soybeans an oestrogen, called Genistein. Few study suggest how its oral and topical administration, are useful in reducing the cell damage by UVR, suggesting a possible adjuvant use of Genistein to phototherapy [54].

Tars

Tars are oily, viscous material, consisting mainly of hydrocarbons, produced by the destructive distillation of organic substances such as wood, coal, or peat. In past, they had been widely used for the topical treatment of psoriasis, both alone or in association to UVR. Because of their antinflammatory and immunosuppressive effects, tars had been also proposed for the treatment of vitiligo [55]. Actually they are not used, not only for the limited data on their effectiveness, but also for their toxicity and carcinogenic effects.

Vitamins

Vitamins are organic compounds, essential for the normal human growth and development, and for its healthy maintenance. Even if some of them are synthesized by the body organs, the others must be assumed with foods or supplements.

Because of the beneficial effects of some vitamins on the skin, since long time dermatologists used to prescribe them for the treatment of different cutaneous diseases. Also for vitiliginous patients, some vitamins have been observed to be useful. Among them, there are: vitamin A, B12, C and E [56].

Different studies underline how an oral supplement of those vitamins is indicated in the treatment of vitiliginous patients, because of their antioxidant properties. Interesting are the good results in term of repigmentation, achieved in vitiliginous patients treated with phototherapy associated to oral vitamins C and E, which are natural photoprotectors [1][57].

In conclusion, a part for well-documented effectiveness of L-phenylalanine, PGE2 and antioxidant agents in the treatment of vitiligo, for the other therapeutical approaches more investigations are needed.

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