Vitiligo and Mental Health

Subjects: Dermatology

Contributor: Luca Di Bartolomeo, Paolo Custurone, Natasha Irrera, Francesco Borgia, Federico Vaccaro, Francesco Squadrito, Mario Vaccaro

Vitiligo is a dermatosis consisting of the appearance of white discoloration patches of the skin, with a prominent pathogenetic factor represented by autoimmunity. Segmental and non-segmental are the two main forms of vitiligo, which may be recognized depending on the onset and localization: the first one is the most common and affects people with autoimmune-prone habits, whereas the non-segmental vitiligo is characterized by symmetrical white macules/patches spread over the skin surface; when untreated it is usually progressive. Macules may appear close to the mucosae (mouth, orbits, genitals, anus) and flexural areas (wrists, axillae and so on) and although they do not immediately affect physical health, they represent not only a cosmetic concern but also a risk for non-melanoma skin cancer (NMSC) development, because of the reduction of sun protection due to the lack of melanin. Different factors have been outlined as possible triggers in the development of the typical lesions, such as the tendency to develop other autoimmune diseases like Hashimoto's thyroiditis, Addison's disease, or alopecia areata as well as oxidative stress, trauma, sunlight exposure, and genetic factors.

Keywords: vitiligo ; oxidative stress ; mental health ; anxiety ; obsessive compulsive disorder ; supplement

1. Main Pathogenetic Pathways of Vitiligo and Mental Disorders Targeted by Natural Compounds

Oxidative stress, autoimmunity, and alteration of melanogenesis are the main pathogenetic mechanisms of vitiligo, and natural compounds counter one or more of these. The overproduction of reactive oxygen species (ROS) and the deficiency of antioxidants enzymes cause an imbalance of cellular redox status and consequently damage melanocytes [1]. Different molecules and pathways targeted by natural compounds are involved in oxidative stress, such as the nuclear factor erythroid 2-like factor 2 (Nrf2), which improves the antioxidant activity of melanocytes. The regulation of melanogenesis and tyrosinase activity is essential in the treatment of vitiligo; melanin production, as well as its transport, may be stimulated by several cytokines, including the α-melanocyte-stimulating hormone (α-MSH) and stem cell factor (SCF). These factors express their signal through several molecular pathways, such as phosphatidylinositol-3-kinase and protein kinase B (PI3K/AKT) or p38 MAP kinase, which converge towards an increase of microphthalmia-associated transcription factor (MITF) expression, thus enhancing RNA levels of tyrosinase (TYR), tyrosine-related protein-1 (TRP-1) and tyrosine-related protein-2 (TRP-2), which produce melanogenesis in melanosomes [2] that can be regulated by natural compounds. One of the most important cytokines involved in vitiligo is INFγ which promotes the skin homing of melanocyte-specific $CD8^+$ cytotoxic T lymphocytes (CTLs) and induces the production of several chemokines, particularly CXCL10. INFγ effects are mediated by the Janus kinase and Signal Transducer and Activator of Transcription (JAK/STAT) pathway [3]. In addition to INFγ, other cytokines contributing to inflammation in vitiligo, such as TNF-α or IL-1β, may be targeted by natural compounds that may have not only well-known anti-inflammatory effects, but may also manage mental disorders. In fact, neuroinflammation represents one of the main causes of mental disorders such as major depression, anxiety, and schizophrenia [4][5]. Innate inflammation and Th1-Th2 cytokine imbalance may activate glial cells, neurotrophism and may affect neurotransmitter levels [6]. Neuroinflammation is characterized by an increase of pro-inflammatory cytokines, such as IL-1β, IL-2, IL-6, TNF-α, and IFN-γ which are produced by microglia, Th1 lymphocytes, and M1 phenotype monocytes/macrophages. One of the pathogenetic theories of depression relates to the monoamine hypothesis, according to which depressive symptoms are caused by the depletion of serotonin, norepinephrine, and/or dopamine levels in the central nervous system [7]. Low levels of the neurotransmitter GABA, as well as the increase of glutamate linked to depression and the use of some natural compounds, may also be useful in regulating these neurotransmitters. In addition, the alteration of the neurotrophic activity of the brain-derived neurotrophic factor (BDNF) may contribute to depression [8]. BDNF stimulates neurogenesis, synaptic plasticity, and neurotransmission. In fact, the reduction of BDNF levels is considered to be an important cause of depressive symptoms [9], therefore BDNF may also be considered an important target for the treatment of depression, and some natural compounds may induce its expression. Additionally, the endocannabinoid system may be targeted by natural compounds, thus increasing serotonin and GABA

levels. In the following sections, the description of natural compounds' efficacy will be reported for the treatment of vitiligo and mental disorders.

2. Baicalein

Baicalein is a flavonoid deriving from *Scutellaria baicalensis Georgi* whose anti-inflammatory and antioxidant effects have been demonstrated [9]. In vitiligo-affected melanocytes, the activation of antioxidant mechanisms, such as that of the nuclear factor erythroid 2-like factor 2 (Nrf2), is impaired [9]. Ndf2 is a transcription factor that activates antioxidant and detoxification genes such as heme oxygenase-1 (HO-1) or superoxide dismutase (SOD) in response to oxidative stress [9], which plays an important role in the pathogenesis of vitiligo [10]. As demonstrated by in vitro experiments, Baicalein may upregulate the Nrf2 signaling pathway in human melanocytes, thus protecting cells from oxidative stress [9]. Moreover, other experimental models showed that Baicalein may exert anti-depressant effects by regulating neurogenesis [11]; in particular, Baicalein may upregulate extracellular signal-regulated kinase (pERK) phosphorylation and BDNF. As with BDNF, ERK, a member of the mitogen-activated protein kinases (MAPKs) family, also has neurotrophic properties and is involved in the neurogenesis of the hippocampus [11]. The activation of these factors would have an anti-depressant effect; also, fluoxetine, an antidepressant drug, acts through ERK1/2 phosphorylation (p-ERK1/2) regulation in the hippocampus.

3. Quercetin

Quercetin is a polyphenolic flavonoid found in fruits such as apples and cranberries, vegetables such as onion and asparagus, and herbs including dill, cilantro, and Camellia sinensis (black tea). Quercetin has anti-inflammatory, antioxidant, anti-cancer as well as neuroprotective properties [12] and seems to be also protective in vitiligo patients. Previous results indicated that quercetin may prevent endoplasmic reticulum (ER) swelling induced by oxidative stress [13], and may modulate the inhibition of tyrosinase observed in human epidermal melanocytes [13]. In fact, like other flavonoids, quercetin stimulates melanogenesis by increasing intracellular tyrosinase activity [14] and melanin in melanoma cells in a dose-dependent manner [15]. Flavonoids influence melanogenesis by activating the MITF, which regulates the expression of the most important melanogenic enzymes, such as tyrosinase, dopachrome tautomerase (DTC, also known as tyrosine-related protein 2, TYRP-2), and tyrosine-related protein 1 (TYRP-1) [16]. Quercetin may be useful for the treatment of psychiatric disorders, as demonstrated by Samad et al. who evaluated the effect of a parenteral administration in anxious and depressed mice: quercetin regulated serotonergic and cholinergic neurotransmission of mice, contrasting anxiety and depression, but also improved memory performance [17]. Moreover, thanks to its antioxidant activity, quercetin can modulate the altered expression of phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), Nrf2 and heme oxygenase-1 (HO-1) observed in depression [18].

4. Kaempferol

Kaempferol is a flavonoid found in many vegetables and fruits as well as plants and herbs, which is well known for its anti-tumor properties [19] thanks to its ability in inhibiting malignant proliferations [20][21]. Previous studies indicated that Kaempferol may promote melanogenesis, although the involved mechanisms are not well-known [22]. Kaempferol was able to promote melanogenesis, melanosome maturation, and melanin transport from perinuclear to dendritic tips of melanocytes [22], and as quercetin, kaempferol may stimulate melanogenesis in a dose-dependent manner [23]. These effects would be mediated by p38/ERK/MAPK phosphorylation and PI3K/AKT signaling downregulation [22]. Together with its anti-cancer effects, kaempferol has neuroprotective properties. For this reason, it has been tested and studied in different neurodegenerative diseases such as Parkinson's and Alzheimer's disease, as well as for the management of depression and anxiety [18]. The antidepressant effects of kaempferol were related to its antioxidant and anti-inflammatory effects through the modulation of different pathways such as AKT and β-catenin and reducing TNF-α and IL-1β levels [23]. The anxiolytic action of kaempferol is supported by in vitro and in vivo studies [24] that demonstrated an anti-anxiety activity like diazepam. The anxiolytic effect of kaempferol is also related to endocannabinoids levels regulation as anandamide, which plays significant anxiolytic effects: kaempferol inhibits the fatty-acid amide hydrolase (FAAH), an enzyme that catabolizes anandamide, in a concentration-dependent manner, thus elevating the levels of anandamide [24].

5. Epigallocatechin-3-Gallate

Epigallocatechin-3-Gallate (EGCG) is a polyphenolic catechin mostly contained in green tea (*Camellia sinensis*). EGCG has anti-cancer, antioxidant, anti-inflammatory, and anti-infective effects, although its low bioactivity after oral administration restricts its use [25][26]. A topical ointment with EGCG is already licensed for the treatment of external genital

warts [25][27], whereas its topical use for vitiligo treatment is still being investigated [28]. In a recent randomized controlled trial, EGCG positive effects on re-pigmentation were observed in vitiligo patients using pimecrolimus ointment [28]. Nevertheless, EGCG does not seem to have a direct melanogenesis-promoting action, even though it might reduce melanin synthesis by inhibiting tyrosinase accumulation [13][15]. Therefore, the usefulness of EGCG in vitiligo patients would not be related to its effects on melanogenesis, but to its antioxidant and anti-inflammatory properties [13][29]. Peracetylated EGCG is the derivative with a greater bioavailability, whose antioxidant effect was observed in human epidermal melanocytes by reducing ROS production [30]. Moreover, the topical administration of EGCG in mice with monobenzone-induced vitiligo reduced serum levels of the pro-inflammatory cytokines TNF-α, IFN-γ, and IL-6, as well as the perilesional CD8+ T cells accumulation [29]. The reduced expression of IFNγ decreases, in turn, the downstream targets JAK2 and STAT1/3, which are particularly involved in the pathogenesis of vitiligo [31]. Moreover, EGCG may reduce IFNγ-induced chemokines such as CXCL10, and the expression of the related receptors including CD11a, CXCR3, and CCR2 in human T lymphocytes [31]. In relation to this evidence, experimental in vivo studies have highlighted the promising properties of EGCG in neuromodulation, thus ameliorating depression-related behaviors and enhancing serotonin levels in the hippocampus [32][33][34]. Moreover, EGCG can decrease IL-6 levels and its downstream transcription factor STAT3 in the hippocampus, counteracting neuroinflammation and reducing anxiety-like behaviors [33]. The anxiolytic properties of EGCG are also related to the modulation of gamma-aminobutyric acid (GABA) receptors and to the inhibition of spontaneous excitatory synaptic transmission [34]. In contrast to its usefulness in depression and anxiety, EGCG did not show antipsychotic effects in patients with schizophrenia and bipolar disorder [35]: no significant difference was observed between placebo and EGCG -treated groups in a double-blind, randomized controlled trial on patients with schizophrenia, schizoaffective disorder, or bipolar disorder [35].

6. Curcumin

Curcumin is a polyphenolic compound taken from turmeric (*Curcuma longa*) which, like the other natural compounds described so far, shows anti-inflammatory, antimicrobial, antioxidant, and anti-neoplastic properties [36]. These pleiotropic effects have raised interest also in the field of dermatology and phytotherapy, so an application for vitiligo was hypothesized. A combination treatment composed of a tetrahydrocurcuminoid cream plus narrowband UVB phototherapy was used in patients suffering from focal or generalized vitiligo. The combination treatment did not improve re-pigmentation compared to the group that received phototherapy only, although this result may be explained by the small sample size [37]. To the best of author's knowledge, no studies reported the possible efficacy of systemic administration of curcumin on vitiligo in animals or humans. Curcumin may activate the Nrf-2 signaling pathway, which is impaired in vitiligo, upregulating antioxidant and detoxification genes and protecting cells from oxidative stress [38]. Moreover, curcumin may inhibit many pro-inflammatory molecules, including IFNγ, which play a critical role in the pathogenesis of vitiligo [39]. The ability of curcumin in inhibiting IFNγ was already demonstrated in psoriasis but was not demonstrated in vitiligo [39], even if curcumin was able to inhibit melanogenesis in an in vitro model, thus reducing melanin content and tyrosinase activity in a dose-dependent manner [40]. The poor bioavailability of curcumin represents the main limitation of its possible use. Therefore, different experimental approaches are aimed at testing new formulations to ameliorate its bioavailability: modified curcumin suppressed melanogenesis by activating the extracellular signal-regulated protein kinase (ERK) pathway [41]. Curcumin supplementation is an efficient alternative treatment for depressive and anxiety symptoms, thus improving the quality of life of patients with chronic disorders [42]. However, the available evidence of curcumin’s effects on vitiligo is still contrasting, therefore new data are required to provide a recommendation for its use in the clinical practice for vitiligo management.

7. Cannabidiol

Cannabidiol (CBD) is a non-psychoactive compound derived from the *Cannabis sativa* L. which, compared to Δ9-*trans*-tetrahydrocannabinol (the main compound extracted from the plant), does not induce intoxication and is not considered a psychoactive drug [43]. Increasing interest has been raised about CBD neuroprotective effects which are currently used for the treatment of refractory epilepsy in children [44]. Moreover, both animal and human studies have shown promising results concerning CBD use for the treatment of depression, anxiety, and psychotic disorders, such as schizophrenia [43]. CBD was also used in many skin disorders, although evidence concerning its use in vitiligo is still lacking [45]. However, the data obtained so far in other experimental models indicated that CBD may protect against oxidative stress by preventing free radical formation and activating Nrf2, improving antioxidant enzyme transcription [46]. Moreover, CBD has significant anti-inflammatory effects, thus reducing pro-inflammatory cytokines release and inhibiting T cell proliferation [46]. Nevertheless, the relationship between melanogenesis and the role of cannabinoids is not completely clear: cannabinoid-1 (CB-1) receptor agonism may induce different responses in melanogenesis, inducing both reduction and induction of this process [47][48]. CBD may play a role as adjuvant therapy in vitiligo thanks to its antioxidant and anti-

inflammatory effects, although its effect should be fully elucidated in melanogenesis. Moreover, cannabidiol-related adverse events should not be underestimated: they may include somnolence, gastrointestinal disorders, an increase in liver function, and drug interactions [49].

8. Glycyrrhizin and Glycyrrhetinic Acid

Glycyrrhizin is a triterpenoid saponin glycoside extracted from licorice (*Glycyrrhiza glabra*), composed of one glycyrrhetinic acid (GA) and two glucuronic acids [50]. Glycyrrhizin has anti-inflammatory, antioxidant, and antiviral activity; in fact, has been recently proposed as an adjunctive treatment for the SARS-CoV-2 infection [51]. The anti-inflammatory effects of glycyrrhizin are related to its ability in inhibiting the high-mobility group box-1 gene (HMGB1), which stimulates pro-inflammatory cytokines production, including TNFα [52] and IL-23 [53]. Moreover, glycyrrhizin was found to protect melanocytes from oxidative stress by inducing the nuclear translocation of Nrf2 in human melanocytes, thus inducing the expression of HO-1, an antioxidant enzyme responsible for heme degradation [54]. The effects of glycyrrhizin on melanocytes also involve the stimulation of melanogenesis: glycyrrhizin may increase tyrosinase mRNA levels as well as TRP-2 expression and melanin content in a dose-dependent manner [50]. In addition, Lee et al. demonstrated that glycyrrhizin may stimulate melanogenesis with a mechanism of action that involves cAMP signaling activation [55]. The oral administration of glycyrrhizin in association with UVB irradiation caused re-pigmentation of lesions in 87.5% of patients, with no appearance of new lesions in previously active vitiligo [56]. Glycyrrhizin also showed anti-depressant effects in patients which were related to its anti-inflammatory properties. The symptomatic improvement was higher in patients that showed high levels of inflammatory markers at baseline [57], even if animal models of depression have shown that the antidepressant activity of glycyrrhizin lies in its ability to block inflammation induced by HMGB1, which is responsible for depressive behaviors in mice [58][59] and the production of IL-33 [60], which also has been demonstrated as an interleukin significantly overexpressed in vitiligo-affected patients [61]. Moreover, glycyrrhizin may regulate neurotransmitter levels in the amygdala of mice which showed a significant alteration of the circadian rhythm of serotonin [62]. Glycyrrhizin may normalize the serotonin fluctuations, thus demonstrating an interesting potential for the treatment of anxiety and stress-related disorders [62].

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