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Harnessing Flavonoids and Nutraceuticals for Vitiligo via Targeting Oxidative Stress and Neural-Melanocyte Crosstalk

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Abstract

Vitiligo, a complex disorder characterized by the progressive destruction of melanocytes, involves a multifaceted pathophysiology driven by oxidative stress, immune dysregulation, and impaired neural-melanocyte signaling. Emerging evidence supports the therapeutic potential of flavonoids and other nutraceuticals in targeting these pathways, yet their precise mechanisms and clinical applications remain inadequately defined. Specific flavonoids, such as quercetin, apigenin, and catechins, demonstrate potent antioxidant effects by scavenging reactive oxygen species (ROS) and modulating redox-sensitive signaling pathways, including nuclear factor erythroid 2–related factor 2 (Nrf2) and mitogen-activated protein kinases (MAPKs). In addition to their role in redox homeostasis, flavonoids exhibit neuroprotective properties by attenuating neuroinflammation through the suppression of pro-inflammatory cytokines (e.g., IL-1β, TNF-α) and enhancing neural-melanocyte communication via upregulation of cyclic adenosine monophosphate (cAMP) and extracellular signal-regulated kinase (ERK) signaling pathways. Further, the combination of flavonoids with antioxidants such as N-acetylcysteine and alpha-lipoic acid offers synergistic benefits by targeting distinct aspects of oxidative stress, including ROS detoxification, mitochondrial function restoration, and lipid peroxidation prevention. These compounds collectively promote melanocyte survival and migration, critical processes for effective repigmentation. Integration with narrowband UVB (NB-UVB) phototherapy offers additional therapeutic potential by enhancing UV-induced melanogenesis while minimizing photodamage through upregulated antioxidant defenses. Specifically, flavonoids may amplify NB-UVB efficacy by stabilizing melanogenic enzymes, such as tyrosinase, and protecting melanocyte stem cells from oxidative insults. Emerging research suggests that flavonoids may exert epigenetic effects on melanocyte stem cell niches, influencing their plasticity and regenerative capacity. Investigating these epigenetic modifications, such as changes in histone acetylation and DNA methylation, could illuminate new pathways for reversing depigmentation and preventing disease recurrence. Integrating flavonoid-based nutraceuticals with NB-UVB therapy offers a targeted strategy to address oxidative stress, immune imbalance, and neural-melanocyte signaling dysfunction in vitiligo, enhancing repigmentation outcomes and reducing relapse rates through synergistic molecular mechanisms.

1. Introduction

Vitiligo is a chronic, progressive depigmenting disorder where there is the loss of functioning melanocytes, which leads to the appearance of white patches on the skin. It affects 1-2% of the world's population with no gender or racial predisposition [1]. Its visible nature translates to a reduced quality of life and psychosocial burden.

It is worth noting that the pathogenesis of vitiligo is complicated by the interactions of genetic, epigenetic, and environmental factors. Melanocyte destruction is primarily mediated by

mechanisms through oxidative stress, immune dysregulation, and neural-melanocyte signaling [1, 2, 3]. It is unpredictable in its course and is currently lacking broadly efficacious therapies, underscoring the need for greater understanding and renewed innovation in better management strategies.

Oxidative stress is a hallmark of vitiligo, in which excessive reactive oxygen species (ROS) dysregulate cellular homeostasis; the buildup then causes melanocyte malfunction and apoptosis [2]. Many factors such as UV exposure, infections, and mitochondrial malfunction generate reactive oxygen species (ROS), whereas a deficiency of enzymatic antioxidants (e.g., catalase, glutathione peroxidase) decreases detoxification mechanisms [2, 3]. This oxidative imbalance triggers the release of autoantigens, which shifts immune pathways towards the destruction of melanocytes [2]. These processes are not independent of each other and collectively contribute to the gradual loss of pigmentation in individuals affected.

While oxidative stress contributes to hypopigmentation, it is the dysregulation of the immunological environment that is the primary factor behind vitiligo's pathology. Abnormal activation of CD8+ T lymphocytes and proinflammatory cytokine secretion (e.g., IFN-γ/gamma) sustains both inflammation and destruction of melanocytes [1, 2]. These immune reactions are often linked to a deficit of regulatory T cells, which promotes autoimmune processes. Another contributor, neural-melanocyte signaling, is impaired in vitiligo and disrupts the survival and migration of melanocytes influenced by elevated neuroinflammation and oxidative stress [2, 3]. Such interactions underline the necessity of precise therapeutic approaches that are able to target these complex networks.

Emerging treatments for vitiligo have centered on flavonoids and nutraceuticals that display promise as therapeutic agents. Flavonoids, including quercetin and apigenin, are naturally occurring polyphenols with potent antioxidant and anti-inflammatory properties [3,4]. Flavonoids maintain cell homeostasis by scavenging reactive oxygen species (ROS) and modulating redox-sensitive pathways, such as the pathways of nuclear factor erythroid 2-related factor 2 (Nrf2) and mitogen-activated protein kinases (MAPKs). In addition, their neuroprotective properties include potent enhancement of the neural-melanocyte latitudinal interaction and suppression of neuroinflammation for the benefit of melanocyte survival. These various benefits make flavonoids an appealing addition to conventional vitiligo treatments, as well as an ideal foundation for exploring combination therapy.

This paper aims to review the metabolic processes, clinical significance, and therapeutic perspectives of flavonoids for treating vitiligo. Combination flavonoid use and narrowband UVB (NB-UVB) phototherapeutic vehicles are also discussed as potential vehicles of synergistic repigmentation. The proposed integrative approaches for vitiligo treatment show potential for addressing the various contributing factors such as oxidative stress, immunological imbalance, and neural signaling dysregulation.

2. Mechanisms of Oxidative Stress and Immune Dysregulation in Vitiligo

In vitiligo, elevated levels of ROS, including hydrogen peroxide and superoxide anions, are a significant contributor to melanocyte vulnerability. Intrinsically, byproducts accumulate during melanogenesis, increasing oxidative stress within melanocytes [5]. In the absence of physiologic stressors, the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, enzymes such as catalase and glutathione peroxidase, and mitogen-activated protein kinase (MAPK) neutralize ROS. However, in pathological states such as inflammation, antioxidant deficiencies, and UV radiation exposure, ROS accumulate. The collection of ROS damages melanocytes by disrupting mitochondrial function, impairing endoplasmic reticulum processes, and triggering apoptosis. This damage amplifies the immune response which creates a positive feedback loop of further ROS production and, consequently, melanocyte destruction. These cumulative cellular changes amplify oxidative stress and the progression of vitiligo [6]. Enzymes like catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPX) play roles in neutralizing ROS and can be measured to indicate the severity of oxidative stress in vitiligo. In vitiligo, reduced levels of CAT and GPX impair the oxidative stress response [7]. Ultimately, persistent imbalance exacerbates ROS accumulation in skin lesions, contributing to melanocyte damage and disease progression.

In addition to oxidative stress, pro-inflammatory cytokines play a significant role in melanocyte

damage in vitiligo by disrupting melanogenesis and inducing apoptosis. Increased levels of TNF-α, IFN-γ, IL-1β, IL-6, and IL-17 are observed in vitiligo lesional skin, contributing to inflammation and melanocyte dysfunction [8]. IL-1β inhibits melanogenesis through inhibiting microphthalmia-associated transcription factor (MITF). TNF-α and IL-17 inhibit melanogenic signaling pathways, reducing melanin synthesis and pigmentation-related gene expression. IFN-γ induces melanocyte apoptosis and impairs melanosome maturation through the STAT1 pathway, while IL-6 suppresses tyrosinase activity, further inhibiting melanogenesis. The imbalance of Th1/Th2 cytokine responses, marked by elevated IFN-γ and reduced IL-4, exacerbates the inflammatory response. This causes disruption of melanocyte homeostasis which leads to melanocyte destruction [9]. Impaired neural-melanocyte signaling in vitiligo is linked to dysfunctional Nrf2-ARE pathway activation, which compromises the antioxidant defenses of melanocytes. Despite the presence of oxidative stress, vitiligo melanocytes exhibit reduced activation of Nrf2, leading to decreased expression of antioxidant genes [10]. The failure to upregulate protective mechanisms exacerbates susceptibility to H2O2-induced oxidative damage. Epigenetic mechanisms such as DNA methylation and histone acetylation contribute significantly in the pathogenesis of vitiligo by regulating gene expression. Studies have identified a negative correlation between DNA methylation levels and gene expression in vitiligo melanocytes, highlighting the impact of methylation changes on functional gene expression [11]. For example, hypermethylation of the Annexin A2 receptor (ANXA2R), which is critical for cell survival, leads to reduced gene expression, promoting melanocyte apoptosis and impairing their survival under oxidative stress [12]. These findings suggest that targeting DNA methylation patterns could offer novel therapeutic approaches for managing vitiligo [11]. Epigenetic interventions hold promise for reversing depigmentation in vitiligo by targeting molecular pathways involved in melanocyte function and survival. MicroRNAs (miRNAs) play a role in regulating gene expression and are implicated in the pathogenesis of vitiligo through their effects on immune response, oxidative stress, and melanocyte activity. These can be used to reduce cytokine production, upregulate antioxidants such as catalase, and protect melanocytes from apoptosis [13]. Overall, melanocyte vulnerability could be reduced under immunological dysregulation and oxidative stress, thereby creating opportunities for novel therapeutic options.

3. Role of Flavonoids in Addressing Vitiligo Pathophysiology

Flavonoids, found in various fruits and vegetables, are well known for their antioxidant properties that counteract oxidative stress, a key driver in the pathophysiology of vitiligo. Specifically, oxidative stress contributes to an overproduction of reactive oxygen species (ROS). Flavonoids, such as Quercetin, have the potential to treat vitiligo as it reduces oxidative mediators including hydrogen peroxide (H_2O_2). In vitiligo, excessive H_2O_2 disrupts the endoplasmic reticulum (ER) in melanocytes, causes swelling, and prevents the proper production of tyrosinase, a critical enzyme in melanin synthesis [14]. This disruption ultimately leads to melanocyte dysfunction and depigmentation. Quercetin maintains melanocyte viability by neutralizing H_2O_2. Additionally, it supports melanogenesis by modulating transcription factors such as microphthalmia-associated transcription factor (MiTF) [15]. MiTF increases expression of melanogenesis related genes, including those responsible for producing tyrosinase, resulting in increased melanin production and pigmentation [15]. Apigenin, another potent flavonoid, protects human melanocytes against oxidative damage by upregulating the Nrf2 pathway. Lin et al. reported that apigenin reduced ROS aggregation, inhibited caspase-3 and PARP activities, and inhibited mitogen-activated protein kinases (MAPKs) in a dopamine induced melanocyte model [16]. Elevated levels of dopamine, a catecholamine, is associated with oxidative stress and has been reported in both the serum and urine of patients with vitiligo [17]. Apigenin's ability to modulate the damaging effects of dopamine induced stress, positions it to be a potential candidate for vitiligo treatment. Epigallocatechin-3-Gallate (ECCG), a flavonoid that is abundant in green tea, also has been shown to have cytoprotective effects. Zhu et al. reported that topical administration of ECCG delayed the time, prevalence, and area of depigmentation by reducing serum levels of the pro-inflammatory cytokines TNF-α, IFN-γ, IL-6, and CD8 [18]. JAK2 and STAT1/3 are downstream targets of IFN-y and key mediators of vitiligo pathogenesis. This finding suggests that ECCG could be preventative against vitiligo. Overall, the antioxidant properties of flavonoids

and their ability to scavenge ROS highlight its potential in treating patients with vitiligo.

Beyond their antioxidant properties, flavonoids have shown neuroprotective effects through their regulation of neural-melanocyte communication and upregulation of signaling pathways. Flavonoids can directly cross the blood-brain barrier to reduce ROS and inflammation, fostering neuronal protection [19]. Hesperidin, a flavonoid found in citrus, has been shown to increase neural crest cell survival [20]. Melanocytes are derived from neural crest cells, making their survival critical to maintain pigment within the skin. Neural-melanocyte communication refers to signals, such as repulsive guidance molecule B (RGMB), between melanocytes and neurons that help regulate melanin production [21]. By promoting neural crest cell survival and protecting melanocytes from oxidative stress and apoptosis, hesperidin can help stabilize the neural-melanocyte communication that is often disrupted in vitiligo. Additionally, neural cells release neurotransmitters that influence melanocyte activity. Excessive neurotransmitter release can lead to oxidative stress, while insufficient release may impair melanocyte stimulation [22]. Furthermore, flavonoids enhance neuroprotection through the intracellular signaling pathways cyclic adenosine monophosphate (cAMP) and extracellular signal-regulated kinase (ERK) [23, 24]. By activating the cAMP/PKA cascade, flavonoids increase cAMP, which has a strong effect on dendrite formation [25]. Dendrites are integral for processing and transferring information to neurons. Dendrite formation and extension in melanocytes allow for the transportation of melanosomes to nearby keratinocytes, promoting skin pigmentation. Similarly, basic fibroblast growth factor promotes melanocyte migration and cytoskeletal rearrangements through PI3K/Akt and ERK signaling pathways, highlighting its potential clinical application in melanocyte transplantation [23]. Another flavonoid, fisetin, upregulates ERK to promote nerve cell differentiation [26]. By promoting proliferation and differentiation of melanocytes, melanocyte regeneration and repigmentation can be achieved. In addition to their individual benefits, flavonoids can demonstrate synergistic potential when combined with other antioxidants such as N-Acetyl Cysteine (NAC) and alpha-lipoic acid (ALA). Tanomrat et al. reported that Quercetin has higher efficacy when used in combination with NAC [27]. NAC, a precursor to glutathione, enhances intracellular antioxidant defenses by replenishing glutathione levels. Glutathione is an antioxidant that protects cells from oxidative stress damage, and in patients with vitiligo its levels are often lower than in healthy individuals [28]. When combined with flavonoids, NAC can strengthen internal antioxidant defences. ALA supplementation can be an effective treatment for repigmentation for patients with vitiligo [29]. Al-Otaibi et al reported Quercetin and ALA complemented each other in protecting the rat brain against oxidative stress induced by aluminium chloride [30]. A similar benefit can be applied to melanocyte survival and function by reducing oxidative damage, improving mitochondrial function, and stabilizing cellular signaling pathways. Utilizing flavonoids in combination with NAC or ALA presents a potential therapeutic strategy for conditions like vitiligo. Further research into the optimal dosages of each antioxidant could enhance their clinical application in repigmentation therapies.

4. Integration of Flavonoids with NB-UVB Phototherapy

Narrowband ultraviolet B (NB-UVB) phototherapy is a cornerstone in vitiligo treatment, utilizing multiple mechanisms to position itself as one of the most effective therapies to date. NB-UVB stimulates dormant or residual melanocyte stem cells within the outer hair root sheath, promoting their proliferation and migration to depigmented areas [31]. Additionally, ultraviolet B (UVB) activates transcription factors that induce melanogenesis, including alpha-melanocyte-stimulating hormone (α-MSH) and the Wnt/β-catenin signaling pathway [32]. NB-UVB also exerts immunomodulatory effects that stabilize the autoimmune destruction of melanocytes. These mechanisms include reducing the release of inflammatory interleukins and chemokines, stimulating the differentiation of regulatory T cells (Tregs)—a process upregulated during anti-inflammatory responses—and increasing tyrosinase activity, which enhances melanin synthesis [33]. Overall, these multifaceted mechanisms underline the efficacy of NB-UVB allowing it to be an integral player in future vitiligo therapies.

Flavonoids possess strong antioxidant and immunomodulatory properties, making them a promising adjunct to NB-UVB therapy for

vitiligo treatment. These plant derived compounds scavenge reactive oxygen species generated by UV radiation, thereby preventing oxidative stress and maintaining the viability of melanocyte stem cells under photodamaging conditions [34]. Their anti-inflammatory effects, particularly the reduction of pro-inflammatory cytokines, help to minimize processes that could harm melanocyte stem cells [34]. Certain flavonoids have been shown to enhance melanogenesis by increasing tyrosinase protein levels and other melanogenesis-related proteins, including MITF, TYR, TRP-1, and TRP-2 [35]. They have also demonstrated efficacy as a pretreatment therapy by reducing melanocyte apoptosis and reactive oxygen species (ROS) production [36]. As a result, their usage can be exponentially beneficial in the treatment of de-pigmentary disorders due to their efficacy and low side effect profile.

Combination therapies are increasingly gaining interest by dermatologists and have the potential to amplify NB-UVB monotherapy in inducing repigmentation in patients with vitiligo [37] Historically, trimethylpsoralen combined with UVA/UVB phototherapy has been a first-line treatment for vitiligo [38]. Antioxidants tablets have been shown to complement NB-UVB therapy, although this has only been reported in one clinical trial thus far [31]. The addition of flavonoids to these therapies is hypothesized to augment melanogenesis while minimizing UVA/UVB exposure [38]. While flavonoids are rarely used in isolation, their inclusion in combination therapies offers numerous benefits, including improved repigmentation outcomes and reduced relapse rates. The synergistic effects of these therapies enhance the speed and extent of pigment restoration, as flavonoids amplify melanogenic activity while protecting melanocytes from further damage [39]. Moreover, their antioxidant and anti-inflammatory properties address the oxidative stress and immune dysregulation that underlie vitiligo, providing a more comprehensive treatment approach. Through these modalities, clinicians can potentially increase repigmentation, shorten the duration of phototherapy, and lessen patient exposure to radiation.

5. Future Implications and Challenges

Reliability in therapeutic applications of flavonoids and other nutraceuticals is significantly limited by the lack of literature establishing their efficacy in clinical studies. Key challenges to clinical application include elucidating their role in signaling pathways and epigenetic modifications, as well as enhancing bioavailability through the development of targeted delivery systems. Current literature examining the effects of flavonoids on melanogenesis primarily focuses on their role in regulating signal transduction pathways. Epigenetic modification of melanogenesis, however, plays a key role in the pathogenesis of pigmentation disorders. Multiple noncoding RNAs, including miR-155, have been implicated in downregulating melanogenesis genes [40]. Flavonoids have been shown to reduce the overexpression of miR-155 in other dermatologic conditions, leading to the attenuation of proinflammatory markers [41]. However, the relationship between flavonoids and noncoding RNAs in the context of melanogenesis remains unexplored. Future studies should investigate the potential of flavonoid-based therapies as an epigenetic modulator of melanogenesis, providing valuable insights into their therapeutic role in managing pigmentation disorders.

One of the challenges in advancing flavonoid-based therapies is their limited bioavailability, which complicates the determination of appropriate therapeutic dosing. The limited oral bioavailability of flavonoids is compounded by poor digestive absorption and conversion into metabolites with altered biological activity. However, advancements in biotechnology may provide a solution, with novel delivery systems in development to improve intestinal absorption. Methods of microencapsulation, such as lipid-based vehicles and nano-delivery systems, aim to enhance flavonoid permeability and provide metabolic stability. Despite their potential, the safety and novelty of these systems come at a high production cost [42]. Balancing improved delivery of nutraceuticals with diligent monitoring of their safety and efficacy is essential. While specific flavonoids demonstrate potent antioxidant effects and immunomodulation, excessive consumption of these compounds can result in the production of free radicals, which may result in potential mutagenic effects. While these negative effects are unlikely to result from the intake of dietary levels of flavonoids, regular supplementation with unregulated formulations could lead to the consumption of toxic levels [43]. The health implications of excessive flavonoids are not limited to direct biochemical pathways; a

bidirectional relationship exists between dietary flavonoids and the gut microbiome. Microbial activity is essential for the metabolism of flavonoids into active metabolites, which, in turn, support the growth of probiotic bacteria through the production of short-chain fatty acids [44]. Therefore, enhancing the oral bioavailability of flavonoids may disrupt the symbiotic relationship with gut microbiota. Consequently, with the development of targeted delivery systems, clinical investigations are required to determine optimal therapeutic and efficacious dosing to avoid the inherent health risks associated with flavonoid supplementation beyond normal dietary intake.

Although improving the bioavailability and therapeutic dosing of flavonoids presents significant challenges, topical application as an adjuvant therapy to narrowband UVB (NB-UVB) may promote repigmentation while offering a more controlled and localized delivery. First-line therapy for the treatment of vitiligo combines NB-UVB with oral or topical preparations of psoralen, though individual results vary. Augmenting treatment with flavonoids may improve outcomes [45]; however, standardized protocols are lacking. *In vivo* studies are required to establish the efficacy of flavonoids as an adjuvant to phototherapy, from which treatment regimens, including dosing, formulation, and application frequency, can be developed. Furthermore, large-scale clinical trials must be conducted to compare the efficacy of psoralen alone with combination psoralen-flavonoid phototherapy, ensuring sufficient patient safety data collection. As the literature on nutraceuticals progresses, therapies tailored to patient-specific molecular profiles, utilizing next-generation sequencing and multi-omics approaches, will enable more personalized treatment strategies. Specific biomarkers may predict therapeutic response to different oral medications, topical emollients, and phototherapies for repigmentation [46]. Flavonoid-based therapies may offer synergist benefits alongside current treatments in individuals with dysregulations in signal transduction or epigenetic modifications in melanogenesis that can be regulated through the application of oral or topical flavonoids.

6. Conclusion

Flavonoids have extensive therapeutic potential in vitiligo treatment. They target various pathways involved in the disease etiology, such as oxidative damage, immunological dysregulation, and neural-melanocyte dysfunction. Bioactive compounds, including quercetin, apigenin, and epigallocatechin-3-gallate (EGCG), have been shown as potent scavengers of reactive oxygen species (ROS), modulators of redox-sensitive signaling pathways, as well as anti-neuroinflammatory agents. Their capacity to enhance melanocyte survival, promote melanogenesis, and support repigmentation may therefore make them a novel therapeutic approach. Moreover, the flavonoids in combination with (NB-UVB) phototherapy amplifies the therapeutic effect by stabilizing melanogenic enzymes, protecting melanocyte stem cells from photodamage, and reducing the recurrence rate. These findings emphasize the potential of flavonoids to enhance current treatments and provide a more comprehensive approach to vitiligo management.

Flavonoids have potential, yet clinical translation is hindered due to bioavailability, optimal doses of the active compounds, and the lack of uniform protocols. Additional research should clarify flavonoid mechanisms of action, develop delivery technologies, and conduct large-scale human clinical trials to ensure safety and efficacy. This highlights the relevance of incorporating flavonoids into individualized and integrative vitiligo therapy strategies, which may elevate vitiligo care to new heights, resulting in an enhanced therapeutic outcome and quality of life for vitiligo patients.

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