VITILIGO AN IDIOPATHIC DISORDER

Abstract

Vitiligo, a hypomelanotic disorder characterized by distinct patches of hypopigmentation. It delves into the clinical manifestations, prevalence, psychiatric morbidity, and social impacts of vitiligo. Furthermore, it explores the condition's pathogenesis, biochemical basis, and the role of key enzymes like tyrosinase in melanin production.

The review assesses the involvement of melanocytes and keratinocytes in melanin synthesis, emphasizing the significance of β 2 adrenergic receptors in elevating melanogenesis. It highlights the potential impact of beta-blockers on vitiligo and discusses the role of antimelanocyte antibodies in melanocyte destruction.

The document examines alternative agents for regulating melanogenesis, such as arbutin, kojic acid, aloesin, and azelaic acid, along with their mechanisms of action. It also discusses the biochemical and adverse effects of hydroquinone, a prominent melanogenesis inhibitor.

Moreover, the review explores immunomodulation, therapeutic approaches, measurement techniques for vitiligo area, and various treatment modalities encompassing topical treatments, systemic therapies, surgical interventions, and their respective successes and side effects.

The abstract concludes by emphasizing the autoimmune hypothesis as the primary etiology of vitiligo, highlighting the significance of ongoing research and clinical trials in unveiling innovative therapeutic pathways for pigmentation modulation."

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I. INTRODUCTION

Vitiligo is a hypomelanotic disease that is acquired and idiopathic in nature, described by distinct hypopigmented patches (Ontonne J P and Bose S K., 1993). This condition involves the degeneration of active melanocytes, contributing to pigmentation disorders. While affecting 1% of the global population, the pervasiveness of vitiligo diverges across populations, ranging from 0.1 - 8.8% (Mosher et al., 1993). Particularly in southern India, this issue is referred to as "ven kushtham," colloquially termed "white leprosy" by (Mosher et al., 1993).

Clinical manifestations of vitiligo include various forms: a) dermatomal and asymmetric dispersal with minimized clinical significance, b) focal vitiligo characterized by a limited amount of scattered small lesions, c) generalized vitiligo, the most frequent type, featuring lesions distributed symmetrically on both sides of the body, and d) universal vitiligo, which involves total or nearly total loss of pigmentation (Mosher et al., 1993).

Psychiatric morbidity affects 16-35% of vitiligo patients. Among this group, instances of dysthymia (17-19%), depression (10%), sleep problems (20%), thoughts of suicide (10%), actual suicide attempts (3.3%), and feelings of anxiety (3.3%) have been noticed. Furthermore, vitiligo can affect how people relate to each other, make them avoid specific social situations, and cause difficulties in sexual relationships (Porter J et al., 1990).

Vitiligo’s pathogenesis is underpinned by 3 major hypotheses: self-destruction, neural factors, and autoimmune mechanisms. This review will delve into novel evidence concerning autoimmune melanocyte destruction, intrinsic biochemical processes, the usage of natural health products, levels of specific enzymes in both blood and skin, as well as the cellular, molecular, and genetic foundations of the condition.

II. BIOCHEMICAL BASIS OF VITILIGO

Melanocytes, specialized cells liable for melanin generation in the skin, are known for their dendritic nature. Dendrites extend into the Malpighian layer of the epidermis, in the skin, they move melanosomes to nearby keratinocytes – a total of around 36 – creating a unit known as the epidermal melanin unit (Shahjil et al., 2006). Apart from the skin, melanocytes are also found in the retinal pigment epithelium, uveal tract, inner ear, and leptomeninges, and they exist in the hair follicle matrix of the lower epidermal layer.
The key player in melanin creation is the enzyme tyrosinase. It starts the process of converting tyrosine into dihydroxyphenylalanine (DOPA), which is a crucial step in making melanin (Hearing VJ, 1999).

After DOPA, it changes into dopaquinone through a process called oxidation. This then turns into DOPAchrome and eventually transforms into 5,6 dihydroxy indole (DHI). With the help of TRP2 (tyrosine-related protein 2), dopachrome becomes dihydroxyindole carboxylic acid (DHICA). This finally leads to eumelanin, where DHI and DHICA come together and form a polymer. In addition, reactions involving cystine/glutathione and dopaquinone create cysteinyldopas, which then undergo more changes to become benzothiazines. These higher forms offer protection against harmful radiation like ionizing radiations (Hearing VJ, 1999).

Keratinocytes, dominant cells comprising the epidermis, serve as reservoirs for melanin storage. With an expression limited to β 2 adrenergic receptors, keratinocytes possess a seven-pass transmembrane G protein-linked receptor. Expression of β 2 AR is more prominent in the basal epidermal layer, diminishing towards stratum corneum. Notably, both melanocytes and keratinocytes express β 2 AR, with keratinocytes capable of producing norepinephrine. Activation of beta 2 AR in melanocytes elevates intracellular cAMP levels, subsequently augmenting melanogenesis. Moreover, the beta 2 AR-mediated melanogenesis pathway in normal melanocytes can be locally stimulated through the endogenous generation of epinephrine by normal epidermal keratinocytes.

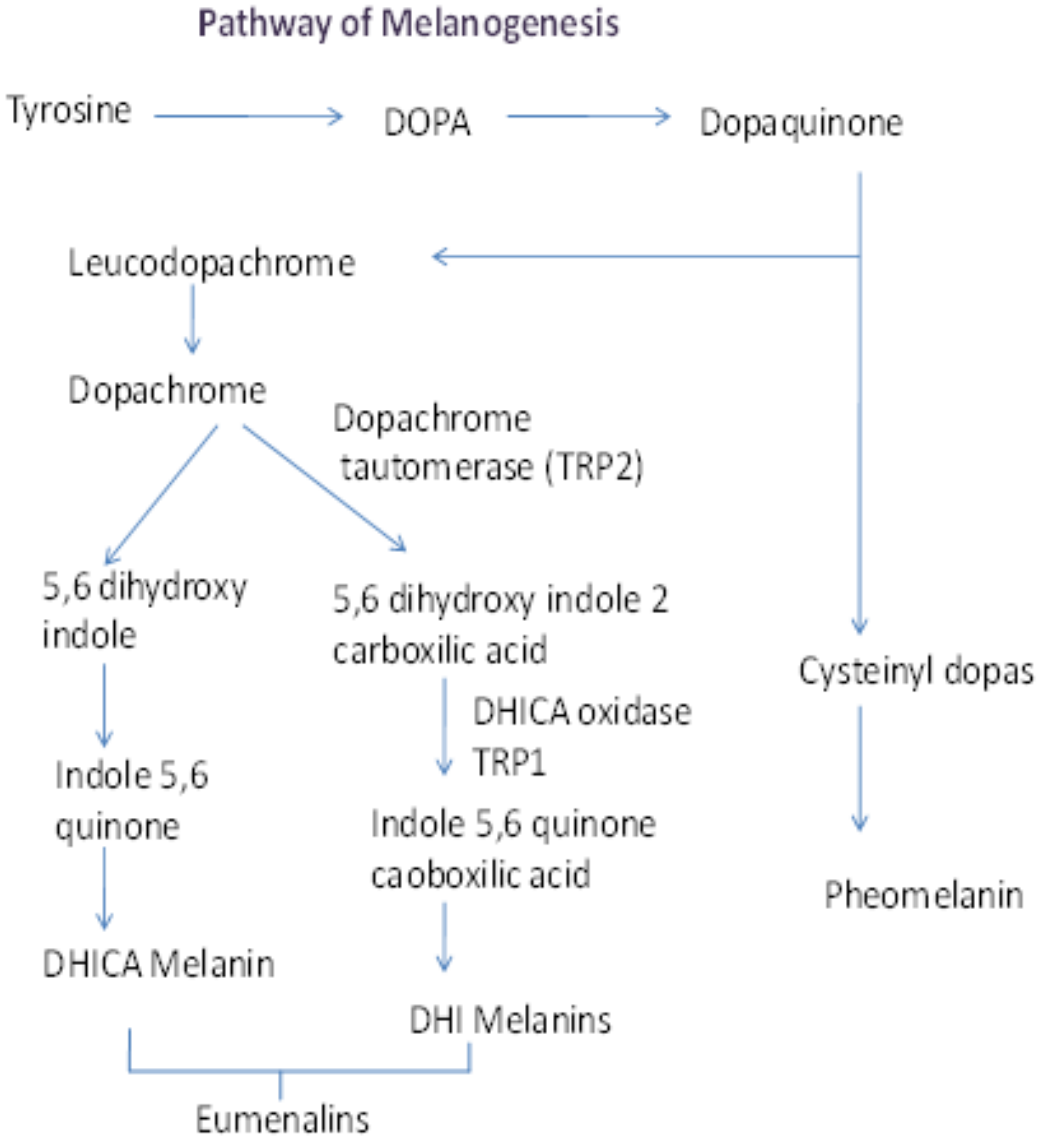

Figure 1: Melanogenesis Pathway

Creating beta-blockers has been linked to the potential worsening of Vitiligo in specific patients. Studies suggest that activating beta 2 adrenergic receptors (AR) can stimulate melanogenesis in a controlled environment. However, blocking beta 2 AR on melanocytes in real-life situations could lead to reduced melanin production in skin affected by Vitiligo. Individuals with Vitiligo often have higher levels of norepinephrine and its breakdown products in their blood and urine (Cucchi ML et al., 2003). There's also an increase in 6BH4 in the affected area (Schallreuter and Wood JM., 1996) along with reduced PNMT activity in keratinocytes. In lab cultures, epidermal keratinocytes from Vitiligo patients' skin show greater expression of beta 2 AR. The presence of these receptors on keratinocytes is influenced by calcium levels and a redox product called 6 biopterin, which is higher in Vitiligo-affected skin (Hasse S et al., 2004). Keratinocytes in Vitiligo-affected skin have higher levels of intracellular calcium. Some patient samples indicate that keratinocytes in Vitiligo skin struggle with calcium influx (Schallreuter KU and Pittelkow MP., 1998), but the role of this in Vitiligo development is not fully understood. Manipulating beta 2 AR through medications could potentially offer a path for treating Vitiligo.

Antimelanocyte antibodies have been found to cause melanocyte death via complement-mediated lysis and antibody-dependent cell-mediated cytotoxicity. The latter mechanism is more effective in killing melanocytes than complement-mediated lysis. Patients with active vitiligo display cytotoxicity for melanocytes in their sera (Yu et al., 1993). Cytoplasmic vacuolation and extracellular granular material, possibly from altered keratinocytes' cytoplasm, Instances of this have been documented, primarily in surrounding unaffected skin in cases of vitiligo and the skin around the edges of the affected areas. Focal vacuolar degeneration has also been noted in the lowest skin layer (Bhawan J and Bhutani KK., 1983).

Vitiligo impacts the complete keratinocyte-Langerhans cell-melanocyte unit (KLM). Langerhans cell density varies in vitiligo, showing decreased, normal, or increased levels. The mechanism for hypopigmentation involves decreased melanin either due to fewer melanocytes or reduced melanin production. Vitiligo's genetic basis is complex, involving multiple genes related to immune function and autoimmune diseases. Certain HLA associations have been reported.

Antibodies that react against substances produced by melanocytes, like tyrosinase, have been detected in the blood of individuals with vitiligo. Melanocyte destruction might be induced by cytotoxic T lymphocytes (CTLs) through perforin/granzyme or Fas/Fas ligand pathways. Type-1 T cells participate in immune responses that involve cell-based inflammation, whereas type-2 T cells are linked to robust antibody reactions. The apoptotic pathway has been implicated in melanocyte death in vitiligo, triggered by cytokines and activated cytotoxic T lymphocytes.

Biological factors like cytokines, inhibitors of melanogenic enzymes, and various compounds have been shown to inhibit tyrosinase and related enzymes' function, often involving down-regulation of MITF. Chemical agents and certain drugs have also been linked to hypopigmentation, often affecting tyrosinase function."

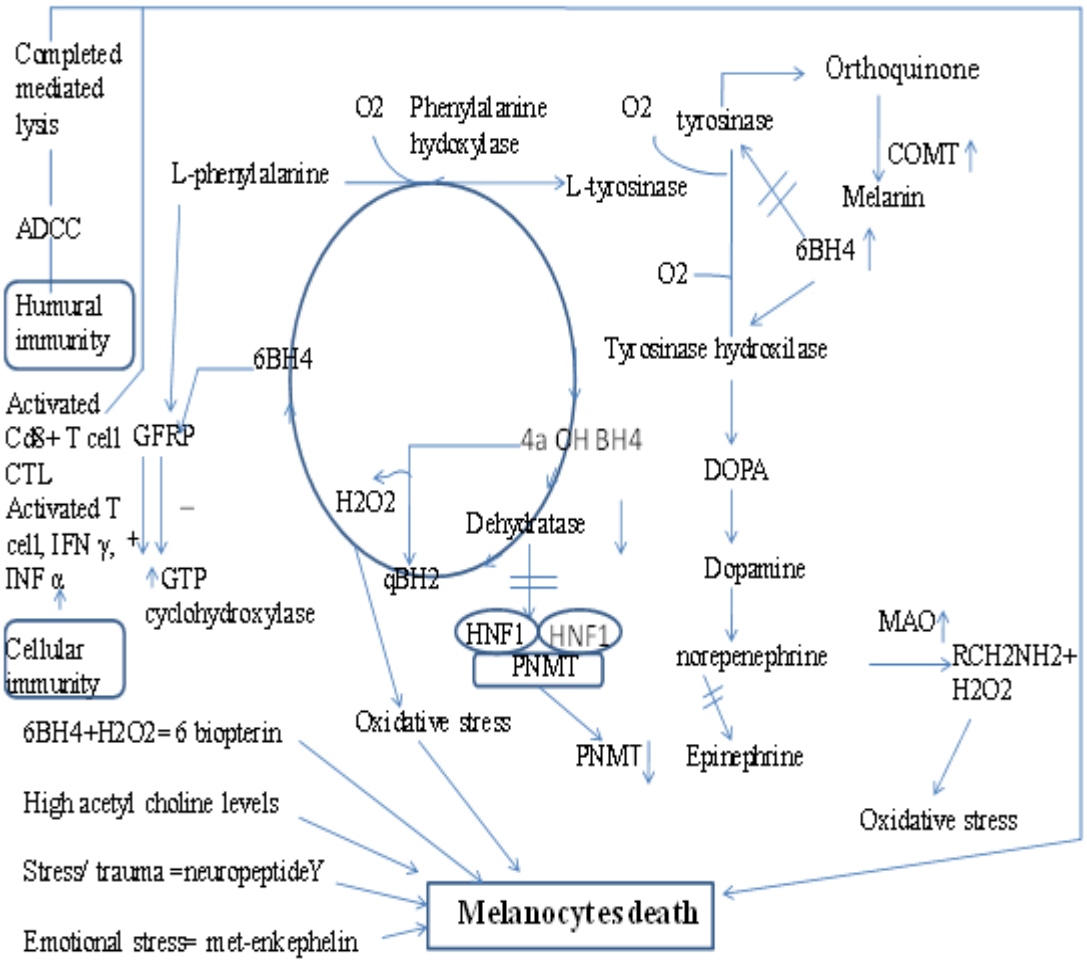

Figure 2: Schemantic Drawing Showing Several Pathways and Factors Responsible For Melanocytes Death.

6BH4 = (6R) - 5, 6, 7, 8-tetrahydrobiopterin, MAO = monoamine oxidase, COMT = Catechol-O- methyl transferase, PNMT = Phenylethanolamine-N-Methyl transferase, GFRP = Growth factor regulatory protein, HNF – 1 = Hepatocyte nuclear factor 1, ADCC = Antibody dependent cell mediate cytotoxicity, qBH2 = quinoid dihydobiopterin, H202 = Hydrogen per oxide.

Phenolic compounds like hydroquinone (HQ) are widely recognized as potent melanogenesis inhibitors and serve as a benchmark for assessing depigmenting agents. HQ exhibits a significant reduction in tyrosinase activity, reaching approximately 90%. This inhibition mechanism is attributed to the generation of quinones and ROS results in oxidative harm to lipids and proteins in cell membranes. HQ interacts with copper and enzyme active sites, impacting melanosome functionality as well (Briganti S et al, 2003).

Nevertheless, it's crucial to highlight that the use of hydroquinone can bring about several undesirable effects. These include contact dermatitis and skin irritation in rare cases, ochronosis, a form of resistant hyperpigmentation that appears blackish and is challenging to treat.

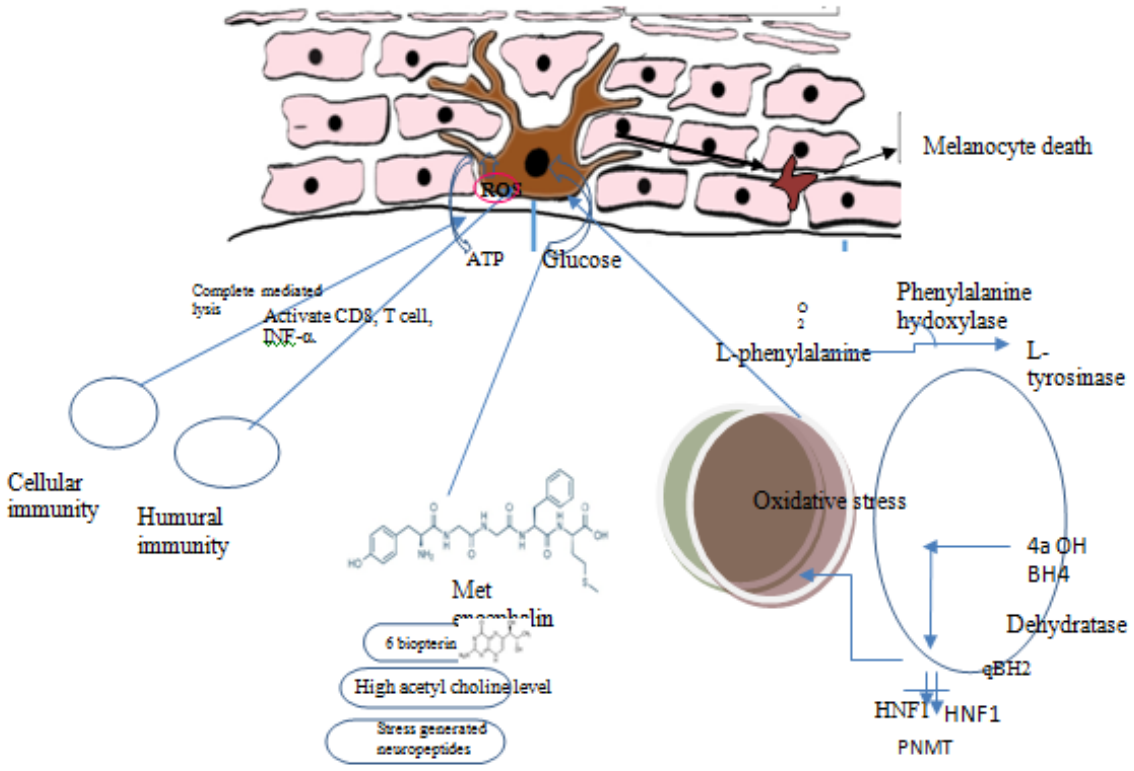

Figure 3: Schematic Diagram Showing Factors Responsible For Death of Melanocytes.

III. ALTERNATIVE AGENTS FOR MELANOGENESIS REGULATION

Arbutin, a natural β-glycoside derived from hydroquinone found in the fruit of Aesculus californica, holds prominence as a potent tyrosinase inhibitor. It stands out due to its more effective artificial α-glycoside structure and its manufactured variation, deoxyarbutin.

Kojic acid, derived from fungal metabolites of Aspergillus and Penicillium species, serves as a recognized skin lightening agent and dietary supplement in Asia. Its mechanism of action involves chelating copper at the enzyme's active site, thereby inhibiting tyrosinase. However, it's noteworthy that when used in combination with other agents, Kojic acid can induce hypersensitivity, including contact dermatitis. Moreover, concerns regarding potential carcinogenic effects have been raised.

A natural compound of aloe vera known as aloesin, displays competitive inhibition of DOPA oxidation and noncompetitive inhibition of tyrosine hydroxylase activity. It effectively combines with arbutin to inhibit UV-induced melanogenesis.

Azelaic acid, a type of dicarboxylic acid obtained from Pityrosporum ovale cultures, demonstrates antiproliferative and cytotoxic impacts. It slightly hampers tyrosinase activity and disrupts mitochondrial oxidoreductase function and DNA synthesis in functioning melanocytes.

Retinoic acid holds a pivotal role in disrupting the transfer of pigment, impeding the dispersion of pigment granules within keratinocytes, promoting epidermal turnover, and inducing desquamation. Despite its effectiveness in treating hyperpigmentation disorders, it's associated with side effects such as peeling, erythema, and post-inflammatory hyperpigmentation.

1. **Immunomodulation in Vitiligo:** Notably, a significant discovery pertains to the use of simvastatin, an immunomodulator. Substantial quantities of simvastatin were observed to efficiently decrease MHC-II expression induced by IFN-γ by activating the CIITA promoter-1. This finding underscores the potential utility of immunomodulators in vitiligo treatment.

2. **Natural Product Interventions:** Various natural products have shown promise in vitiligo treatment. Ginkgo biloba demonstrated heightened efficacy against vitiligo, though it was associated with a few cases of nausea. Khellin exhibited similar results as PUVA (Psoralen + Ultraviolet A) therapy, and certain mixtures, like Xiabai mixture, yielded favorable outcomes in repigmentation.

3. **Therapeutic Approaches in Vitiligo:** Amelanotic melanocytes within the hair follicle's external root sheet have been studied extensively. Through the use of psoralens and UVA therapy, it was discovered that non-dendritic pigment cells transform into fully mature, dendritic melanocytes with tyrosinase activity. These melanocytes then replenish the basal cell layer. Hair follicles serve as a reservoir for melanocytes, contributing to repigmentation.

IV. MEASUREMENT OF VITILIGO AREA AND EVALUATION

The absence of a standardized method for assessing affected areas in vitiligo hampers the comparison of therapeutic outcomes. Two crucial methods, the Vitiligo Area Scoring Index (VASI) and Dermatology Life Quality Index (DLQI), offer tools for quantifying vitiligo areas and evaluating patient satisfaction, respectively.

1. **Vitiligo Therapy:** Initial treatment for depigmentation in vitiligo primarily involves medical therapy. Topical treatments are recommended for cases where depigmentation covers less than 10-20% of the skin surface. Systemic therapies might be considered if localized treatments fail. Repigmentation is a gradual process, necessitating patient compliance and persistence.Various therapeutic categories include corticosteroids, immunomodulators, ultraviolet radiation, lasers, alternative therapies, depigmentation, and psychological support. Corticosteroids suppress the immune response, particularly antibody-mediated cytotoxicity in contradiction of pigment cells. Tacrolimus, an immunomodulator, regulates cytokine expression and impacts melanocyte growth and migration during repigmentation.

V. SURGICAL INTERVENTIONS

Surgical Techniques Include Procedures Like non-cultured epidermal suspension, dermo-epidermal grafts, suction epidermal grafts, mini grafting, punch grafting, and in-vitro

cultured epidermis with melanocytes. Success depends on patient selection and the surgeon's expertise. Surgical side effects may include infection, post-inflammatory hyperpigmentation, and irregular pigmentation.

VI. CONCLUSION

Current research strongly supports the autoimmune hypothesis as the basis for vitiligo's etiology. Progress in understanding melanogenic pathway regulators opens avenues for innovative approaches to pigmentation modulation. Thorough clinical trials are essential for assessing the safety and effectiveness of these therapies.

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