A Comprehensive Analysis of Vitiligo's Epidemiology, Causes, Pathogenesis, and Pharmacotherapy

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***Abstract*- Vitiligo is a pigmentary disorder characterized by the development of white macules due to melanocyte loss. It is prevalent in the US and Europe, with a higher prevalence in women. Half of patients develop the disease before 20 years, raising concerns about associated diseases like thyroid dysfunction, rheumatoid arthritis, diabetes mellitus, and alopecia areata. Generalized vitiligo is the most common clinical presentation, often affecting the face and acral regions. The disease's course is unpredictable, and treatment response varies. Depigmentation can cause severe psychological distress, reduced quality of life, and increased risk of psychiatric morbidity. This two-part series discusses the clinical presentation, histopathologic findings, and various hypotheses for vitiligo's pathogenesis based on past and current research.**

Introduction:

All ages and genders are susceptible to vitiligo, an idiopathic, acquired skin depigmentation condition. [1] A frequent, but not always present, acquired pigmentary condition called vitiligo is characterised by distinct, irregularly shaped depigmented macules and patches.

Fig no.1 Vitiligo on hands and face

Only on the face, hands' dorsa, nipples, axillae, umbilicus, sacral, inguinal, and anogenital areas, all of which are encircled by healthy skin [2]. Vitiligo's pathophysiology is now clearly classified as an autoimmune illness due to significant recent advancements in our understanding of the condition. It is linked to both hereditary and environmental variables, as well as anomalies in cell detachment, oxidative stress, metabolism, and stress levels. Moderately successful medications such as systemic treatment (corticosteroid), topical treatment (calcineurin inhibitors, corticosteroid), and phototherapy (psoralen combination with ultraviolet A and narrowband ultraviolet B [NB-UVB]) are nonetheless monetarily and practically onerous. (5) Vitiligo can have mentally devastating repercussions and can significantly interfere with daily living, so it is important not to disregard it as a minor or cosmetic condition [6]. Melanocyte destruction is a feature of both segmental vitiligo (SV) and nonsegmental vitiligo (NSV). However, it is unclear if the autoimmune response or underlying cellular abnormalities are responsible for the destruction of melanocytes in SV. [7] Taking into account that NSV is more common [8] According to a 2018 study by Diana et al., 108 people, or 0.46% of the population, had vitiligo in the dermatology and venereology polyclinic of Dr. Moewardi General Hospital Surakarta, with a male frequency of 52.78%. [9] Collective The goals of corticosteroid therapy are to stabilise vitiligo lesions, slow the pace of recurrence, and prevent the depigmentation process from progressing further. [10].

Definition:

Skin depigmentation resulting from melanocyte malfunction is the cause of vitiligo, an autoimmune skin disorder. [10] It can also refer to an illness that is chalky or ivory-white in colour.

White pimples on the skin's surface [11] When vitiligo affects the hair, the hair turns white. [12] Vitiligo stability is characterised by the disease being regressive for two months to two years and the absence of new lesions, the enlargement of previous lesions, or the Koebner phenomenon in the first year. Although the exact length of stable vitiligo is unknown, it typically lasts between six months and two years [13].

Varieties of vitiligo:

There are two main types of vitiligo: segmental and non-segmental vitiligo. A portion of this classification is predicated on the unique prognosis and treatment response. Between these two principal categories.[14]

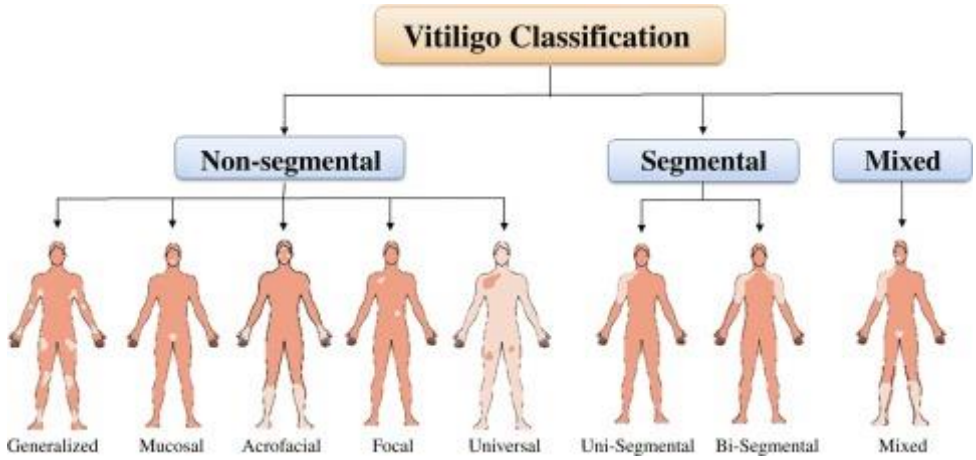

Fig no.2 classification of Vitiligo

I.Non-segmental vitiligo :

It is a condition characterised by depigmentation of the skin, often resulting from exposure to chemicals. [15] It can be focal, mucosal, acrofacial, generalised, universal, mixed, or other rare variants. Focal vitiligo is stable over a two-year period, while mucosal vitiligo involves multiple depigmented patches. [16] Acrofacial vitiligo is limited to the face and distal extremities. Generalised vitiligo involves scattered patches with a widespread distribution. Mixed vitiligo is a combination of segmental and other non-segmental forms. [17]

II.Segmental vitiligo:

It is a less common variant of vitiligo, characterised by a block-like patch in one or multiple body segments. It progresses rapidly over a six-month-to-two-year period, halts spontaneously, is associated with leukotrichia, and is less responsive to treatment. It is more common in paediatric patients. [18,19,20]

Epidemiology:

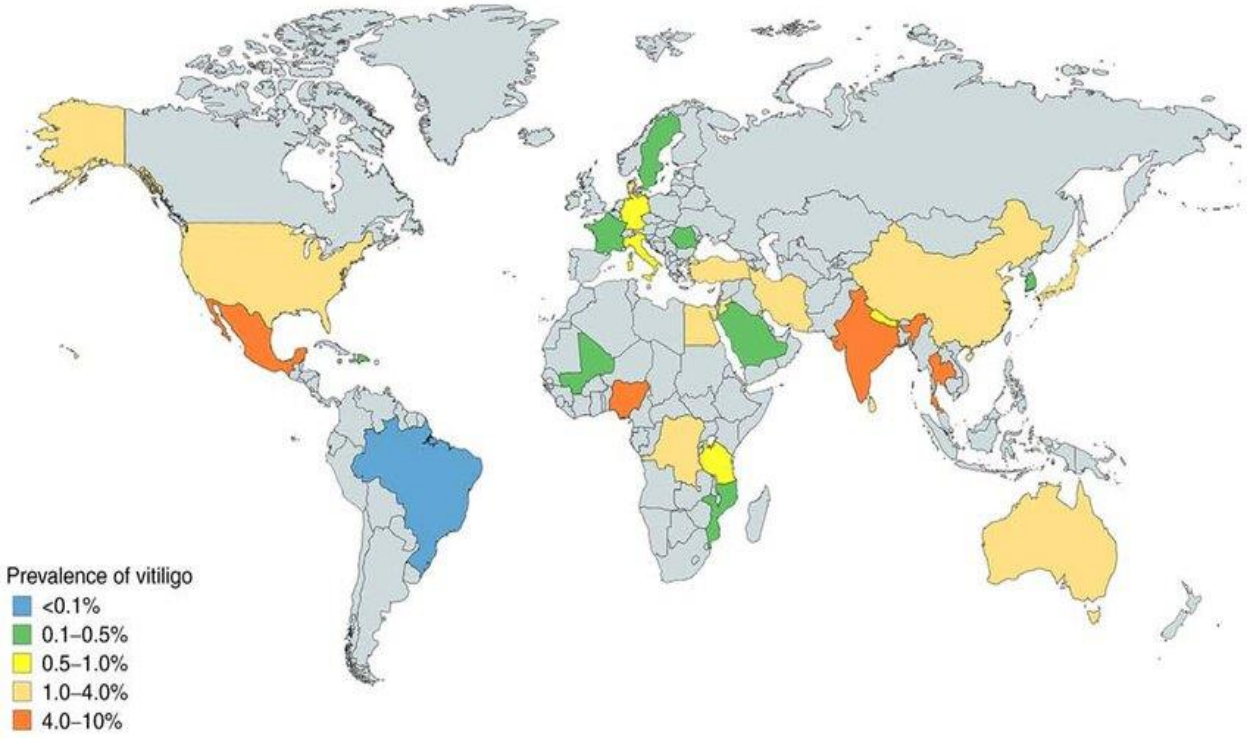

Fig no. 3 Epidemiology of Vitiligo.

Vitiligo is a common depigmenting skin disorder affecting 0.5–2% of the global population, affecting ethnic groups and people of all skin types. [20] Geographical differences exist, with some regions experiencing high rates, such as India, due to the inclusion of cases with chemical and toxic depigmentation [21]. A meta-analysis of over 50 worldwide studies found that the prevalence ranges from 0.06% to 2.28%. Males and females are equally affected, with women and girls seeking consultation more frequently due to the greater negative social impact. The disease affects 25–50% of patients before the age of 10, almost half before 20 years, and 70–80% before 30 years. Most populations have mixed age-of-onset groups and double peaks, with the earliest reported onset being immediately after birth and the latest being 54 years. [22,23,24] The mean age of onset is 15.6 years, with most cases being less than 3 years in duration at referral. [25].

Causes

The multifactorial condition vitiligo is typified by the depletion of viable melanocytes [14, 30].

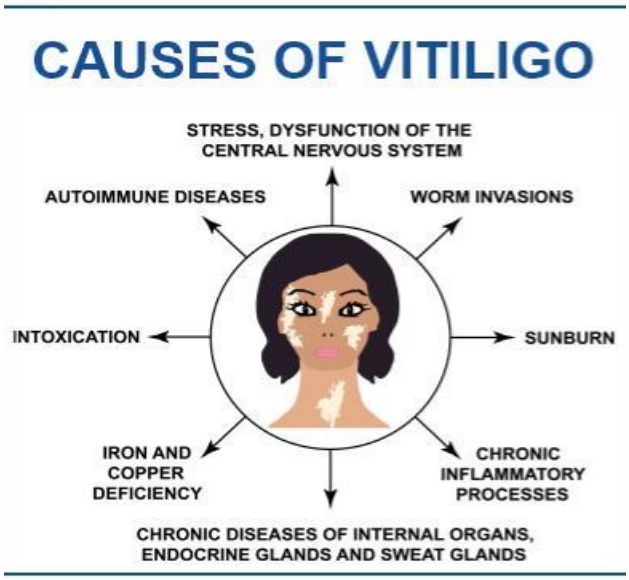

Fig no. 4 Causes of Vitiligo

I.Genetics of Vitiligo

Vitiligo is a genetic condition with a 23% concordance rate in monozygotic twins. It is associated with a 6–18% risk for relatives and a 6% risk for individuals with first-degree relatives. [31,32] Genome-wide association studies have identified 50 genetic loci that confer risk for vitiligo, many of which are shared with other autoimmune diseases. [34,35] Single-nucleotide polymorphisms in multiple-risk genes are related to the emergence of vitiligo. Over 40 susceptibility loci have been identified, with HLA-A polymorphisms conferring the most significant genetic risk. Tyrosinase, an enzyme in vitiligo, is a major autoantigen. A genome-wide association study has discovered a susceptibility variant for NSV in TYR in European white people. [35,36,37].

II.Oxidative Stress

Research suggests that oxidative stress may be the initial cause of melanocyte destruction in vitiligo. Melanocytes from vitiligo patients are more susceptible to oxidative stress and are more difficult to culture ex vivo [38,39].This imbalance between pro-oxidants and antioxidants leads to increased sensitivity to external stimuli, DNA damage, protein oxidation, and lipid peroxidation, impairing cellular function [40,41]. The production of melanin is toxic to melanocytes, and oxidative stress can cause tyrosine-related protein 1 to interact with the calnexin complex, leading to the production of toxic melanin intermediates. Melanocytes are also susceptible to oxidative stress, as enzymatic redox-cycling of phenol can result in the formation of phenoxyl radicals that compromise antioxidant defense mechanisms [41,42].

Mechanisms of Autoimmune Killing:

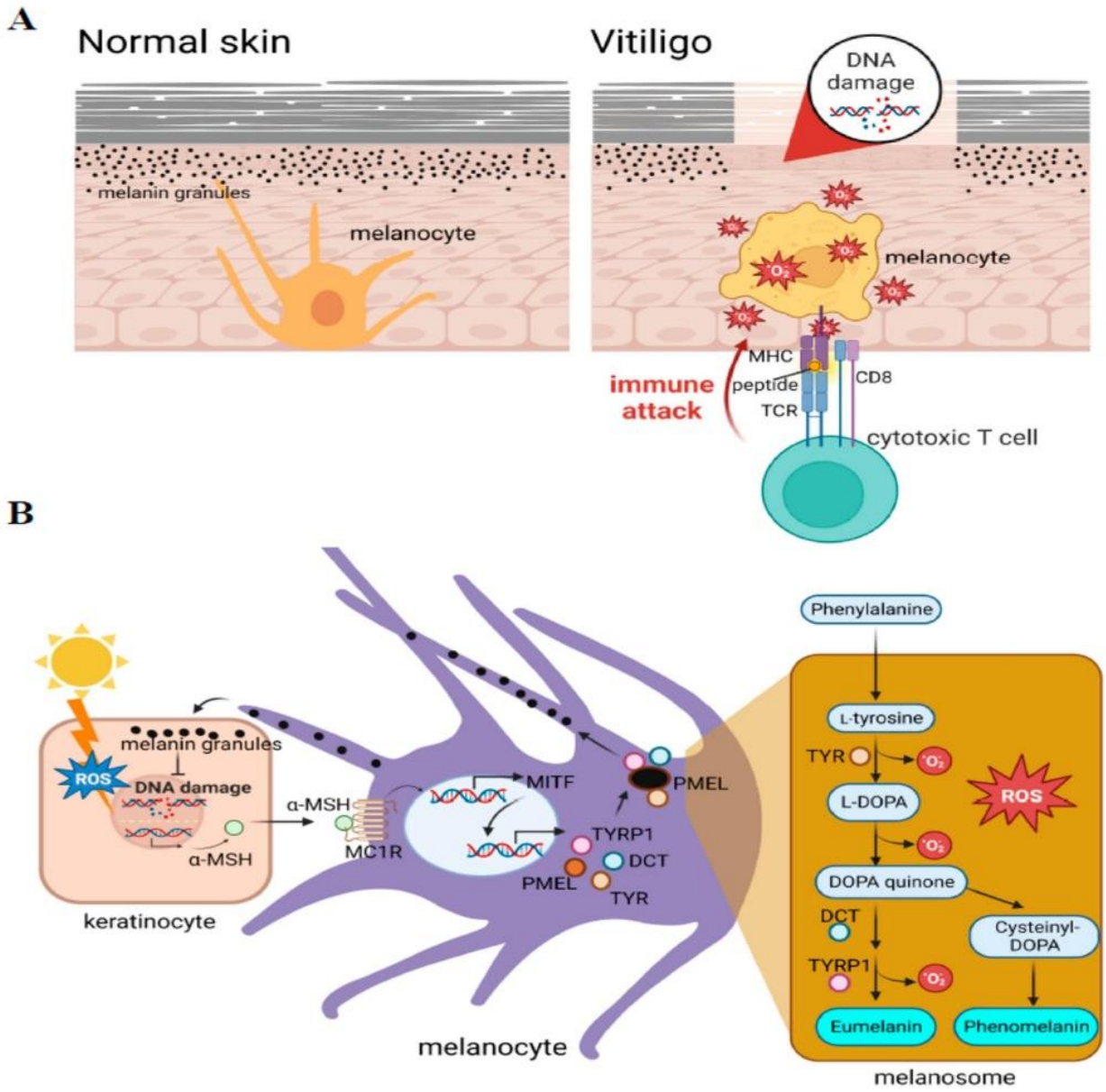

Fig no.5 Mechanisms of Autoimmune Killing

Cytokines like perfin, granzyme, and Fas Ligand are believed to be used by cytotoxic T cells for melanocyte elimination in vitiligo and melanoma immunotherapy [43,44,45]. However, the exact mechanism used by these cells is still unclear due to different intracellular signaling pathways and potential differences in mechanisms for autoimmunity compared to tumors and viral-infected cells. Further studies are needed to understand this process [45,46].

Pathogenesis:

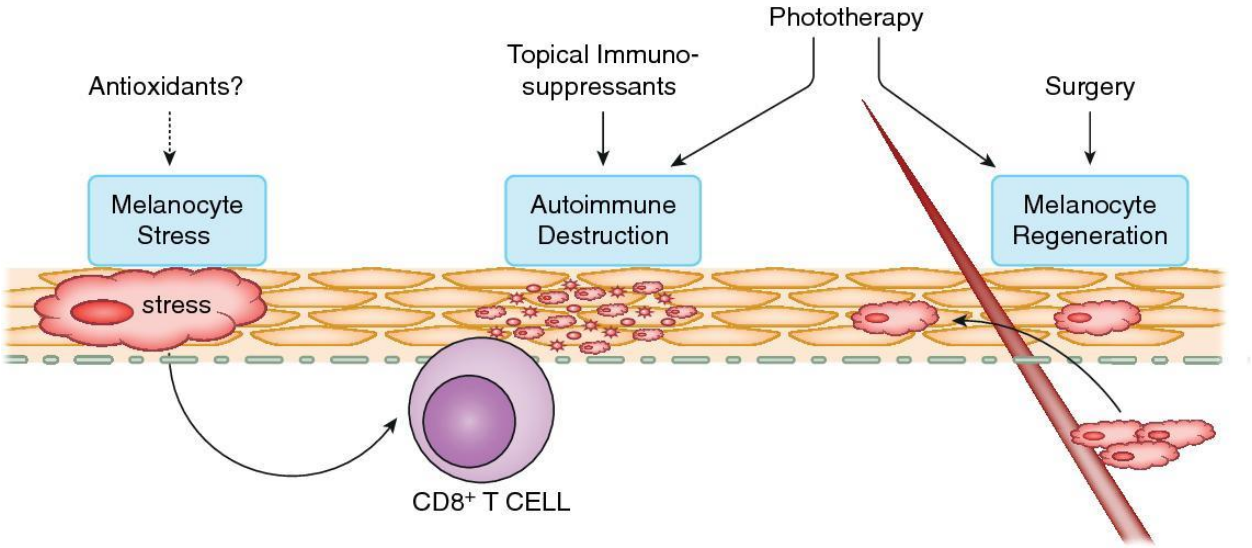

Fig no. 6 Pathogenesis And Emerging Treatment

Vitiligo is a skin disorder characterised by the loss of functional melanocytes. Multiple mechanisms have been proposed for melanocyte destruction, including genetics, autoimmune responses, oxidative stress, inflammatory mediators, and melanocyte detachment [47,47,49]. Both the innate and adaptive immune systems are involved. The autoimmune nature of vitiligo is now a consensus [50].The "convergence theory" suggests multiple mechanisms may work together in vitro, leading to the same clinical result. Recent evidence suggests an overlapping inflammatory pathogenesis for both SV and NSV, with the nervous system contributing to the disease [52,53].

Diagnosis:

Vitiligo is a depigmentation disorder characterised by the loss of melanin pigment in the epidermis and the absence of melanocytes [54]. The diagnosis is straightforward, based on the presence of amelanotic, non-scaly, chalky-white macules with distinct margins. The absence of melanocytes can be assessed noninvasively through in vivo confocal microscopy or a skin biopsy [55] Lymphocytes may be noted at the advancing border of the lesions.

VARIOUS APPROACHES OF TREATMENT :

a. Immunomodulating/suppressing agents

Immunomodulating agents like growth factor and leukotrienes are used to treat vitiligo, which is believed to be an immunological aberration, with their practical utility being spadreno-cortico trophic hormones (ACTH) [56].

- Levomisole [57]
- Cyclophosphamide[58]
- topical fluorouracil[59]
- human placental extract.[60]
- polypodium leucotomos.[61]
- Penicillamine.[62]
- suplatast tosilate [63].

b. Topical/intra lesional corticosteroids :

Initial studies used betamethasone-17 valerate for vitiligo treatment, with variable results depending on duration and stages [64]. Propionate cream was later tried, with fluticasone propionate and mometasone being added for less skin atrophy. Topical corticosteroids can be first-line therapy for vitiligo, but they should be monitored for side effects [64].

c. Herbal Concoctions:

Herbal remedies of various kinds and effects have been used to cure vitiligo since ancient times. a succinct summary of the herbal remedies that are available for the sickness of the pigments [65]

d. **Ginkgo biloba** :

This extract is effective in treating various diseases like allergies, varicose veins, premenstrual syndrome, headaches, and vertigo. Its anti-inflammatory, immunomodulatory, and antioxidant properties make it safe and well-tolerated at therapeutic dosages (120 mg/day) [66]. Patients on anticoagulants should take them under medical supervision.

e. Cucumis melo :

Cucumis melo extract, rich in antioxidants, has been shown to prevent melanocyte deconstruction in vitiligo. Preliminary studies have evaluated the efficacy of a topical preparation containing Cucumis melo SOD and catalase, with phenylalanine, Cucumis melo extract, and acetyl cysteine being promising [69].

f. Khellin :

The Amni visnaga plant has been used in medicine for treating vitiligo, with analogues providing safer and better efficacy. These analogues stimulate melanocyte proliferation and melanogenesis, with topical khellin 4% being successfully used [70].

A. Ayurvedic medicine:

1. Picrorhiza kurroa :

Chemical constituents: picroside I and picroside II Improved repigmentation outcomes were observed when Picrorhiza kuroda, a herbal extract with immune-modulating and antioxidant qualities, was studied in conjunction with phototherapy as a possible treatment for vitiligo [71].

2. Polypodium leucotomos

Many skin conditions, including psoriasis and atopic dermatitis, are treated with Polypodium leucotomos [72].

B. Miscellaneous topical/oral therapies:

1. Calcipotriol:

Calcium hemostasis may cause vitiligo-affected skin. Vitamin D3 receptors in melanocytes can be used as an alternative therapy. Topical vitamin D3 ointment and solar irradiation can be used as an alternative. Adding calcipotriol ointment to PUVA or NB-UVB therapy improves repigmentation [73].

2. Topical prostaglandin analogue:

Prostaglandins stimulate melanosomes in melanocytes and produce eumelanogenesis in Cynomolgus monkeys' iridium melanocytes. A preliminary study found marginal repigmentation in vitiligo patients treated with topical prostaglandin E2, but further research is needed. [74].

3. Sex-steroid and thyroid powder mixture:

Four patients were treated with a sex-steroid + thyroid powder combo (Metharmon-F; two tablets daily), and all of the patients showed histological and clinical improvement. Ichimyja [75] looked into this feature and discovered that the review of the worldwide prevalence of

Vitiligo in children, adolescents, and adults causes melanocytes to produce and proliferate via boosting the alpha-melanocyte stimulating hormone (a-MSH). This medication was found to be effective in treating non-segmental vitiligo and to have no significant side effects [76] .

4. **Other therapies :**

Although there have been occasional advancements in chemotherapeutic drugs, they have not consistently demonstrated efficacy. Among these, clofazimine stands out [123].

- clofazimine [77]
- tar/anthraline [78]
- topical minoxidil [79]
- thiambutosine [80]
- antimalarials [81]
- iontophoresis with 1% sodium salt of meladinine [82]

i. Nutritional therapy :

Nutritional therapy is crucial in vitiligo treatment, especially in developing countries where malnourished children are more susceptible to the disease. Conservative management with adequate vitamins, trace elements, and protein supplementation can stabilize the disease process, especially in children [83].

ii. Role of vitamin cyanocobalamin (B12) and folic acid:

A study of 100 vitiligo patients found that folic acid and vitamin B12, along with sun exposure, led to repigmentation in over half of them. The administration of these vitamins and B12 resulted in a noticeable improvement of the lesions [84].

iii. Other vitamins and trace elements :

Zinc, manganese, nickel, cobalt, calcium, iron, ascorbic acid, and alpha tocopheral influence pigmentation in vitiligo. Ferrous ions may increase pigmentation. Studies on psoralen and ultraviolet A (PUVA) with or without vitamin E found that vitamin E prevents oxidative stress from PUVA therapy, despite not affecting clinical improvement outcomes [85].

Conclusion:

Vitiligo is an acquired skin pigmentation condition that causes the loss of melanocytes, leading to depigmented regions. This condition can affect individuals of all ages, ethnicities, and genders and may be caused by autoimmune or hereditary reasons. Predisposition and environmental stimuli. Although there is no cure for vitiligo, therapies include topical corticosteroids, phototherapy, and skin grafting can alleviate symptoms and enhance aesthetic appearance. Current study strives to better understand the underlying causes of vitiligo and find more effective treatments. The main goal is to provide a complete review of the topic while also documenting the natural repercussions. This review could be beneficial for future study.

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