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An Overview of Aetiology, Types, Pathophysiology and Treatment of Vitiligo

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ABSTRACT
Vitiligo is a chronic skin condition characterized by the loss of melanin, resulting in white patches on the skin. Its etiology is multifactorial, involving genetic predisposition, autoimmune responses, and environmental triggers. The disorder often presents with asymptomatic depigmented macules and patches that can appear on any part of the body, leading to significant psychological impact and social stigmatization. The pathogenesis of vitiligo is complex, involving the destruction of melanocytes—cells responsible for skin pigmentation. Autoimmune mechanisms, where the body's immune system mistakenly attacks its own cells, play a crucial role. Genetic factors may also contribute to susceptibility, while stress, sunburn, and certain chemicals can exacerbate the condition. Treatment options for vitiligo aim to restore skin color or achieve an even skin tone. Therapies include topical corticosteroids, calcineurin inhibitors, and phototherapy, which stimulate regimentation. In more severe cases, depigmentation of unaffected skin may be considered for cosmetic uniformity. Psychosocial support is essential, as vitiligo can significantly affect quality of life. Ongoing research continues to explore more effective therapies and a deeper understanding of the underlying mechanisms of this complex condition.

Keywords: etiology, predisposition, physiological, melanocytes, regimentation, effective, underlying.

I. INTRODUCTION

A chronic skin condition called vitiligo is typified by a progressive loss of melanocytes that results in skin patches that are depigmented.

This condition can affect individuals of all ages and ethnic backgrounds, with its impact often extending beyond physical appearance to encompass psychological and social dimensions. The pathogenesis of vitiligo remains complex and multifactorial, involving autoimmune mechanisms, genetic predispositions, and environmental triggers.

Clinically, vitiligo can present in various forms, including generalized, localized, and segmental types, each with unique patterns and progression. Despite its non-life-threatening nature, vitiligo can significantly affect quality of life, leading to issues such as low self-esteem and social anxiety. Current treatment options range from topical therapies and phototherapy to more advanced interventions like depigmentation and skin grafting, yet achieving satisfactory regimentation remains challenging for many patients.

This review aims to provide a comprehensive overview of vitiligo, exploring its etiology, clinical manifestations, and therapeutic approaches. By synthesizing current research findings and clinical practices, we hope to enhance understanding of this complex condition and foster better management strategies for affected individuals.

Key points

- Vitiligo is a pigmentation illness that affects both sexes equally and can occur at any age.
- It is disorder of the skin and mucous membranes that develops over time, vitiligo is typified by well-defined, depigmented macules and patches that result from the selective death of melanocytes.
- It can manifest at any age; instances have been documented as early as six weeks following the usual CAPSULE SUMMARY. A pigmentary illness that causes white macules to emerge at any stage in life, vitiligo can have serious psychological effects. It affects all skin types equally frequently in men and women.
- A biopsy is rarely required to diagnose vitiligo, despite the fact that a wide differential exists for illnesses involving pigment loss.
- There have been several aetiology theories put up, however the strongest evidence points to an autoimmune phenomenon linked to underlying genetic predisposition at birth.

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- Affected individuals make up between 0.5% and 1% of the population, with nearly half having symptoms before turning 20.
- Its frequency does not seem to alter based on race or skin type, and it appears to be equally common in men and women. Vitiligo may be a psychologically distressing condition, particularly for those with darker skin tones as it is more evident in them.
- It seems to have a polygenic/multifactorial genetic transmission pattern. The true etiology is controversial but has been linked to oxidative stress, sympathetic neurogenic disturbance, and/or autoimmune (AI) reasons.
- Segmental (SV) and nonsegmental (NSV), which is the more common kind, are the two main types of vitiligo.
- NSV is described as "an acquired chronic pigmentation disorder characterized by white patches, often symmetrical, that usually increase in size with time" by the Vitiligo European Task Force (VETF), NSV is defined by the Vitiligo European Task Force (VETF) as "corresponding to a significant loss of functioning epidermal and occasionally hair follicle melanocytes." SV can develop in a unilateral distribution that matches a dermatome entirely or in part. Vitiligo lesions tend to be itchy and sunburn easily.
- There is a common Koebner phenomenon. A rare and perifollicular pattern of spontaneous regimentation is seen in vitiligo, a chronic, persistent condition. A lot of folks don't know enough about what they have.
- According to one study, 51.3% of patients said that receiving subpar medical care was the reason for their vitiligo, while 30% blamed their own behavior, 25% pointed to their food, 21.3% to their mental health, and 20% pointed to pollution.

EPIDEMIOLOGY

➢ **Key points**

- The prevalence of vitiligo is likely less than 1%, but varies based on region.
- Females usually acquire the disease earlier than males.

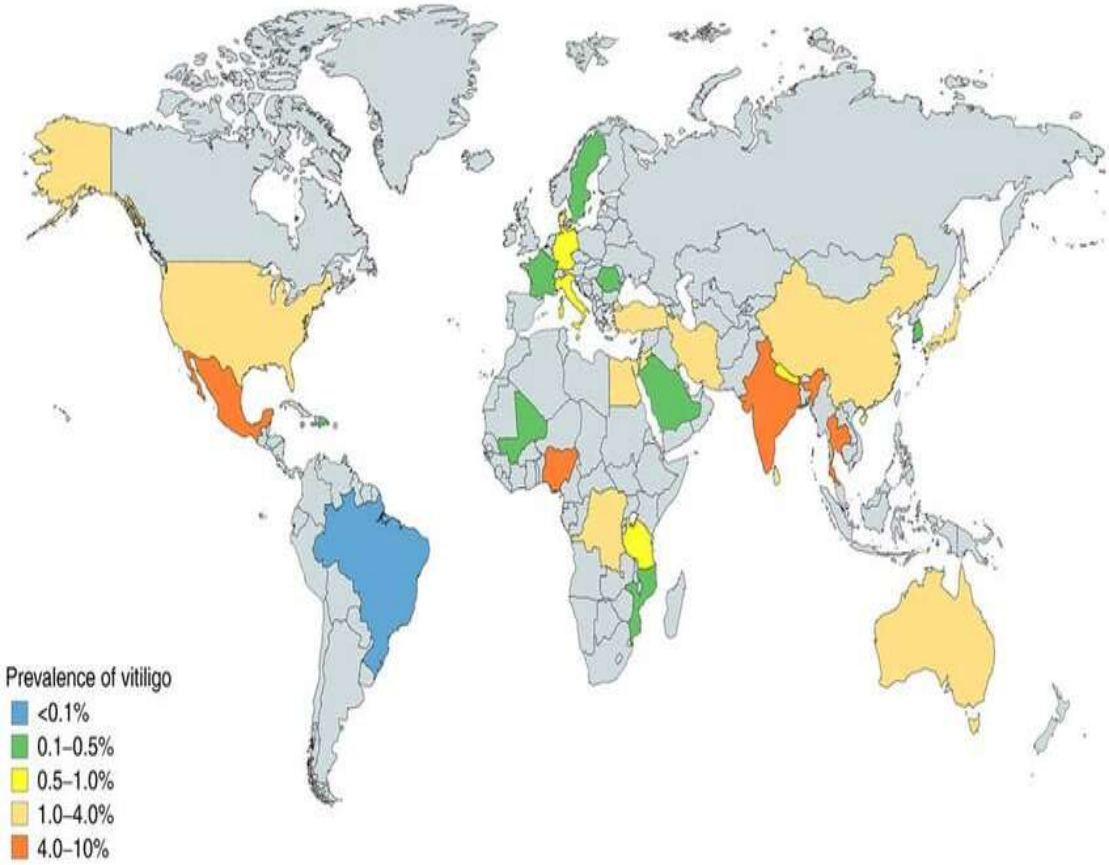

FIG.NO. 1 (Prevalence of vitiligo in different countries)

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Vitiligo is the most common depigmenting skin disorder, affecting 0.5–2% of the adult and pediatric populations worldwide. However, there seem to be notable regional differences. For example, a study conducted in the Shaanxi Province of China revealed a frequency as low as 0.093%, although rates in other regions of India reached as 8.8%. This high score In 1977, 0.38 percent of people on the Danish island of Bornholm developed vitiligo, according to one of the largest and longest epidemiological surveys ever carried out. People of all skin tones and races are susceptible to vitiligo.

E could be attributed to the inclusion of cases with toxic and chemical depigmentation or to the high prevalence of a single skin institute in Delhi. Moreover, there may be a mismatch in the prevalence estimates due to a rise in data reporting in places with high rates of social and cultural shame or where darker-skinned individuals tend to have more noticeable lesions. A comprehensive examination of prevalence data from over 50 research studies conducted worldwide indicates that the prevalence of vitiligo ranges from a low of 0.06% to a high of 2.28%. A meta-analysis comprising 103 papers assessed the prevalence of vitiligo; the combined frequency from 82 population- or community-based studies was 0.2%, and from 22 hospital-based studies it was 1.8%. Published studies indicate that between 5 and 30% of people have SV. This mismatch in epidemiological statistics could be explained by differences in disease classification from previous years, variations in patient reporting, and differing demography.

Figure 2: A person suffering from vitiligo

Vitiligo is the most common pigmentary problem, happens worldwide,15 with a frequency pace of somewhere in the range of 0.1% and 2%, regardless old enough, race, ethnic beginning or skin colour. The rate of vitiligo in those with racially pigmented skin is higher, albeit solid figures are not available. The commonness has been accounted for ashigh as 4% in some South Asian, Mexican and US populations.The two genders are similarly afflicted. In certain examinations,a female dominance has been reported, however the disparity has been credited to an assumed expansion in announcing of restorative worries by female patients. Albeit familial bunching of cases is generally seen, legacy happens in a non-Mendelian pattern. Sporadically, it is accounted for that vitiligo is discourage mined by an autosomal predominant quality of variablepenetrance. It has likewise been accounted for in monozygoticm twins.

Vitiligo usually starts in youth or youthful adulthood, with top beginning of 10-30 years, however, it can create at any age. A few studies report that half of cases show up before the age of 20 years. It is seldom found in outset or old age. The occurrence diminishes with expanding age. Barona tracked down that in patients with one-sided vitiligo, the mean age at beginning was 16.3 years (95% certainty span [CI] = 12-19 years), contrasted with 24.8 years (95% CI = 22-28 years) in patients with reciprocal vitiligo. One review showed that a high extent of patients with vitiligo

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were understudies or students or of a high socio-proficient level. Most patients with vitiligo quality the beginning of their illness to explicit life occasions (actual injury, sun related burn, profound injury, sickness or pregnancy). Except for Koebner peculiarities, there is no verification that these variables cause or partake in vitiligo.

Roughly 20% of patients with vitiligo have something like one first-degree relative with vitiligo, and the general gamble for first-degree family members of vitiligo patients is expanded byfold.

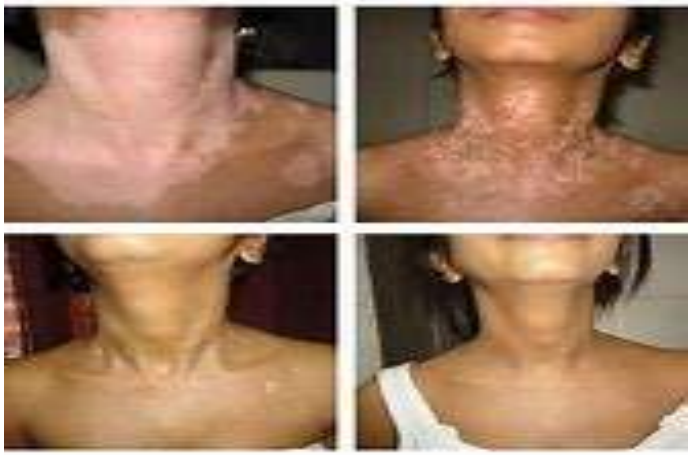

FIG NO. 3 Patient suffering from severe Vitiligo

Types of vitiligo:

- Type A
- Type B

In the past, hypotheses concerning the pathogenesis of vitiligo have been confusing and contradictory. However, autoimmune mechanisms have been considered important by many authors. We have suggested that vitiligo can be divided into two types:

- Type A: caused by autoimmune mechanisms.
- Type B: which results from the dysfunction of sympathetic nerves in the affected area.

If this is the case, the clinical course and features of the two types should be different, and this has been investigated in the present study.

Generalized Vitiligo: The most common form, where white patches appear on various parts of the body in a symmetrical pattern.
Segmental Vitiligo: Affects one side of the body or a specific area, often starting at a younger age and progressing more slowly than generalized vitiligo.
Focal Vitiligo: Characterized by one or a few small white patches that are localized to a specific area.
Mucosal Vitiligo: Affects the mucous membranes, such as those in the mouth or around the eyes.
Universal Vitiligo: A rare form where nearly all skin loses pigment, leading to a very light appearance overall.
Acrofacial Vitiligo: Involves the face and extremities, with patches appearing on hands, feet, and facial areas.

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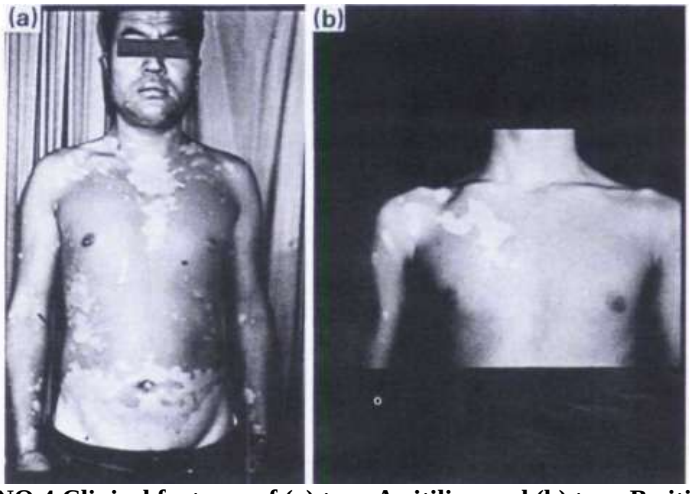

FIG NO.4 Clinical features of (a) type A vitiligo and (b) type B vitiligo

Clinical data When patients were seen for the first time a detailed history was taken, including age at onset of vitiligo, progression of the vitiligo and any associated diseases in the patients and their close relatives. After analyzing the distribution pattern of the depigmented patches, the patients were split into two groups: type B, which comprised all cases of vitiligo not included in type B, and type A, which included depigmented patches restricted to a specific dermatome similarly to herpes zoster.

The depigmented patches in type A vitiligo were distributed irregularly, although they tended towards a symmetrical distribution during the progression of the disease (Fig. 4). All patients were examined for halo naevi or occurrence of Kobner's phenomenon. In the course of treatment over many years the appearance of new depigmented patches was carefully recorded. Statistical analysis the results were analysed using the Wilcoxon rank sum test. Fisher's exact test and the test.

ETIOLOGY OF VITILIGO:

It is still unclear exactly what causes vitiligo, including its many varieties such acral, mucosal, and localized vitiligo. StillNumerous variables have been linked to its growth, including the primary reasons are:

- **AUTOIMMUNE FACTOR:** It is believed that vitiligo, especially its segmental and generalized variants, is primarily caused by immunological systems. In these instances, the immune system of the body attacks and kills resulting in depigmentation due to melanocytes. Immune Factors could include cytokines, T cells, and melanocyte antigen-targeting autoantibodies.
- **GENETIC PREDISPOSITION:** Evidence suggests that numerous genes are involved in the hereditary component of vitiligo.vulnerability Numerous genetic loci have been found.is linked to vitiligo, include genes implicated in oxidative stress, melanocyte function, and immunological modulationreaction to stress.
- **OXIDATIVE STRESS:** that oxidative stress is the primary cause of vitiligo, a condition marked by damage to melanocytes.Redox equilibrium is upset by this stress, which results in an imbalance brought on by the overproduction of reactive ROS (reactive oxygen species)and inadequate scavenging mechanisms. But the disparity in oxidative antioxidant defines systems and stress within the pathophysiology of vitiligo has been linked to the skin.Higher levels of oxidative stress may cause melanocyte apoptosis and damage, which lead to depigmentation.

- **Neurochemical Factors:**
  Neurochemical mediators that affect melanocyte function and aid in the formation of melanocytes include neuropeptides and neurotransmitters. Neuropeptides and neurotransmitters are examples of neurochemical mediators that may affect melanocyte function and aid in the formation of vitiligo.
- **Changes in Pigmentation of Mucous Membranes:** Rarely, vitiligo may also impact mucous membrane pigmentation, including the

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tissues inside the mouth and nose. It's crucial to remember that vitiligo symptoms can differ greatly from person to person and that not everyone who has the condition will have all of these symptoms. Furthermore, there are differences in the intensity and course of vitiligo; some people only have mild depigmentation, while others may have enormous patches that cover a significant portion of the body.

- **Sensitivity to Sunlight:**In areas that are depigmented, some vitiligo patients may become more sensitive to sunlight. These places may burn more easily or become more visible after being exposed to the sun.
- **Progressive Spreading:** Over time, vitiligo spots may progressively grow larger or spread. There's a chance that new patches will appear, which would further depigment.
- **Hair Discoloration:** Vitiligo can cause hair in the affected areas to turn white or lose pigment in addition to damaging the skin.

SIGN AND SYMPTOMS OF VITILIGO:

Vitiligo is a long-term skin disorder that results in lighter regions of skin due to pigmentation loss. These are a few typical indications and symptoms:

1. **Light Skin Patches:** The appearance of lighter skin patches is the main symptom. These patches can vary widely in size and shape; they usually begin tiny but have the potential to spreads.
2. **Symmetrical Patterns**: Although this isn't always the case, the lighter patches frequently show up symmetrically on both sides of the body.
3. **Alterations in Pigmentation**: The skin that is impacted may become paler in comparison to the surrounding skin. In regions where there is greater pigment contrast, as on darker skin, it could be more apparent.
4. **Changes in Hair:** White or grey hair can occur from pigment loss in vitiligo-affected sections of the hair. This can happen on the eyebrows, eyelashes, scalp, and other places.
5. Sensitive Skin: Due to a lack of the protective pigment melanin, the affected parts of the skin may be more susceptible to sunburn and UV radiation.
6. **Sensitive Skin**: Due to a lack of the protective pigment melanin, the affected parts of the skin may be more susceptible to sunburn and UV radiation.
7. **Itching or Inflammation**: While less often, the affected skin may occasionally itchy or inflame.
8. **Periodic Depigmentation:** Vitiligo can occasionally also damage mucous membranes, such as those within the mouth and nose, resulting in lighter patches in these regions.

FIG NO.5 (SYMPTOMS OF VITILIGO)

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Pathogenesis of Vitiligo

Vitiligo is a multifactorial disorder characterized by the destruction of functional epidermal melanocytes.Functional epidermal melanocytes are destroyed in vitiligo, a multifactorial condition . There is still substantial disagreement about the numerous ideas regarding the loss of melanocyte function, and the exact etiology and pathophysiology are complicated. Numerous pathophysiological explanations have been hypothesized, such as oxidative stress, autoimmunity, genetics, and neurological system dysfunction. Therefore, none of these pathways can fully account for all vitiligo phenotypes, and diverse mechanisms may even contribute to the same clinical outcome .

As a result, the convergence theory—which integrates all previous hypotheses into a single, complete theory—was put forth. It holds that a number of factors contribute to the decline in melanocyte viability. It is now accepted that the oxidative stress and autoimmune theories are the primary mechanisms in the pathogenesis of vitiligo, even if there is ongoing debate over each of these pathogenetic ideas.

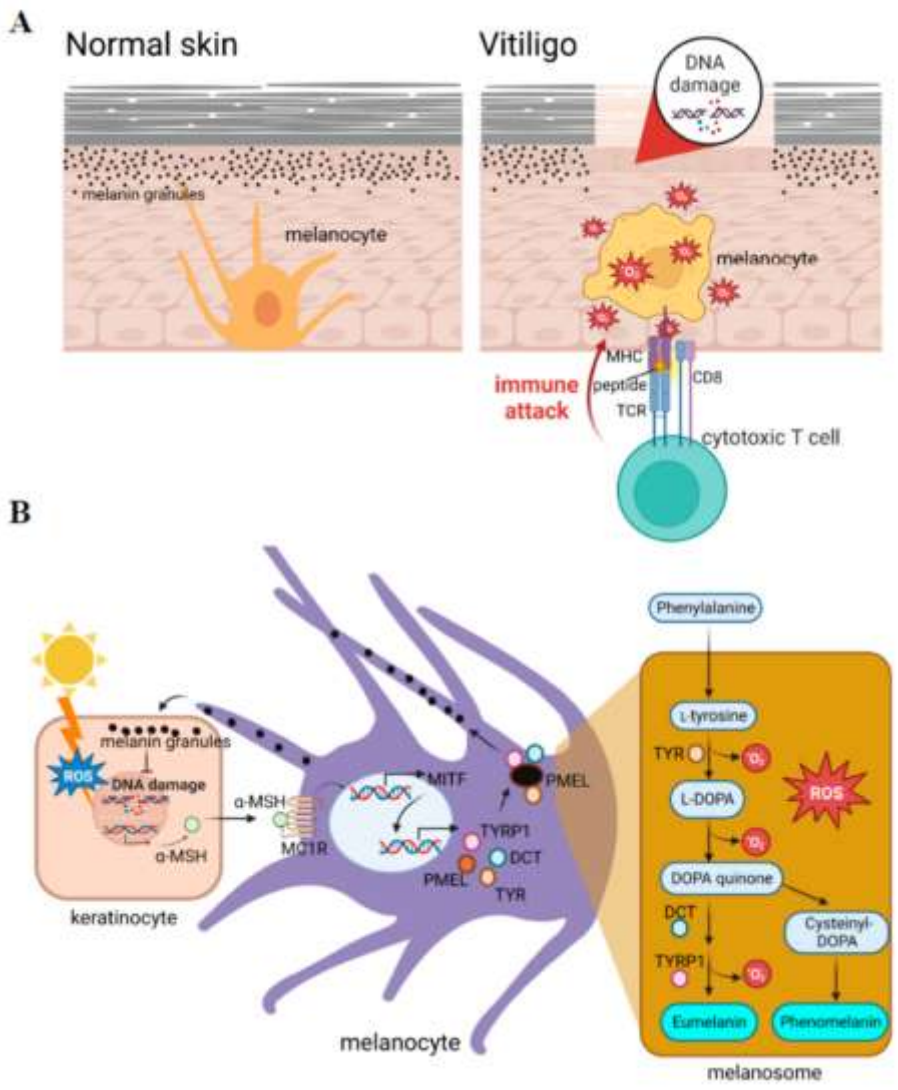

FIG NO. 6 (ROS MECHANISM)

ROS (REACTIVE OXYGEN SPECIES)

The primary species for assessing the degree of oxidative stress are reactive oxygen species (ROS), which include O2−, -OH, and H2O2. Both external exposure and cellular metabolic activities can cause ROS. Apart from

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mitochondrial metabolism, one of the main intracellular stressors that generate reactive oxygen species (ROS) is melanin production. Melanin synthesis is one of the processes in cells that has two opposing effects: on the one hand, it is a photosensitizer that produces a lot of intracellular reactive oxygen species (ROS); on the other hand, it is a photoprotector that shields DNA from UV damage. Under normal physiological settings, the antioxidant system transforms trace levels of reactive oxygen species (ROS) into harmless compounds. Overproduction of ROS can happen in individuals with a genetic predisposition, which can lead to cell damage, or in pathological conditions like inflammation.

When chronic inflammation persists, as it does in neurodegenerative diseases, aging, and chronic illness, antioxidant defenses may be overpowered. Numerous factors that cause inflammation, including as TNF-α (tumor necrosis factor-α), lipopolysaccharide (LPS), and thrombin, affect the generation of ROS by means of the mitochondria and nicotinamide adenine dinucleotide phosphate (NOX) oxidase. Increased intracellular ROS levels progressively increase the risk of skin conditions.When oxidative stress is identified in a patient, it can give important information about the state of their illness and direct treatment plans. By using fluorescent probes and chemiluminescence assays to evaluate the degrees of protein oxidation, lipid peroxidation, and DNA/RNA damage from patient plasma or serum, oxidative stress can be indirectly assessed. Enzymatic antioxidant activities such glutathione peroxidase, gluetathione S-transferases, catalase (CAT), and superoxide dismutase (SOD) can also be used to evaluate oxidative stress.When oxidative stress is found in a patient, treatment strategies can be guided and vital information about the patient's condition can be obtained. Oxidative stress can be indirectly measured by measuring the levels of protein oxidation, lipid peroxidation, and DNA/RNA damage from patient plasma or serum using fluorescent probes and chemiluminescence assays. Oxidative stress can also be assessed by enzymatic antioxidant activities such superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase, and gluetathione S-transferases.

By evaluating the levels of the antioxidant enzymes SOD and CAT, current research have demonstrated significant levels of antioxidant activity in cases of active vitiligo in comparison to stable vitiligo and healthy controls. According to one study, people with non-segmental vitiligo may exhibit varying degrees of activity based on the blood oxidative stress indicator, total antioxidant capacity (TAC), malondialdehyde (MDA), and 8-hydroxy-2′-deoxyguanosine (8-OHdG). A precise diagnosis and further treatment for patient management are provided by such assessments of oxidative stress in the blo8od and skin patch areas of patients. This paper describes what happens to cells when there are too many reactive oxygen species in vitiligo skin.

Vitiligo is a chronic skin disorder characterized by the progressive loss of melanocytes, leading to depigmented patches on the skin. This condition can affect individuals of all ages and ethnic backgrounds, with its impact often extending beyond physical appearance to encompass psychological and social dimensions. The pathogenesis of vitiligo remains complex and multifactorial, involving autoimmune mechanisms, genetic predispositions, and environmental triggers.

Genetics Vitiligo
(Molecular Biology)

Clinically, vitiligo can present in various forms, including generalized, localized, and segmental types, each with unique patterns and progression. Despite its non-life-threatening nature, vitiligo can significantly affect quality of life, leading to issues such as low self-esteem and social anxiety. Current treatment options range from topical therapies and phototherapy to more advanced interventions like depigmentation and skin grafting, yet achieving satisfactory repigmentation remains challenging for many patients.

This review aims to provide a comprehensive overview of vitiligo, exploring its etiology, clinical manifestations, and therapeutic approaches. By synthesizing current research findings and clinical practices, we hope to enhance understanding of this complex condition and foster better management strategies for affected individuals.

Numerous investigations have provided compelling evidence in favor of the multifactorial, polygenic inheritance of vitiligo. The estimated risks for genetic and environmental variables are 20% and 80%, respectively. Vitiligo has been shown in several epidemiological studies to cluster within families. In summary, approximately 20% of patients report having at least one first-degree relative affected, and approximately 23% of monozygotic twins have concordance.

About 71% of the overall vitiligo heritability and 53% of the total risk are accounted for by common genetic variations (risk allele

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frequency > 0.01), while rare variants account for the remaining 29% of the heritability and 23% of the total risk.

The most effective method for comprehending the intricate polygenic inheritance of vitiligo is a DNA sequence analysis. At least 54 vitiligo susceptibility loci have been found thus far by Genome-Wide Association Studies (GWAS), which have been carried out on populations in Asia and Europe. Most of them have to do with immune system modulation, melanocyte recognition and death, and several have similarities to other autoimmune disorders such thyroid disease, type 1 diabetes, and rheumatoid arthritis.

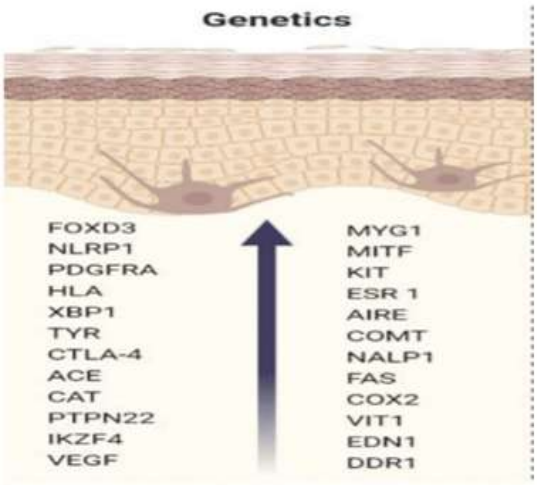

Fig no. 7 pathogenesis of genetic vitiligo

The TYR gene, which codes for tyrosinase, a crucial enzyme in the manufacture of melanin, is an exception. It was discovered in a genome-wide association study (GWAS) conducted on European White individuals suffering from nonsegmental vitiligo.

Seven putative susceptibility loci for vitiligo were identified by genome-wide linkage analysis; five of these loci—FOXD3 (Forkhead Box D3), NLRP1 (NLR family pyrin domain containing 1), PDGFRA (Platelet-Derived Growth Factor Receptor Alpha), HLA (human leukocyte antigen), and XBP1 (X-box binding protein 1)—have been linked to a causal gene.

Mutations in FOXD3 appear to disrupt melanoblast development by causing transcriptional upregulation. NLRP1 plays a crucial role in controlling the innate immune system, particularly in the skin. It initiates the inflammasome in response to particular stimuli and converts pro-IL1β into its active form, IL1β, which controls T cell polarization towards Th17 and sustains the inflammatory response.

As with other autoimmune disorders, vitiligo is known to feature Th17 cells and high amounts of IL17; however, it is yet unknown what function these cells serve in the pathophysiology of the condition. Additionally, a number of studies have shown a strong relationship between the duration, severity, and activity of the disease and the serum levels of Th17 and IL17. Additionally, research indicates that NB-UVB improves vitiligo lesions by lowering the expression of IL-17. Numerous theories have been put out on the potential role that IL17 generated by Th17 cells may have in the onset of disease. The first theory focuses on the chemokine CCL20 that IL-17 produces. As a homing molecule, this cytokine would, in fact, draw CD8+ T lymphocytes, which have been linked to the direct destruction of melanocytes in vitiligo mice. The stimulation of endothelial expression of E- and P-selectins and the adhesion molecules ICAM-1 and VCAM-1 is another way that IL-17 may be involved. This could lead to neutrophil migration, which would encourage the production of several ROS that are essential for the destruction of melanocytes.

The PDGFRA gene is linked to aberrant melanocyte migration and plays a crucial role in the differentiation, survival, and regulation of pigmentation of melanocytes during embryonic development.

HLA alleles linked to vitiligo might not be disease-specific. HLA-DRB4*0101, HLA-DQB1*0303, HLA-DRB1*03, HLA-DRB1*04, HLA-DRB1*07, and HLA DRB1A*04-(DQA1*0302)-DQB1*0301

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are the HLA alleles that have been linked to vitiligo thus far.

A transcription factor called XBP1 may interact with HLA-DR molecules to affect the course of vitiligo.

Numerous other genes, including CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4), ACE (Antigen Converting Enzyme), CAT (Catalase), PTPN22 (Protein Tyrosine Phosphatase Non-Receptor Type 22), MYG1 (MYG1 Exonuclease), MITF (Melanocyte Inducing Transcription Factor), KIT (KIT Proto-Oncogene, Receptor Tyrosine Kinase), ESR 1 (Estrogen Receptor 1), AIRE (Autoimmune Regulator), COMT (Catechol-O-methyltransferase), and NALP1 (Nucleotide-binding oligomerization domain, Leucine rich again and Pyrin domain containing), FAS (Fas Cell Surface Death Receptor), EDN1 (Endothelin 1), COX2 (Cyclooxygenase 2), VIT1 (Vacuolar iron transporter 1), IKZF4 (IKAROS Family Zinc Finger 4), and DDR1 (Discoidin Domain Receptor Tyrosine Kinase 1) . One of the main regulators of angiogenesis that has been researched in several malignancies and chronic disorders is vascular endothelial growth factor (VEGF) . A noteworthy correlation has been noted ($p = 0.04$) between the GG genotype and an older age at vitiligo onset.

Neural Hypothesis

According to the neural theory, the cytotoxic damage and death of the melanocytes are caused by neurochemical mediators produced from cutaneous nerve terminals. This exchange of information between the skin and the neurological system is suggested by several clinical observations.

First, the distribution of vitiligo patches is symmetrical in non-segmental vitiligo, but nearly dermatomal in segmental vitiligo. In reality, vitiligo of the segmental form only affects a single body segment; nevertheless, it rarely stays within the dermatomal boundaries and instead spreads to nearby dermatomes.Moreover, vitiligo has been reported to appear in individuals with diabetic neuropathy, transverse myelitis, and in places where nerve injury has occurred.

Numerous discoveries supporting the involvement of neuropeptides, the sympathetic nervous system, and morphologic changes to dermal nerves support the neural theory.

The autonomic nervous system malfunction that results in elevated adrenergic tone and decreased parasympathetic tone, which causes three times higher cutaneous blood flow on segmental vitiligo lesions compared to normal skin, appears to have an impact on melanin formation. Patients with vitiligo also exhibit elevated urinary catecholamine catabolite concentrations and plasma norepinephrine levels, both of which are linked to disease activity. Melanocytes die as a result of vasoconstriction, hypoxia, and ROS overproduction brought on by catecholamines.

Neutrophil-associated neuropeptide Y (NPY) is elevated in the skin of vitiligo lesional and perilesional areas. Significantly elevated levels of nerve growth factor (NGF), which is likewise inducedby stress, have also been linked to vitiligo.Ultimately, the dermal nerves of the vitiligo skin examined under an electron microscope revealed ultrastructural alterations, including a modest axon degeneration and an increased thickness of the Schwann cell basement membrane.

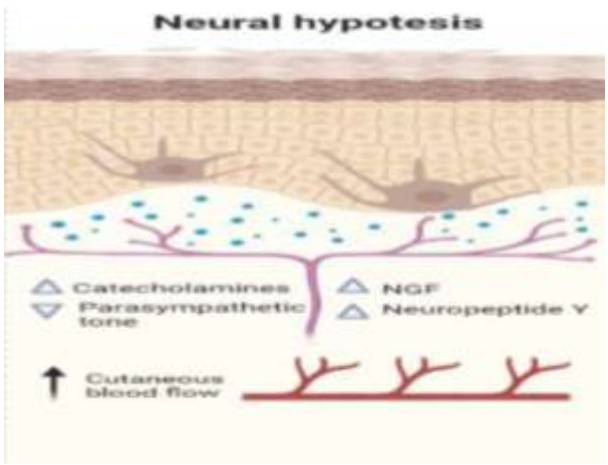

Fig. 8 Mechanism of Neural Hypotesis

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Immunity (Autoimmunity)

The autoimmune theory of vitiligo suggests that mechanisms related to autoimmunity play a role in the destruction of melanocytes. The correlation between vitiligo and various autoimmune disorders, such as autoimmune thyroid diseases, alopecia areata, halo nevi, and Addison's disease, reinforces the notion of an autoimmune origin for vitiligo. In the sera of individuals with vitiligo, several circulating autoantibodies specific to pigment cells have been identified. Notably, antimelanocyte antibodies, particularly those targeting tyrosinase isoforms TRP-1 and TRP-2, are present at elevated levels in approximately 10% of patients. However, the precise function of these antimelanocyte antibodies in the context of vitiligo remains inadequately understood. Currently, these autoantibodies are thought to arise as a secondary humoral response to the destruction of melanocytes. Research indicating the presence of CD4+ and CD8+ lymphocytes at the dermal-epidermal junction in skin regions adjacent to vitiligo lesions points to the involvement of cell-mediated immunity in the condition. Cytotoxic CD8+ T cells, which target melanocyte-specific antigens such as tyrosinase, Melan-A/MART-1, gp100, TRP-1, and TRP-2, have been observed to display anti-melanocytic cytotoxic effects in vitro. Additionally, increased levels of tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), as well as IL-10 and IL-17, have been recorded in the blood and tissues of individuals with vitiligo.

Biochemical Theory

The biochemical theory posits that the buildup of harmful intermediate metabolites resulting from melanin synthesis, coupled with insufficient defense against free radicals, leads to elevated levels of hydrogen peroxide (H2O2), which can result in the destruction of melanocytes. Various theories propose that genetic factors, structural and functional defects in melanocytes, as well as a deficiency in factors necessary for melanocyte development, all play a role in the process of depigmentation. While there is a consensus that vitiligo is classified as an autoimmune disease, the precise contribution of each of these mechanisms remains a topic of ongoing discussion. Furthermore, none of the proposed hypotheses adequately accounts for the diverse phenotypes observed in vitiligo. Nevertheless, the manifestation of the disease is influenced by environmental factors.

TREATMENT OF VITILIGO USING CORTICOSTEROIDS TOPICALLY

For all kinds of vitiligo with an affected body surface area of less than 3%, topical corticosteroids are the recommended therapy (limited vitiligo). This treatment works especially well for dark skin types, new lesions, and the face and neck area. On the face, however, it causes issues because of its adverse effects. In patients with vitiligo with an affected BSA of less than 20%, topical corticosteroids of classes III and IV showed a similar therapeutic efficacy (75% regimentation), amounted to 56% and 55%, respectively, in a meta-analysis [35]. Comparative research indicates that topical calcineurin inhibitors (tacrolimus and pimecrolimus) and topical corticosteroids of class IV (clobetasol propionate) or class III (metemetasone furoate) are equally effective in treating conditions related to the face and neck.

Topical corticosteroids can cause skin atrophy, albeit this is not a typical adverse effect. Telangiectasias, hypertrichosis, striae, acneiform responses, and perioral dermatitis are less common side effects. When administering high-potency corticosteroids to extensive regions of the body, particularly in intertriginous areas and children, systemic absorption must be taken into account. The face and neck usually react to therapy the best. \

The first-line treatment for extra facial involvement and minimal vitiligo is topical corticosteroids. There is no research on the best application schedule (interval or permanent). Strong corticosteroids (class III) with an enhanced therapeutic index, like mometasone furoate, are advised, for instance, for three months at a time (once daily) or six months at a time (once daily for 15 days each, separated by 14 days). Children can also benefit from this therapy. Here, large-surface treatment in intertriginous areas requires consideration of systemic resorption.

Topical inhibitors of calcineurin

Through case reports and case series, the beneficial effects of topical calcineurin inhibitors (tacrolimus and pimecrolimus) in vitiligo have been known for nearly 20 years. A small number of small-scale randomized controlled trials (RCT) highlight the beneficial effects of pimecrolimus 1% and tacrolimus 0.1%, respectively, in adults and children [36–39]. After applying tacrolimus for six months, regimentation of more than 50% of face lesions was achieved in 58% of children treated with 0.1% tacrolimus ointment. When compared to

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a control group that received clobetasol propionate treatment, there was no difference.

Topical calcineurin inhibitors generally have a very good therapeutic impact on the face and neck, while in other body regions there is little to no benefit. Whether tacrolimus is more effective than pimecrolimus is unknown. Additionally, topical tacrolimus seems to work effectively in SV. Erythema formation and burning and itching sensations are uncommon side effects of alcohol usage.

Topical calcineurin inhibitors are useful for both maintenance therapy of previously induced regimentation (even after phototherapy and focused light therapy) and initial therapy of vitiligo (Figure 1). The administration of 0.1% tacrolimus ointment twice a week significantly decreased the recurrence risk from 48.4% to 26.4% in the first year of a placebo-controlled randomized clinical trial involving 78 individuals with vitiligo.

Photomedicine

For many years, phototherapies have been one of the most significant forms of vitiligo treatment. Heliotherapy, psoralen plus solar exposure [PUVAsol], psoralen plus UVA [PUVA], phenylalanine plus UVA [PAUVA], khellin plus UVA [KUVA], broadband UVB [BB-UVB], and narrowband UVB [NB-UVB] are among the numerous phototherapeutic techniques that have been used in the past to treat vitiligo; currently, NB-UVB is primarily used for full-body irradiation. Since the early 2000s, medical technology has advanced to the point that high-intensity UVB light sources have been introduced. These light sources can be used to selectively irradiate areas with vitiligo. In particular, segmental vitiligo is covered by this (see targeted UV therapy).

Combination treatments

Several research have attempted to enhance the phototherapy's regimentation efficacy in vitiligo by combining it with systemic or external therapies. Most of the evidence that is now available comes from very heterogeneous, non-controlled studies that typically have a maximum intervention length of six months and rather small case numbers. Therefore, it is yet unclear if adjuvant therapy will ultimately lead to superior therapeutic outcomes or if it is A

Treatement	Approaches	Indication	Defects/SideEffect
Topical Corticosteroids	Betamethasone dipropionate, clobetasoldipropionate, mometasone furoate.	Localized vitiligo, both on adults and children.	Skin atrophy, telangectasias,folliculittis, acneic lesions, hypertrichosis and striae distensae.
	Tacrolimus, pimecrolimus		
Topical Immunomodulators		Adult patients, as a substitution option of corticosteroids.	Photosensitivity, burningsensation, erythema, pruritus, flushing, increased risk of cutaneous and noncutaneous lymphomas.
	Vitamin C,vitaminE, superoxide dismutase, polypodium leucotomos		
Antioxidants		In association with all kinds of treatment options.	No obvious side effects reported while treatment effect is not obvious.
	NB-UVB, PUVA		

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Phototherapy		Generalized vitiligo both in adults and children. Usuallly combine with additional drugs.	Hyperpigmentation,erythema, burning and blistering, increased risk of skin cancer.

Other treatment surgical therapies,

depigmentation, cosmetics approaches.

II. CONCLUSION:

Vitiligo, a chronic skin condition characterized by the progressive loss of pigment-producing cells, presents significant challenges for patients and healthcare providers alike. This review highlights the multifaceted nature of vitiligo, from its diverse clinical manifestations to its potential autoimmune and genetic underpinnings. Advances in research have improved our understanding of the pathophysiology and led to more targeted therapeutic approaches, including emerging treatments like JAK inhibitors and cellular therapies. However, gaps remain in fully elucidating the mechanisms driving vitiligo and optimizing long-term management strategies. Future research should focus on personalized treatment plans, incorporating patient-specific factors and genetic profiles, to enhance therapeutic outcomes. Additionally, addressing the psychological impact of vitiligo through integrated care models could significantly improve patients' quality of life. Overall, a multidisciplinary approach combining medical, psychological, and supportive care is essential for advancing the treatment and management of vitiligo.

REFERENCES

[1]. AL-smadi K, Imran M, Leite-Silva VR, Mohammed Y. Vitiligo: a review of aetiology, pathogenesis, treatment, and psychosocial impact. Cosmetics. 2023 May 27;10(3):84.

[2]. Baumrin E, Loren AW, Falk SJ, Mays JW, Cowen EW. Chronic graft-versus-host disease. Part I: Epidemiology, pathogenesis, and clinical manifestations. Journal of the American Academy of Dermatology. 2024 Jan 1;90(1):1-6.

[3]. Bellei B, Papaccio F, Picardo M. Regenerative Medicine-Based Treatment for Vitiligo: An Overview. Biomedicines. 2022 Oct 28;10(11):2744.

[4]. Beebeejaun M, Haslinger J, Beuttel C. Topically Applied Therapies for the Treatment of Skin Disease: Past, Present, and Future. Pharmacological reviews. 2024 Sep 1;76(5):689-790.

[5]. Chakraborty GS, Mandal SD, Agrahari R, Mishra R. Vitiligo Induction Methods: A Review Update.

[6]. Diotallevi F, Campanati A, Martina E, Radi G, Paolinelli M, Marani A, Molinelli E, Candelora M, Taus M, Galeazzi T, Nicolai A. The role of nutrition in immune-mediated, inflammatory skin disease: a narrative review. Nutrients. 2022 Jan 29;14(3):591.

[7]. Frączek A, Owczarczyk-Saczonek A, Placek W. The role of TRM cells in the pathogenesis of vitiligo—a review of the current state-of-the-art. International Journal of Molecular Sciences. 2020 May 18;21(10):3552.

[8]. Goh CL, Kang HY, Morita A, Zhang C, Wu Y, Prakoeswa CR, Sau NH, Kerob D, Flament F, Wei L. Awareness of sun exposure risks and photoprotection for preventing pigmentary disorders in Asian populations: Survey results from three Asian countries and expert panel recommendations. Photodermatology, Photoimmunology & Photomedicine. 2024 Jan;40(1):e12932.

[9]. Gopinath D, Koe KH, Maharajan MK, Panda S. A comprehensive overview of epidemiology, pathogenesis and the management of herpes labialis. Viruses. 2023 Jan 13;15(1):225.

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Volume 9, Issue 5 Sep - Oct 2024, pp: 873-887 www.ijprajournal.com ISSN: 2456-4494

[10]. Joge RR, Kathane PU, Joshi SH. Vitiligo: a narrative review. Cureus. 2022 Sep;14(9).
[11]. Júnior DS. Environmental and individual factors associated with protection and predisposition to autoimmune diseases. International Journal of Health Sciences. 2020 Nov;14(6):13.
[12]. Kang H, Lee S. Prevalence and incidence of vitiligo and associated comorbidities: a nationwide population-based study in Korea. Clinical and Experimental Dermatology. 2023 May;48(5):484-9.
[13]. Karkoszka M, Rok J, Wrześniok D. Melanin Biopolymers in Pharmacology and Medicine—Skin Pigmentation Disorders, Implications for Drug Action, Adverse Effects and Therapy. Pharmaceuticals. 2024 Apr 18;17(4):521.
[14]. Kubelis-López DE, Zapata-Salazar NA, Said-Fernández SL, Sánchez-Domínguez CN, Salinas-Santander MA, Martínez-Rodríguez HG, Vázquez-Martínez OT, Wollina U, Lotti T, Ocampo-Candiani J. Updates and new medical treatments for vitiligo. Experimental and therapeutic medicine. 2021 Aug 1;22(2):1-1.
[15]. Lu M, DiBernardo E, Parks E, Fox H, Zheng SY, Wayne E. The role of extracellular vesicles in the pathogenesis and treatment of autoimmune disorders. Frontiers in Immunology. 2021 Feb 24;12:566299.
[16]. Nirojini PS, Vijay A, Raja AB, Murugan A. A Review on Unraveling the Complexity of Autoimmune Skin Disorders: Genetic Influences, Environmental Triggers and Innovative Management Approaches. Indian Journal of Pharmacy Practice. 2024;17(2).
[17]. Malhotra N, Dytoc M. The pathogenesis of vitiligo. Journal of Cutaneous Medicine and Surgery. 2013 May;17(3):153-72.
[18]. Pala V, Ribero S, Quaglino P, Mastorino L. Updates on Potential Therapeutic Approaches for Vitiligo: Janus Kinase Inhibitors and Biologics. Journal of Clinical Medicine. 2023 Dec 4;12(23):7486.
[19]. Pala V, Ribero S, Quaglino P, Mastorino L. Updates on Potential Therapeutic Approaches for Vitiligo: Janus Kinase Inhibitors and Biologics. Journal of Clinical Medicine. 2023 Dec 4;12(23):7486.
[20]. Premkumar M, Kalarani IB, Mohammed V, Veerabathiran R. An Extensive Review of Vitiligo-Associated Conditions. International Journal of Dermatology and Venereology. 2024 Mar 30;7(01):44-51.
[21]. Perez-Bootello J, Cova-Martin R, Naharro-Rodriguez J, Segurado-Miravalles G. Vitiligo: Pathogenesis and new and emerging treatments. International Journal of Molecular Sciences. 2023 Dec 9;24(24):17306.
[22]. Premkumar M, Kalarani IB, Mohammed V, Veerabathiran R. An Extensive Review of Vitiligo-Associated Conditions. International Journal of Dermatology and Venereology. 2024 Mar 30;7(01):44-51.
[23]. Rao M, Young K, Jackson-Cowan L, Kourosh A, Theodosakis N. Post-inflammatory Hypopigmentation: review of the etiology, clinical manifestations, and Treatment options. Journal of Clinical Medicine. 2023 Feb 3;12(3):1243.
[24]. Renert-Yuval Y, Ezzedine K, Grimes P, Rosmarin D, Eichenfield LF, Castelo-Soccio L, Huang V, Desai SR, Walsh S, Silverberg JI, Paller AS. Expert Recommendations on Use of Topical Therapeutics for Vitiligo in Pediatric, Adolescent, and Young Adult Patients. JAMA dermatology. 2024 Apr 1;160(4):453-61.
[25]. Singh N, Kumari V, Agrawal K, Kulshreshtha M. Molecular Pathway, Epidemiological Data and Treatment Strategies of Fungal Infection (Mycoses): A Comprehensive Review. Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents). 2024 Apr 1;24(1):68-81.
[26]. Sharma N, Chaudhary SM, Khungar N, Aulakh SK, Idris H, Singh A, Sharma K. Dietary Influences on Skin Health in Common Dermatological Disorders. Cureus. 2024 Feb;16(2).
[27]. Shakhbazova A, Wu H, Chambers CJ, Sivamani RK. A systematic review of nutrition, supplement, and herbal-based adjunctive therapies for vitiligo. The Journal of Alternative and Complementary Medicine. 2021 Apr 1;27(4):294-311.
[28]. Speeckaert R, Lambert J, Bulat V, Belpaire A, Speeckaert M, van Geel N.

Autoimmunity in segmental vitiligo. Frontiers in Immunology. 2020 Oct 27;11:568447.

[29]. Shah H, Eckembrecher FJ, Eckembrecher DG, Nouri K. Current and emerging immunobiologic therapies for atopic dermatitis. Drugs & Therapy Perspectives. 2024 Jun 13:1-2.

[30]. Srivastav Y, Hameed A, Srivastav A, Ahmad MI, Singh J. A COMPREHENSIVE DESCRIPTION OF VITILIGO DISEASE AND ITS MEDICATION BASED MANAGEMENT. International Journal of Medical Sciences (IJMS). 2024 Jan;2(1).

[31]. SWATI ST, DEVI N, GUPTA J. UNDERSTANDING VITILIGO; CAUSES, SYMPTOMS AND PHARMACOLOGICAL TREATMENT OPTION.

[32]. Taylor SC, editor. Diagnosing Skin Disease in Skin of Color, An Issue of Dermatologic Clinics, E-Book. Elsevier Health Sciences; 2023 May 26.

[33]. Thawabteh AM, Jibreen A, Karaman D, Thawabteh A, Karaman R. Skin pigmentation types, causes and treatment—a review. Molecules. 2023 Jun 18;28(12):4839.

[34]. Tanemura A. Understanding of pathomechanisms and clinical practice for vitiligo. Annals of Dermatology. 2023 Oct;35(5):333.

[35]. Xia J, Melian C, Guo W, Usmani H, Clark R, Lozeau D. Vitiligo and metabolic syndrome: systematic review and meta-analysis. JMIR dermatology. 2022 Mar 16;5(1):e34772.

[36]. Zhu Y, Wang B, Hao Y, Zhu R. Clinical features of myasthenia gravis with neurological and systemic autoimmune diseases. Frontiers in immunology. 2023 Sep 14;14:1223322.