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THE VITILIGO IS THE HUMAN SKIN'S PIGMENTARY CHALLENGE STILL: AN UP-TO-DATE REVIEW

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The vitiligo is a cutaneous pigmentary disease. It is one of the most common skin conditions challenging most dermatologists all over the world. The purpose of the study is to shed a light on available data of this skin lesion regarding its epidemiology, pathogenesis, etiology and genetic causes. Additionally theories and hypotheses related to its occurrence and clinical characteristics of various distinguishable types are considered. The diagnosis and treatment of this skin disorder using different medications and management lines or procedures, particularly recently discovered ones, may positively input into treatment of these skin disorders. The article is based on comprehensive data obtained from such well-known scientific databases as Web of Science, Medline, EMBASE, Pubmed Central, PubMed, Scopus, and Cochrane Library.

K e y w o r d s : vitiligo; hypo-pigmentation, melanin, melanocyte.

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Introduction

The word vitiligo comes from a Latin name "Vitellius" that means "calf", because the white spots of this skin disorder resembled calf patches. Furthermore, some authors claimed that "vitium", which means "fault", might cause vitiligo or leukoderma. It is an acquired illness that occurs from the death of epidermal melanocyte cells, resulting in well-defined whitish patches which are in general distributed symmetrically [1].

It is naturally non-contagious. The specific etiology of this characteristic is unknown; however it might be a combination of environmental and hereditary factors. Some researchers found that a single stimulus, such as mental discomfort or sunburn, can cause this skin lesion [2].

Although this illness is not physically unpleasant, the social and psychological consequences have been thoroughly documented. It is especially offensive to children and those with dark complexion [3].

Materials and methods

This study was established by searching several well-known scientific databases such as Web of Science, Medline, EMBASE, Pubmed Central (PMC), PubMed, Scopus, and Cochrane Library until December 2021. The following sentences and words were deeply searched in the article title, abstract, summary, keywords, introduction, and heading: vitiligo, pigmentation, hypopigmentation, depigmentation, repigmentation, melanin, skin pigment, cutaneous pigment, melanocyte, Köebner phenomenon, vitiligo causes, vitiligo epidemiology, vitiligo etiology, vitiligo pathogenesis, vitiligo clinical features, vitiligo types, vitiligo diagnosis, vitiligo prognosis, vitiligo management, vitiligo treatment, vitiligo drug, and vitiligo theories. The Boolean survey strategy was utilized (or, and, or not). All the scientific articles, such as systemic reviews, original articles, meta-analyses, case reports, and even the references of all these scientific articles, were thoroughly searched, evaluated, and recorded. Then all the accumulated information was filtrated, assessed, clarified, and organized in a precise scientific manner. However, the current review is completely based on previously accomplished studies, and therefore, the author conducted no new research on animals or human individuals.

Results and discussion

Epidemiology

It's a depigmentation disorder that affects people of all ethnicities and has a significant aesthetic impact. In different parts of the world, the prevalence ranges between 0.5 and 4%. Although both genders are impacted equally, females may be assigned to pay more attention (and express more attention to) any cosmetic imperfection. This condition is more prevalent in sun-exposed areas and among people with dark skin. Despite the fact that the most common age of onset was 15–35 years old, half of all cases had an onset in their early twenties [4].

Individuals with racially significant pigmented skin have a big social influence, and the prevalence is high. Despite this, around half of the population with this skin illness appears to get it before maturity, and about ninety-five percent develops it before the age of forty. It often affects people of all races, ethnicities, and genders [5].

Besides, some inherited factors may be causative, and there is a high frequency of vitiligo in certain families as a result of these. Approximately half of vitiligo patients have a favorable family history (i.e. grandparent, uncle, aunt, and even cousin). The risk of developing vitiligo in the offspring of afflicted people is estimated to be around five times higher [6].

Pathogenesis and etiology

Vitiligo is a kind of systemic illness with extracutaneous clinical signs and symptoms affecting the nervous

and endocrine systems. Vitiligo patients frequently attribute the disease's start to a particular sickness, life crises, or incident. Many people associate it with an accident, the death of a close relative, a serious chronic systemic disease, or even the loss of a certain career. A specific physical event, such as an abrasion or cut, may trigger the start in some people [7]. As a result, the Köebner phenomenon refers to the formation of a vitiliginous skin lesion near the injury site, which affects around one-third of patients. Many people with vitiligo blame it on excessive sun exposure, which can trigger the Köebner phenomenon in those who are prone to it. Different ideas have been proposed for the disease's origin; a single cause cannot apply to all patients [8].

Genetics

Familial vitiligo instances are prevalent, suggesting that the condition has a hereditary basis. Thirty to forty percent of people have a good vitiligo history in their family. The frequency in main families of vitiligo sufferers is roughly 6–7%, which is twenty-fold higher than that found in the general population. The occurrence of around 23% conformity in identical twins adds to the hereditary predisposition to vitiligo [9].

Vitiligo does not have a straightforward autosomal recessive or dominant pattern of transmission. However, this transmission is more sophisticated, and it is most likely governed by a number of genes with varying expression levels. The results of many reports on the association between vitiligo and the human leukocytes antigen (HLA) systems were mixed [10].

Vitiligo susceptibility is a complex hereditary characteristic that can affect various genes involved in the manufacture of melanin pigment. Many family-based correlation and case-control studies have highlighted a link between vitiligo and catalase gene (CAT). This gene was chosen as a susceptible gene due to a decrease in catalase enzyme activity. It's been connected to vitiligo sufferers' epidermis accumulating hydrogen peroxide. One of the three CAT gene indicators described was useful for genotypic testing among Caucasian vitiligo patients and healthy controls [11].

Theories of vitiligo occurrence

Many studies on vitiligo suggest that it is an autoimmune condition affecting melanin pigmentary cells. These are some of them:

1. Association with Autoimmune Diseases: Initially, the autoimmune theory focused on the link between vitiligo and other autoimmune disorders such pernicious anemia, rheumatoid arthritis, alopecia areata, autoimmune thyroid diseases, systemic lupus, and adult-onset autoimmune diabetes mellitus. These connections may promote certain people's autoimmune responses to play a key part in vitiligo development [12–14].

2. Humoral Immunity Theory. Various diffuse auto-antibodies were detected in the serum of vitiligo individuals. These instances have been implicated to antibodies against non-pigment cellular antigen (common tissues antigen), pigment cellular surface antigen, and cytoplasmic pigment cellular antigen. Antibodies against the enzyme anti-tyrosinase were found in some of the individuals with active illness [15].

A small number of these autoantibodies are specific to pigment cells. It produced an antigen on the surface of its cells in order to be destroyed by a particular antibody. Only tyrosinase related protein 1 (TRP1) was revealed to have an expression on the surface of melanocyte cells. TRP1 monoclonal antibodies may cause vitiligo-related depigmentation and melanoma regression in certain animals when administered. Autoantibodies that interact with a variety of antigens do more than only reveal an expression on the pigment cells. However, their contentious pathogenic function might imply that the humoral response is a subsequent reaction to the loss of melanocytes by a fundamental mechanism, such as the cytotoxic impact of CD8 T-cells [16–18].

3. Cellular Immunity Theory:

i. ***T-Cell Participitation.*** The observation of a T-cell infiltration in the border of an inflammatory vitiligo is the first indication that cellular immunity was involved in vitiligo etiology. Cells of the CD4 and CD8 types have been discovered. They revealed local immune reactivity in generalized vitiligo, but it has yet to be discovered in segmental vitiligo. According to the clinical phenomenology of vitiligo, such data also point to a variety of pathogeneses. With the release of IFN-γ and TNF-α, both cytotoxic and helper T-cells enhance the Th1 respond. TNF-α level is greater in vitiligo skin, according to these data. Elevated concentrations of soluble IL-2 receptors with presentation of the skin lymphocyte antigens in few infiltrated T-cells have all been reported, suggesting that circulatory T-cells have been activated and recruited to such vitiligo skin [3, 19].

The CD4/CD8 ratio is inverted in vitiligo skin, with CD8 T-cells predominating. Melan-A specific CD8 cells were found in exceptionally large numbers, which appear to be linked to the degree of the sickness [20]. A recent knowledge of the conditions of CD8 T-cell melanocyte killing has been obtained. Both systemic immunization-induced CD4 T-cell assistance and/or local inflammations are necessary to disrupt MHC class-I-restricted-cell tolerance [21].

Monocytes from individuals with active illness release more CD68 macrophages and proinflammatory cytokines are prevalent in dermal layer, implicating myeloid cells. The participation of dendritic cells in vitiligo etiology is still unknown, and the researchers published various contradictory findings. However, recent findings imply that dendritic cell-mediated death of stressed epidermal melanocytes may play a role in vitiligo depigmentation [22].

ii. ***B-Cell Participation.*** It's unknown what function B-cells play in vitiligo pathogenesis. Several articles reported no infiltration of B-cell into the vitiligo lesion. Infiltration of B-cells in depigmented areas was discovered in some researches, while other researchers discovered that MC1R is B-cells auto-antigen in vitiligo. In addition, with antibodies opposed such receptors being produced, supporting their role in this disease. As a result, inhibiting such receptors can change the signaling

route that controls melanocytes activity, changing pigment cells behavior [23].

Zinc (Zn) and copper (Cu) are well-known immunomodulators that interfere with immune response and slow the progression of autoimmune illness. Copper-containing enzymes were used to influence melanogenesis. They discovered that vitiligo patients had copper metabolism problems. A considerable rise in plasma Zn, Cu, and Cu/Zn ratio levels has been discovered. These trace elements were related to the size of the lesions and fluctuated with therapy. The ratio may be tracked via Cu/Zn [24].

4. Neural Theory. Lerner pioneered the neurological theory of vitiligo, basing his concept on the following criteria: clinical scientific evidence of dermatomal and segmental vitiligo; increased vasoconstriction and sweating in vitiliginous sites indicating higher adrenergic performance; depigmentation in some experimental models with injured nerve fibers [7, 25].

Many alterations had been seen in other investigations, including color decrease in brown-eyed rabbits with sympathectomized irises; and higher cholinergic action, as evidenced by sweat generation and high skin temperature, as well as delayed bleeding time in depigmented patches. It was also shown that keratinocytes and melanocytes from the affected skin had higher monoamine oxidase levels. The activity of these cells producing 4-folds more than of norepinephrine and approximately 6.5-folds less than of epinephrine compared to the control keratinocytes. Whereas melanocytes, which come from the cells of neural crest, may found close to the nerve terminals in depigmented areas, but this is uncommon in the normal epidermis. In the periphery and center of depigmented patches, they saw regenerative and degenerative autonomic nerves, as well as thicker basement membrane in Schwann cells [21, 26, 27].

Individuals with vitiligo had higher levels of TNF, interferon-gamma, and intercellular adhesion molecule–1 in their perilesional skin. Neurotensin, a neuropeptide, caused 500-fold more TNF production from melanocytes than normal. Also, 50-fold more than UVB radiation *in vitro*, implying that neurogenic regulation can be possible. In individuals with recently active or early active vitiligo, increased urine elimination for homovanillic acid, which is a dopamine mediator, and also vanilmandelic acid, which is an epinephrine and norepinephrine mediator, all had been identified. Overexpression of some catecholamine metabolites throughout the urine or plasma of individuals with active depigmentation might be a side effect or it could be the depigmentation causes [15, 20, 28].

5. Self-Destruction Theory. This shows that the melanocytes self-destruct caused by a flaw in a normal defensive process that clears out harmful melanin pigment precursors. This concept depends upon clinical aspects of vitiligo with the cutaneous experimental depigmentation created by using chemical agents with a selective fatal impact on functioning melanocytes. These chemicals may cause a kind of leukoderma that looks identical to vitiligo caused by idiopathic causes. With reduced catalase concentration in vitiligo epidermis, some believe that faulty keratinocyte metabolism plays a crucial role. Another theory that has been proposed to explain the etiology of this condition involves faulty tetrahydrobiopterin and catecholamine production [8, 26, 29, 30].

6. Other Hypotheses. Several studies have found that vitiligo patients have higher levels of oxidative stress across their epidermis. Other pathomechanisms could include: a dysregulation of melanocytes apoptosis, a viral origin, a lack of melanocytes growth factor, an underlying defect in the function and structure of rough endoplasmic reticulum within melanocytes of vitiligo patients, and primary disturbances of T lymphocyte leading to the formation of forbidden clones of the autoreactive lymphocytes within the epidermis [11, 20, 22, 31].

T-cells that express cutaneous lymphocytes-binding antigen, which is characteristic for skin-homing T-cell, have been discovered around the edges of vitiligo patches, indicating that biological processes are involved in the etiology. This data supports a theory that the patchy death of cutaneous melanocytes in vitiligo is caused by lesional T cells rather than systemic anti-melanocytic antibodies. According to the evidence, vitiligo may be caused by a variety of pathogenic processes that result in the loss of follicular and epidermal melanocytes. Genetic variables, stress, toxic chemical buildup, infections, mutations, autoimmunity, decreased melanocytes proliferation and migration, and a changed cellular environment, are all thought to have a role in the occurrence, according to the convergence theory [9, 10, 16, 32, 33].

Clinical Features

Vitiligo can appear at any age; however it usually appears before the age of twenty. The illness progresses gradually, sometimes dramatically over many months and then lying dormant for several years. Hypomelanotic macules commonly appear initially on sun-exposed parts of the skin, like the face or the dorsum of the hand. These regions are prone to sunburn; itching may develop even if there is no sunburn. The isomorphic or Köebner phenomenon occurs when normal skin is damaged, resulting in a depigmented region [3, 28, 34].

The amelanotic macules with vitiligo were discovered in places that are ordinarily hyperpigmented, such as the face, groins, areolae, axillae, and genitalia. Areas that are prone to frequent friction and damage, like the dorsum of the hands, feet, elbows, ankles, and knees are likely to be impacted. The lesions are generally symmetrical in distribution; however they can sometimes be unilateral and have a dermatomal layout. Complete vitiligo is uncommon; however a few colored spots are always present [22, 35].

Pigment loss can be full or partial, or both can happen at the same time at the same location (trichrome vitiligo). The macules are convex in shape, grow in size unevenly, and combine with other lesions to generate intricate patterns. The hairs situates in these patches are typically colored normally, while earlier lesion's hairs

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are frequently amelanotic. Lesions' margins could be hyperpigmented. However, few patients appear due to exposure to sunburn at the amelanotic regions, the main symptom is aesthetic impairment [18, 36].

When vitiligo spreads to the point where only a small amount of normal melanin persists, the residual areas of normal skin pigment have curved margins, which would be a diagnostic indicator that differentiates this condition from the hyperpigmented cutaneous macules found on perfectly natural, absolutely fair skin [3, 36, 37].

Vitiligo Types. The vitiligo patterns listed below are the most common:-

A. ***Focal Vitiligo.*** It's either a solitary macule or just few distributed macules. The size and quantity of the macules were limited by a vague norm. Around 20% of children suffering vitiligo have a concentrated pattern [35, 38].

B. ***Segmental Vitiligo.*** Unilateral macules were seen in a dermatomal or quasi-dermatomal distribution. They assumed it was a rare form of vitiligo with such a predictable course. There is no association with the thyroid diseases or other vitiligo-related conditions. Vitiligo that occurs sooner and lasts longer than widespread vitiligo is known as segmental vitiligo. Köebnerization is a rare occurrence. This pattern can be present in about 5% of adult individuals and also more than 25% in children associated with vitiligo disease. The trigeminal region, which accounts for more than half of all cases, is the most prevalent single location of involvement. Poliomyelitis (white hairs) is associated with nearly half of all occurrences, with up to 13% of cases involving several locations. Several studies found that the segmental pattern was present in ranging from 5% to 28% of people [28, 38–40].

C. ***Generalized Vitiligo.*** With a wide spectrum of macules, it is the most common kind of vitiligo. These macules, which are normally symmetrically positioned, frequently involve extensor surfaces. Vitiligo macules can affect the skin around the mouth, nose, eyes, ears, and anus. Lip-tip vitiligo is a kind of periungual vitiligo that affects certain mucosal surfaces (nipples, distal penis, and lips). Acrofacial vitiligo affects the periorificial face and distal fingers [9, 39, 41].

D. ***Universal Vitiligo.*** It defines vitiligo that is so pervasive that only a few typical macules of pigmentation remain; this form is linked to a variety of endocrinopathies. Mucosal involvement can occur everywhere on the body, including the lips, nipples, genitalia, and gingiva. Palms and soles involvement is uncommon, however it has been observed, especially in fair-skinned people [12, 38, 42].

Other kinds of vitiligo, like halo naevi, where a halo of depigmentation arises surrounding a pigmented naevus, may also be described by certain writers. Grey hair is frequent in vitiligo sufferers, as the disease affects the melanocytes in the hair bulbs, resulting in premature greying. In individuals with severe vitiligo, ocular vitiligo can develop, although the color of the eyes remains unchanged; nonetheless, slit-lamp examination can show alterations just in the uvea and retina pigmentary epithelium. Finally, occupational (chemical) vitiligo can be due to a wide-range of substituted phenolic chemicals, such as para-tertiary butyl-phenol and monobenzyl ether of hydroquinone [2, 10, 20, 22, 43].

Diagnosis of Vitiligo

Vitiligo is a disorder that is easily detected and seldom requires further testing. The utter lack of melanin and melanocyte cells from the epidermis, whether incomplete in early lesions or complete lack in late creamy white regions. Investigation of vitiligo with Wood's light, that will emphasize the hypopigmented regions, which most often fluoresce an ivory appearance when investigated under Wood's light [3, 20, 23, 44].

Differential Diagnosis

According to most of the available medical textbooks, the localized and diffuse systemic disorders are two types of systemic diseases that cause skin hypopigmentation. Oculocutaneous albinism (OCA) is a kind of widespread hypopigmentation that involves a group of hereditary melanin production abnormalities. It manifests clinically as a global pigmentary loss of skin, hair, and eyes. OCA1A is the most severe variant, resulting in a complete lack of melanin formation throughout one's life. The milder variants of OCA4, OCA3, OCA2, and OCA1B, on the other hand, show less melanin accumulation over time. Mutations mostly in P (type II) or tyrosinase (type I) genes cause this illness. The most severe kind is accompanied with a complete deficit in enzyme activity [2, 45].

Hermansky-Pudlak syndrome (HPS) seems to be autosomal recessive disease, which influences only a small percentage of the population. Because nine subtypes are present, it demonstrates genetic heterogeneity. OCA, bleeding diathesis due to apparent platelet storage pool decrease, and ceroid lipofuscin accumulation in lysosomes are all characteristic clinical features [46].

Another uncommon congenital, autosomal recessive immunodeficiency condition is Chédiak-Higashi syndrome (CHS). OCA is the most common symptom. Giant melanosomes induce disruptions in the migration of melanin pigments, resulting in this condition [10].

A phenylalanine hydroxylase (PAH) deficiency in the liver causes phenylketonuria (PKU). As a result, excessive amounts of L-phenylalanine in PKU patients' serum result in hypopigmentation of their hair and skin, as well as mental retardation [9, 20].

Cystathionine beta-synthase (CBS) deficiency causes homocystinuria. It's a trans-sulfuration hereditary disorder that causes lower plasma cysteine levels and higher methionine and homocysteine levels. Homocysteine inhibits tyrosinase, a key pigment enzyme, halting the formation of melanin [7, 10, 16].

Sarcoidosis is a multisystemic inflammatory illness with non-caseating granulomas as its hallmark. The growth of these granulomas and their buildup is the basic aberration that occurs in sarcoidosis. They're compact, having a centrally located concentration of epithelioid and macrophage cells surrounded by lymphocytes. Localized areas of hypopigmentation can be detected in

sarcoidosis owing to the inflammatory process. Furthermore, earlier literatures have shown dermal nodules surrounded by hypopigmented areas and macular hypopigmented regions [6, 29, 47].

Waardenburg syndrome is an uncommon condition that is characterized by deafness and other pigmentary abnormalities in the hair, skin, and eyes. It's a kind of neuropathy marked by aberrant embryonic survival or migration of two neural crest cell-derived components, one of which is melanocytes. A mutation in a gene that controls the differentiation of melanocytes from neural crest cells during embryonic development causes this condition [10, 16, 48].

Scleroderma is a rheumatic autoimmune disease that manifests as vitiligo-like leukoderma in its clinical features. It's comparable to idiopathic vitiligo, which starts repigmenting following therapy when the normal pigmentary process's perifollicular macules appear within depigmented areas. The presence of these macules with varying degrees of pigmentation might lead to a scleroderma diagnosis rather than vitiligo. Other illnesses that should be separated from vitiligo include onchocerciasis, Vogt-Koyanagi-Harada syndrome, and melanoma-associated leukoderma [29, 36, 38, 49].

Clinical Course and Prognosis

Vitiligo has an unpredictably bad prognosis and progress. Vitiligo's initial clinical subtype has little bearing on subsequent anatomical areas of involvement or disease activity [34, 38].

Vitiligo Treatment

Vitiligo therapy is ineffective, and patients are encouraged to seek efficient cosmetic concealment for the lesions over exposed parts of skin in most situations. Nonetheless, several studies have demonstrated that successful therapy and complete recovery may be achieved. Only 15–25% of people have spontaneous repigmentation, which can take months or even years [18, 22, 37].

The goal of therapy is to drive remaining melanocytes inside the afflicted epidermis and/or external roots sheaths of white follicles of the hair to develop and cover the vitiliginous patches, or to have melanocyte cells migrating from neighboring normal skin, particularly in tiny lesions [2, 26, 29, 43].

A. Emotional Support. Psychotherapy by the use of a mild tranquilizer is often necessary in people with vitiligo who are experiencing psychological distress [7, 18, 41].

B. Topical Therapy*:*

i. ***Sunscreen:*** Vitiligo is normally not a severe aesthetic issue in fair-skinned people; nevertheless, the disease becomes more noticeable in the summer season when tanning highlights normal skin. The use of appropriate sunscreens with a sufficient sun protection factor (SPF) can assist to keep vitiliginous patches from burning as well as healthy skin from tanning. The most suitable for these dual uses are opaque sunblocks with an SPF of above 30 and incorporating Zinc Oxide (ZnO) or/and Titanium Dioxide (TiO2) [11, 15, 24, 50].

ii. ***Cosmetics:*** They cover-ups are a beneficial therapy option for many individuals, particularly those with localized vitiligo. Leukoderma patches, particularly on the hands, face, and neck that have been covered with traditional make-up, self-tanning creams, or other topical dyes. Cosmetics are inexpensive, have fewer adverse effects, and are simple to use. In addition, most of those cover-ups may be customized to match the patient's natural skin color [18, 25, 37].

iii. ***Topical Corticosteroids:*** Although most experiences is anecdotal, it demonstrated that topical corticosteroids can cure small regions of vitiligo and are frequently the first line of treatment for youngsters. The correct reaction to topical corticosteroids appears to be on the face; lesions mostly on neck and extremities (excluding the toes and fingers) also respond well, albeit at the cost of considerable atrophy. This therapy is frequently resistant to acral and trunk lesions [6, 20, 32, 35, 51].

iv. ***Topical Immunomodulators:*** The calcineurin inhibitor topical tacrolimus ointment 0.03% to 0.1%, formerly known as FK 506, is a microlactam medication that inhibits T-cell stimulation triggered by antigen. When paired with excimer (308 nm) laser or UVB treatment, it was proven to be more efficient. Tacrolimus ointment is thought to be safer in children versus topical steroids. Untreated regions of vitiligo develop new patches, implying there's no systematic impact [22, 51, 52].

v. ***Topical Calcipotriol:*** In some vitiligo patients, topical calcipotriol 0.005% causes aesthetically acceptable repigmentation. In the management of vitiligo, a topical calcipotriol is administered, which acts by stimulating keratinocytes to produce mediators. It is used in conjunction with NB-UVB. This combination yet results in early pigmentation dramatically lower UVB dosage, and less adverse effects, as well as a shorter treatment time and reduced cost. Topical calcipotriol coupled with PUVA (psoralen and sunshine) proved extremely effective and acts quicker than PUVA itself [25, 37, 53].

vi. ***Pseudocatalase:*** Catalase, a skin enzyme that protects against free radical damage, has been discovered to be deficient in the epidermis of vitiligo sufferers. In uncontrolled studies, a replacement treatment employing a mimic of catalase (pseudocatalase) in conjunction with NB-UVB phototherapy was found to repigment certain vitiligo individuals and limit disease development [20, 37, 53].

vii. ***Fluorouracil:*** Five percent fluorouracil cream is administered under occlusion about 1–10 days after dermabrasion using a dermabrasion equipment or sandpaper. Re-pigmentation can occur as soon as a month following the dermabrasion procedure [43, 54].

viii. ***Topical Coal Tar:*** For almost a hundred years, coal tar has been utilized to treat vitiligo. The usage of coal tar has decreased significantly in comparison to other medications [18, 22, 25, 37, 44].

ix. ***Using Gold Salt to Tattoo Achromatic Patches*****:** It is done every week, with 4 to 12 treatments typically being sufficient. On the neck and face, it had the finest

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benefits. Erythema should appear without bleeding after tattooing [37, 47].

x. ***Topical iodine tincture:*** For many years, iodine tincture was applied topically for vitiligo and was shown to be effective, especially in individuals with localized vitiligo. The 5% iodine tincture demonstrated moderate to notable improvement in 65.5% of the treated patches. Because it is inexpensive and has few side effects, iodine tincture can be a useful alternative to methoxy-psoralen in the management of isolated areas of vitiligo. The so-called irritating hypothesis is most likely the principal mechanism for 5 percent iodine tincture. These therapies are likely to cause mild inflammation, which provokes keratinocytes to expose inflammatory mediators, such as basic fibroblast growth factor (bFGF), which stimulates melanocyte hypertrophy and proliferation. Also, by discharging other intermediaries from keratinocytes, such as IL-1, which facilitates α-MSH binding to cells. *In vitro*, leukotriene C4 and D4 stimulate melanocyte proliferation, whereas leukotriene C4, transforming growth factor (TGF-α), and cause melanocyte cells migration, and endothelin-1 induces melanocyte migration, resulting in re-pigmentation. Any irritating substance applied to a vitiligo patch may cause re-pigmentation, according to the theory [20, 26, 43, 55, 56].

It was recently discovered that a 5% of iodine solution, a 15% of lactic acid solution, and 0.07% methoxsalen with UV radiation all have identical therapeutic effects [57].

xi. ***Infrared Radiation:*** Infrared technique is a simple procedure treating localized vitiligo for use alone or in conjunction with other treatments for some people [37, 58].

xii. ***Direct Electrical Current Therapy:*** A particular device is designed to deliver a voltage and amperage-appropriate direct electrical impulses to lesions. A little direct electrical charge was applied to the vitiligo patches with this device [59].

xiii. ***Topical Sour Orange and UVA Singly or in Combination:*** It was for a six-month period, and it involved two-times weekly sessions. When compared to 20% sour orange solution alone (56.2%), the reaction of a combined of 20% sour orange solution and UVA showed a substantial improvement of (62.2%), while those with UVA exhibited a 20% improvement [23, 60].

xiv. ***Vitiskin:*** It is a hydrogel containing superoxide dismutase, catalase, reductase from Saccharomyces cerevisiae yeast-Dismutine BT. The detoxifying and antiradical capabilities of this compound are beneficial. This has the potential to boost the cell's overall metabolism. Vitiskin as a skincare therapy in combination with UVB improves vitiligo spots dramatically, especially when used for 10 weeks [21, 57].

C. Systemic Therapy:

i. ***Psoralen–UVA:*** In individuals with severe vitiligo, oral PUVA treatment is employed. It's crucial to clarify the odds of repigmentation, as well as the short- and long-term consequences. Patients subjected to UVA, starting at 1–2 j/cm^2 (rising by 0.2 j/cm^2 in skin type I and II and by 0.5 j/cm^2 in skin types III to IV), twice to triple times a week, till erythema occur. This method causes re-pigmentation of vitiligo patches for reasons that are unclear. In unaffected skin, PUVA promotes tyrosinase activity and melanogenesis. PUVA is also immunosuppressive locally, as evidenced by lower expression of antigens in vitiligo-associated melanocyte. Melanocytes in the hair follicle's bulb and infundibulum are frequently killed in vitiligo, while the lower and middle areas of the follicle, and even the external root sheath, are preserved. Because of the production of cytokines and chemotactants by epidermal keratinocytes, PUVA induces follicular melanocyte cells to migrate further into epidermis and colonizes the neighboring depigmented skin. Patients who have a more widespread involvement or who do not react to topical PUVA are given oral psoralens [11, 15, 21, 26, 31].

However 70–80% of individuals will have pigment induction with psoralen orally, less than 25% of patients will achieve entire re-pigmentation, and 30-40% of individuals will only see a partial therapeutic response. Because of their enhanced tolerance to higher cumulative UVA doses, darker pigmented individuals respond positively to PUVA treatment, and children also undergo more re-pigmentation than adults [8, 18, 37, 43, 58].

ii. ***PUVA Sol (Psoralen and Sun Light):*** By employing trioxsalen instead of 8-methoxy psoralen, which is less phototoxic. It's taken in a 5mg dosage for every 20–25 pounds (9–11) kilogram of body weight prior 2–4 hours of sunlight exposure. Usually twice to three times a week should individuals be treated. In the treatment of vitiligo, a mixture of PUVA sol with topical calcipotriol is extremely successful and performs better, and it may be used to abbreviate the PUVA therapy [22, 37, 57, 61].

iii. ***Excimer Laser:*** Its effectiveness in treating vitiligo has been tested in various trials. Treatments were shown to be most successful when administered three to four times weekly, with intervention intervals of over 12 weeks required to achieve adequate re-pigmentation. The first dosage ranges between 50 and 100 mJ/cm^2. The face, like with regular phototherapy, responds best to excimer laser treatment; the feet and hands are the least sensitive [58, 62, 63].

iv. ***Systemic Steroids:*** In a considerable number of individuals, systemic steroids can stop the course of vitiligo and lead to repigmentation, although they can also have unfavorable side effects. In certain vitiligo patients, oral mini-pulse treatment with 5mg dexamethasone/betamethasone was observed to stop the disease progression and produce spontaneous repigmentation. Eighty percent of patients began spontaneous repigmentation within 2–4 months [43, 63, 64].

v. ***Levamisole:*** The use of levamisole to treat vitiligo for a long time reduced and stopped the illness from spreading. It regulates disease activity and causes vitiliginous regions to re-pigment. To induce a faster reaction rate of re-pigmentation, mix levamisole with additional therapy approaches like topical corticosteroids [51, 57, 65].

vi. ***Vitamin C and E Antioxidant Use:*** It was discovered that in the mild type (i. e. earlier than usual in the disease's duration because when disease remains active), oxidative stress significantly decreased after therapy

with antioxidant medications, and this could have therapeutic implications, implying that antioxidants could help to reduce oxidative stress only when taken early in the disease's duration [15, 66].

D. Surgical Treatment:

Surgical options are available if PUVA or topical steroid therapy fails to repigment. Because surgical treatments are time-consuming, they are often confined to localized or segmental vitiligo, albeit they may be effective in generalizing illness for stable cases of vitiligo [17, 22, 28, 37, 57].

i. ***Epidermal Grafting (Suction Blister Grafts):*** The procedure's goal is to replace achromic epithelial layers with normal epidermis-bearing melanocyte cells obtained by suction and applied to the afflicted region [54, 65, 67].

ii. ***Autologous Minigrafting:*** Multiple, tiny biopsy specimens of 1–2 mm were taken from an unknown donor location and placed close together at the recipient intervention site to reduce scarring; UVA radiation may aid in re-pigmentation [54, 57, 68].

iii. ***In Vitro-Cultured Epidermis Transplantation:*** Blisters are produced at both the recipient and donor locations using liquid nitrogen or suction, with the epidermis of the donor area is excised, as well. Approximately 1–10 cm^2 pigmented epidermis shave biopsy samples can also be utilized. The melanocyte cells were extracted and cultivated in cell culture for three weeks after the epidermis was processed with trypsin. The melanocytes stick to vaseline gauze which has been separated and applied to the recipient's vitiliginous skin's denuded patches. With an elastic bandage, a dressing is placed [57, 69].

iv. ***Transplantation of Non-Cultured Melanocytes:*** This approach is similar to *vitro*-cultured melanocyt cells, except it uses non-cultured melanocyte cells extracted from numerous two cm2 occipital cutaneous samples collected using the dermatome. The melanocyte cells were trypsin-processed, then EDTA-treated, put in a saline solution, then injected like a clear suspension into liquid nitrogen-created blisters at recipient area. Non-grown melanocytes re-pigment a bigger vitiliginous region quicker than that *in vitro* cultured melanocyte cells, according to the researchers [31, 57, 63, 69].

E. Depigmentation:

When the vitiliginous region exceeds the usual skin area, it's used in broad generalized vitiligo [18, 20, 22, 34, 38, 43, 57].

i. ***Vitiligo Therapy with Phenol:*** According to several researches, phenol's major action in melanocytes is to block melanogenesis, resulting in a reduced number of such cells. Because it does not enter the dermis and hence has minimal systemic impact, depigmentation with 88 percent phenol is harmless. This treatment is also advantageous because of its inexpensive cost and favorable aesthetic outcomes [2, 25, 38, 42].

ii. ***Monobenzyl Ether of Hydroquinone (Monobenzone):*** It's the only treatment for depigmenting normal skin in people with severe vitiligo that's popular in USA and Europe. Monobenzone is just a phenolic toxin which kills epidermal melanocytes when used over an extended period of time. As a result, it can provide a homogeneous depigmented condition that is more visually appealing than that of the distinction between normal and afflicted skin for too many individuals. It comes as a 20% cream and may be made with up to a 40% concentration. Monobenzone users could perhaps avoid direct applying with others for one hour after administration to avoid depigmenting others' skin. Monobenzone may irritate the skin and cause allergic sensitization [57, 70].

iii. ***Ruby Laser:*** It's also utilized since it's a good, quick, and safe way to get rid of the aesthetically bothersome vestiges of natural pigmentation in vitiligo sufferers [58, 64].

iv. ***Lactic Acid:*** In a colorless or light yellow dilute aqueous solution, hydroscopic liquid with a somewhat but not unpleasant odor and a little acidic taste. Because lactic acid is an alpha hydroxyl acid, it is used to manage dry skin, follicular hyperkeratosis, ichthyosis, seborrhoeic keratosis, verrucae vulgaris, and actinic keratoses, by diminishing corneocyte cohesiveness and thereby reducing stratum corneum thickness. Lactic acid seems to be an antioxidant that may aid in the repigmentation of vitiligo patches. A novel technique of treatment for localized varieties of vitiligo is a topical 15% of lactic acid solution. The skin is not affected by this therapy, hence it is not carcinogenic [15, 26, 43, 60, 62].

F. Phototherapy with Narrow-Band Ultraviolet B. In 1997, Westerhof and Nieuweboer-krobotova were the first to report using NB-UVB phototherapy treating vitiligo. He contrasted NB-UVB phototherapy with topical PUVA phototherapy twice a week. Patients receiving NB-UVB phototherapy demonstrated re-pigmentation in 67 percent of cases after four months, compared to 46 percent of patients getting topical PUVA [53, 58, 62].

In vitiligo, the precise mechanism of NB-UVB phototherapy is unknown. A previous study discovered that UVB irradiation elevated the IL-1, expression of endothelin-1, and tyrosinase in the human keratinocyte cells *in vivo* and *in vitro*, indicating a mechanism for UVB-induced repigmentation [21, 53, 71].

Conclusions

Vitiligo is a challengeable cutaneous disorder that stands up to most of the world's dermatologists. This review is a straightforward attempt to gather the most up-to-date medical information regarding the vast number of scientific articles that explain, discuss, or even mention this cutaneous lesion from different medical points of view. The current review concentrates on the modern drugs, procedures, and line management that were discovered to treat vitiligo. These data require a careful, inquisitive scientific eye to extract, clarify, evaluate, categorize, and arrange these valuable obtained data in a simple, brief medical form. It is the fundamental goal behind the present study.

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