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Holistic Approaches to Vitiligo Treatment: A Review of Pharmacological and Traditional Indian Therapies

Shivani Agarwal[1]; Kartikay Prakash[2]; Rahul Chauhan[3]; Akash Sharma[3]
[1]Moradabad Educational Trust Group of Institutions Faculty of Pharmacy, Moradabad, Uttar Pradesh, India, 244001.
[2]Ankerite College of Pharmacy, Lucknow, Uttar Pradesh,226001.
[3]Moradabad Educational Trust Group of Institutions Faculty of Pharmacy, Moradabad, Uttar Pradesh, India, 244001.

Abstract:- Vitiligo is a complex skin disorder characterized by the loss of melanocytes, leading to patchy depigmentation of the skin. Although the exact etiology remains uncertain, factors such as genetics, autoimmune responses, and oxidative stress have been implicated in its development. The Indian system of medicine and modern pharmacological treatments have been explored for managing vitiligo. This review paper provides a comprehensive overview of the pharmacological treatment of vitiligo, emphasizing three major classes of treatment: topical, systemic, and depigmentation therapies. Topical treatments include corticosteroids, calcineurin inhibitors, vitamin D3 analogues, pseudocatalase, 5-fluorouracil, methotrexate, PF2A, basic fibroblast growth factor (bFGF), and Janus kinase (JAK) inhibitors. These treatments target immune responses and promote melanocyte function to restore skin pigmentation. Systemic treatments involve corticosteroids, apremilast, JAK inhibitors, minocycline, statins, methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil, aiming to suppress immune activity and stabilize the progression of vitiligo. Therapies for depigmentation aim to lighten the remaining pigmented areas, providing a more uniform skin tone. By examining the effectiveness and safety of these treatment options, this paper aims to guide clinicians in selecting the most appropriate pharmacological interventions for vitiligo patients. Additionally, insights into the Indian system of medicine offer potential alternatives for treatment.

Keywords:- *Vitiligo Treatment, Topical Therapy, Systemic Therapy, Depigmentation Therapy, Indian System of Medicine and Autoimmune Response.*

I. INTRODUCTION AND BACKGROUND

Vitiligo is a skin condition that causes loss of pigmentation due to the depletion of melanocytes, leading to patches of skin that lack color. A hallmark of the condition is the presence of clear, sharply defined white patches on the skin [1]. Recent advances have provided insights into the causes of vitiligo, recognizing it as an autoimmune disorder influenced by metabolism, oxidative stress, and various genetic and environmental factors. Vitiligo can be psychologically distressing and impact daily life, emphasizing the need to treat it as more than just a cosmetic concern [2]. In 2011, a global consensus distinguished between two types of vitiligo: nonsegmental vitiligo (NSV) and segmental vitiligo (SV). The term "vitiligo" was agreed to encompass all types of NSV (such as acrofacial, mucosal, generalized, universal, mixed, and other variations). One key decision was to differentiate SV from other types of vitiligo due to its different prognosis. Vitiligo is widely recognized by dermatologists and the general population, as its primary symptom is patches of hypopigmented skin, typically appearing on areas such as the fingers, knuckles, lips, eyes, toes, and genital regions [3]. Two main processes lead to the skin turning white: the production of melanin by melanocytes, which is then transferred to surrounding keratinocytes; and the transport of melanin through the epidermis. Various conditions can inhibit melanin production, resulting in hypopigmentation [4]. The overall loss of melanocytes in vitiligo patients appears to stem from three key factors: the presence of three "vitiligo" alleles that predispose individuals to melanocyte degeneration; differences in the melanocytes of vitiligo patients compared to those without the condition; and environmental factors that trigger immune responses leading to melanocyte destruction [5]. Vitiligo primarily affects melanocytes, but it can also cause damage to keratinocytes, leading to functional changes in the skin. Merkel cells, important for neurosensory functions, are not typically found in depigmented skin. Changes in the function of sweat glands and alterations in the skin's cholinergic response have also been observed in vitiligo [6]. The term "segmental" vitiligo refers to unilateral depigmentation that is not dermatomal, and it typically starts in childhood or early adulthood, progressing for a short period before stabilizing. Unilateral vitiligo differs from bilateral vitiligo in terms of the distribution and progression of the condition, as well as the recurrence of depigmentation in specific areas [7,8]. Segmental vitiligo may resemble nevus depigment Osus and café-au-lait spots in terms of distribution and appearance. This suggests a potential similarity in the embryological development of melanocytes between segmental vitiligo and nevus depigment Osus [9].

➢ *Epidemiology*

The global prevalence of vitiligo varies between 0.4% and 2.0%, with the highest rates observed in India, followed by Mexico and Japan [10,11]. Studies from India show that vitiligo affects between 0.25% and 4% of dermatology outpatients. This condition can impact both sexes, with childhood vitiligo commonly beginning before age 20, and in adults, onset ranges from 18 to 32 years [12,13]. Among the various triggers, such as chemicals, allergens, occupational factors, diet, systemic illnesses, and sunlight,

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skin trauma seems to be the most significant cause of vitiligo, affecting both the onset and progression of the condition and leading to lesions in trauma-prone areas (Koebner's phenomenon). Koebner's phenomenon occurs in approximately 20%–60% of vitiligo patients and supports this theory [14]. The percentage of affected patients with a positive family history varies globally; in India, it ranges from 6.25% to 18% [15].

➢ *Classification of Vitiligo*

Vitiligo is typically classified into different subtypes based on the distribution and progression of depigmentation:

- **Segmental Vitiligo:** This type is characterized by depigmentation on one side of the body, often following a dermatome. It is typically less common and occurs at a younger age.
- **Non-Segmental Vitiligo:** The most common type, which involves bilateral and symmetrical depigmentation on various parts of the body. Subtypes include:

✓ **Generalized Vitiligo:** Widespread depigmentation across multiple areas.
✓ **Acrofacial Vitiligo:** Depigmentation on the face and extremities, especially around the mouth and eyes.
✓ **Universal Vitiligo:** Involves over 80% of the body surface with depigmentation.
✓ **Focal Vitiligo:** A small, localized area of depigmentation.
✓ **Mucosal Vitiligo:** Involves depigmentation on mucous membranes such as the lips or genitals.

Table 1 Classification of Vitiligo

Vitiligo Subtype	Distribution	Characteristics
Segmental Vitiligo	Unilateral (one side)	Usually follows dermatomes, occurs at a younger age
Generalized Vitiligo	Widespread	Most common form, symmetrical depigmentation
Acrofacial Vitiligo	Face and extremities	Includes areas around mouth, eyes, and fingers
Universal Vitiligo	Over 80% of body	Extensive depigmentation, rare
Focal Vitiligo	Localized area	Small, confined patches of depigmentation
Mucosal Vitiligo	Mucous membranes	Depigmentation on lips, genitals, or other mucous membranes

➢ *Rational/Etiology of Vitiligo*

Vitiligo is a complex disorder with a multifactorial etiology, involving a combination of genetic, immunological, and environmental factors:

- **Genetic Factors:** Vitiligo has a hereditary component, and several genes have been linked to the condition, including those associated with immune system function.
- **Autoimmune Mechanism:** Vitiligo is often considered an autoimmune disorder where the immune system mistakenly attacks and destroys melanocytes.
- **Oxidative Stress:** Increased levels of reactive oxygen species (ROS) and a decrease in antioxidant defenses in the skin may contribute to melanocyte damage.
- **Neural Factors:** Neurogenic factors, such as the release of neuropeptides or catecholamines, may play a role in melanocyte dysfunction.
- **Other Factors:** Trauma, stress, and infections have also been suggested as triggers for the onset or exacerbation of vitiligo.

➢ *Pathophysiology of Vitiligo*

The pathophysiology of vitiligo involves the destruction or loss of melanocytes, the cells responsible for producing melanin in the skin:

- **Melanocyte Destruction:** Autoimmune attacks and oxidative stress lead to the destruction of melanocytes, causing depigmentation.
- **Melanin Biosynthesis Impairment:** Reduced activity of tyrosinase (the key enzyme in melanin synthesis) can result from the loss of melanocytes or oxidative stress.
- **Immune-Mediated Inflammation:** Immune cells such as T cells may play a role in attacking melanocytes, resulting in localized or generalized inflammation.
- **Neurogenic Factors:** Neurotransmitters and neuropeptides from nerve endings in the skin may affect melanocyte function, contributing to depigmentation.

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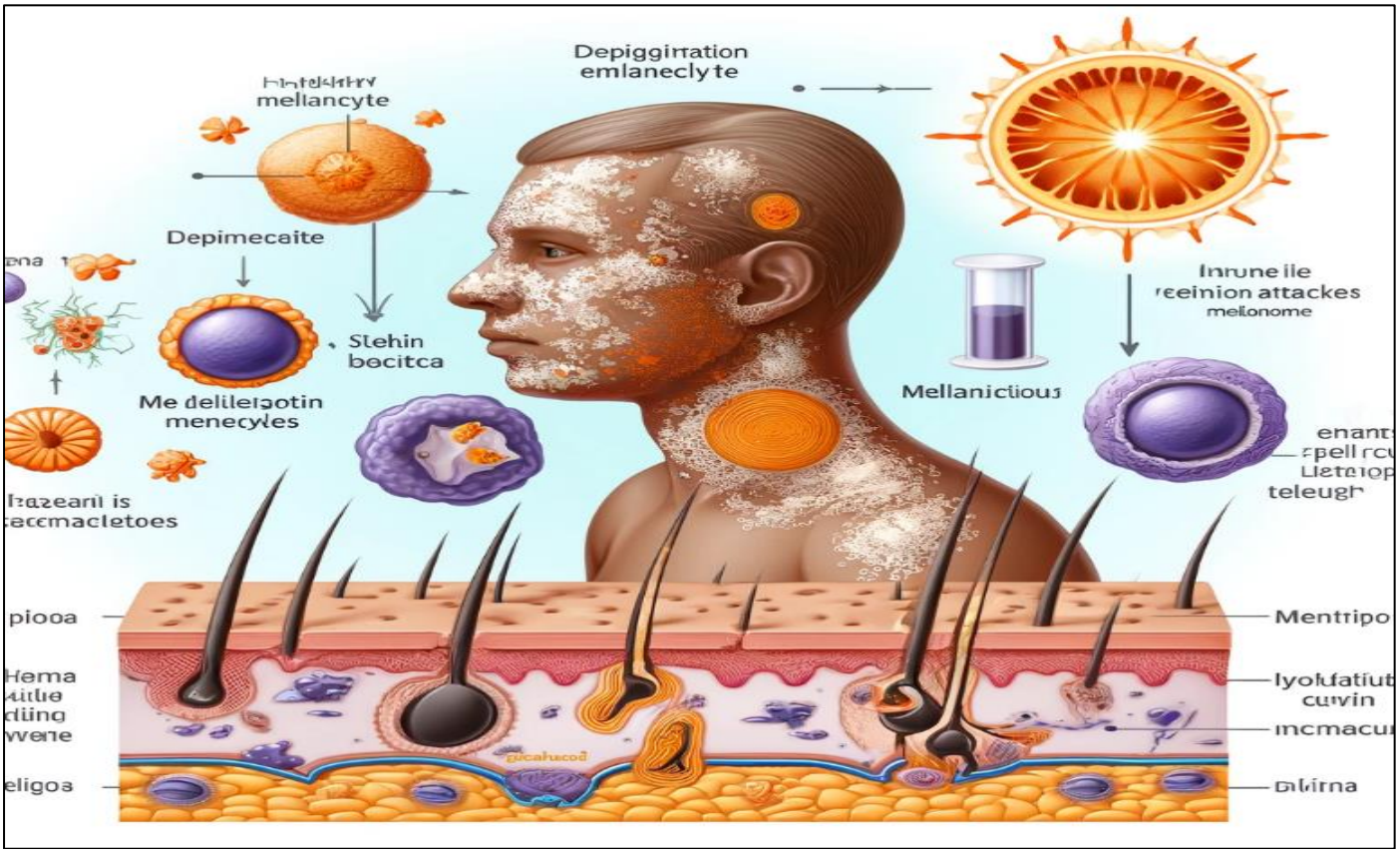

Fig 1 Pathophysiology of Vitiligo

II. PHARMACOLOGICAL TREATMENT

A. Topical Treatment

➢ *Corticosteroids*.

Corticosteroids are effective in treating vitiligo by modulating and inhibiting inflammation [16]. Topical corticosteroids (TCS), such as potent betamethasone valerate and very potent clobetasol propionate, are typically the initial treatment for vitiligo [17]. Sun-exposed areas tend to respond better to treatment, while extremities often show limited improvement. High potency TCS are suitable for treating small areas; for sensitive regions like the face, neck, genitals, or skin folds, where absorption is higher and side effects are more likely, topical calcineurin inhibitors (TCI) or milder steroids are preferred. Daily application of TCS for up to 3 months is recommended [18], followed by intermittent usage for up to 6 months. If there is no improvement after 3-4 months, treatment should be discontinued [19]. A meta-analysis revealed that both potent (56%) and very potent (55%) TCS achieved similar levels of effectiveness in treating localized vitiligo, with ≥75% repigmentation [20]. To improve therapeutic outcomes when using TCS alone, very potent TCS may be favored. TCS side effects include skin thinning, stretch marks, dilated blood vessels, excessive hair growth, and acne-like reactions. The most common local side effect is skin thinning, influenced by factors such as age, application site, TCS potency, and occlusion. Prolonged treatments may be necessary in vitiligo [21]. "Corticosteroid holidays," or periods without TCS, combined with a gradual reduction from high to mild potency, can help manage side effects. Systemic absorption might lead to adrenal suppression, as shown in a retrospective study of pediatric vitiligo patients treated with moderate to high potency TCS [22,23], where 29% had abnormal cortisol levels, particularly those with lesions on the head and neck. To minimize these risks in children, soft steroids like mometasone furoate and methylprednisolone aceponate can be used, as they provide anti-inflammatory effects while causing fewer systemic side effects [24-25].

➢ *Calcineurin Inhibitors*

Calcineurin inhibitors are a class of immunomodulators that can be used off-label to treat vitiligo [26]. These inhibitors work by blocking the action of calcineurin, a protein involved in inflammatory processes in immune cells that triggers the production of interleukin (IL) 2 and tumor necrosis factor α (TNF α). By inhibiting calcineurin, these drugs reduce cytokine production and stimulate the growth of melanocytes and melanoblasts . Topical calcineurin inhibitors (TCIs), such as tacrolimus (0.03% or 0.1%) and pimecrolimus (1%), are recommended for use on the head and neck areas due to their minimal side effects, including a lower risk of skin atrophy [27]. TCIs can be applied twice daily for at least six months, with treatment duration adjustable based on observed improvement. Moderate daily sun exposure is also advised during treatment. TCIs can also be part of an intermittent treatment strategy alongside topical corticosteroids (TCS), providing continuous care on days when TCS is not applied. A systemic review and meta-analysis found that using TCIs alone resulted in ≥25% repigmentation in 55% of patients, ≥50% repigmentation in 38.5%, and ≥75% repigmentation in 18.1% of patients. In children, these figures were even

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higher, with ≥25% repigmentation observed in 66.4% and ≥75% in 31.7% of patients [28]. The best results were seen in the face and neck, followed by the trunk and limbs, with the least success on the hands and feet. Chang et al. conducted a meta-analysis comparing TCIs and TCS, finding TCIs less effective than TCS for achieving ≥50% repigmentation but similar in achieving ≥75% repigmentation. TCIs can be used alone or in combination with other treatments. Ebrahim et al. compared the use of tacrolimus 0.1% alone to its use in combination with microneedling in patients with localized stable vitiligo. Both groups applied tacrolimus daily, while the combination group also received biweekly microneedling and tacrolimus treatment over 12 sessions. The combination group experienced earlier repigmentation, with ≥75% pigmentation in 50% of patients, compared to 29.92% in the monotherapy group [29]. A randomized placebo-controlled study involving patients with stable generalized vitiligo, treating three similarly sized lesions per patient differently. One lesion received daily tacrolimus 0.03%, another monthly microdermabrasion plus daily tacrolimus 0.03%, and the last received placebo treatment. The combination group showed moderate to excellent repigmentation (≥50%) in 65.7% of lesions, compared to 25.8% with tacrolimus monotherapy. TCIs may cause side effects such as burning sensations, itching, and increased risk of infection (e.g., herpes simplex and molluscum contagiosum) [30].

- *Vitamin D3 Analogs.*

Vitamin D can be obtained from the diet or synthesized by the skin through the action of UVB light on 7 dehydrocholesterol [31]. The primary method of producing the biologically active form of vitamin D is through hydroxylation to 25 hydroxyvitamin D3, primarily in the liver. This form is then transformed to 1,25 hydroxyvitamin D3 in the kidney, which is the active form of the vitamin [32]. CYP11A1 is responsible for producing physiologically active metabolites that activate vitamin D3 through an alternate route. Antigen presenting cells, T cells, and B cells are responsible for synthesizing active vitamin D3 [33]. These types of cells can also react to the stimulation of vitamin D, which could be linked to their ability to maintain self-tolerance and enhance protective immunity against infections [34]. Topical vitamin D3 analogs (D3A) are not successful as a standalone treatment for vitiligo. However, they can be beneficial when used alongside other therapies because of their immunomodulatory actions, which decrease T cell activity, promote melanocyte growth, and induce melanogenesis [26, 34, 35]. The recommended maximum dosage is 100 grams per week, applied to 30% of the body surface area. This should be done using a combination of calcipotriol 0.005% and betamethasone 0.05% in the form of an ointment for 4 weeks, or a cream for 8 weeks. A randomized controlled trial to investigate the effectiveness of the combination therapy of calcipotriol 0.005% and betamethasone dipropionate 0.05% in patients with localized vitiligo. The study compared the use of each drug individually with their combined use. Repigmentation ranging from 50% to 75% was observed in 6.7% of patients treated with calcipotriol, 13.3% of patients treated with betamethasone, and 26.7% of patients treated with the combination of both drugs. Repigmentation of moderate extent (25-50%) was observed in 33.3% of patients in the calcipotriol group, 46.7% in the betamethasone group, and 46.7% in the combination group. None of the patients attained more than 75% repigmentation, but, the combined therapy led to a quicker process of repigmentation [36]. Microneedling can enhance the transdermal administration of medicines. Ibrahim et al [37] conducted a study comparing the combination of microneedling with calcipotriol 0.05 mg/g and betamethasone 0.5 mg to microneedling with tacrolimus 0.03%. The patients underwent both treatments for two distinct lesions. The creams were administered on a daily basis, while microneedling was conducted every 2 weeks, with a maximum of 12 sessions. The combination of calcipotriol and betamethasone, when used with microneedling, resulted in 76-100% repigmentation in 60% of patients. In comparison, the combination with tacrolimus only achieved 32% repigmentation. This study concludes that the calcipotriol and betamethasone combination with microneedling is superior and effective in treating areas that are resistant to therapy, such as the elbow, knees, extremities, and acral area. D3A is considered to be safe for individuals of all ages, including both children and adults. However, it has been observed to cause only minor irritation in certain cases.

- *Pseudocatalase/Superoxide Dismutase*

Vitiligo is thought to be influenced by oxidative stress and the buildup of hydrogen peroxide. The epidermis of the lesions experiences a buildup of elevated concentrations of Hydrogen Peroxide. These substances are harmful to melanocytes, they prevent the action of tyrosinase, and they deactivate catalase, an enzyme found in peroxisomes that helps reduce hydrogen peroxide to water and oxygen [38]. The effectiveness of topical pseudo catalase might vary. Naini et colleagues conducted a pilot study that was randomized and placebo controlled. They used a topical gel containing pseudo catalase/superoxide dismutase. The study found no significant alterations in the size of the lesions or the pigmentation around the hair follicles. A study examined the effects of treating juvenile patients with pseudo-catalase PC KUS triggered with low dose narrow band UVB (nb UVB), applied twice daily. The findings indicated that disease progression was stopped in 70 out of 71 patients. In 92.9% of children with lesions on the face/neck, more than 75% repigmentation was obtained. On the trunk, 78.6% of children experienced more than 75% repigmentation, while on the extremities, the percentage was 72.7%. Only 9.4% of children with lesions on the hands/feet achieved more than 75% repigmentation [39]. In a study, the effectiveness of topical pseudo-catalase and nb UV was assessed in a double-blind, placebo-controlled, randomized, single-centre experiment involving patients with active vitiligo. The combined therapy [40] did not provide any further advantages. In a study, the effectiveness of tacrolimus 0.1% ointment was compared to tacrolimus 0.1% ointment combined with topical pseudo-catalase/superoxide dismutase gel for treating localized vitiligo in children. The study found that there was no significant variation in repigmentation percentages between the two groups.

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Nevertheless, there is a dearth of evidence regarding the adverse effects and safety of pseudo-catalase [41]. The current findings do not support the presence of an extra impact of topical catalase as compared to UVB alone [42].

- *Fluorouracil (5-FU)*

Topical 5 FU is primarily employed for the management of premalignant and malignant skin lesions [43]. The identification of increased pigmentation as a result of treatment with this medication prompted its application in the treatment of vitiligo [43]. The repigmentation mechanisms of 5 FU may involve the activation of follicular melanocytes and their migration during epithelization, as well as an increase in the number of melanosomes in keratinocytes [44,45]. Tsuji Takuo and Hamada [43] have reported the effectiveness of using 5 FU as a single treatment. After epidermal abrasion, a cream containing 5-FU was administered once daily for a period of 7 to 10 days. In 64% of patients, more than 75% repigmentation was observed [43]. Multiple trials have integrated laser therapy with topical 5 FU, as evidenced by references 44, 46, and 47. Abdelwahab et al [44] conducted a study to evaluate the impact of 5 FU used alone versus its combination with ablative erbium: YAG (2,940 nm) laser in non-segmental vitiligo. The surgical handpiece was used to apply an Erbium: YAG laser with a spot size of 4 mm and a fluence of 60 J/cm2. A cumulative total of two to three applications were administered, resulting in precise bleeding at the targeted site, with each treatment session occurring every 4 to 6 weeks. The application of 5-fluorouracil cream was performed on a daily basis for a duration of two weeks following each treatment session. The combination treatment resulted in a repigmentation range of 0-70%, with less than 25% repigmentation observed in 73.3% of patients and 50-75% repigmentation observed in 10% of patients. In contrast, the monotherapy group only achieved a repigmentation range of 0-5% [44]. Anbar et al [46] also employed the erbium-YAG laser in conjunction with topical 5-FU, specifically for the treatment of periungual vitiligo. The laser was utilized with a spot diameter of 5 millimeters and a fluence of 2.1 joules per square centimeter. The endpoint exhibited precise and localized bleeding, typically necessitating three passes. The topical 5-FU cream was used daily until there was inflammation characterized by redness, mild discharge, and the formation of crusts. The erbium-YAG laser treatments were repeated until complete repigmentation was obtained, or a maximum of three consecutive sessions were performed without any additional improvement noticed. The study found that 33.3% of patients achieved repigmentation of 75% or more, 33.3% achieved repigmentation between 26% and 74%, and 33.3% achieved repigmentation of 25% or less, or no repigmentation at all [46]. The study conducted by Mohamed et al [47] examined the use of a CO2 laser combined with topical 5 FU in treating acral vitiligo. The laser was utilized at a frequency of 12 Hz in level 2 pulse control and a power of 0.9 W to administer individual pulses using the single spot handpiece. Within the area that had been scraped, a daily application of 5 FU was administered for a duration of 7 days. Additionally, CO2 laser sessions were conducted on a monthly basis, either until the area had fully healed or a maximum of 5 sessions had been completed. The findings revealed that more than 75% of the lesions showed repigmentation in 49.8% of the cases, whereas 6.1% of the lesions exhibited repigmentation ranging from 50% to 75% [47]. Mina et al [48] conducted a study that compared the efficacy of microneedling with either topical tacrolimus or topical 5 FU. Two patches of vitiligo were treated in each subject. Initially, microneedling was conducted using a Dermapen at the slowest speed and a depth of 0.25-0.50 mm, tailored to the specific location. Subsequently, one patch was treated with a solution containing 5 FU (50 mg/ml), while the other patch was treated with tacrolimus 0.03% ointment. Patients were instructed to maintain their treatment regimen by applying either 5 FU or tacrolimus daily for a period of 2 weeks, as appropriate. A series of microneedling sessions, combined with topical therapy, were conducted every 2 weeks for a maximum of 12 sessions. The combination of 5 FU was shown to be highly effective, with over 75% repigmentation observed in 48% of patients. Additionally, 51% of patients achieved 75% repigmentation, while 26% achieved 50% repigmentation. In comparison, the tacrolimus group had repigmentation rates of 16%, 24%, and 36% for the relevant levels of repigmentation. The group treated with 5 FU also had a more rapid reaction to repigmentation, as reported in reference 48. Common adverse reactions associated with 5 FU include hyperpigmentation, scarring, infection, ulceration, and delayed wound healing [42,48].

- *Methotrexate*

Methotrexate, often known as MTX. MTX is a substance that inhibits folate and reduces the amount of T cells that produce TNF α. As a result, it has anti-inflammatory, immunomodulatory, and antiproliferative properties. A recent case study [49] documented substantial repigmentation in a patient with stable vitiligo who underwent a 12-week therapy regimen of applying topical MTX 1% gel twice daily, in addition to folic acid intake. There were no documented adverse effects. However, additional research is necessary to ascertain the effectiveness and safety of MTX [49].

- *Analoges of Prostaglandin F2 Alpha*

Prostaglandin F2 alpha analogs (PF2A) are frequently used to treat ocular hypertension [50]. The identification of iris and periocular skin darkening in glaucoma patients prompted its application in vitiligo [50]. The cause of this hyperpigmentation appears to be an upregulation of melanogenesis [51]. Kanokrungsee et al [52] conducted a preliminary investigation to evaluate the effectiveness of bimatoprost 0.01% solution in patients with non-segmental facial vitiligo, comparing it to tacrolimus 0.1% ointment. Both topical medications were administered twice daily for a duration of 12 weeks. Repigmentation was detected in 60% and 50% of the patients in the bimatoprost and tacrolimus groups, respectively. Furthermore, more than 50% of patients in the bimatoprost group experienced repigmentation, compared to 10% in the tacrolimus group. However, there were no statistically significant differences between the two groups [52]. The effectiveness of Latanoprost was assessed in a double-blind clinical trial

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conducted by Nowroozpoor Dailami et al [53]. The recruited patients had either widespread or localized vitiligo that affected their eyelids. The application of Latanoprost 0.005% gel occurred twice daily over a period of 12 weeks, and it was compared to a placebo. The case group showed a significant improvement in pigmentation, with an increase of 45.66±14.87%, compared to the control group which only had a 2.32±0.85% increase [53]. The adverse effects of PF2A are negligible and periorbital hyperpigmentation is rare [23].

- *Basic Fibroblast Growth Factor*

Peptide produced from basic fibroblast growth factor (bFGF). The action of bFGF in vitiligo is achieved through the migration of melanocytes [54]. Kamala Subhashini et colleagues [54] conducted a comparative study to evaluate the effectiveness of bFGF as a standalone treatment. The study involved patients who received either a 0.1% solution of bFGF or a 0.1% ointment of betamethasone valerate as monotherapy. Both groups administered their respective medication on a daily basis for a duration of 16 weeks. The bFGF group observed repigmentation of over 75% in 45% of patients, repigmentation between 50% and 75% in 35% of patients, and repigmentation of 50% in 22.5% of patients in the combination group. In comparison, only 6.8% of patients in the monotherapy group experienced repigmentation [55]. The adverse consequences encompass xerosis, stinging, and dermal irritation [23].

- *Janus Kinase (JAK) Inhibitors*

Janus kinase (JAK) inhibitors are drugs that inhibit the activity of Janus kinases. The JAK inhibitors utilized for treating vitiligo include tofacitinib, which inhibits JAK1/3, and ruxolitinib, which inhibits JAK1/2 [56]. Their mode of action involves the downregulation of the JAK STAT pathway, resulting in a drop in interferon gamma (IFN γ) levels. This decrease is also linked to the impairment of cell-mediated immunity in vitiligo [56]. Hamzavi et al [57] conducted a phase 2 open-label clinical trial involving 11 patients diagnosed with vitiligo. The administration of Ruxolitinib 1.5% cream occurred twice daily for a duration of 20 weeks. The cream was administered to a maximum of 10% of the body surface area or 3.75 g per application. The results were assessed using the vitiligo area scoring index (VASI) [57]. There was a statistically significant average improvement of 27% in patients who finished the study. Lesions on the face showed a better response compared to lesions in other areas [58]. In a recent phase 2 research conducted by Rosmarin et al [59], the effectiveness and safety of ruxolitinib cream were assessed at three varying doses (0.15%, 0.5%, and 1.5%) in comparison to a placebo, over a period of 52 weeks. The patients were categorized into four distinct groups based on the dosage of ruxolitinib they received: 1.5% administered twice daily, 1.5% administered once daily, 0.5% administered once daily, and 0.15% administered once daily. The efficacy of the treatment was assessed by measuring the percentage of patients who achieved a 50% or greater improvement in their baseline face VASI (F VASI50) score. At the 24-week mark, the groups who received ruxolitinib 1.5% once and twice daily obtained a F VASI50 in 50% and 45% of patients, respectively, compared to just 3% in the placebo group [59]. Mobasher et al [60] conducted an open-label research using tofacitinib 2% cream administered twice daily in a cohort of 16 patients diagnosed with vitiligo. Significantly, patients were permitted to utilize TCS (topical corticosteroids), TCI (topical calcineurin inhibitors), vitamins, or phototherapy concurrently during the research. 81.2% of patients exhibited repigmentation. Furthermore, a repigmentation rate of over 90% was found in four patients, while five patients saw repigmentation ranging from 25% to 75%. Four patients showed repigmentation between 5% and 15%, two patients showed no change, and one patient experienced sluggish progression. Notably, facial lesions showed greater improvement compared to other affected areas [60]. Common adverse effects of JAK inhibitors include skin redness (erythema), itching (pruritus), darkening of the skin (hyperpigmentation), and temporary acne. These side effects have been documented in studies [58,59].

III. SYSTEMIC TREATMENT

- *Corticosteroids*

The primary goal of utilizing systemic corticosteroids (SCS) is to inhibit the immunological response, thereby stabilizing the condition and promoting repigmentation [61]. SCS is administered to treat actively progressing vitiligo [16]. Utilizing pulse therapy with SCS is the preferred method for reducing the potential negative effects [62]. Patients receiving SCS therapy should be regularly checked for blood pressure, glucose levels, weight, waist circumference, and infections. Additionally, an ocular examination should be conducted every 6 to 12 months [23]. Multiple strategies for SCS have been documented. Imamura and Tagami [63] conducted a study involving 17 individuals with global vitiligo and five patients with localized vitiligo. Various oral corticosteroids, including prednisolone, betamethasone, paramethasone acetate, and methylprednisolone, were administered at varying dosages. These dosages were gradually reduced to a maintenance dose, and the effectiveness of the treatment was evaluated after 6 months. The findings indicated that more than 75% of patients with global vitiligo experienced pigmentation in at least one patch, with this occurring in 35% of patients. Additionally, repigmentation became noticeable within 4 weeks in the majority of instances [63]. Kim et al [61] conducted a trial where they continuously used SCS in individuals who had active vitiligo. The administration of oral prednisolone commenced at a dosage of 0.3 mg/kg of body weight for the initial two months. In the third month, the dosage was reduced to half of the original dose, and in the fourth month, it was further reduced to half of the previous dose. The findings demonstrated that 87.7% of patients experienced a halt in the course of vitiligo, while 70.4% of patients experienced the restoration of pigmentation [61]. Applying the identical approach, Banerjee et al [64] reported a 90% rate of patient arrest and a 76% rate of patient repigmentation in active vitiligo cases.

Pasricha and Khaitan [65] implemented a therapeutic approach involving the administration of either

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betamethasone or dexamethasone pulses orally at a dosage of 5 mg for two consecutive days per week. The treatment was maintained until complete repigmentation was achieved or for a duration of four months with no additional progress. After 1-3 months of treatment with a 5 mg dose, 89% of patients saw a cessation of active illness, and after 2-4 months, 80% of patients observed repigmentation. The degree of repigmentation was 76-99% in 15.0% of patients, 51-75% in 7.5% of patients, 26-50% in 25.0% of patients, 10-25% in 17.5% of patients, and less than 10% in 35.0% of patients [65]. Kanwar et al [66] conducted a retrospective analysis with 444 patients with active vitiligo. They used a low-dose oral mini-pulse treatment, administering a dosage of 2.5 mg/day on 2 consecutive days every week. Out of the individuals studied, 91.8% were able to stop the progression of the disease. However, throughout the follow-up period, 12.25% of these patients had one or two instances of the disease becoming active again. Radakovic-Fijan et al [67] implemented an alternative method of oral pulse treatment, in which they administered a dosage of 10 mg of dexamethasone for two consecutive days over a period of 24 weeks. 88% of patients with active vitiligo successfully halted the progression of the condition, but the majority of patients (72.4%) did not have any improvement in repigmentation [67].

Seiter et al [62] also utilized a therapy including pulses, administered intravenously. Over a period of three consecutive days, methylprednisolone was delivered intravenously at a dosage of 8 mg per kilogram of body weight. If the medication was well tolerated, it was administered again at 4 and 8 weeks. 85% of patients experienced a cessation of active vitiligo development, whereas 71% of patients observed repigmentation. Patients with persistent vitiligo experienced no alteration in pigmentation [62]. The adverse effects of SCS include increased body weight, temporary muscle weakness, tiredness, difficulty sleeping, skin breakouts, restlessness, disruptions in menstrual cycle, high blood pressure, metallic taste in the mouth, itching, headaches, flushing, and excessive hair growth [62,65,67].

- *Apremilast*

Apremilast is a medication that inhibits phosphodiesterase 4, which works by raising the levels of cyclic adenosine monophosphate (cAMP) inside cells [68]. The application of Apremilast in vitiligo is attributed to its immunomodulatory qualities. This medication increases the concentration of cAMP, which leads to a reduction in the synthesis of pro-inflammatory mediators (such as IL 23, IL 17, TNF α, and IFN γ) and an increase in anti-inflammatory mediators, such as IL 10 [68]. Apremilast is authorized for the management of moderate to severe plaque psoriasis [68]. The initial instance of its application in vitiligo was documented by Huff and Gottwald [69] in a patient who did not respond to alternative treatments. Apremilast was given at a dosage of 30 mg twice daily for a duration of 13 months, and two injections of 60 mg of triamcinolone acetonide were injected into the muscle at the same time. The findings demonstrated a repigmentation rate of 60-70% in the chest and extremities [69]. A recent pilot study conducted by Majid et al [68] presented a case series of 13 individuals suffering with fast advancing non-segmental vitiligo. These patients were treated with a dosage of 30 mg of apremilast twice daily for a period of 3 months, following an initial adjustment of the dosage. The patients may apply topical tacrolimus to the areas of the body that are not covered. All patients experienced stabilization of their condition, and 61.5% of patients showed partial repigmentation [68]. Apremilast may cause various adverse symptoms such as headache, nausea, vomiting, weight loss, depression, and stomach pain [68,69].

- *JAK Inhibitors*

JAK inhibitors have use beyond topical usage. Craiglow and King (70) documented a case of a 50-year-old woman with extensive and advancing vitiligo. The patient was administered oral tofacitinib citrate at a daily dosage of 5 mg for a period of 5 months. As a result, there was a significant restoration of pigmentation on the forehead and hands, whereas other regions saw only partial repigmentation (70). Two case reports of female patients with rheumatoid arthritis showed that treatment with tofacitinib 5 mg twice daily also resulted in improvement of vitiligo [71,72]. Liu et al [56] presented a collection of cases involving 10 patients who were administered tofacitinib at a dosage of 5-10 mg, either once or twice daily, for a minimum duration of 3 months. During the trial, suction blister sampling was conducted on both responding and nonresponding sites, which revealed a suppression of the autoimmune response in both areas. The study found that 50% of patients experienced repigmentation at areas treated with low dose nb UVB phototherapy or exposed to sunlight. Based on these results, the authors propose that melanocyte regeneration and repigmentation during treatment with JAK inhibitors may necessitate the presence of low level light. The observed adverse effects were upper respiratory infections, weight gain, arthralgia, and a little increase in cholesterol levels [56].

- *Minocycline*

Minocycline, an oral antibiotic, was investigated as a potential treatment for vitiligo based on in vitro research indicating its ability to shield melanocytes from oxidative stress and prevent their depletion during the initial phases of the disease [73]. In order to assess this, Parsad and Kanwar [74] conducted a research including 32 individuals who had vitiligo that was steadily worsening over time. Patients received a daily dose of 100 mg of minocycline for a duration of 3 months. This treatment resulted in the cessation of disease activity in 90.6% of patients, and 21.8% of patients experienced mild to substantial repigmentation [74]. Singh et al [75] conducted a randomized.

A controlled trial was conducted to assess the effectiveness and tolerability of oral minocycline in comparison to oral micro pulse corticosteroids in patients with active vitiligo. The minocycline group was administered a daily dose of 100 mg, whereas the corticosteroid group received dexamethasone at a dosage of 2.5 mg on two consecutive days every week. The effectiveness of the treatment was assessed using the vitiligo

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disease activity score (VIDA) [76] and VASI. While not reaching statistical significance at the end of therapy, both groups experienced a decrease in VIDA and VASI scores with similar outcomes. This suggests that both medicines are successful in stopping vitiligo activity [75]. In a study conducted by Siadat et al [77], minocycline 100 mg daily was compared to nb UVB phototherapy in individuals with unstable vitiligo over a 3-month treatment period. At the start of the experiment, all patients had active vitiligo. However, after treatment, the percentage of patients with active vitiligo dropped to 66.1% in the minocycline group and 23.8% in the nb UVB group [77]. Minocycline can cause adverse effects such as nausea, gastrointestinal issues, headaches, and hyperpigmentation of the nails, oral mucosa, or skin [75,77].

Cholesterol-lowering medications called statins. Statins are pharmaceutical agents used to reduce levels of lipids in the body. Their involvement in vitiligo is attributed to their anti-inflammatory and immunomodulatory properties, which result in the suppression of CD8 T cell proliferation, chemokines, proinflammatory mediators, and the production of proinflammatory adhesion markers [78,79]. Furthermore, the suppression of IFN γ production leads to a decrease in the expression of major histocompatibility complex II, as well as the inhibition of activated T cell [78-81].

- *Statins*

Statins have the ability to increase the activity of a transcription factor called nuclear erythroid 2 related factor, which leads to a decrease in reactive oxygen species and the activation of the antioxidant response in melanocytes [78]. Statins enhance the synthesis of tyrosinase mRNA and amplify the impact of α melanocyte stimulating hormone on melanocytes, leading to enhanced melanogenesis [78]. There is a single case report documenting an unforeseen improvement of vitiligo in a patient who received a high dosage of simvastatin [82]. Nevertheless, research conducted with statins has indicated that there is no advantageous effect on vitiligo [80,81,83].

- *Methotrexate (MTX)*

MTX is frequently employed in the treatment of several inflammatory and autoimmune conditions [84]. The majority of the original findings on the improvement of vitiligo treated with MTX were observed in individuals who were also using it to manage coexisting rheumatoid arthritis or psoriatic arthritis. The MTX dosage ranged from 7.5 to 25.0 mg per week, in addition to taking folic acid supplements. The outcomes varied from the cessation of vitiligo progression to substantial restoration of skin pigmentation [84,85]. A study conducted by Nageswaramma et al [86] involved the treatment of 20 patients with unstable vitiligo using a weekly dosage of 15 mg of MTX together with folic acid therapy. 70% of patients experienced moderate repigmentation, whereas 90% of patients saw a halt in the course of their condition. Nevertheless, the effectiveness of MTX in treating vitiligo varies. Alghamdi and Khurrum conducted an uncontrolled pilot research [84] where they administered MTX 25 mg weekly for a duration of 6 months. However, no clinical improvement was found throughout this period. In a randomized comparison trial conducted by Singh et al [87], the effectiveness of MTX 10 mg administered weekly was compared to that of oral corticosteroid mini pulses consisting of 2.5 mg of dexamethasone taken on 2 consecutive days for a duration of 24 weeks. Both groups experienced a comparable decrease in the VIDA score by the conclusion of the trial. During treatment, further lesions emerged in 23% of patients in the MTX group and 28% of patients in the corticosteroid group [87]. ElGhareeb et al [88] conducted a study including 42 patients to evaluate the effectiveness and safety of oral methotrexate (MTX) and oral micro pulse of dexamethasone, whether taken individually or in combination. The patients were allocated into three groups using randomization. Group A was administered a total of 15 mg of MTX, which was divided into three doses and given at weekly intervals of 12 hours. Group B was administered a daily dosage of 5 mg of dexamethasone for two consecutive days each week. Group C was administered a hybrid of both procedures. The treatment was administered to all groups for a duration of 3 months. The findings indicated a notable reduction in the spread of the disease in group C when compared to the other groups [88]. MTX can cause hepatotoxicity, idiosyncratic pulmonary toxicity, pancytopenia, as well as symptoms such as nausea, vomiting, and diarrhea [23].

- *Azathioprine*

Azathioprine is a type of medication that suppresses the immune system by preventing the manufacture of DNA in cells that are involved in immunological responses [42]. A study conducted by Madarkar et al [89] examined the use of azathioprine 50 mg twice daily compared to betamethasone 5 mg on 2 consecutive days every week for 6 months in the treatment of vitiligo. The authors found significant advancements in both groups and concluded that both therapy are equally efficacious in treating vitiligo [89]. Radmanesh and Saedi [90] conducted a study involving 60 patients who were randomly assigned to two groups. The initial cohort was administered azathioprine at a dosage of 0.60-0.75 mg/kg per day (with a maximum limit of 50 mg), in combination with twice weekly oral psoralen (methoxypsoralen at a dosage of 0.3-0.4 mg/kg) along with UVA treatment. The second group exclusively received oral psoralen with UVA (PUVA). Both cohorts were observed for a duration of 4 months. The previous findings shown that repigmentation occurred quicker after 5 oral PUVA sessions, and there was a higher level of repigmentation (58.4%) in the combination group compared to the oral PUVA monotherapy group after 8 sessions, which resulted in 24.8% repigmentation [90]. Azathioprine can cause myelosuppression, hepatotoxicity, gastrointestinal discomfort, increased vulnerability to infections (such as herpes simplex and human papillomavirus), and hypersensitivity syndrome [23].

- *Cyclosporine*

Cyclosporine is a medication that inhibits calcineurin and has the ability to modify the immune system. Taneja et al [91] conducted an open-label, single-arm trial with 18 patients with progressive vitiligo. The patients were

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administered cyclosporine at a dosage of 3 mg/kg/day, divided into two doses, for a duration of 12 weeks. Out of the individuals studied, 61% saw a halt in the advancement of vitiligo, while 81% showed signs of repigmentation [91]. Mutalik et al [92] conducted a pilot research on patients with localized stable vitiligo who were treated with autologous nonculture melanocyte keratinocyte cell transplant (NCMKT). The aim was to evaluate the effectiveness of cyclosporine in preventing the perilesional depigmentation halo that occurs after NCMKT surgery. The experimental group was administered cyclosporine after the surgery for a duration of 3 weeks at a dosage of 3 mg per kilogram per day, followed by a 6-week period of cyclosporine at a dosage of 1.5 mg per kilogram per day. The cyclosporine group achieved a repigmentation rate of over 75% in all patients, while only 28% of patients in the untreated group experienced the same level of repigmentation. Within the latter group, the majority of patients (52%) acquired repigmentation ranging from 25% to 50%. According to the authors' findings, the use of postoperative cyclosporine resulted in consistent and total restoration of skin pigmentation after NCMKT [92]. Cyclosporine can cause several side effects including renal failure, hypertension, gingival hyperplasia, hypercalcemia, hyperuricemia, nausea, abdominal discomfort, tremor, headache, arthralgias, and hypertrichosis [23,91].

- *Mycophenolate Mofetil (MM)*

MM hinders the production of new purines in T and B lymphocytes by blocking the activity of the enzyme inosine 5' monophosphate dehydrogenase [93]. Bishnoi et al [93] assessed the effectiveness of MM in stabilizing non-segmental vitiligo. A comparison was made between the administration of up to 1 g of mycophenolate mofetil twice daily and the administration of 2.5 mg of dexamethasone on two consecutive days each week for a period of 180 days. Disease activity was successfully halted in 80% of patients in the corticosteroid group, while 72% of individuals in the MM group experienced the same outcome. The predominant adverse effects observed in the MM group were nausea and diarrhea. Two patients in the MM group had their treatment interrupted due to leucopenia and transaminitis, respectively [93].

IV. TREATMENTS FOR DEPIGMENTATION

These therapies are typically suggested for severe and resistant cases of vitiligo, when more than 50% of the body surface is affected or when cosmetically sensitive areas are primarily involved. The Monobenzyl ether of hydroquinone (MBEH) at a concentration of 10% is administered topically once daily during the initial month. Subsequently, the concentration is increased to 20% and applied daily for another month. After this period, the application frequency is increased to twice daily. If the areas are unresponsive and tolerated, the concentration can be increased to 30-40%. Typically, patients experience loss of pigmentation in areas farther away from the application site after a period of 3 to 6 months. Additional treatment alternatives include 4 methoxyphenol, an 88% phenol solution, laser therapy, and cryotherapy.

Table 2 Pharmacological Treatment of Vitiligo

Class	Subclass	Medication	Uses	Mechanism of Drug	Side Effects
Topical	**Corticosteroids**	Hydrocortisone	Reduces inflammation and immune response	Anti-inflammatory and immunosuppressive	Skin thinning, stretch marks
		Clobetasol propionate	More potent than hydrocortisone	Anti-inflammatory and immunosuppressive	Skin atrophy, acne
	Calcineurin Inhibitor	Tacrolimus	Reduces inflammation and immune response	Inhibits calcineurin, suppresses T-cell activation	Burning, stinging, irritation
		Pimecrolimus	Similar to tacrolimus	Inhibits calcineurin, suppresses T-cell activation	Skin irritation, redness
	Vitamin D3 Analogues	Calcipotriol	Modulates immune response	Binds vitamin D receptor, modulates T-cell function	Skin irritation, hypercalcemia
		Calcitriol	Modulates immune response	Binds vitamin D receptor, modulates T-cell function	Skin irritation, hypercalcemia
	Pseudocatalase	PC-KUS	Reduces oxidative stress	Catalyzes breakdown of hydrogen peroxide	Skin irritation
	5-Fluorouracil	5-FU	Potential adjunctive treatment	Antimetabolite, disrupts DNA and RNA synthesis	Skin irritation, photosensitivity
	Methotrexate	Methotrexate	Reduces inflammation	Folate antagonist, inhibits cell division	Skin irritation, liver toxicity
	PF2A	PF2A	Reduces oxidative stress	Not well-documented	Unknown
	bFGF	bFGF	Promotes melanocyte proliferation	Growth factor for melanocyte proliferation	Limited information
	JAK Inhibitors	Tofacitinib	Reduces inflammation and	Inhibits Janus kinase pathways	Skin irritation, infections

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			immune response		
		Ruxolitinib	Similar to tofacitinib	Inhibits Janus kinase pathways	Skin irritation, infections
Systemic	**Corticosteroids**	Prednisone	Reduces inflammation and immune response	Anti-inflammatory and immunosuppressive	Weight gain, osteoporosis
		Dexamethasone	More potent than prednisone	Anti-inflammatory and immunosuppressive	Hypertension, diabetes
	Apremilast	Apremilast	Reduces inflammation	Inhibits phosphodiesterase 4 (PDE4)	Nausea, diarrhea
	JAK Inhibitors	Tofacitinib	Similar to topical	Inhibits Janus kinase pathways	Infections, liver toxicity
		Ruxolitinib	Similar to topical	Inhibits Janus kinase pathways	Infections, liver toxicity
	Minocycline	Minocycline	Anti-inflammatory properties	Inhibits matrix metalloproteinases (MMPs)	Photosensitivity, dizziness
	Statins	Atorvastatin	Potential adjunctive treatment	Inhibits HMG-CoA reductase, reduces cholesterol	Muscle pain, liver toxicity
	Methotrexate	Methotrexate	Similar to topical	Folate antagonist, inhibits cell division	Liver toxicity, anemia
	Azathioprine	Azathioprine	Immunosuppressive	Inhibits DNA and RNA synthesis	Bone marrow suppression
	Cyclosporine	Cyclosporine	Immunosuppressive	Inhibits calcineurin, suppresses T-cell activation	Nephrotoxicity, hypertension
	Mycophenolate Mofetil	Mycophenolate mofetil	Immunosuppressive	Inhibits inosine monophosphate dehydrogenase (IMPDH)	GI disturbances, leukopenia

➢ *Indian System of Medicine Treatment of Vitiligo*

Here is a table presenting the treatment of vitiligo according to the Indian system of medicine, which includes Ayurveda, Siddha, and Unani. The table lists different treatments, their uses, mechanisms, and potential side effects.

Table 3 Indian System of Medicine Treatment of Vitiligo

Class	Subclass	Medication	Uses	Mechanism of Drug	Side Effects
Topical	**Herbal Oils**	Neem oil	Soothes the skin and reduces inflammation	Antibacterial, antifungal, and anti-inflammatory	Skin irritation
		Babchi oil (Bakuchi oil)	Promotes repigmentation	Phototoxic effect, stimulates melanin production	Photosensitivity
		Coconut oil	Moisturizes skin and reduces irritation	Contains antioxidants and anti-inflammatory properties	None reported
		Turmeric paste	Reduces inflammation and oxidative stress	Contains curcumin with antioxidant and anti-inflammatory	Skin staining
	Herbal Creams	Manjistha cream	Promotes skin health and pigmentation	Contains natural compounds that improve skin quality	None reported
		Ammi majus cream	Encourages repigmentation	Contains psoralen, which enhances UV exposure	Photosensitivity
Systemic	**Herbal Remedies**	Babchi capsules (Bakuchi)	Promotes repigmentation and skin health	Contains psoralen and other active compounds	Photosensitivity
		Guduchi (Tinospora cordifolia)	Boosts immunity and reduces inflammation	Contains bioactive compounds that modulate immune response	None reported
		Khadira (Acacia catechu)	Promotes skin health and pigmentation	Contains catechins and flavonoids with antioxidant effects	None reported

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		Shankhpushpi (Convolvulus pluricaulis)	Calming and neuroprotective effects	Contains bioactive compounds that support mental health	None reported
		Giloy (Tinospora cordifolia)	Boosts immunity and reduces inflammation	Contains bioactive compounds that modulate immune response	None reported
Therapies	**Panchakarma**	Basti (enema therapy)	Detoxifies the body and supports skin health	Ayurvedic detoxification therapy	Mild discomfort
		Virechana (purgation therapy)	Eliminates toxins and supports overall health	Ayurvedic detoxification therapy	Gastrointestinal discomfort
	Raktamokshana	Leech therapy	Removes impure blood to improve circulation and skin health	Leeches remove stagnant blood	Mild irritation at application site

V. CONCLUSION

Vitiligo remains a challenging condition to manage due to its complex etiology and varied response to treatments. A comprehensive approach involving pharmacological treatments such as topical, systemic, and depigmentation therapies can offer promising outcomes for patients. Topical treatments such as corticosteroids, calcineurin inhibitors, and vitamin D3 analogues have shown efficacy in promoting repigmentation, while systemic treatments like corticosteroids, JAK inhibitors, and immunosuppressants help manage the immune response associated with vitiligo. Therapies for depigmentation provide an option for patients with extensive vitiligo who may prefer a more uniform skin tone. The Indian system of medicine presents additional treatment avenues worth exploring for its potential benefits. Future research is needed to optimize treatment regimens and explore novel therapeutic approaches. Personalized treatment plans, taking into account the patient's specific needs and response to therapy, will lead to improved management of vitiligo and enhanced quality of life for those affected.

- *Future Aspects*

The future of treating vitiligo lies in a multidisciplinary approach that combines the best parts of modern drug therapies with the tried-and-true remedies of traditional Indian medicine. This will provide better and more complete care for people who have this difficult condition.

- *Competing Interests*

The authors declare no competing of Interest, financial or otherwise authors contributions.

- *Authors Contribution*

All authors participated in the conception and design of the study. Shivani Agarwal and Rahul Chauhan conducted the material preparation, data collecting, and analysis. Shivani Agarwal composed the initial draft of the book, and all writers reviewed and endorsed the final version.

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- *Availability of data and material*

The authors confirms that the data supporting the findings of this study are available within the article.

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