Acad Med J 2025;5(Suppl 1):S42-S51.
UDC: 616.5-003.829-085
https://www.doi.org/10.53582/AMJ255142d
Review article

VITILIGO: WHAT'S OLD, WHAT'S NEW?

Dimova Maja, Simeonovski Viktor, Telenta Mitrova Julija, Pollozhani Nora

University Clinic for Dermatology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
e-mail: dimovamaja@hotmail.com

Abstract

Vitiligo is a chronic, inflammatory, autoimmune disorder resulting from a selective destruction of melanocytes and the appearance of depigmented skin patches. It affects all ethnic groups and genders equally, with a slight female predominance. It is estimated that approximately 0.5-2% of the global population suffer from vitiligo, making this dermatosis the most common pigmentation disorder. Vitiligo is a complex disease with complex etiology and pathogenesis. It is currently accepted that genetic predisposition and environmental factors lead to melanocyte oxidative stress, and activation of abnormal immune response, but the overall contribution of each of these processes remains insufficiently clear.

Historically, vitiligo was recognized in ancient times, with evidence found in ancient Egyptian, Greek, and Indian texts. Early interpretations associated this skin disease with divine punishment or contagion, leading to quarantines and stigmatization. Today, vitiligo is classified as an autoimmune disease, with autoimmune attack on melanocytes considered the primary factor leading to the appearance of depigmented macules. The skin and gut microbiome and neural hypothesis have recently gained attention as emerging factors in the pathogenesis of vitiligo.

The treatment of vitiligo remains a significant challenge. It includes local and systemic immunosuppressives, phototherapy, surgical techniques, as well as other therapeutic approaches, including traditional medicine, camouflage, depigmentation, and psychological interventions. However, vitiligo has a long treatment cycle, and all current treatments provide only short-term benefits, with relapse of the disease being common once treatments are discontinued. In recent years targeted therapies such as JAK inhibitors are actively being developed.

Keywords: vitiligo; melanocyte destruction; microbiome; neural hypothesis; JAK inhibitors

Introduction

Vitiligo is the most frequent acquired pigmentary disorder characterized by the progressive loss of melanocytes, leading to well-defined depigmented macules [1]. It affects approximately 0.5–2% of the global population, with no clear predilection for sex or ethnicity, though some studies suggest a slight female predominance [2]. The disease is more noticeable in individuals with darker skin types, which may contribute to higher reported prevalence in these populations. Vitiligo is a chronic, inflammatory, autoimmune disease that is not simply cosmetic. Despite being a non-life-threatening condition, vitiligo has profound psychological and social consequences, significantly impacting patients' quality of life [3,4,5].

Historically, vitiligo was described in ancient medical texts, but its pathogenesis remained elusive for centuries. Early theories ranged from infectious causes to purely

psychological explanations[6,7]. Over a long period of time, research has refined our understanding, and vitiligo is now recognized as an autoimmune disease with complex genetic, environmental, and neural influences [8,9,10]. Emerging evidence suggests that the skin and gut microbiome plays a critical role, with alterations in microbial diversity potentially contributing to melanocyte dysfunction and immune activation [11]. Additionally, the neural hypothesis proposes that neurogenic factors, including stress-induced neurotransmitters and neuropeptides, may contribute to melanocyte destruction, particularly in segmental vitiligo [12]. These insights offer a more comprehensive view of vitiligo as a multifaceted disorder rather than a purely immune-driven condition. The management of vitiligo has also evolved. Traditional therapies, such as corticosteroids and phototherapy, remain mainstays, but new targeted treatments, including Janus kinase (JAK) inhibitors, are reshaping the therapeutic landscape. Recent breakthroughs in vitiligo pathogenesis, including the role of the microbiome and neural factors, are opening new avenues for intervention.

This review explores the historical perspectives of vitiligo, current treatment strategies, and the latest advancements in our understanding of the pathogenesis. In particular, the final section highlights emerging concepts and novel therapeutic approaches that may transform vitiligo management in the near future.

What's ancient old?

The understanding of vitiligo has evolved significantly over centuries. One of the oldest known medical texts, describes a skin condition resembling vitiligo. Ancient Egyptians associated depigmentation with supernatural or divine influences and sometimes linked it to leprosy (Ancient Egyptian Medicine (c. 1550 BCE): The *Ebers Papyrus*) [6]. In *Sushruta Samhita*, an early Sanskrit medical text, a condition called *Switra* or *Kilasa* is described, which closely resembles vitiligo. It was thought to result from dietary imbalances or past sins, and treatments included herbal applications, dietary restrictions, and sun exposure (Indian Ayurvedic Texts (c. 600 BCE) [7]. Hippocrates and other Greek physicians described skin disorders that could correspond to vitiligo, but they often confused it with leprosy and other pigmentary disorders (Ancient Greek Medicine c. 400 BCE) [6]. There have been many misconceptions and superstitions over ancient times. Biblical and religious sources have mistaken vitiligo for leprosy, leading to social stigmatization and isolation due to the belief that it was a contagious disease or punishment. During the Middle Ages, vitiligo was sometimes attributed to "bad blood," imbalances in bodily humors, or even witchcraft. Treatments ranged from bloodletting to herbal concoctions. Early Scientific Theories (17th–19th century) came with the advance of medicine, when vitiligo was distinguished from leprosy. By the late 19th century, the term *vitiligo* became widely accepted in dermatology, and researchers started recognizing that it was non-contagious and possibly linked to nerve function [13,14]. These historical perspectives highlight how vitiligo was long misunderstood, often linked to supernatural beliefs or lumped together with other skin diseases. Modern science has since provided a more accurate understanding, particularly in terms of autoimmunity, genetics, and environmental factors.

What's old and generally accepted?

Today it is widely accepted that vitiligo arises from a complex interplay between genetics, environmental factors and autoimmunity [12,15]. While genetic susceptibility is the main culprit, environmental triggers such as UV-radiation and chemical exposures can initiate or exacerbate the disease. Autoimmune mechanisms, including melanocyte-specific T-cell responses and inflammatory cytokines, drive the progression of depigmentation [12,15].

Genetics: The Main Culprit?

Genetic predisposition plays a crucial role in vitiligo, as evidenced by familial clustering and twin studies. Genome-wide association studies (GWAS) have identified over 50 susceptibility loci, many linked to immune regulation and melanocyte function. Key genes include: HLA genes: involved in antigen presentation; NLRP1: a regulator of the inflammasome, influencing immune activation. PTPN22: a key player in immune tolerance, associated with multiple autoimmune diseases. TYR (Tyrosinase): essential for melanin production, highlighting a direct link to melanocyte vulnerability [16,17,18]. Genetics alone does not elicit disease, but is the foundation where environmental factors and immune attack build, leading to visible disease.

Among others environmental triggers, the most important are chemical exposure, UV radiation, mechanical and thermal trauma, involved in melanocyte oxidative stress and increased reactive oxidative species (ROS) in melanocytes which trigger autoimmune response and recruit autoreactive cytotoxic T-lymphocytes. As immune cells attack melanocytes, further oxidative stress and inflammation are generated, sustaining disease progression [19,20,21].
Chemicals directly implicated in vitiligo are many, such as monobenzyl ether of hydroquinone (MBEH) discovered by Oliver et al. in a tanning factory, but includes many others as well [22]. In his 2017 review, Chemical-Induced Vitiligo, Harris JE explores the role of chemical exposure in triggering and exacerbating vitiligo. Chemicals can induce vitiligo by causing oxidative stress and directly damaging melanocytes, leading to autoimmune responses. Certain substances, such as phenolic compounds found in hair dyes, rubber, and industrial chemicals, are particularly implicated. These chemicals generate reactive oxygen species (ROS), which damage melanocytes and make them vulnerable to attack by immune cells. Occupational exposure in industries like hairdressing and manufacturing has been linked to a higher prevalence of vitiligo. Harris emphasizes that genetic susceptibility plays a key role in determining whether an individual develops vitiligo upon exposure to these chemicals, as not everyone exposed will experience the condition [22,23]. Ultraviolet (UV) radiation plays a significant role in the pathogenesis and treatment of vitiligo [24]. While excessive UV exposure can trigger or exacerbate the condition by inducing oxidative stress and immune responses that damage melanocytes, controlled UV therapy is a cornerstone in vitiligo management. Sunburns are more frequent in vitiligo patients, due to loss of melanocytes and skin protection. Sunburns in these areas can cause lesions to increase in size and may lead to the appearance of new lesions due to the Koebner phenomenon. Physical trauma can also initiate or worsen vitiligo through the Koebner phenomenon. Vitiligo is a true example of Koebner phenomenon, together with other dermatological diseases like psoriasis and lichen planus [25]. It is considered that immunological disorders, oxidative stress, defective melanocyte adhesion and growth factor deficiency are the main pathological mechanisms of vitiligo Koebner phenomenon [25,26]. If genetics may predispose an individual to vitiligo, environmental triggers catalyze the cascade that leads to autoimmunity and vitiligo.

The Herald of Immune Attack in Vitiligo is the JAK-STAT pathway.

The Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway is a critical signaling cascade involved in immune responses and inflammation [27]. In vitiligo, this pathway plays a pivotal role in the immune-mediated destruction of melanocytes, bridging innate and adaptive immunes system [28,29]. The JAK-STAT pathway is first activated by cytokines, such as IFN-γ**,** released from innate immune cells (macrophages, dendritic cells, and natural killer cells) in response to tissue damage or stress in the skin. IFN-γ is a key cytokine that signals the presence of a foreign or damaged tissue and activates both innate and adaptive immune responses through the JAK-STAT pathway. The dendritic cells activated by

the JAK-STAT pathway process and present melanocyte-specific antigens to CD8+ T cells, triggering the adaptive immune response.

T helper (Th) cells, including Th1 cells, further contribute to the immune attack by releasing more pro-inflammatory cytokines, which stimulate cytotoxic T lymphocytes (CTLs) to target melanocytes. Thus, the JAK-STAT pathway acts as a signal transducer that facilitates the cross-talk between the innate immune system initial response and the adaptive immune system targeted attack [28,29].

This connection highlights the central role of the JAK-STAT pathway in vitiligo and explains why targeting it can have therapeutic benefits by inhibiting both arms of the immune response[30].

This multifaceted understanding of vitiligo has not only refined diagnostic approaches but has also paved the way for targeted therapeutic strategies.

What's new in pathogenesis?

In recent years, our understanding of vitiligo pathogenesis has expanded beyond the classical autoimmune paradigm to welcome novel contributing factors, including the role of the skin and gut microbiome and the neural hypothesis. These emerging perspectives provide fresh insights into disease mechanisms and potential therapeutic targets [31].

The Microbiome and Vitiligo

The skin microbiome, composed of a diverse array of bacteria, fungi, and viruses, plays a critical role in maintaining cutaneous homeostasis and immune balance. Disruptions in this delicate microbial community, known as dysbiosis, have been implicated in various dermatological conditions, including vitiligo [11,32]. Studies have demonstrated alterations in the microbiome composition in vitiligo patients, suggesting a potential link between microbial imbalances and disease progression. Certain bacterial species, such as *Cutibacterium* acnes and *Staphylococcus aureus*, have been shown to modulate immune responses, influencing melanocyte survival and function. Additionally, microbial-derived metabolites and toxins may exacerbate oxidative stress, a well-known trigger in vitiligo pathogenesis. Future research exploring microbiome-targeted therapies, such as probiotics, prebiotics, and bacteriophage-based treatments, may offer novel avenues for managing vitiligo [33,34].

The gut microbiome alterations are also linked to several skin diseases [35]. The gut microbiome, known as an immune system regulator, by providing immune tolerance and reducing inflammation, is crucial for skin immune homeostasis and plays a role in the development of autoimmune diseases [36]. In recent years, studies have increasingly begun to explore the relationship between the gut dysbiosis and vitiligo through several mechanisms involving immune system dysregulation, oxidative stress, and systemic inflammation. Recent studies have found that vitiliginous skin has altered gut microbiome, with increase in the proinflammatory bacteria (*Proteobacteria, Streptococcus*) and decrease in the beneficial gut bacteria (*Bifidobacterium, Lactobacillus*), leading to gut dysbiosis and intestinal permeability "leaky gut". This allows microbial components to enter circulation, promoting inflammation, cytokine production and melanocyte destruction and shift from a tolerant immune state to a dysregulated one [37].

Do microbes also have something to say?

There have been some reports of microorganisms in vitiligo with proposed potential mechanism of action which might offer new insights in vitiligo development, and offer new treatment strategies. Among others, bacteria like *Helicobacter pylori* and viral infections including hepatitis, human immunodeficiency virus, cytomegalovirus are implicated. *H. Pylori*, a Gram-negative bacterium, known for colonizing the gastric mucosa, is also found

provoke extra-gastric manifestations and is related to body immune reaction and serious autoimmune diseases, like IBD, autoimmune metabolic disorders and liver disease. Recent studies show that dermatological autoimmune diseases are not excluded. Vitiligo is among them, as it is an autoimmune disease [11].

A prospective study conducted at Ankara Education and Research Hospital in Turkey explored the association between *Helicobacter pylori* infection and vitiligo. The study included 68 patients diagnosed with vitiligo and 65 patients with telogen effluvium (TE) as controls. All participants underwent testing for *H. pylori* infection using the urea breath test (UBT), as well as assessments for *H. pylori*-specific IgG antibodies and the cytotoxin-associated gene A (CagA) protein. The study found that the vitiligo group exhibited significantly higher rates of *H. pylori* positivity (60.3%) compared to the controlled -TE group (41.5%). Additionally, the presence of *H. pylori* CagA and IgG antibodies was more prevalent in the vitiligo group. Patients with vitiligo had higher incidence of gastric symptoms such as bloating and upper gastrointestinal discomfort, than those in the control group. However, no significant relationship between *H. pylori* infection status and vitiligo activity and pattern was found [38].
A study by Bakry et al. examined the association between *H. pylori* infection and vitiligo disease activity. The research involved 75 patients with non-segmental vitiligo and an equal number of age- and gender-matched healthy controls. *H. pylori* infection was diagnosed using stool antigen tests and serum IgG antibody levels. The results indicated a significantly higher prevalence of *H. pylori* infection among vitiligo patients (65.3%) compared to the control group (24%). Furthermore, the presence of *H. pylori* infection was correlated with increased vitiligo disease activity, as reflected by higher Vitiligo Disease Activity (VIDA) scores and more active disease states. Based on these findings, the study suggests that screening for H. pylori in vitiligo patients, particularly those with active disease, may be beneficial. The authors propose further clinical trials to investigate whether eradicating *H. pylori* could influence the progression of vitiligo [39].

Another study by Rifaioğlu et al. investigated the frequency of *H. pylori* infection in vitiligo patients using the carbon-14 urea breath test (C14 UBT). The study included 34 vitiligo patients and 30 age- and sex-matched healthy controls. The results showed that *H. pylori* infection was significantly more frequent in vitiligo patients (64.7%) compared to the control group (33.3%), with statistical significance ($P = 0.012$). The authors suggest that this study is the first to report the prevalence of *H. pylori* infection in vitiligo patients. They recommend further research to clarify whether *H. pylori* plays an etiological or initiating role in vitiligo pathogenesis [40].

These studies open questions about the possible pathogenic mechanism by which bacteria are implicated in vitiligo autoimmunity. There is no clear answer of the potential pathogenic mechanism of *H. pylori* on vitiligo. Oxidative stress and cytotoxic T-cell destruction of melanocytes are suggested mechanisms. Cytokines like INF-gama, Il-1, Il-6 are implicated in vitiligo. Meanwhile, research has shown that the levels of cytokines such as IFN-γ, TNF-α, and IL-1 are high in the stomachs of *H. pylori*-positive patients. This is a probable and suspected mechanism, but more research is needed to understand the underlying mechanism.

Emerging research suggests potential associations between certain viral infections and the development or exacerbation of vitiligo. The exact nature of these relationships is not fully established, but immune dysregulation, molecular mimicry, and oxidative stress are under suspicion.

HCV is known to trigger systemic immune activation, leading to chronic inflammation and autoimmune reactions. One possible mechanism is molecular mimicry, where viral antigens resemble melanocyte antigens, triggering cross-reactive immune responses that lead to melanocyte destruction. Additionally, HCV-associated liver dysfunction may alter immune

homeostasis, potentially influencing the development of autoimmune conditions like vitiligo. Some studies have indicated a link between chronic HCV infection and vitiligo. For instance, a study found that 65.3% of vitiligo patients tested positive for HCV antibodies, compared to 24% in a control group, suggesting a significant association between HCV infection and vitiligo. However, other research has not found a significant relationship between HCV and vitiligo, indicating that the connection remains inconclusive [41,42].

CMV, a latent herpesvirus, has been implicated in autoimmunity due to its ability to manipulate immune responses. CMV infection may induce chronic immune activation and an imbalance in regulatory T cells, leading to increased autoreactive immune responses against melanocytes. Some studies suggest that CMV-induced oxidative stress and inflammatory cytokine production may contribute to melanocyte apoptosis. The role of CMV in vitiligo pathogenesis is also under investigation. A study detected CMV DNA in skin biopsy specimens from some vitiligo patients, suggesting a possible involvement of CMV in the development of the disease. However, subsequent studies have produced mixed results, and the exact role of CMV in vitiligo remains unclear [43,44].

HIV, due to its profound impact on the immune system, has also been associated with vitiligo, particularly in patients undergoing immune reconstitution after antiretroviral therapy (ART). The phenomenon of immune reconstitution inflammatory syndrome (IRIS) may unmask or exacerbate autoimmune conditions, including vitiligo, as the recovering immune system aggressively targets latent autoantigens, including melanocytes. Additionally, chronic HIV infection and systemic inflammation can disrupt normal immune tolerance mechanisms, further predisposing individuals to vitiligo. Vitiligo has been reported in individuals with HIV infection, either as a direct manifestation of the virus or as a complication of antiretroviral therapy. The immunological alterations caused by HIV, such as changes in CD4+ and CD8+ T-cell populations, may contribute to the development of autoimmune conditions like vitiligo. However, the precise mechanisms linking HIV to vitiligo are not fully understood [11].

The Neural Hypothesis in Vitiligo

The neural hypothesis of vitiligo proposes that neurogenic factors play a significant role in melanocyte dysfunction and destruction. This concept is supported by clinical observations, such as the tendency for vitiligo lesions to develop along dermatomes and the association with stress-related triggers. Melanocytes share embryological origins with neural crest cells and interact closely with nerve endings. Neurotransmitters, neuropeptides, and oxidative stress induced by neuronal activity may contribute to melanocyte apoptosis and immune activation. Increased levels of catecholamines, such as norepinephrine, have been detected in vitiliginous skin, suggesting heightened sympathetic nervous system activity in affected areas. Moreover, neuroinflammation and the release of damage-associated molecular patterns (DAMPs) may further drive autoimmune responses against melanocytes [12].

Vitiligo treatment continues to be a big challenge for dermatologists. The profound and complex pathogenesis makes the challenge even bigger, as key therapies arise from understanding the underlying immune attack of melanocytes. Conventional therapy includes topical and systemic immunosuppressants and phototherapy. Topical corticosteroids remain first-line therapy for non-segmental vitiligo. They achieve clinical response by inhibiting the production of cytokines like IFN-γ**.** While effective, they are not a cure and may have side effects with prolonged use. Systemic corticosteroids in vitiligo are mainly used in unstable and rapidly evolving vitiligo, as in generalized and refractory cases. Their desired effect is often overshadowed by the numerous side effects on the skin, but also in general. Other topical immunosuppressants in the therapy of vitiligo, are the calcineurin inhibitors. Topicals like tacrolimus and pimecrolimus target T-cell activation, reducing the immune response

against melanocytes. They are often used in sensitive areas like the face and genitals where steroids may be less suitable.

Other used tools like camouflage, depigmentation, natural remedies are unsatisfactory. Surgery, with melanocyte transplantation and skin grafting are also available, but difficult to access and complicated [45,46].

Phototherapy, nb-UVB, involves exposing the skin to narrowband ultraviolet B light, which suppresses the immune response and induces melanocyte proliferation. UVB light also reduces the expression of inflammatory cytokines and can trigger repigmentation in patients with active vitiligo. Phototherapy is often combined with topical and systemic immunosuppressants, for achieving much successful repigmentation [47].

The recent and most promising in the treatment of vitiligo is the targeted therapy with JAK-inhibitors. These JAK-STAT inhibitors are targeting the JAK-STAT pathway, the immune signal that drives initiation, progression and persistence of melanocyte destruction and vitiligo. They achieve their effect by blocking one or more Janus Kinase molecules (JAK1, JAK2, JAK3, or TYK2), involved in transmitting signals from cytokine receptors on the cell surface to the nucleus, where they initiate gene expression. By inhibiting JAKs, the downstream effects of cytokine signaling are reduced. They prevent the inflammatory pathways that contribute to depigmentation, and help restoring the function and survival of these pigment-producing cells, which can lead to repigmentation of depigmented skin areas. These drugs are particularly effective in patients with more widespread or refractory vitiligo and offer an alternative to traditional immunosuppressive therapies [28].

Of the JAK inhibitor family, only one topical JAK inhibitor is approved in vitiligo therapy. Ruxolitinib cream was approved in 2022, after the completion of two large phase -3 double-blind placebo-controlled studies. The studies involved over 600 participants (aged 12 years and older) with moderate to severe vitiligo affecting the face or body. Patients were randomly assigned to either the ruxolitinib treatment group or a placebo group, with both groups applying their respective creams twice daily. The results were compelling. After 24 weeks of treatment, a significantly higher percentage of patients in the ruxolitinib group achieved at least 75% improvement in the Vitiligo Area Scoring Index (VASI 75) compared to those in the placebo group. This improvement was especially noticeable on the face, a common site of vitiligo distress. Additionally, patients reported significant improvement in their quality of life, reflecting the impact of repigmentation on both their physical and psychological well-being. The treatment was generally well-tolerated, with only mild to moderate side effects, most commonly application site reactions, like acne and pruritus [48].

Implications for Future Research and Therapy

These novel insights into vitiligo pathogenesis underscore the multifaceted nature of the disease and highlight potential new therapeutic strategies. Modulating the skin microbiome, targeting neurogenic inflammation, and integrating these approaches with established immunomodulatory therapies could lead to more comprehensive and effective treatment options for vitiligo patients. Future research should focus on elucidating the precise interactions between microbes, neural elements, and immune mechanisms to pave the way for innovative, personalized therapies.

Conclusion

The viewpoint that vitiligo is not caused only by predisposing mutations, or only by melanocytes responding to chemical/radiation exposure, or only by hyperreactive T cells, but rather results from a combination of etiologic factors that impact melanocyte viability, has certainly stood the test of time. New findings have contributed to better description of progressive depigmentation. Understanding the relative importance of such etiologic factors

combined with a careful selection of the most targetable pathways will continue to drive the next phase in vitiligo research: the development of effective therapeutics. In that arena, it is likewise important to acknowledge that pathways affected in some patients may not be altered in others. Taken together, the convergence theory continues to provide a comprehensive viewpoint of vitiligo etiology. The theory serves to intertwine etiologic pathways, helping to define the way amenable to disease intervention in individual patients.

Conflict of interest statement. None declared.

References:

1. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. *Lancet*. 2015 Jul 4;386(9988):74–84. doi:10.1016/S0140-6736(14)60763-7
2. Bibeau K, Pandya AG, Ezzedine K, Jones H, Gao J, Lindley A, Harris JE. Vitiligo prevalence and quality of life among adults in Europe, Japan and the USA. *J Eur Acad Dermatol Venereol*. 2022 Oct;36(10):1831–1844. doi:10.1111/jdv.18257
3. Amer AA, Gao XH. Quality of life in patients with vitiligo: an analysis of the dermatology life quality index outcome over the past two decades. *Int J Dermatol*. 2016 Jun;55(6):608–614. doi:10.1111/ijd.13198
4. Bae JM, Lee SC, Kim TH, Yeom SD, Shin JH, Lee WJ, et al. Factors affecting quality of life in patients with vitiligo: a nationwide study. *Br J Dermatol*. 2018 Jan;178(1):238–244. doi:10.1111/bjd.15560
5. Yang TT, Lee CH, Lan CE. Impact of Vitiligo on Life Quality of Patients: Assessment of Currently Available Tools. *Int J Environ Res Public Health*. 2022 Nov 13;19(22):14943. doi:10.3390/ijerph192214943
6. Millington GW, Levell NJ. Vitiligo: the historical curse of depigmentation. *Int J Dermatol*. 2007 Sep;46(9):990–995. doi:10.1111/j.1365-4632.2007.03226.x
7. Prasad PV, Bhatnagar VK. Medico-historical study of "Kilasa" (vitiligo/leucoderma) a common skin disorder. *Bull Indian Inst Hist Med Hyderabad*. 2003 Jul-Dec;33(2):113–127.
8. Arcos-Burgos M, Parodi E, Salgar M, Bedoya E, Builes J, Jaramillo D, et al. Vitiligo: complex segregation and linkage disequilibrium analyses with respect to microsatellite loci spanning the HLA. *Hum Genet*. 2002 Apr;110(4):334–342. doi:10.1007/s00439-001-0719-4
9. Chang WL, Lee WR, Kuo YC, Huang YH. Vitiligo: An Autoimmune Skin Disease and its Immunomodulatory Therapeutic Intervention. *Front Cell Dev Biol*. 2021 Dec 14;9:797026. doi:10.3389/fcell.2021.797026
10. Matarrese P, Puglisi R, Mattia G, Samela T, Abeni D, Malorni W. An Overview of the Biological Complexity of Vitiligo. *Oxid Med Cell Longev*. 2024 Dec 19;2024:3193670. doi:10.1155/2024/3193670
11. Liu X, Liu J. Vitiligo: are microbes to blame? *Biosci Microbiota Food Health*. 2025;44(1):16–25.
12. Marchioro HZ, Silva de Castro CC, Fava VM, Sakiyama PH, Dellatorre G, Miot HA. Update on the pathogenesis of vitiligo. *An Bras Dermatol*. 2022 Jul-Aug;97(4):478–490. doi:10.1016/j.abd.2022.03.002
13. Nazzaro G. Vitiligo: historical perspectives and the evolution of treatment. *J Dermatol Treat*. 2017;28(1):23–28. doi:10.1080/09546634.2016.1186328
14. Gauthier Y, Bérard F. Historical perspectives of vitiligo and leprosy: From the Middle Ages to modern times. *Int J Dermatol*. 2015;54(9):1030–1037. doi:10.1111/ijd.12929
15. Kundu RV, Mhlaba JM, Rangel SM, Le Poole IC. The convergence theory for vitiligo: a reappraisal. *Exp Dermatol*. 2019 Jun;28(6):647–655. doi:10.1111/exd.13925

16. Finkel TH, Bourke EJ. Genetic and immune mechanisms in vitiligo. *J Invest Dermatol*. 2020 Jul;140(7):1325–1334. doi:10.1016/j.jid.2019.12.013
17. Rees JL, Laddha SD. Genetics of vitiligo: Theories and insights. *Br J Dermatol*. 2017 Apr;176(4):1275–1284. doi:10.1111/bjd.15034
18. Yang S, et al. Genetic and epigenetic factors in vitiligo: A review of molecular mechanisms. *Front Genet*. 2019;10:907. doi:10.3389/fgene.2019.00907
19. Faraj S, Kemp EH, Gawkrodger DJ. Patho-immunological mechanisms of vitiligo: the role of the innate and adaptive immunities and environmental stress factors. *Clin Exp Immunol*. 2022 Jan 28;207(1):27–43. doi:10.1093/cei/ixab107
20. Manga P, Elbuluk N, Orlow SJ. Recent advances in understanding vitiligo. *F1000Res*. 2016 Sep 6;5:F1000 Faculty Rev-2234. doi:10.12688/f1000research.9280.1
21. Huggins RH, Davis LA. The role of the immune system in vitiligo. *J Dermatol Sci.* 2017 Feb;85(2):81–89. doi:10.1016/j.jdermsci.2016.11.008
22. Harris JE. Chemical-Induced Vitiligo. *Dermatol Clin*. 2017 Apr;35(2):151–161. doi:10.1016/j.det.2016.11.006
23. Ghosh S, Mukhopadhyay S. Chemical leucoderma: Indian scenario, prognosis, and treatment. *Indian J Dermatol*. 2010 May-Jun;55(3):250–254. doi:10.4103/0019-5154.68223
24. Goldstein NB, Koster MI, Hoaglin LG, Spoelstra NS, Kechris KJ, Robinson SE, Robinson WA, Roop DR, Norris DA, Birlea SA. Narrow Band Ultraviolet B Treatment for Human Vitiligo Is Associated with Proliferation, Migration, and Differentiation of Melanocyte Precursors. *J Invest Dermatol*. 2015 Aug;135(8):2068–2076. doi:10.1038/jid.2015.112
25. Zhang X, Lei L, Jiang L, Fu C, Huang J, Hu Y, Zhu L, Zhang F, Chen J, Zeng Q. Characteristics and pathogenesis of Koebner phenomenon. *Exp Dermatol*. 2023 Apr;32(4):310–323. doi:10.1111/exd.14628
26. Shin JU, Roh MR, Lee JH. Vitiligo following intense pulsed light treatment. *J Dermatol*. 2010 Jul;37(7):674–676. doi:10.1111/j.1346-8138.2010.00988.x
27. Shreberk-Hassidim R, Ramot Y, Zlotogorski A. Janus kinase inhibitors in dermatology: A systematic review. *J Am Acad Dermatol*. 2017 Apr;76(4):745–753.e19. doi:10.1016/j.jaad.2016.12.034
28. Qi F, Liu F, Gao L. Janus Kinase Inhibitors in the Treatment of Vitiligo: A Review. *Front Immunol*. 2021 Nov 18;12:790125. doi:10.3389/fimmu.2021.790125
29. Inoue S, Suzuki T, Sano S, Katayama I. JAK inhibitors for the treatment of vitiligo. *J Dermatol Sci*. 2024 Mar;113(3):86–92. doi:10.1016/j.jdermsci.2023.11.008
30. Karagaiah P, Schwartz RA, Lotti T, Wollina U, Grabbe S, Goldust M. Biologic and targeted therapeutics in vitiligo. *J Cosmet Dermatol*. 2023 Jan;22(1):64–73. doi:10.1111/jocd.15358
31. Bertolani M, Rodighiero E, de Felici Del Giudice MB, Lotti T, Feliciani C, Satolli F. Vitiligo: What's old, what's new. *Dermatol Rep*. 2021 Sep 15;13(2):9142. doi:10.4081/dr.2021.9142
32. Zeeuwen PL, Kleerebezem M, Timmerman HM, Schalkwijk J. Microbiome and skin diseases. *Curr Opin Allergy Clin Immunol*. 2013 Oct;13(5):514–520. doi:10.1097/ACI.0b013e328365a3da
33. Ni Q, Ye Z, Wang Y, Chen J, Zhang W, Ma C, Li K, Liu Y, Liu L, Han Z, et al. Gut microbial dysbiosis and plasma metabolic profile in individuals with vitiligo. *Front Microbiol*. 2020;11:592248. doi:10.3389/fmicb.2020.592248
34. Lu H, Xu J, Hu Y, Luo H, Chen Y, Xie B, Song X. Differences in the skin microbial community between patients with active and stable vitiligo based on 16S rRNA gene sequencing. *Australas J Dermatol*. 2021;62:e516–e523. doi:10.1111/ajd.13563

35. Mahmud MR, Akter S, Tamanna SK, Mazumder L, Esti IZ, Banerjee S, Akter S, Hasan MR, Acharjee M, Hossain MS, et al. Impact of gut microbiome on skin health: gut-skin axis observed through the lenses of therapeutics and skin diseases. *Gut Microbes*. 2022;14:2096995. doi:10.1080/19490976.2022.2096995
36. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. *Nat Rev Immunol*. 2017;17:219–232. doi:10.1038/nri.2016.142
37. Luan M, Niu M, Yang P, Han D, Zhang Y, Li W, He Q, Zhao Y, Mao B, Chen J, et al. Metagenomic sequencing reveals altered gut microbial compositions and gene functions in patients with non-segmental vitiligo. *BMC Microbiol*. 2023;23:265. doi:10.1186/s12866-023-02914-9
38. Doğan Z, Özdemir P, Ekşioğlu M, Filik L. Relationship between Helicobacter pylori infection and vitiligo: a prospective study. *Am J Clin Dermatol*. 2014 Oct;15(5):457–462. doi:10.1007/s40257-014-0097-8
39. Bakry OA, Basha M, El Hefnawy S, Mekkawy S. Relationship between Disease Activity and Helicobacter pylori Infection in Patients with Vitiligo. *Indian Dermatol Online J*. 2018 Jan-Feb;9(1):59–61. doi:10.4103/ijdvl.ijdvl_282_17
40. Rifaioğlu EN, Aydoğan F. Investigation Into The Frequency Of Helicobacter pylori Infection With Carbon 14 Urea Breath Test In Patients With Vitiligo. *Turk J Med Sci.* 2014;44(6):1075–1080. doi:10.3906/sag-1401-30
41. Akbayir N, Gökdemir G, Mansur T, Sökmen M, Gündüz S, Alkim C, Barutcuoğlu B, Erdem L. Is there any relationship between hepatitis C virus and vitiligo? *J Clin Gastroenterol.* 2004 Oct;38(9):815–817. doi:10.1097/01.MCG.0000139052.74801.98
42. Fawzy MM, Hammad NM, Sharaf AL, Khattab F. Hepatitis C virus infection could be a risk factor for adult-onset vitiligo in Egyptian patients: A cross-sectional study. *J Cosmet Dermatol*. 2022 Oct;21(10):4983–4989. doi:10.1111/jocd.14946
43. Grimes PE, Sevall JS, Vojdani A. Cytomegalovirus DNA identified in skin biopsy specimens of patients with vitiligo. *J Am Acad Dermatol*. 1996 Jul;35(1):21–26. doi:10.1016/S0190-9622(96)90490-9
44. Zhuang T, Yi X, Chen J, et al. Intracellular virus sensor MDA5 exacerbates vitiligo by inducing the secretion of chemokines in keratinocytes under virus invasion. *Cell Death Dis*. 2020;11:453. doi:10.1038/s41419-020-2665-z
45. Seneschal J, Boniface K. Vitiligo: Current Therapies and Future Treatments. *Dermatol Pract Concept.* 2023 Dec 1;13(4S2):e2023313S. doi:10.5826/dpc.1304a27
46. Sritanyarat T, Wongpraparut C, Jansuwan N, Yothachai P, Nuntawisuttiwong N, Silpa-Archa N. Outcomes of autologous non-cultured melanocyte keratinocyte transplantation in vitiligo and nevus depigmentosus. *J Dermatolog Treat*. 2022 Mar;33(2):935–940. doi:10.1080/09546634.2021.1962230
47. Rathod DG, Muneer H, Masood S. Phototherapy. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. 2023 Feb 16. doi:10.48550/arXiv.
48. Rosmarin D, Passeron T, Pandya AG, Grimes P, Harris JE, Desai SR, Lebwohl M, Ruer-Mulard M, Seneschal J, Wolkerstorfer A, Kornacki D, Sun K, Butler K, Ezzedine K; TRuE-V Study Group. Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo. *N Engl J Med*. 2022 Oct 20;387(16):1445–1455. doi:10.1056/NEJMoa2205809