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Vitiligo: An Ayurvedic and Allopathic Perspective

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ABSTRACT :-

Vitiligo is a widely recognized depigmenting skin disorder, affecting an estimated 0.5% to 2% of the global population. This condition is characterized by the presence of non-scaly, chalky white macules resulting from a selective loss of melanocytes. Recent years have seen significant progress in understanding the pathophysiology of vitiligo, leading to the conclusion that it is an autoimmune disorder. While often dismissed as merely a cosmetic concern, vitiligo can have profound psychological effects and can greatly disrupt daily life. In 2011, an international consensus distinguished segmental vitiligo from other forms, defining "vitiligo" to encompass all non-segmental types. This review aims to provide a thorough overview of the current understanding of vitiligo and its future treatment options. The defining features of vitiligo include a complete absence of melanocytes observed microscopically, along with acquired, idiopathic, progressive, localized hypomelanosis affecting the skin and hair. Vitiligo is a significant skin condition that can severely impact a patient's quality of life. Although the precise causes remain unclear, it seems to be influenced by a combination of neurological, immunological, and genetic factors. Additionally, vitiligo may coexist with conditions such as malignant melanoma, Sutton or halo nevus, and other autoimmune diseases. The considerable disfigurement associated with vitiligo can lead to significant emotional distress for those affected, necessitating treatment. Due to the still unclear pathogenesis, a wide range of treatment options exists. The most commonly used treatments for localized and generalized vitiligo include topical steroids and narrowband ultraviolet B monotherapy, respectively. Cosmetic improvements can also be achieved through the use of camouflage products and self-tanning dyes. The progression of vitiligo is often unpredictable, with some cases showing spontaneous repigmentation.

KEY WORDS:- VITILIGO, AYURVEDIC, MELANIN, PIGMENTATION, ALLOPATHIC

1. INTRODUCTION:-

The societal stigma surrounding vitiligo has been evident since ancient times, as it is referenced in Egyptian and Indian texts dating back 3,500 years. The Atharvaveda, an ancient Indian scripture composed between 1500 and 1000 BCE, the Egyptian Ebers Papyrus from 1500 BCE, and the book of Leviticus in the Hebrew Bible from a similar era all mention white skin patches. Indian literature describes it as "abhorred" for a son or daughter to marry an individual with these depigmented spots.

Early Buddhist texts indicated that individuals with vitiligo were deemed unfit for ordination, while Hindu writings suggested that such individuals might have a history of theft related to clothing. Vitiligo manifests as patchy skin depigmentation that can occur on any part of the body. It affects approximately 1% of the global population, with no significant differences in prevalence based on sex, ethnicity, or geographic location.

Like in previous times, vitiligo continues to inflict considerable psychological distress and diminish self-esteem, adversely impacting the quality of life for those affected. This decline in quality of life is comparable to that experienced by individuals with other skin disorders, such as eczema and psoriasis. The visible skin lesions associated with vitiligo can lead to feelings of sadness, anxiety, and embarrassment. Patients often express concern that the condition may progress and become more pronounced in visible areas, such as the hands and face.

Fig.1: Disease of Vitiligo

The significant social stigma and prevalent misconceptions surrounding vitiligo continue to impact individuals affected by the condition. Patients with vitiligo may encounter various challenging situations. For instance, during a flight to our clinic, one of my patients, J.E.H., was seated next to a woman who requested a seat change due to his vitiligo, despite being informed that the condition is not contagious.

In another instance, a young child in New York City approached a woman with vitiligo on the subway and exclaimed, "You look like a monster, but I know you're not!" Additionally, a Pakistani man now living in the UK inquired about the possibility of amputating his arm to eliminate his vitiligo, fearing rejection from his family, although he believed they would accept him if he lost a limb instead. This highlights the urgent need for a more profound understanding of the pathophysiology of vitiligo to develop more effective treatments for those affected.

Vitiligo is a disfiguring medical condition of unknown origin that leads to the destruction of melanocytes in the skin, mucous membranes, eyes, and occasionally hair follicles. The loss of these cells results in a reduction of pigment, altering the structure and function of the affected organs. Melanocytes are responsible for producing melanin, the pigment that imparts color to the skin, hair, and eyes. When these cells die or fail to produce melanin, the skin becomes lighter or white. Although individuals of different races possess a similar density of melanocytes, variations in skin pigmentation among ethnic groups arise from differences in the rate of melanin production.

Approximately one percent of the global population is affected by this condition. While vitiligo can develop at any age, it most commonly appears between the ages of 10 and 30. It is rarely observed in very young children or the elderly. About 30% of patients exhibit familial clustering of cases, and the incidence tends to decrease with age. Although vitiligo can manifest anywhere on the body, the initial signs are most frequently observed on the hands, feet, arms, face, and lips. Additionally, ocular pigmentary abnormalities are present in 40% of patients.

2. PATHOGENESIS:-

2.1 AUTOIMMUNE COMPONENT :-

Autoimmunity has been suspected to significantly contribute to the onset of vitiligo, and recent research is shedding light on the immune system's involvement in this condition. Individuals with vitiligo exhibit higher levels of CD8+ T cells that specifically target and eliminate melanocytes, with their numbers correlating with the severity of the disease. In earlier studies, Harris and his team utilized a mouse model to identify interferon (IFN)-γ as a key factor in the progression of vitiligo lesions, noting that it enhances the expression of CXCL10, a chemokine that recruits CD8+ T cells to the epidermis and hair follicles. Additionally, IFN-γ was found to be part of a "signature cytokine profile" in an avian model, particularly in the Smyth line (SL) of chickens, which naturally develop a depigmentation disorder akin to human vitiligo, characterized by the autoimmune loss of feather melanocytes. As the condition progresses, the expression of IFN-γ increases. More recently, Yang et al. proposed a more direct involvement of IFN-γ in vitiligo, demonstrating that IFN-γ produced by cytotoxic T cells can directly trigger apoptosis in melanocytes. Harris also provided an editorial that contextualizes these findings within a broader framework.

Interleukin-17 (IL-17) and T helper type 17 (Th17) cells, which secrete this cytokine, are increasingly acknowledged as significant players in autoimmune disorders. Singh and his colleagues recently examined the potential role of Th17 in vitiligo, observing elevated levels of IL-17 in blood, tissue, and cells, with a positive correlation between IL-17 levels and disease severity. Zhou et al. further supported this by showing that Th17 cells, along with the cytokines TGF-β and IL-21 (which also increased in the SL avian model as the disease progressed), are linked to the activity of generalized vitiligo. Singh

et al. also explored how treatments for vitiligo, such as UVB phototherapy, may influence IL-17 levels, indicating new therapeutic avenues that could target the IL-17 pathway.

The clinical inhibition of IL-17 is a relatively recent development, whereas TNF-α inhibitors have been utilized for more than ten years. Research presents mixed findings regarding TNF-α levels in vitiligo; some studies indicate elevated levels, while others do not. Webb et al. reported that inhibiting TNF-α halted disease progression in three patients with vitiligo, suggesting that earlier research may have missed this effect by concentrating on TNF-α's role in facilitating repigmentation. Additionally, the paradoxical emergence of vitiligo has been documented in patients with other autoimmune disorders undergoing treatment with TNF-α inhibitors, particularly in those with psoriasis.

Zhou et al. highlighted increased levels of IL-21, prompting inquiries into T follicular helper (Tfh) cells, a subset of T cells that produce IL-21 and engage with B cell regions in lymphoid tissues, and their involvement in vitiligo. Tfh cells and IL-21 are essential for B cell activation and are increasingly acknowledged in the context of autoimmune dysregulation. Furthermore, IL-21 is significant in mouse models of autoimmune diabetes, where it enhances the proliferation of CD8+ T cells and amplifies their cytotoxic responses.

Research has also established connections between vitiligo and major histocompatibility (MHC) loci located on chromosome 6p21.3. In a recent genome-wide association study involving 2,853 Caucasian patients with vitiligo, Spritz, Dinarello, and their team identified three single nucleotide polymorphisms (SNPs) situated within a predicted super-enhancer region between HLA-DRB1 and HLA-DQA1. These SNPs were associated with heightened MHC class II protein expression on monocytes from individuals possessing the high-risk haplotype. When stimulated with microbial products, these monocytes exhibited 2.5 to 5 times greater production of IFN-γ and IL-1β compared to those with the low-risk haplotype, indicating a potential relationship between MHC class II expression and cytokine responses that could trigger or maintain an autoimmune reaction. Additionally, they discovered a haplotype linked to vitiligo susceptibility at the MHC class I locus, which encompasses a transcriptional regulator located downstream of HLA-A, with carriers demonstrating elevated levels of HLA-A RNA transcripts. The HLA-A *02:01:01:01 allele, associated with vitiligo, exhibits autoantigens derived from melanocytes. When it interacts with additional risk alleles, this regulatory region promotes increased expression of HLA-A2, thereby improving the presentation of melanocyte antigens to cytotoxic T cells.

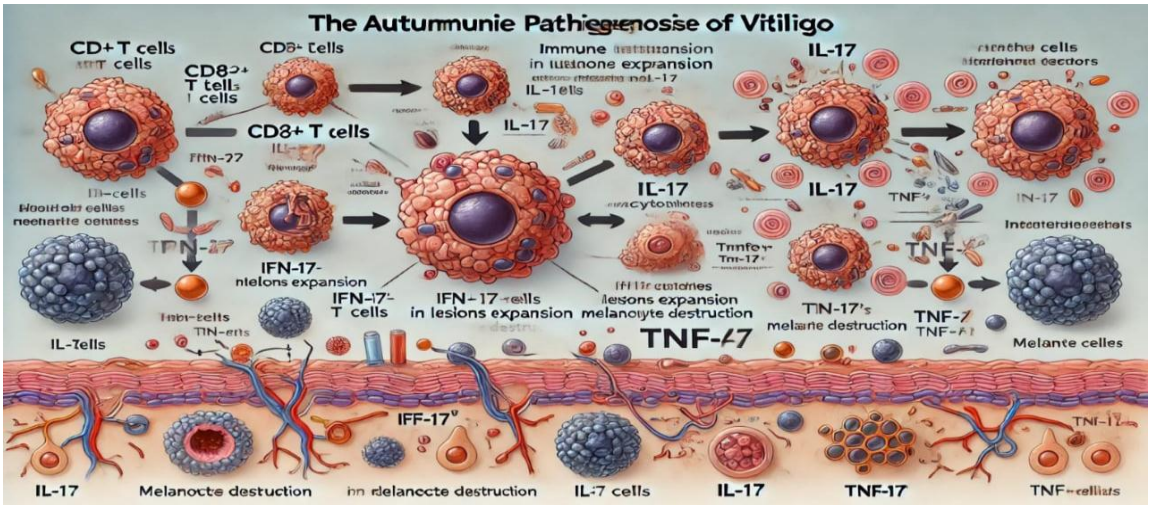

Fig.2 : Pathogenesis Of Vitiligo

3. GENETICS :-

Vitiligo is a prevalent dermatological condition characterized by the depigmentation of certain skin areas due to the depletion of melanocytes, the cells responsible for pigment production. It impacts approximately 0.1% to 2% of the global population, with incidence rates varying among different demographic groups. The genetic underpinnings of vitiligo are complex and do not adhere to straightforward inheritance patterns. Rather, the condition is shaped by a multitude of genetic factors, some of which may not lead to the manifestation of the disease even in the presence of the associated genes. Furthermore, environmental influences contribute to its development, although genetics is regarded as a significant factor. Research, particularly studies involving twins and familial patterns, has demonstrated a robust genetic component to vitiligo; however, the precise interactions among these genes remain unclear. Several genomic regions have been associated with the condition, including chromosomes 4q13–q21, 1p31, 7q22, 8p12, and 17p13. Nonetheless, additional regions on chromosomes 6p, 6q, 14q, 9q, 13q, 19p, and 22q require further exploration. Despite the challenges in fully elucidating the genetic causes of vitiligo, recent advancements in genetic research provide optimism. The strides made in the past five years have brought researchers closer to identifying the intricate genetic factors associated with vitiligo, potentially paving the way for improved treatments and preventive strategies in the future. The continued investigation into the complex genetic architecture of vitiligo holds significant promise for enhancing care and developing innovative therapies for individuals affected by this condition.

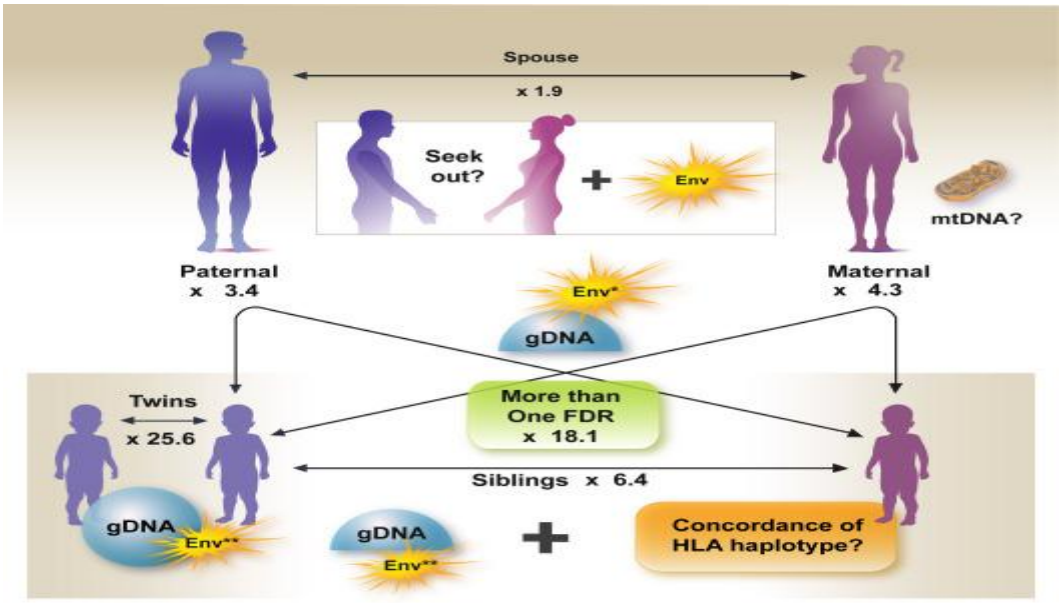

Fig.3 : Genetics Of Vitiligo

3.1 OXIDATIVE STRESS :-

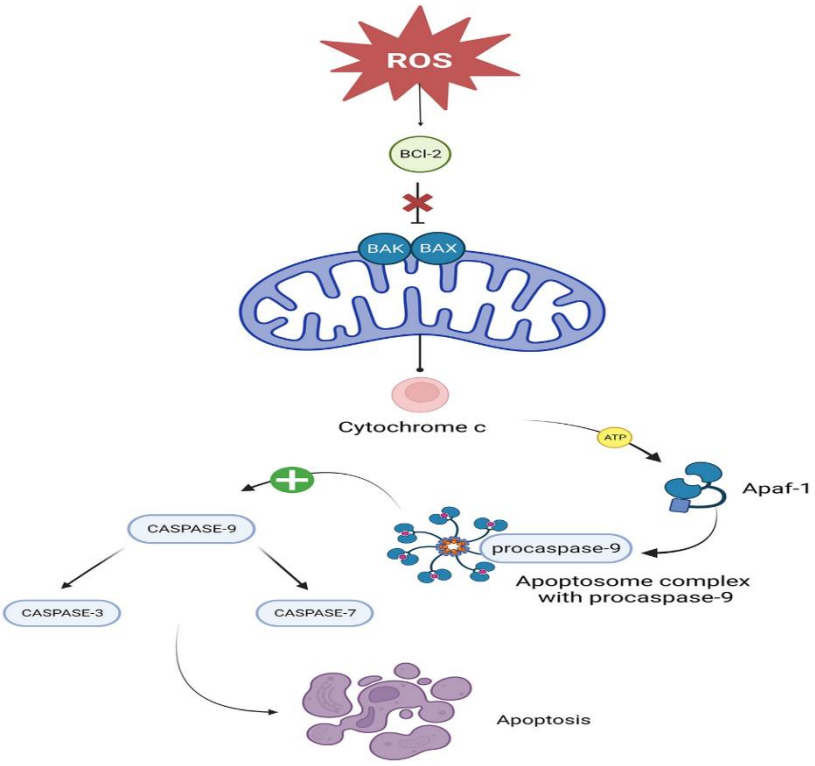

Fig.4 : Oxidative Stress

Melanocytes are continuously exposed to oxidative stress from various external environmental factors, and individuals with vitiligo exhibit a heightened vulnerability to oxidative damage compared to their healthy counterparts. Several theories have been proposed to elucidate this increased sensitivity. During melanin synthesis (melanogenesis), the production of free radicals occurs, which contributes to oxidative stress and undermines the stability of tyrosinase-related protein 1. Consequently, this leads to the formation of detrimental melanin intermediates, resulting in damage to melanocytes. Furthermore, in genetically predisposed individuals, the mechanisms that neutralize free radicals are less efficient, intensifying the damage and stress experienced by melanocytes.

This oxidative stress has been shown to influence the expression of E-cadherin in melanocytes. E-cadherin is essential for securing melanocytes to the basal layer of the epidermis. A reduction in E-cadherin expression compromises the stability of melanocytes in the basal layer, prompting their migration to the upper skin layers, which ultimately results in programmed cell death (apoptosis) of these cells. Importantly, this decline in E-cadherin expression can occur even in skin regions that appear unaffected by vitiligo. Consequently, areas of the body that frequently experience mechanical friction—such as the elbows, knees, ankles, and other extremities—are more susceptible to depigmentation in non-segmental vitiligo. This phenomenon may also account for the observed resistance to treatment in these specific regions.

4. DIAGNOSIS OF VITILIGO:-

The identification of vitiligo is typically straightforward due to the presence of distinct, amelanotic, nonscaly, chalky-white patches with clear edges located in specific regions, including the mouth, tips of the lower limbs, genital area, and sites prone to friction. Diagnosis usually does not require chemical tests, and skin biopsies or additional examinations are seldom necessary unless there is a need to exclude other conditions. Non-invasive techniques, such as in vivo confocal imaging or skin sampling, can verify the absence of melanocytes in the affected regions.

Histological analysis of the center of a vitiligo patch reveals a total lack of melanin pigmentation and melanocytes within the epidermis. Occasionally, lymphocytes may be present at the periphery of expanding lesions. Portable UV-A devices, such as a Wood's lamp, assist in detecting vitiligo by highlighting depigmented areas that are not visible to the naked eye, particularly in individuals with lighter skin. Under Wood's light, vitiligo patches manifest as bright blue-white spots with well-defined borders. Dermoscopy can also aid in differentiating vitiligo from other depigmenting conditions, which may not exhibit perifollicular pigmentation and telangiectasia—characteristics commonly associated with vitiligo. This technique can also indicate disease progression, showing perifollicular pigmentation in advancing lesions and perifollicular depigmentation in stable or regressing ones.

It is essential to differentiate vitiligo from other hypopigmented disorders. Hypopigmented spots can occur in various conditions, making it vital to distinguish vitiligo from melanoma-associated leukoderma, which may present prior to a melanoma diagnosis. Despite their similar appearances, melanoma-associated depigmentation can be identified through antibodies to MART1 (melanoma antigen recognized by T cells 1). Segmental hypopigmentation, or nevus depigmentosus, typically emerges at birth or within the first year and remains stable, although it may evolve as the child matures.

In contrast to vitiligo, this condition typically features melanocytes that produce less melanin. This reduced melanin production is observable under Wood's light, where the difference between the affected skin and healthy skin is not as stark as it is in vitiligo.

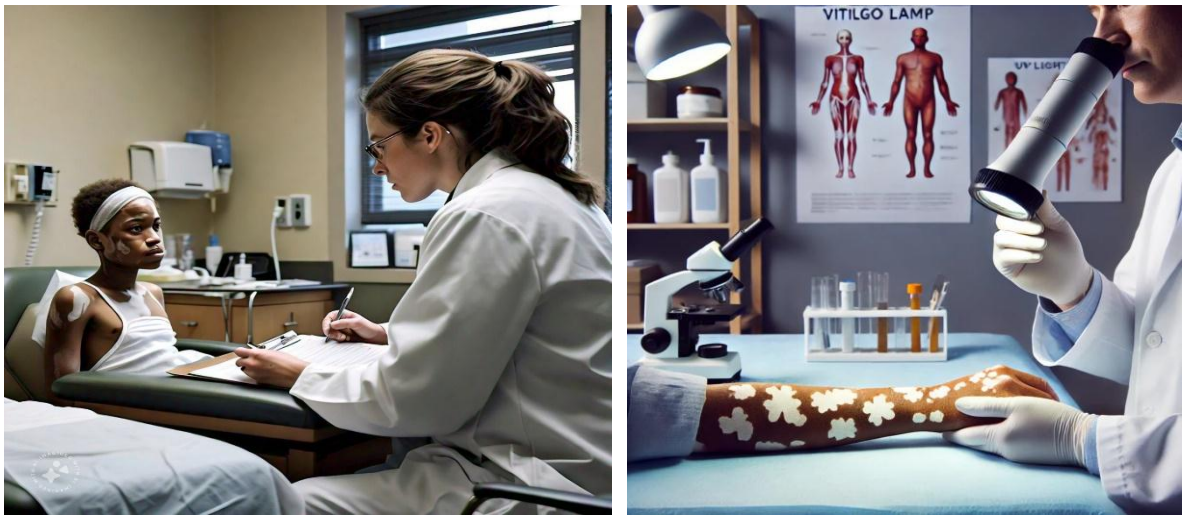

Fig.5 : Diagnosis Of Vitiligo

5.COMPREHENSIVE STUDIES OF VITILIGO TREATMENT :-

5.1 AYURVEDIC PERSPECTIVE :-

In the field of biomedicine, the skin condition known as "vitiligo" is comparable to Shwitra or Shwet-Kushtha as described in Ayurveda. Ayurveda identifies the skin, referred to as twak in Sanskrit, as a primary sense organ that houses the energies of Vata and bhrajaka pitta. Given that the skin envelops the entire body, it is essential to maintain a balance of bhrajaka pitta, which necessitates continuous care. An imbalance in Vata and bhrajaka pitta can result in various skin disorders. The Ayurvedic approach to treating vitiligo begins with purification therapies (shodhana karma) that utilize herbal decoctions from Psoralea corylifolia (bakuchi kwatha) and Euphorbia neriifolia (snuhi), aimed at facilitating multiple rounds of purgation (Step 1). The subsequent phase (Step 2) involves oil massages, with the selection of oil based on a comprehensive patient evaluation (rogi pariksa) and analysis

of the condition (roga). In Step 3, the affected skin areas are subjected to sunlight exposure for as long as the patient can endure it, a practice known as Soorya pada santhapam in Ayurveda.

Herbomineral therapies encompass the topical application of herbal pastes (Lepa), medicinal plant powders (Curna), ghee-based herbal formulations (Ghrita), semi-solid oral preparations (Avaleha), herbal oils (Thaila), fermented solutions (Asava-Arista), and tablets (Vati/Gutika). Additionally, minerals and metallic salts (Rasousadha) are incorporated into the treatment regimen. Bakuchi oil, derived from the dried fruits of P. corylifolia, along with sesame oil, is frequently employed in Ayurveda for the treatment of vitiligo due to their psoralen content, which aids in stimulating melanocytes upon exposure to UV light. While the specifics of these treatments are elaborated upon, further research is necessary to scientifically substantiate the efficacy of these remedies.

In Ayurveda, vitiligo is referred to as "shwitra" and is categorized into two distinct types: Kilas and Varuna, although some references treat them as identical. Contemporary medical science attributes vitiligo to an irregular distribution of melanin, which is linked to impaired production of melanocytes beneath the skin's surface. This condition may be hereditary, induced by medications (due to toxicity), or a consequence of radiation or chemotherapy. In numerous instances, however, it arises without identifiable causes and is classified as idiopathic leukoderma. Ayurveda recognizes shwitra as a skin disorder.

Fig.6: Ayurvedic Remedy Of Vitiligo

Fig.6.1: Ayurvedic Herbs For Vitiligo

5.1.1 ETIOLOGY (NIDANA) :–

In Ayurveda, the underlying causes of skin disorders (Kusta) and vitiligo (Shwitra) are regarded as analogous, affecting the same fundamental body tissues (dhatu). Shwitra is unique among skin ailments as it specifically targets the “skin tissue” (twak), resulting in discoloration (twak vaivarnyata) without any exudation (aparisravi).

Ayurvedic literature identifies various factors that may directly or indirectly contribute to the onset of vitiligo (Shwitra). These factors encompass Viruddhahara (the intake of incompatible foods), chardivegadharana (suppressing the urge to vomit), atibhojana (excessive eating), and the overconsumption of certain tastes, including sour, sweet, salty, and pungent (Atyamla, Lavana, Madhura, Katu Rasa Sevana). Additional factors include the excessive consumption of fresh grains, curd, and fish (navanna, dadhi, matsyabhakshana), as well as behaviors such as mocking or disrespecting elders (vipra-guru gharshana).

5.1.2 AYURVEDIC PATHOPHYSIOLOGY :- (SAMPRAPTI)

As a result of one or more of the aforementioned factors, the three doshas—Vata, Pitta, and Kapha—experience aggravation, which impacts the skin, blood (Rakta), muscles (Mamsa), and bodily fluids (Udaka). These components interact at various levels, resulting in a range of skin disorders. When lymph (Rasa) and blood (Raktha) are predominantly affected, vitiligo, also known as shwitrakushta, may arise. Among the different dosha types, conditions associated with Vata are particularly difficult to treat, those linked to Pitta are even more challenging, while Kaphaja conditions are nearly impossible to manage. Based on the characteristics of the lesions, those that are new, thin, possess black hair, and are neither matted nor caused by burns can be treated. Conversely, lesions that are very white and have persisted for a long time are deemed incurable. Furthermore, vitiligo lesions located on the palms, soles, genitalia, and lips are classified as untreatable.

5.2 ALLOPATHIC PERSPECTIVE :-

In contrast to the majority of autoimmune disorders, vitiligo is entirely reversible. This condition primarily affects the melanocytes, the pigment-producing cells found in the epidermis between hair follicles (interfollicular epidermis). Notably, melanocytes within the hair follicles are often preserved due to the immune privilege associated with this area, akin to other protected regions containing melanocytes, such as the brain, eyes, and inner ear. Additionally, hair follicles house melanocyte stem cells that can regenerate the epidermis in vitiligo-affected areas with functional, newly differentiated melanocytes, thereby restoring normal pigmentation. Consequently, clinical repigmentation in vitiligo lesions typically manifests in a punctate, perifollicular pattern, while regions devoid of hair or with white hairs—where autoimmunity has affected the follicular melanocyte populations—do not exhibit repigmentation.

Historical treatments for vitiligo documented in ancient texts include cow dung, urine, elephant feces, cobra bones, topical acids, and heavy metals like arsenic. Fortunately, these methods have been largely abandoned; however, one ancient remedy remains in use today. In the past, ancient Indian and Egyptian practitioners treated vitiligo with specific herbs applied topically or ingested, followed by exposure to sunlight. These herbs have been found to contain psoralens, which are now utilized in purified forms in conjunction with UVA light to address skin conditions, a therapy known as PUVA (psoralen plus UVA light). Thus, a version of this contemporary vitiligo treatment was employed over three thousand years ago and was rediscovered in the twentieth century. In rare instances, vitiligo may regress spontaneously without treatment, likely due to sun exposure. However, most patients require therapeutic intervention to achieve significant improvement in their condition. As is typical for autoimmune diseases, immunosuppression plays a crucial role in the clinical management of vitiligo.

Topical corticosteroids and calcineurin inhibitors facilitate repigmentation, while systemic corticosteroid therapy aids in stabilizing highly active disease. Achieving successful repigmentation in vitiligo necessitates two primary treatment objectives: the suppression of autoimmunity and the regeneration of melanocytes from their stem cell niche located in the hair follicle. PUVA therapy employs UVA light to transform psoralen compounds into DNA-reactive oxidative chemicals that both inhibit immune function and promote melanocyte proliferation and pigmentation. The dual immunosuppressive and pigment-stimulating effects may account for the notable effectiveness of PUVA in treating vitiligo.

However, recent clinical research indicates that narrow-band UVB (nbUVB) phototherapy offers superior repigmentation of vitiligo lesions with fewer side effects, including a reduced risk of skin cancer, which has been associated primarily with PUVA therapy. Like PUVA, UVB light also suppresses skin immunity while encouraging melanocyte proliferation and pigmentation. Consequently, nbUVB has largely supplanted PUVA as the preferred first-line treatment for vitiligo, with current therapeutic approaches integrating nbUVB phototherapy alongside topical corticosteroids and/or topical calcineurin inhibitors.

Despite advancements, existing treatments for vitiligo are still far from optimal, as they do not yield consistent results across all patients, fail to repigment all anatomical areas, and can be burdensome for patients. Phototherapy necessitates multiple weekly appointments with a dermatologist, while topical treatments must be applied twice daily to all affected areas. Additionally, all current therapies offer only temporary relief, with a relapse rate of 40% observed within the first year after treatment cessation. Therefore, although many earlier treatments have been replaced by safer alternatives, the quest for more effective and targeted therapies continues.

Vitiligo typically manifests in individuals prior to reaching 30 years of age, and due to its infrequent spontaneous regression, it allows for meticulous monitoring of the condition and its evolution over many years. This characteristic, combined with its significant prevalence and the ease of accessing affected skin, has facilitated extensive research into vitiligo through translational methods over the years. Such efforts have established a robust basis for contemporary investigations aimed at elucidating the intricate mechanisms underlying its pathogenesis. The current insights into vitiligo present an exceptional opportunity for the advancement of more effective treatment options.

1) Ruxolitinib -

Ruxolitinib, recognized as the first Jakinib to receive FDA approval, is a JAK inhibitor that was initially sanctioned for the treatment of polycythemia vera and intermediate- to high-risk primary myelofibrosis. Research has demonstrated that, in addition to its role as a JAK inhibitor, ruxolitinib also inhibits the differentiation and migration of dendritic cells (DCs) in vitiligo, thereby enhancing CD8+ cytotoxic T cell responses. In a double-blind phase 2 clinical trial, 157 participants with vitiligo were randomly assigned in a 1:1:1:1:1 ratio to receive topical erythroxylenic cream at concentrations of 1.5% BID, 1.5% QD, 0.5% QD, 0.15% QD, or a placebo for a duration of 24 weeks. The results indicated a significant reduction in CXCL9 and CXCL10 expression in the groups receiving 1.5% BID and 1.5% QD treatments. Furthermore, a greater number of patients in the groups treated with ruxolitinib cream at 1.5% BID, 1.5% QD, and 0.5% QD achieved F-VASI50, with the 1.5% BID group exhibiting the most substantial responses, achieving F-VASI50 (58%), F-VASI75 (52%), and F-VASI90 (33%).

2) Baricitinib –
Baricitinib is a selective inhibitor of JAK1 and JAK2, which disrupts the signaling pathways of various pro-inflammatory cytokines and has been authorized for the management of rheumatoid arthritis (RA). To date, there is a singular case report documenting pigmentation alterations in a vitiligo patient who received a daily dosage of 4 mg of baricitinib for rheumatoid arthritis. Additionally, a phase 2 clinical trial is underway, assessing the effectiveness of a combination therapy that includes 4 mg doses of baricitinib alongside phototherapy in patients.

3) Ifidancitinib (ATI-50002) –
Ifidancitinib, a dual inhibitor of JAK 1 and 3, is being investigated in phase 2 clinical trials for its potential efficacy in treating vitiligo, following its use in managing alopecia areata. In a study involving patients with facial non-segmental vitiligo (NSV) (NCT03468855), those treated with topical ATI-50002 twice daily for 24 weeks showed significant improvements in both the Facial Vitiligo Area Severity Index (F-VASI) and the Vitiligo Noticeability Scale (VNS).

4) Ritlecitinib (PF-06651600) and Brepocitinib (PF-06700841) –
Ritlecitinib functions as an irreversible inhibitor of JAK3 and tyrosine kinase, utilized in the management of moderate to severe rheumatoid arthritis (RA). Meanwhile, Brepocitinib, which acts as a TYK2/JAK1 inhibitor, is presently being studied for its effectiveness and safety in treating active nonsegmental vitiligo (NSV) when used in conjunction with phototherapy. The objective of this research is to explore the potential synergistic effects of these treatments to promote skin repigmentation and enhance the quality of life for individuals suffering from this condition.

5) Cerdulatinib (PRT062070) –
Cerdulatinib, a dual kinase inhibitor targeting SYK and JAK, has undergone evaluation (NCT04103060) to assess its safety and tolerability for the treatment of vitiligo in a topical formulation (0.37% cerudulatinib gel applied twice daily). Further studies are essential to determine the most effective medication, treatment regimen, and suitable dosage forms to optimize therapeutic results while reducing toxicity. Given the instances of depigmentation that can occur after discontinuing JAK inhibitors, it is crucial to explore the underlying mechanisms further. Moreover, additional research is required to validate the effectiveness of combining these inhibitors with other therapeutic approaches.

6) IFN-γ and the inhibitors –
The IFN-γ-CXCL9/10-CXCR3 pathway may significantly contribute to the pathogenesis of vitiligo, potentially affecting the progression of the disease by impairing melanogenesis, inducing apoptosis in melanocytes, and altering T-cell function within the skin. Research has indicated an elevated expression of IFN-γ mRNA in both non-stabilized and prestabilized skin, particularly in cases of active vitiligo, which correlates with disease activity. Furthermore, anti-IFN-γ has demonstrated efficacy in treating conditions such as rheumatoid arthritis (RA), multiple sclerosis (MS), preventing corneal rejection, and various autoimmune skin disorders.

7) CXCL10 and the inhibitors –
Recent research has demonstrated a Th1/IFN-γ immune response in both human subjects and a murine model of vitiligo, characterized by increased production of CXCL9, CXCL10, and CXCL11. Among these, CXCL10 plays a significant role in the targeted migration of T cells, which initiates immune cell infiltration during the early stages of the condition and contributes to the downregulation of the keratinocyte glycoprotein non-metastatic melanoma protein B (GPNMB). Furthermore, a study found that mice treated with CXCL10-neutralizing antibodies showed enhanced pigmentation after four weeks, with this effect continuing for an additional four weeks. This finding underscores the potential of CXCL10 suppression as an effective therapeutic approach.

8) CXCR3 antibodies -
CXCR3 has been identified in skin lesions, autoreactive T cells, and a significant proportion of CD8+ resident memory T cells that infiltrate the skin, facilitating the secretion of IFN-γ and TNF-α. In a study conducted on vitiligo mice exhibiting less than 75% depigmentation on their tails, researchers administered antibodies that target and deplete CXCR3 over a period of 7 to 8 weeks. This intervention resulted in a notable enhancement of the mice's clinical condition, marked by a perifollicular pattern of repigmentation.

7. FUTURE SCOPE:-

1) To slow the advancement of vitiligo, it is essential to create innovative treatment strategies. Among these strategies, the targeting of the IFN-γ–CXCL9/10–CXCR3 pathway has been the subject of clinical studies involving OPZELURA.

2) OPZELURA has been utilized as a topical solution for treating nonsegmental vitiligo in both adult and pediatric patients who are 12 years of age and older.

3) Furthermore, it is crucial to select an appropriate vector system while ensuring both chemical and biological stability.

4) In recent years, adoptive Treg cell therapy has gained significant attention in research; however, there are ongoing challenges related to safety and the creation of an effective delivery mechanism.

5) The management of vitiligo continues to pose a significant therapeutic challenge.

6) This paper illustrates that a broader array of precision therapies is currently being explored, bolstered by enhanced understanding of the disease's underlying mechanisms.

7) The confirmation of these therapeutic targets allows for patient stratification, thereby promoting the adoption of personalized treatment strategies.

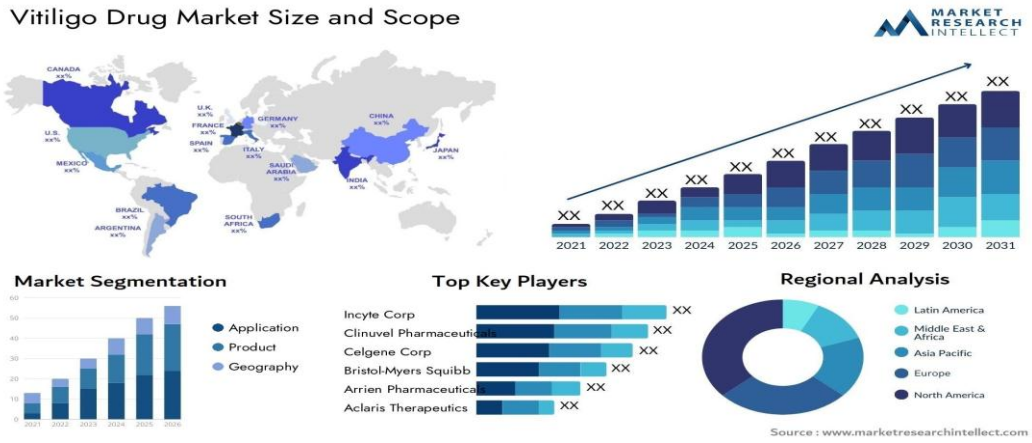

Fig.7: Future Scope and Market Size

8. CONCLUSION :-

Vitiligo is a complex skin disorder with multifactorial origins and intricate pathophysiological mechanisms. Although there have been significant advancements in our comprehension of this condition, the underlying causes and processes of vitiligo are still not fully understood. The degeneration of melanocytes, a key aspect of this disorder, requires further investigation to clarify its etiology. Natural therapies that target specific cytokines have shown promise in managing immune-mediated skin conditions, such as psoriasis and vitiligo. These treatments function by modulating the inflammatory pathways linked to disease progression, potentially leading to improved symptom management and repigmentation of lesions. By concentrating on critical cytokines involved in the development of these disorders, such therapies may offer more precise and effective management options. Consequently, addressing the interferon (IFN)-chemokine axis with either existing or innovative therapeutics presents a compelling approach. However, the variability in treatment outcomes and the recurrent nature of vitiligo can be disheartening. It is crucial to create individualized treatment plans that consider the specific type of vitiligo, its current activity level, and the side effects associated with the prescribed therapies.

At present, the treatment options for vitiligo are limited, and none have been proven to achieve consistent repigmentation across all patients. Continued scientific and therapeutic research is vital to develop new treatment approaches and to deepen our understanding of vitiligo's etiology. A variety of new therapeutic agents are emerging, with much of the evidence regarding their effectiveness coming from case studies or individual reports. Additional randomized controlled trials are needed to rigorously assess their efficacy.

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