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# The Etiological Features and Treatment of Vitiligo: A Pilot Study Prospective to Indian Scenario

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***Abstract-*** Despite studies of Vitiligo pathogenesis still evades its exact pathway, causes, a cast effective therapy challenge for Indian. Vitiligo is an acquired disorder of pigmentation, caused by decreased production of melanin as a result of dysfunction of melanocytes. In Indian tradition system plants medicine using for treatment of leucoderma but still no effective medicine cure the vitiligo. Indian studies of vitiligo find higher prevalence of vitiligo in Gujarat, Rajasthan, Madhya Pradesh, main possible causes are genetic, cellular, triggering, environmental effects, these gene polymorphism of candidate gene that are part of the immune system or part of melanocytes have both been associated with vitiligo and other autoimmune disorders. Environment Pollution like water, air and food pollution effects human health and increasing in villages and cities of India, environment pollution management and some diseases still gap in knowledge which are challenge for India.

***Keywords-*** Autoimmunity; Etiology, Gene Polymorphism, Genetic Susceptibility, Melanocyte, Pigmentation, Vitiligo, ACE, Neural Factors, Oxidative Stress, Vitiligo Associated Disorders Idiopathic Achroma

## INTRODUCTION

Vitiligo or Leucoderma in India refer to as “Ven kustam” meaning white leprosy,[10] is a chronic skin condition that causes loss of pigment due to destruction of melanocytes, resulting in irregular pale and white patches of skin [19] may also be associated with autoimmune diseases in human[24]. The cause of vitiligo is unknown, but research suggests that it may arise from autoimmune, genetic, oxidative stress, neural, or viral. The most common form is non-segmental vitiligo, which tends to appear in symmetric patches, sometimes over large areas of the body. The patches are initially small; they often enlarge and change shape. When skin lesions occur, they are most prominent on the face, hands and wrists; depigmentation is particularly noticeable around body orifices, such as the mouth, eyes, nostrils, genitalia and umbilicus [19].

Prevalence of vitiligo affects 1 - 4% of the world’s population, irrespective of gender and races[23], In India there is a stigma associated with vitiligo and effected person and their families particularly girls are society ostracized for marital purpose[18], Gujarat and Rajasthan states have the highest prevalence that is, around 8.8% [39],its prevalence is varying from 0.46 to 8.8% in rest of India [12].

Recent studies suggest that genetic factors may play a major role in the pathogenesis of vitiligo. Study suggests that almost 1.93% of Gujarat patients with vitiligo exhibited positive family history and 13.68% patients had at least one affected first-degree relative [36].In south Indian population also find the polymorphism of angiotensin converting enzyme (ACE) gene is capable of modulating cutaneous neuro-genic inflammation and autoimmunity with the development of vitiligo.[9]However Vitiligo patients present with progressive depigmentation involving progressive loss of melanocytes from skin and incidence vitiligo varies up to 2% in Madhya Pradesh [1]

*Historical Background of treatment of Vitiligo:* The symptom and sign of vitiligo in human last many centuries was shown, as a oldest information the treatment of vitiligo is about Pharaonic medicine in the Ebers Papyrus, shown in Pharaoh, king of Ancient Egypt, showing white patches (Vitiligo),[42].The oldest reference vitiligo treatment in the period of Aushooryan (2200 BC) as described in Tarikh-e-Tibb-Iran and Information concerning treatment of vitiligo the pharaonic medicine in the Ebers Papyrus (1550 BC) there was two types of diseases affecting color of the skin, One with tumors and mutations, probably leprosy and other

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probably vitiligo which according to Ebers Papyrus was treatable. As a Buddhist sacred book Vinay pitch (624-544 BC) was shown 'White spots' on the skin [43].In Indian tradition use Ayurvedic medicine for treatment of vitiligo: sacred Indian book Atharva Veda (1400 BC) the medicine are Shweta Kushta vitiligo Babchi seeds (Black seeds of Psoralea corylifolia "Bavachi") and from thirteen century Ibn El Bitar in Egypt treated vitiligo with the extract from the fruit of the plant known as Ammi majus[11].

*Cause of vitiligo and their effects in human health:* Most of Indian people suffering from genetic and pathogenic disease in cities and villages, so many disease are curable but for some disease are still gape in knowledge, one of these disease is Vitiligo, the population generally accepts that it is the concept of the "autoimmune destruction of pigment-producing cells called melanocytes" however, this assertion has not been fully substantiated. The exact pathogenesis is unknown, but research shows that it is complex, involving the interplay of multiple factors, many of which are not elucidated.

In the last century, much research has been dedicated to vitiligo and several overarching theories of its pathogenesis have emerged. In India and elsewhere also men, women and children with vitiligo face severe psychological and social problems. It is more acute in the case of young women and children. It is thus an important skin disease having major impact on the quality of life of patients suffering from vitiligo. Appearance of this disease can affect an individual self-image, and any pathological alteration can have psychological consequences [9]. In India and abroad the current therapeutic modalities are directed toward increasing melanocyte melanin production, few treatment modalities address the immunologic nature of the disease (1).

## GENETIC EFFECTS

A genome wide association study found 10 independent susceptibility loci for generalized vitiligo, responsible for 7.4% of the genetic risk. A family based association method revealed biased transmission of specific alleles from heterozygous parents to affected offspring for the TAP1 gene, as well as for the closely linked LMP2 and LMP7 genes encoding subunits of the immunoproteasome. No association with vitiligo was found for the MECL1 gene, which encodes a third immunoproteasome subunit and is unlinked to the MHC class II region. These results suggest a possible role for the MHC class I antigen processing and/or presentation pathway in the antimelanocyte autoimmune response involved in vitiligo pathogenesis (Casp et,al,.2003). Whereas our earlier studies on CAT, GPX, MBL-2, ACE and PTPN22 polymorphisms did not show significant association [15].

The missense R620W polymorphism in the PTPN22 gene, which encodes lymphoid protein tyrosine phosphatase (LYP), has been associated with susceptibility to autoimmune disorders and also associated with generalised (nonsegmental) vitiligo, polymorphism may have an influence on the development of generalised vitiligo and provide further evidence for autoimmunity as an aetiological factor with respect to this disease [15].

Genome vide Associations have yielded substantial progress in identifying genes involved in risk of GV, with 17 loci now confirmed (*HLA* class I, *HLA* class II, *HLA* class III,*PTPN22*, *RERE*, *FOXP1*, *LPP*, *TSLP*, *CCR6*, *IL2RA*, *TYR*, *GZMB*, *NLRP1*, *UBASH3A*, *XBP1*, *C1QTNF6*, and *FOXP3*): 16 in European-derived white individuals and four in Chinese people, and, for a few genes, in both. Nevertheless, the 16 loci identified in European-derived white individuals together account for only 10% of the total genetic risk of GV in that group, indicating that additional loci probably remain to be discovered, with a few common and perhaps numerous rare variants accounting for disease risk at each locus, the identification of GV susceptibility genes may enable identification of individuals at high genetic risk, enabling relatively direct analysis of potentially causal gene environment interactions, both retrospectively in patients with relatively recent disease onset, and prospectively in individuals who are at high genetic risk [45].

Vitiligo is a polygenic disease, several candidate gene listed in Table-1 that are involved in regulation of immunity have been tested for genetic association with generalized vitiligo, the process shown in fig-1(b).

 

Table -1, Susceptible genes of Vitiligo Pathogenesis [30] and [13]

| Name of Gene | Full Name gene | Biological Vitiligo effect's |
|---|---|---|
| MHC | Major histo- compatibility | Autoimmune diseases, Generalized Vitiligo candidate gene |
| ACE | Angiotensin-converting enzyme | Sensory nerves in the skin under noxious stimuli like chemical and mechanical injury, |
| CAT | Catalase | reduction of Catalase enzyme activity during vitiligo condition |
| CTLA4 | Cytotoxic T lymphocyte-associated antigen 4 | Mutation in CTLA4 cause autoimmune diseases |
| COMT | Catechol O-methyl transferase | It is reported that COMT-158 polymorphism reduced COMT enzyme activity, this may caused overproduction of toxic radicals in the melanocyte microenvironment. |
| ESR-1 | Estrogen receptor 1 | Important for hormone binding, DNA binding, and activation of transcription. |
| CTLA4 | cytotoxic T lymphocytes | mediate melanocyte killing in GV and perhaps also participate in immune surveillance for melanoma cells |
| HLA | Human leukocyte antigen | Autoimmune diseases, Generalized Vitiligo candidate gene strong association of generalized vitiligo |
| XBP1 | X box binding protein 1 | XBP1 gene is considered to be a candidate gene for vitiligo due to its plausible role in the onset of the disease through its interaction with HLA-DR |
| FOXP3 | forkhead box P3 | Generalized Vitiligo candidate gene |
| IL-2RA | interleukin 2 receptor, α | Generelized Vitiligo candidate gene |
| PTPN22 | Protein tyrosine phosphatase, non-receptor type 22 | Generelized Vitiligo candidate gene |
| PDGFRA | platelet-derived growth factor receptor, alpha polypeptide | Elated autoimmune susceptibility. |
| FOXP1 | forkhead box P1 | Generelized Vitiligo candidate gene |
| MYG1 | Melanocyte proliferating gene 1 | atopic eczema |
| MIFT | Microphthalmia- associated transcription factor | Encodes a specialized transcription factor that binds to & activates target genes required for development of pigment cells. |
| VIT1 | Vitiligo-associated protein 1 | VIT1 gene in melanocytes of Vitiligo patients and potential function in pathogenesis. |
| FOXD3 | Forkhead box D3 | it are affected with vitiligo and that had a - 639G>T promoter mutation in FOXD3, which significantly increased transcriptional activity of the gene. |
| CD117 | Cluster of differentiation 117 | Mutations in the human CD117 gene caused Piebaldism, a rare autosomal dominant disorder of melanogenesis which is characterized by depigmentation of skin patches |

 

| | | |
|---|---|---|
| FAS | participated in apoptotic signaling | Mutation of in FAS gene defet;s the signaling pathways which leads to vitiligo. |
| COX2 | Cyclooxygenase-2 | It plays an important role in the production of prostaglandin E2 (PGE2), which is made by epidermal keratinocytes in response to ultraviolet radiation (UVR). PGE2 is important for the proliferation and melanogenesis of epidermal melanocytes, the loss of which leads to vitiligo. |
| EDN1 | Endothelin-1 | The role of genotyping and allele frequencies of EDN1 in the onset of vitiligo. |
| AIRE | The autoimmune regulator | Vitiligo is commonly associated with autoimmune polyglandular syndrome type 1 (APS1). |

In the major histocompatibility complex (MHC) region, which controls the immune system, major association signals were identified in the class I gene region (between HLA-A and HLA-HGC9) and class II gene region (between HLA-DRB1 and HLA-DQA1) and association signals were identified near RERE, PTPN22, LPP, IL2RA, GZMB, UBASH3A and C1QTNF6 genes, which are associated with other autoimmune diseases. The genotype–phenotype correlation between CTLA-4, IL-4 and TNFA gene polymorphisms supported the autoimmune pathogenesis of vitiligo in Gujarat population [7] patients with vitiligo from North India and Gujarat suggesting an autoimmune link of vitiligo in these cohorts (Singh , Sharma *et al.,* 2012). Similarly the studies reported TYR encodes tyrosinase, which is not a component of the immune system, but is an enzyme of the melanocyte that catalyzes melanin biosynthesis, and a major autoantigen in generalized Vitiligo [2].

## CELLULAR EFFECTS

The perilesional skin of patients suffering from inflammatory vitiligo was evaluated. Inflammatory vitiligo is a relatively rare subtype of vitiligo in which perilesional skin is red, itchy, and irritated, and inflammation progresses outwards into unaffected skin, melatonin research have clearly demonstrated that melatonin and its metabolites (such as N1-acetyl- N2-formyl-5-methoxykynuramine, AFMK) exert powerful direct, non-receptor-mediated bioregulatory actions [30].

Consequently, the investigators hypothesized that the inflammatory process may play a role in the elimination of melanocytes. Thus, using antibodies, they examined the inflammatory infiltrates of the perilesional skin and determined their composition. Specifically, they used antibodies for melanocytes, T-cells (CD2, CD3, CD4, and CD8), Langerhans cells, and macrophages (CD36 and CD68). Recently, the vacuolation was attributed to H2O2-mediated lipid peroxidation [38].

The study in vitro conditions, this oxidative stress continues in epidermal melanocytes and keratinocytes established from patients with vitiligo [38] patients with acute vitiligo have low epidermal catalase levels and protein expression in their entire epidermis , although the expression of catalase mRNA is unaltered [29]. H2O2 concentrations in the mM range deactivate catalase due to oxidation of the porphyrin ring as well as methionine and tryptophan residues in the structure of the enzyme-active site and the cofactor NADPH-binding site [41].

Oxidative stress is a cause for Vitiligo suggests that patients with vitiligo have an imbalanced redox (reduction-oxidation) state of the skin, resulting in the excess production of reactive oxygen species (ROS, *e.g.,* H2O2). These disturbances and ROS accumulation can have toxic effects on all components of the cell (*e.g.,* proteins, lipids), and could potentially result in the destruction of melanocytes creating the depigmented macules observed in [1].

## ENVIRONMENT EFFECTS

Most environmental exposure to harmful substances will occur at work, but exposure may occur at home or during normal day-to-day activities, the precise modus operandi for vitiligo pathogenesis has remained elusive. Theories regarding loss of melanocytes are based on autoimmune, cytotoxic, oxidant–antioxidant and neural mechanisms.

 

Reactive oxygen species (ROS) in excess have been documented in active vitiligo skin. Numerous proteins in addition to tyrosinase are affected. It is possible that oxidative stress is one among the main principal causes of vitiligo. However, there also exists ample evidence for altered immunological processes in vitiligo, particularly in chronic and progressive conditions. Both innate and adaptive arms of the immune system appear to be involved as a primary event or as a secondary promotive consequence. There is speculation on the interplay, if any, between ROS and the immune system in the pathogenesis of vitiligo process shown in fig-1(d). The scientific evidences linking oxidative stress and immune system to vitiligo pathogenesis giving credence to a convergent terminal pathway of oxidative stress– autoimmunity-mediated melanocyte loss [20].

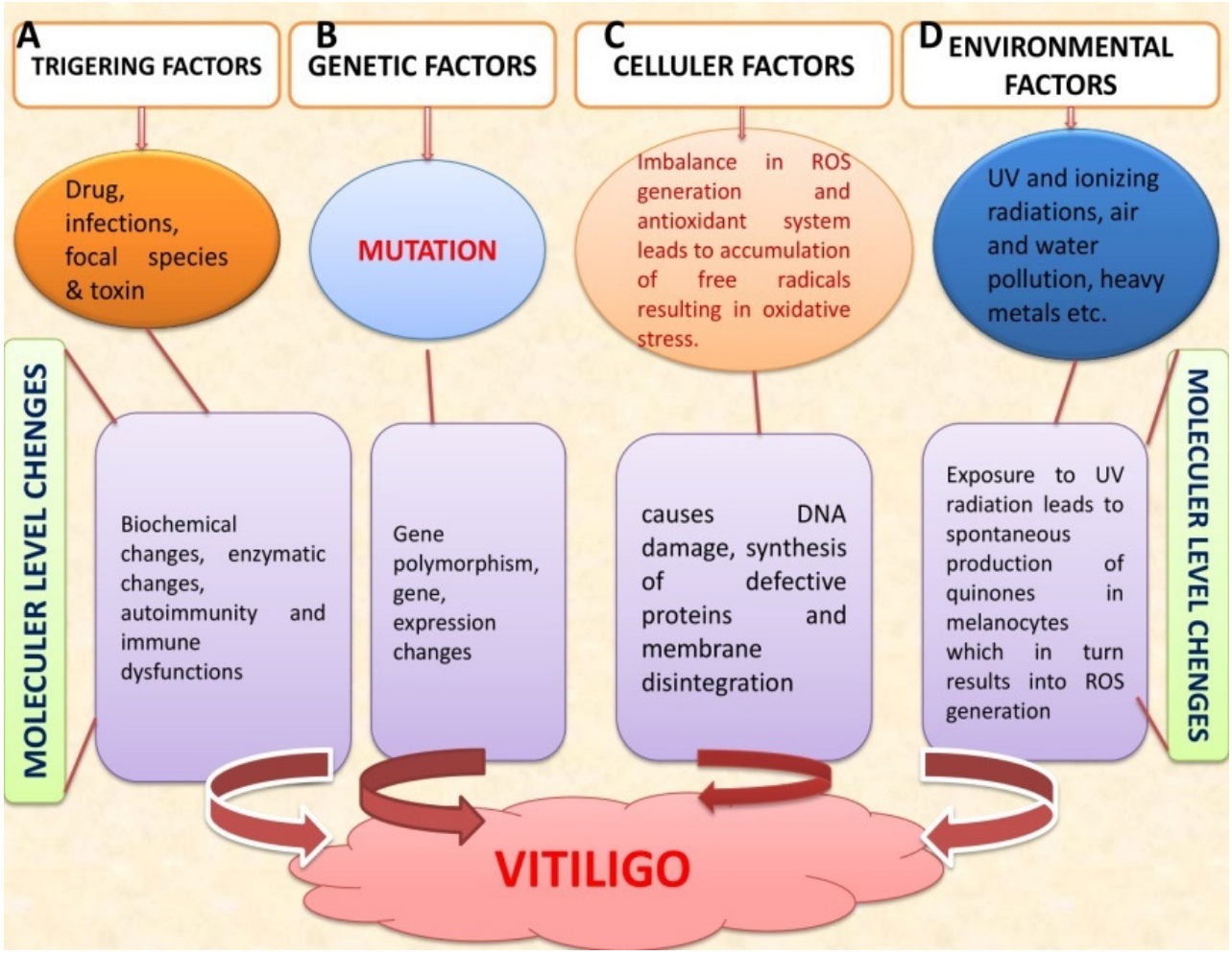


Fig-1, Different factors of vitiligo pathogenesis :( a), (b), (c) & (d)

## THE EARLIEST THERAPIES ARE USE FOR TREATMENT OF VITILIGO IN INDIAN

The treatment of Vitiligo many therapies are using in India and abroad like topical treatment, Immunosuppressant, Phototherapy, chemotherapy etc. The collection of information regarding plants having potential in treatment in vitiligo, used in the traditional Indian system of medicine, according to "ayurveda and unani" medical discipline for treatment of vitiligo, treatment of vitiligo including remedies used, type of formulation used by vaidhy as and tribal people, active components of the plants, their role in treatment of vitiligo and amount to be given as therapeutic against vitiligo, plants are collected and kept in herbarium for further [33]

*Psoralen and Ultraviolet-A:* This therapy use for repigmentaion of skin of vitiligo patients but PUVA is reported to cause phototoxic reaction, cutaneous malignancy [37]

 

*Immunosuppressants:* Anecdotal reports also exist on the off-label use of some immunomodulating biologics in vitiligo[37]

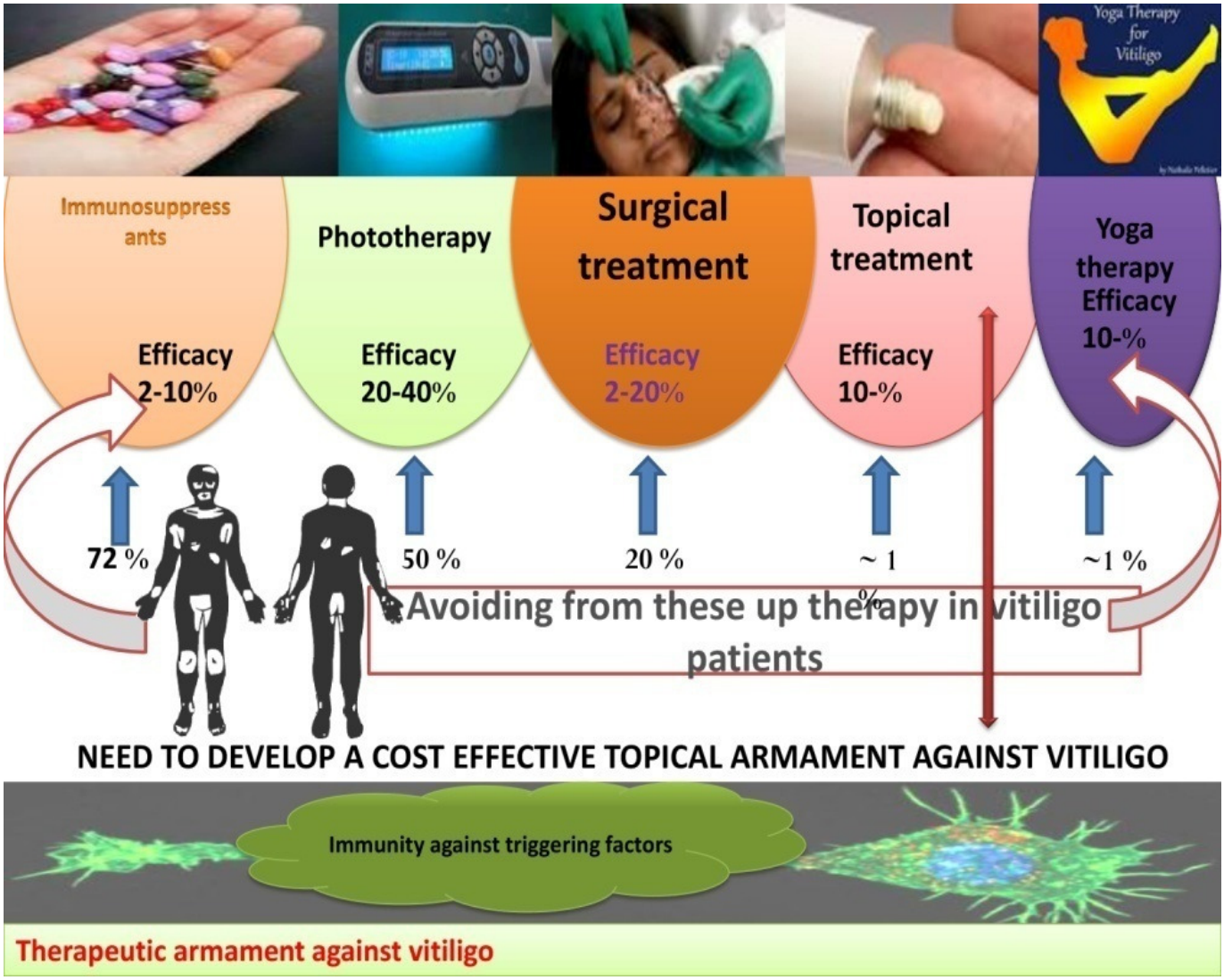


Fig-2, Therapies of Vitiligo treatments in Indian tradition system

## SURGERY

Surgical procedures aim to replace the melanocytes with ones from a normally pigmented autologous donor site. Several melanocyte transplantation techniques can be performed under local anaesthesia in an outpatient facility. However, transplantation for extensive areas may require general anaesthesia. All methods require strict sterile conditions. Punch grafting (tissue graft) is the easiest and least expensive method, but it is not suitable for large lesions and seldom produces even repigmentaion, epidermal blister grafting gives excellent cosmetic results, but it is time-consuming, and large areas cannot be treated, [37],[24].

## CONCLUSION

Today, India stands at cross roads of history. In order to plan for, and Implement, economic and social development, scientific research, it is necessary to have reliable and detailed data on size, distribution and composition of population, pathogenesis of vitiligo in India has yet to be elucidated; however, years of research have provided us with a framework.

The treatment options in India limited success which is often quite dependent on course and location of vitiligo and problem in evaluating treatment efficacy is the present availability of studies and usually uncontrolled pilot studies and case reports it is impossible to name one single

 

treatment modality as the most effective for a particular form of vitiligo, the pilot studies indicating more genetic predisposition to developing the disease is involved.

The studies of vitiligo in India find most of people have genetic defects in pigmentation and cellular activities in body. Vitiligo pathogenesis due genes mutations is environmental factor which are Water pollution, air pollution due to pharmaceutical companies, lather industries, are increasing day by day.

The Reactive Oxygen Species Model suggests that faulty oxygen metabolism results in the excess production of reactive oxygen species, which causes melanocyte destruction and genetic factors likely precede neurogenic factors which, influenced by mental stress, may act via the aforementioned Cytotoxic and immune mechanisms to cause destruction of melanocytes and resulting skin depigmentation.

In India should be manage and decreases the environment pollution because many diseases which are gap in knowledge can be eradicate from India, future research would elucidate the therapy of vitiligo pathogenesis as well as strategies of targeting pathways would potentially advance our cost effective therapeutic armament against vitiligo pathogenesis.

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