Nanogel based drug delivery system for the treatment of vitiligo; systemic review

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Abstract -

Vitiligo is a chronic, non-congenital skin disorder characterized by the loss of melanocytes, leading to white patches predominantly on sun-exposed areas such as the face, neck, and arms. Affecting approximately 0.5–1% of the population, it often presents symmetrically and tends to run in families, suggesting a polygenic inheritance pattern. The exact cause remains unclear, but several hypotheses have been proposed, including autoimmune destruction of melanocytes, oxidative stress, and genetic predisposition involving immune-related genes such as HLA and CTLA-4. Clinically, vitiligo manifests in segmental, non-segmental, and mixed forms, with non-segmental being the most prevalent. Immune-mediated mechanisms involving T cells, antigen-presenting cells, and inflammatory cytokines like IFN-γ and TNF-α play a central role in melanocyte damage.

Treatment aims to restore pigmentation and includes topical corticosteroids, phototherapy, laser therapy, and in some cases, melanocyte transplantation. However, therapeutic success is limited due to the complex etiology. Emerging technologies such as nanogels offer promising drug delivery platforms for targeted therapy. Nanogels are nanoscale, highly absorbent polymeric networks capable of encapsulating drugs through various interactions. Their stability, biocompatibility, and modifiable surfaces make them suitable for delivering bioactive molecules, particularly in protein and gene therapy. Various fabrication methods, including emulsion techniques and self-assembly, support their development for clinical use in treating vitiligo.

Key Words- vitiligo, treatment, nanogel, melanocytes, depigmentation,

1. INTRODUCTION –

skin due to the targeted destruction or death of melanocytes. It affects around 0.5–1% of the population.[1] Depigmentation typically appears on parts of the body that are regularly exposed, such as the face, neck, and arms[1] The most common sites of involvement are the face (24.5%), neck (18.8%), and scalp (11.2%)[2,4]. While both men and women experience the condition at similar rates, women are generally more likely Vitiligo is a non-congenital skin condition of unknown cause, marked by the formation of white patches on the to acknowledge the cosmetic impact and pursue treatment options.[1].The precise cause of vitiligo remains unclear. It is thought to be a polygenic condition, and the most widely accepted explanation is the convergence theory, which integrates aspects of various proposed causes to account for the range of how the disease presents.(2,3)Vitiligo frequently shows a noticeable pattern of occurring within families, with approximately 20% of affected individuals having relatives who also suffer from the condition. People with a family history of vitiligo tend to develop symptoms at a younger age and often experience the disease for a longer period than those without such a background.[1]Vitiligo is a long-term condition that progresses unpredictably, often in flare-ups. While no reliable biological markers exist, certain clinical signs—like inflammatory borders, the Koebner phenomenon, and confetti-like depigmentation—indicate active disease. Early detection is crucial for timely treatment to stop progression.[5,6]Current treatment options for vitiligo aim to restore pigment in affected areas and include medications like topical corticosteroids, narrow-band UVB (NB-UVB) phototherapy[8], and excimer laser therapy[7]. In stubborn cases, autologous melanocyte transplantation may be considered. However, due to the complex and not fully understood causes of the disease, treatment results remain limited.[9]In this disease, antigen-presenting cells stimulate T cells by presenting melanocyte antigens, which leads to the direct destruction of melanocytes by the T cells[13,14]. Studies have shown that both endogenous killer cells and inflammatory dendritic cells are overly active in individuals with vitiligo.

Additionally, a range of cytokines such as INF-γ[15], CXCL10[16], TNF-α, IL-6, and IL-17 are released by innate immune cells as part of the autoimmune response[17,18].

2. ETIOLOGY AND PATHOGENESIS-

The loss of melanocytes and the formation of white patches in vitiligo are associated with several possible mechanisms, including genetic factors, neural influences, autoimmune responses, oxidative stress, inflammatory mediator production, and other processes leading to melanocyte detachment.[25]

2.1 GENETICS THEORY

-Only about 23% of monozygotic twins exhibit concordance, suggesting that non-genetic factors play a significant role in the development of vitiligo. However, because vitiligo is considered a polygenic disorder, multiple candidate genes have been implicated, such as the major histocompatibility complex (MHC), angiotensin-converting enzyme (ACE), catalase (CAT), cytotoxic T lymphocyte antigen-4 (CTLA-4), protein tyrosine phosphatase, human leukocyte antigen (HLA), and interleukin-2 receptor A (IL2RA). These genes, which are mainly involved in immune regulation, have been studied for their potential genetic association with generalized vitiligo.[27,28]

2.2 AUTO IMMUNE THEORY-

The most widely accepted explanation is the autoimmune theory, which proposes that an abnormal immune response leads to the destruction of melanocytes through autoimmune effector pathways, involving either memory cytotoxic T cells or autoantibodies directed against melanocyte surface antigens.[27]

2.3 OXIDATIVE STRESS THEORY-

In the process of melanogenesis, free radicals are generated, resulting in oxidative stress and instability of tyrosine-related protein 1. Consequently, toxic melanin intermediates are formed, which contribute to melanocyte damage.[29,30]. At such concentrations, H_2O_2 induces mitochondrial alterations that trigger apoptosis and subsequent death of melanocytes. In individuals with vitiligo, disturbances in redox balance are often observed (Figure 1). Key biomarkers associated with this include malondialdehyde (MDA), selenium, vitamins C and E, glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT).[31]

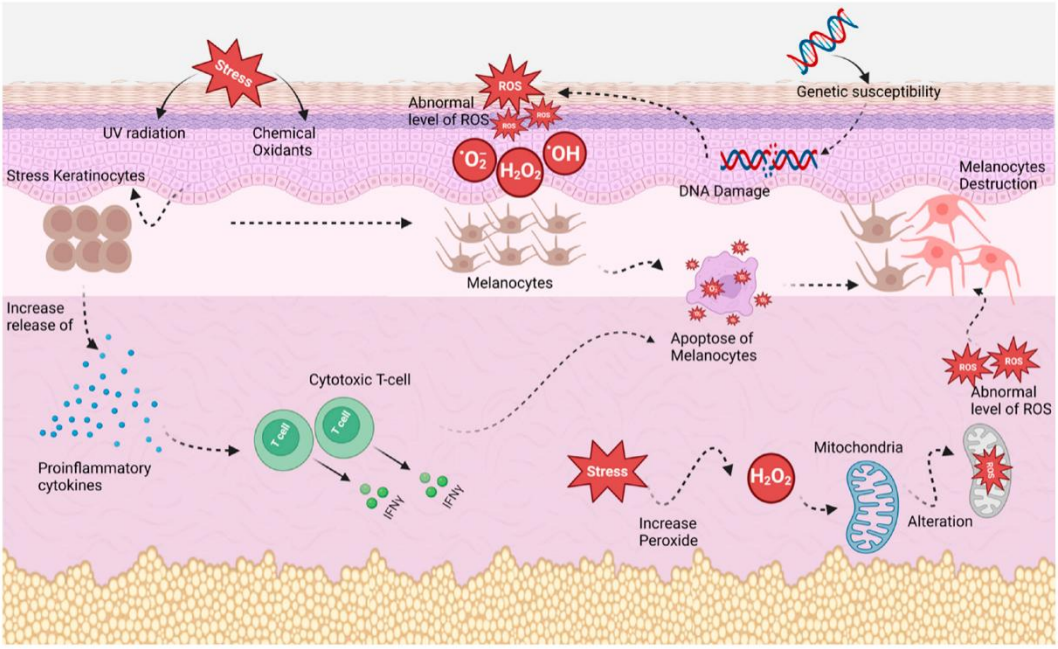
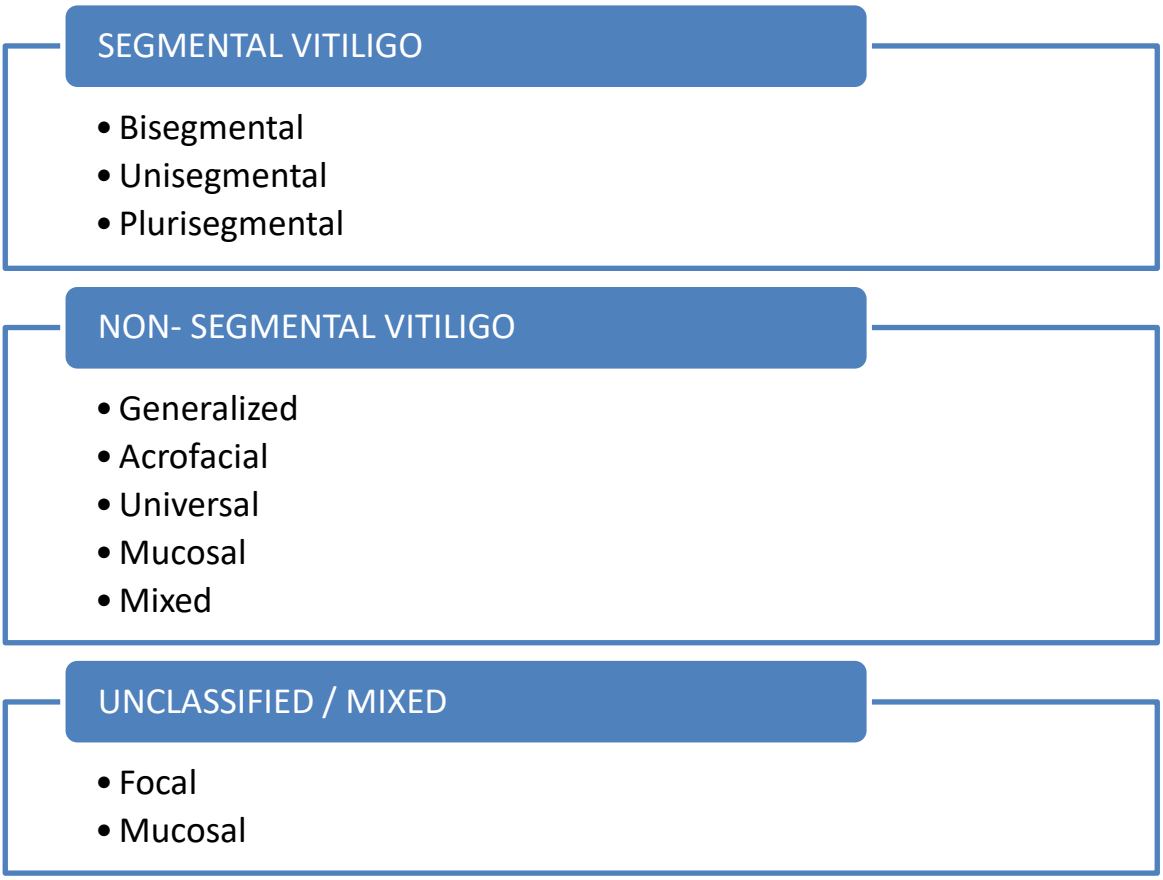


Figure- Oxidative stress is a major factor in vitiligo, causing mitochondrial damage, melanocyte apoptosis, DNA injury, and elevated proinflammatory cytokines and cytotoxic T cells. Excess ROS, generated by UV exposure or mitochondrial dysfunction, further disrupts cellular processes, triggers immune responses, and results in melanocyte loss.

3. TYPES OF VITILIGO-

Vitiligo can present in three distinct clinical forms—segmental, non-segmental, and mixed or unclassified—based on the classification proposed by the Vitiligo Global Issues Consensus Conference conducted between 2011 and 2012.[22]



A] segmental vitiligo-Segmental vitiligo is a long-term acquired pigmentation disorder characterized by white patches that appear on one side of the body, often following the pattern of a dermatome either partially or entirely.[23]Compared to other forms of the condition, it generally responds less effectively to medical treatments.[24]

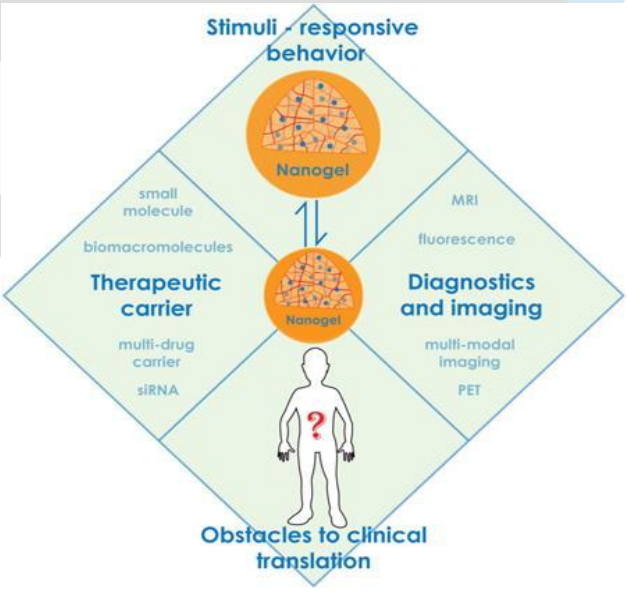
B] non segmental vitiligo- Non-segmental vitiligo (NSV) is the most prevalent form of vitiligo, accounting for 80–90% of all cases. It is a long-standing acquired pigmentation disorder characterized by white patches that appear on both sides of the body, often symmetrically, and tend to expand over time. This type is typically

associated with a significant loss of functional melanocytes in the epidermis, and to some extent, in the hair follicles.[25]

C] mixed and unclassified vitiligo-Mixed vitiligo (MV) is diagnosed when both segmental vitiligo (SV) and non-segmental vitiligo (NSV) are present in the same individual.[25]A halo nevus, also called a Sutton nevus, refers to the loss of pigmentation around an existing mole, forming a halo-like appearance. The presence of multiple halo nevi often indicates an autoimmune response targeting pigment-producing cells, which may raise the likelihood of developing vitiligo[26].

4. NANOGEL-

Nanogels are highly absorbent structures capable of loading over 30% of their weight in biological molecules or drugs. This is achieved through electrostatic, van der Waals, hydrophobic interactions, or covalent bonding with their polymer networks[10]. When drugs are loaded into nanogels, the gels collapse into stable nanoparticles that trap the biological agents inside. To prevent these particles from clumping together, hydrophilic polymers like PEG can be incorporated into the nanogel structure.[11] "They possess exceptional thermodynamic stability, high solubilization capacity, relatively low viscosity, and the ability to withstand rigorous sterilization processes."[20] Nanogels are capable of encapsulating drugs and biomolecules, making them highly suitable for applications in protein and gene delivery.[21].Modifying the surface of nanogels can enhance their ability to selectively accumulate in specific tissues or cells.[12]



4.1 DEVELOPMENT OF NANOGEL-

Nanogel preparation techniques can be divided into two main categories: chemical crosslinking and physical self-assembly. These methods differ based on the particular nanogel architectures and the types of building blocks used.[19]

1] emulsion solvent diffusion

2] nano- precipitated

3] emulsion solvent evaporation

4]reverse micellar

5]modified emulsification – diffusion

4.2 PROPERTIES OF NANOGEL-

A] Degradability and biocompatibility -

Nanogels are composed of natural or synthetic polymers and, due to their biocompatible and biodegradable nature, they do not accumulate permanently in organs. Polysaccharides are carbohydrate polymers made up of repeating monosaccharide units linked by glycosidic bonds. In their natural form, they are stable, biodegradable, hydrophilic, and non-toxic.[32]

B]Swelling in an aqueous medium-

Nanogels are tiny, flexible structures that can expand when exposed to aqueous environments. Environmental factors such as pH, ionic strength, and the types of ions present in the solution play a crucial role in the behavior of polyelectrolyte gels. Additionally, temperature significantly influences the swelling of thermoresponsive gels.[33] Due to their ability to swell and take up large amounts of water, nanogels are expected to offer a higher drug-loading capacity compared to conventional dosage forms.[34]

C] permeability and particle size-

Nano delivery systems' permeability can be enhanced by adjusting particle size, surface charge, or hydrophobicity. While crossing the blood–brain barrier is challenging, nanogels sized 20–200 nm may traverse it with minimal disruption.[34]

D) colloidal stability-

Nanogels, or polymeric micelles, are more stable than surfactant micelles due to their lower CMC, slower dissociation, and prolonged drug retention. Like other colloidal carriers—liposomes, lipid emulsions, and nanoparticles—they can be modified in vivo to reduce protein binding and evade phagocytic clearance, extending their circulation time.[34].

E] Stimuli activated nanogel –

- pH-responsive nanogels can be triggered by environmental pH changes. Positively charged nanoparticles tend to aggregate and clear quickly due to serum interaction, while negatively charged ones have longer plasma half-life and resist protein binding.[36]
- Temperature-responsive polymers like polyisopropylacrylamide and polyvinylcaprolactam have a lower critical solution temperature (LCST) of about 32 °C in water. Nanogels made from these polymers swell at lower temperatures and shrink at higher temperatures, exhibiting a volume phase transition around this critical temperature.[37,38]
- Enzyme-responsive nanogels contain moieties that change their chemical or physical properties upon enzyme activation. Often made from natural peptides or polymers, they are highly biocompatible, selective, and recognizable, making them promising for biomedical applications.[39]

5. THERAPEUTIC APPROACHES-

The main goals of vitiligo treatment are to halt the spread of depigmented patches, stimulate repigmentation, and lessen psychological impact. Current treatments primarily involve drug therapy and phototherapy. First-line drugs, such as corticosteroids like betamethasone dipropionate, clobetasol dipropionate, and mometasone furoate, are preferred for their anti-inflammatory and immunosuppressive actions.[41] Clinical studies indicate that calcineurin inhibitors can be as effective as glucocorticoids, particularly for facial leukomas. Additionally, the buildup of oxidative products in the skin plays a key role in melanocyte dysfunction.[41,42]. Oral antioxidants like polypodium leucotomos, vitamins C and E, and minocycline are employed as part of an antioxidative treatment approach for vitiligo. Besides pharmacological therapy, phototherapy methods such as narrow-band UVB (NB-UVB) and psoralen UVA (PUVA) offer relatively safe physical treatment options.[43,44,45].

5.1 TOPICAL CORTICOSTEROIDS –

Topical corticosteroids (TCS), such as potent options like betamethasone valerate or very potent ones like clobetasol propionate, are commonly used as the first-choice treatment for vitiligo.[46,47]. Daily use of topical corticosteroids is advised for a period of up to three months. If effective, treatment can then continue on an intermittent basis for up to six months. However, if there is no noticeable improvement within three to four months, the treatment should be stopped.[48,49,50].Corticosteroids (CS) were more effective than topical calcineurin inhibitors (TCI) in achieving 50% repigmentation, although both treatments showed similar results when it came to reaching 75% repigmentation.[51].Skin atrophy is the most common side effect of topical corticosteroids, often appearing within two weeks. This risk can be minimized by using lower-potency steroids, limiting high-potency use, and stopping treatment once recovery is achieved.[52].Vitiligo treatment often involves extended use of these medications, exceeding the typically recommended safe durations for inflammatory skin conditions. This prolonged use can lead to notable side effects such as skin atrophy, excessive hair growth, and hypopigmentation around the treated areas, which can limit therapy. Clearly, current dosage forms do not offer targeted drug delivery to specific sites.[53]

5.2 CALCINEURIN INHIBITORS-

Calcineurin inhibitors, including tacrolimus and pimecrolimus, are among the latest topical medications introduced in dermatology.[54,55]. Their mechanism of action involves blocking calcineurin, a protein that promotes inflammation in lymphocytes and dendritic cells by triggering the production of interleukin (IL)-2 and tumor necrosis factor-α (TNF-α).[56]By inhibiting this process, cytokine production is reduced, which also promotes the growth of melanocytes and melanoblasts. Topical calcineurin inhibitors (TCIs) like tacrolimus (0.03% or 0.1%) and pimecrolimus (1%) are preferred for use on the head and neck due to their lower risk of side effects, particularly the absence of skin atrophy.[56,48,58]One lesion was treated with daily tacrolimus 0.03%, another with monthly microdermabrasion plus daily tacrolimus 0.03%, and the last with a placebo. The combination treatment led to moderate to excellent repigmentation (≥50%) in 65.7% of lesions, compared to 25.8% with tacrolimus alone.[59].A recent study showed that using pimecrolimus after microdermabrasion significantly improved repigmentation. This suggests that carrier-mediated drug delivery can boost effectiveness by bypassing the skin barrier and delivering the drug directly to melanocytes and keratinocytes.[60]. Topical calcineurin inhibitors (TCIs) may cause side effects such as a burning sensation, itching, and a higher risk of infections like herpes simplex and molluscum contagiosum.[61]

5.3 PHOTOTHERAPY-

Topical psoralen photochemotherapy (PUVA) is commonly used in individuals with mild vitiligo involving less than 20% of the body. It is also suitable for children aged 12 and above with localized vitiligo patches.[62] UVB radiation (280-320 nm) is more effective than UVA (320-400 nm). Narrowband UVB phototherapy (311 nm) helps treat vitiligo by suppressing the immune response, promoting melanocyte detachment, boosting melanin production, and encouraging melanocytes to move from nearby skin into the affected areas.[63,64]Narrowband UVB (311 nm) phototherapy works in vitiligo by suppressing the immune system, promoting melanocyte differentiation, increasing melanin production, and encouraging melanocyte migration from surrounding skin. It is recommended for extensive vitiligo affecting more than 15-20% of the body or for cases with rapid progression.[57,65,66]Treatment response should be evaluated after 18 to 36 sessions, but due to some patients responding slowly, continuing therapy for at least 72 sessions is advised before stopping. For patients with skin phototypes IV to VI, there is no set maximum number of sessions, while no guidelines exist for other phototypes. The maximum recommended dose is 1,500 mJ/cm² for the face and 3,000 mJ/cm² for the body.[67]PUVA therapy (320-340 nm) stimulates melanin production by suppressing the immune system and promoting melanocyte development. This second-line treatment typically involves applying psoralen topically or taking it orally, followed by UVA exposure. When taken orally, psoralens are ingested 1-3 hours before UVA treatment.[68].Other physical treatment options include the use of combined Fraxel Erbium and UVA1 lasers, as well as excimer laser (EL) therapy.[69].

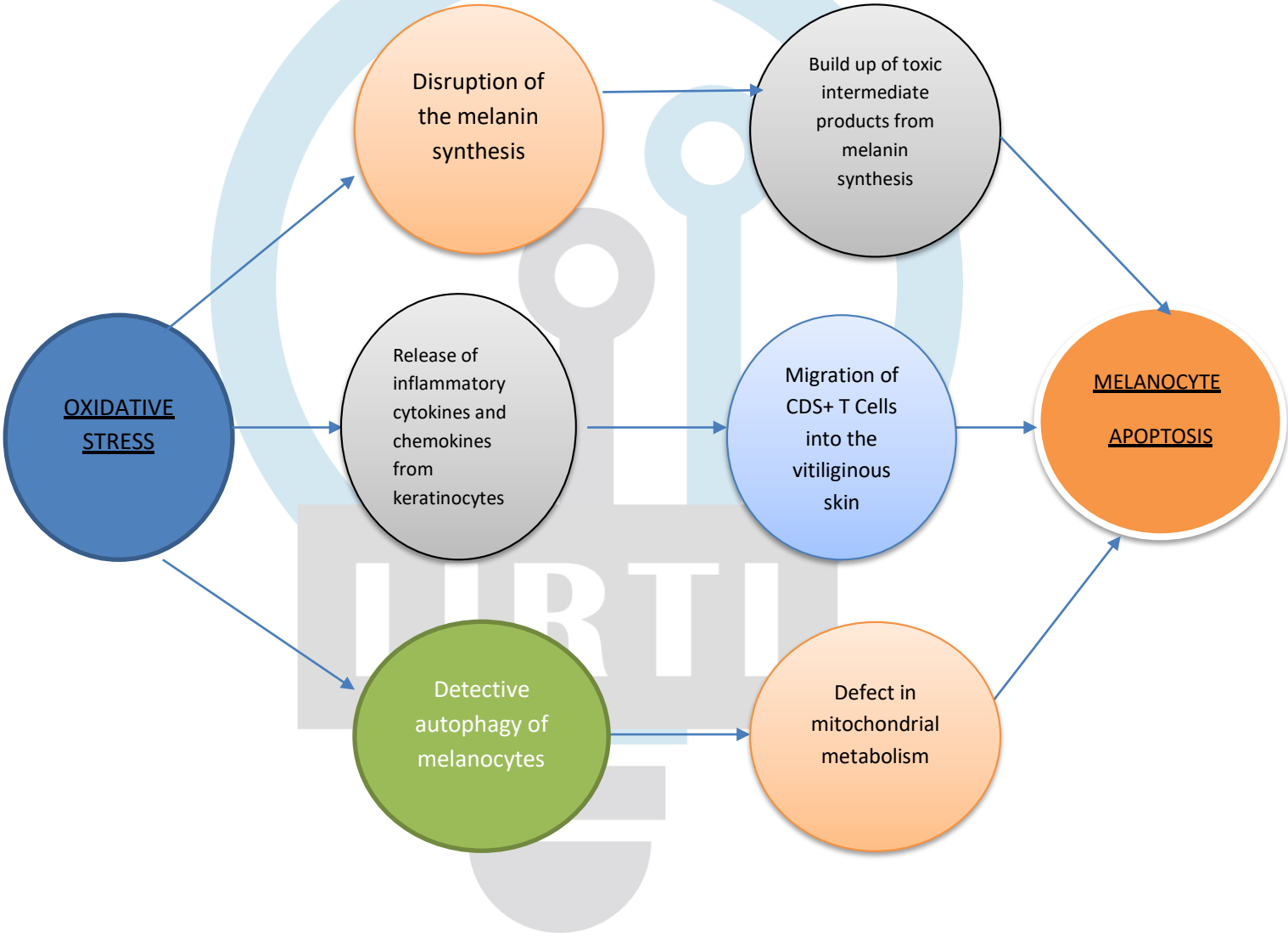
5.4 CALCIUM MODULATORS-

Recently, calcium modulators such as vitamin D3 analogues (calcipotriol and tacalcitol) have been explored as potential treatments for vitiligo. Studies have found impaired calcium transport in melanocytes and keratinocytes from vitiligo patients, and vitamin D3 has also been shown to stimulate melanin production.[72,73] Vitamin D3 analogues (D3As) alone are not highly effective for vitiligo but can boost results when combined with other treatments. They help regulate immunity, support melanocyte growth, and promote melanin production. The suggested dose is 100 g per week on up to 30% of the body, using ointment for 4 weeks or cream for 8 weeks, often alongside calcipotriol 0.005% and betamethasone 0.05%.[74]. Another source of active vitamin D3 is its production by antigen-presenting cells, as well as T and B lymphocytes.[75]Vitamin D3 analogues (D3As) have been found to be safe for use across all age groups, including both children and adults. Clinical observations and studies have shown that these agents are generally well-tolerated, with minimal side effects. The most commonly reported adverse effect is mild skin irritation, which tends to be temporary and not severe enough to require discontinuation of treatment. This favorable safety profile makes D3As a suitable option for long-term use, particularly when used in combination with other therapies for managing vitiligo.[61]

5.5 ANTIOXIDANTS-

Oxidative stress and the buildup of hydrogen peroxide (H2O2) are thought to contribute to vitiligo, with elevated H2O2 levels found in the epidermis of affected areas.[70] A study by Alshiyab et al. (46) compared the effectiveness of tacrolimus 0.1% ointment alone versus tacrolimus 0.1% ointment combined with topical pseudocatalase/superoxide dismutase gel in treating children with localized vitiligo. The results showed no significant difference in repigmentation rates between the two groups.[71]Patients have been reported to exhibit decreased levels of antioxidants, including catalase and superoxide dismutase.[76].Nrf2 is also involved in the process of melanogenesis in normal human melanocytes, where it inhibits melanin production

by downregulating the expression of tyrosinase and TRP1 via modulation of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway.[77] Clinically, studies have shown that enhanced Nrf2-mediated transcriptional activity is necessary to maintain redox balance in individuals with vitiligo.[78]Various organic compounds, including simvastatin, aspirin, vitamin D, and minocycline, along with herbal agents such as glycyrrhizin, afzelin, 6-shogaol, geniposide, 8-methoxypsoralen, and cinnamaldehyde, have been reported to safeguard human melanocytes from oxidative stress by stimulating the Nrf2/ARE signaling pathway.[79,80,81,82,83].

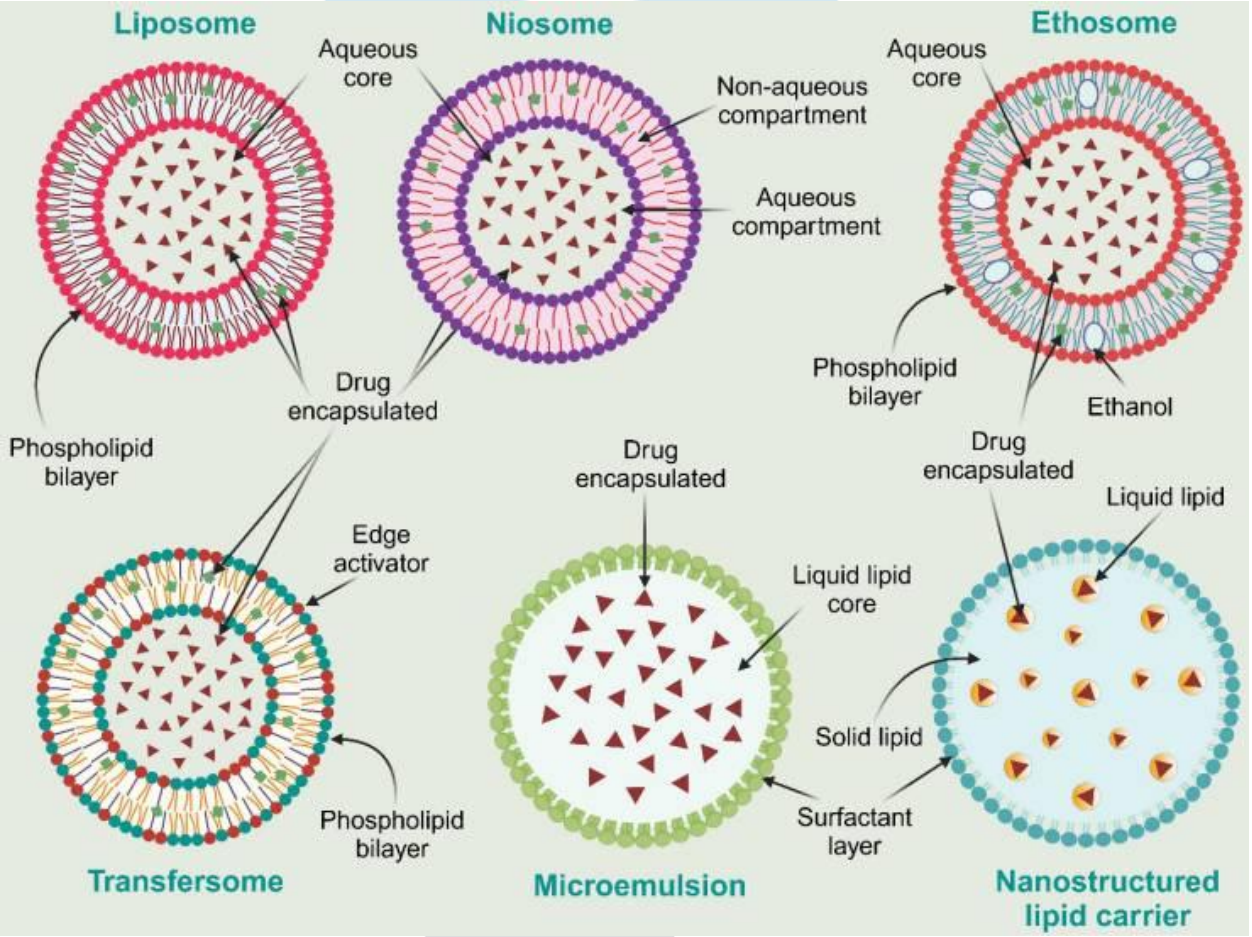


- Fig. Role of oxidative stress in vitiligo.

6. NANO-DRUG DELIVERY SYSTEM IN THE TREATMENT OF VITILIGO –

Human skin, the body's largest organ, performs numerous vital functions. It serves as a physical barrier, supports immune defense, helps regulate body temperature, protects against UV radiation, and maintains moisture balance.[84]. Lipid-based nanoparticles (LNPs) present a promising strategy for topical vitiligo treatment by overcoming limitations of conventional drug delivery. Their unique structure and physicochemical properties enhance drug penetration, stability, and therapeutic efficacy. Types of LNPs, such

as liposomes, niosomes, ethosomes, transfersomes, microemulsions, and nanostructured lipid carriers, mimic the skin's lipid composition, facilitating interaction with the stratum corneum and improving delivery to deeper layers[85,86,87]. LNPs can carry both hydrophilic and lipophilic drugs, offering controlled release and sustained action while minimizing drug degradation. Their small size ensures uniform distribution across depigmented areas, and their biocompatibility reduces skin irritation, supporting long-term use. Furthermore, LNPs can be modified with penetration enhancers or targeting ligands to increase drug localization at melanocytes, making them an effective and patient-friendly platform for vitiligo therapy.[88]



6.1 LIPOSOMES-

Liposomes are vesicles made from phospholipids that facilitate drug delivery through the skin because their structure resembles that of natural cell membranes. They can carry both water-soluble and fat-soluble drugs, enhancing drug solubility, stability, and enabling controlled release.[89,90]. Liposomes are mainly customized for particular skin conditions, such as vitiligo, by altering their composition, size, and surface characteristics. This customization enhances drug retention in the stratum corneum and epidermis, resulting in longer-lasting effects and improved bioavailability.[91,92].Liposomes containing Baicalin and Berberine showed significantly improved drug penetration into the deeper skin layers. They exhibited strong antioxidant and photoprotective properties and enhanced tyrosinase activity along with melanin production.[93]Liposomes incorporating 8-Methoxypsoralen enabled continuous drug release for nearly 24 hours and facilitated deeper penetration of the drug into the skin layers, enhancing its delivery efficiency.[57]Treatment of 3T3 fibroblasts and HaCaT keratinocytes with liposomes significantly boosted melanogenic activity, reaching up to 145% at higher doses. Baicalin and berberine co-loaded liposomes also

enhanced tyrosinase activity to 136% at lower concentrations. Similarly, Sinico et al. developed 8-methoxypsoralen-loaded liposomes using the thin-film hydration method.[57]Resveratrol activates mitogen-activated protein kinase (MAPK) signaling and exhibits strong antioxidant properties. Optimization studies identified the best formulation based on particle size, PDI, and zeta potential. The co-loaded liposomes were produced using a modified film hydration method, resulting in particles around 120 nm in size with drug loading efficiencies ranging from 2.5% to 5%.[98,99].

6.2 NIOSOMES-

Niosomes are single or multilayered vesicles formed by hydrating non-ionic surfactants, with or without cholesterol. They are biodegradable, biocompatible, non-immunogenic, and structurally flexible, offering low toxicity and effective targeted drug action[97]. Niosomes are tiny vesicular structures made from non-ionic surfactants, developed as a substitute for conventional liposomes.[95]Niosomes are promising carriers for both dermal and transdermal drug delivery, providing benefits like improved skin penetration, formulation flexibility, higher stability, minimal irritation, better bioavailability, and targeted action. They alter the stratum corneum's structure to increase permeability, and the inclusion of non-ionic surfactants in their formulation further enhances drug penetration through the skin.[96].

6.3 MICRO-EMULSION -

Microemulsions are clear, thermodynamically stable colloidal systems composed of oil and water stabilized by surfactants, often with a cosurfactant. Their structure depends on the composition and properties of the ingredients. Due to their ability to enhance drug solubility and penetration, microemulsions serve as an effective system for transdermal drug delivery. A clobetasol propionate-loaded microemulsion gel has been shown to overcome the drug's poor solubility successfully.[100,101]. The formulated microemulsion containing *B. gaudichaudii* extract demonstrated controlled skin permeation compared to the free extract. Skin irritation tests indicated minimal irritation potential. Additionally, the formulation promoted melanocyte migration and pigmentation, suggesting that encapsulating *B. gaudichaudii* extract in a microemulsion could be an effective strategy for topical treatment of vitiligo. [88].Nanoemulsions and microemulsions for vitiligo treatment should offer prolonged skin retention, sustained drug release, and high permeability.[102]. A microemulsion gel containing clobetasol propionate was shown to enhance the drug's solubility and bioavailability, maintain longer skin presence, and improve pigment deposition and therapeutic outcomes compared to the control.[94]

6.4 TRANSFEROSOME-

Transfersomes are highly flexible lipid vesicles engineered to improve transdermal drug delivery. Made from phospholipids and edge activators such as sodium cholate, their exceptional deformability allows them to pass through pores smaller than their diameter, effectively penetrating the stratum corneum and delivering drugs to deeper skin layers or the bloodstream.[103,104]. The composition of transfersomes includes amphipathic ingredients, primarily lipids, which form the vesicle's bilayer structure. Surfactants or edge activators, typically 10–25%, are added to destabilize the bilayer and enhance its permeability. Alcohol, present at 3–10%, acts as a solvent, while a hydrating medium facilitates bilayer hydration and promotes the self-assembly of lipid molecules into transfersomes.[105]

6.5 ETHOSOMES

Treating vitiligo remains challenging, and various approaches are used. Topical corticosteroids are applied for their immunosuppressive and anti-inflammatory effects, while calcineurin inhibitors and vitamin D analogues serve as alternative topical therapies. Oral mini-pulse corticosteroids with minocycline can help stabilize active vitiligo. Narrow-band UVB therapy promotes melanocyte differentiation and melanin production. Surgical options like skin grafting are considered for localized patches, and cosmetic agents such as foundations or sunless tanners can provide temporary camouflage[106]. The ethosomal hydrogel was prepared by incorporating the optimized 8-MOP ethosomal formulation into a Carbopol 934P gel base for topical use. Carbopol was dispersed in warm water, agitated for complete solubilization, and neutralized with triethanolamine. The ethosomal dispersion was mixed into the gel in a 4:1 ratio to form the final ethosomal hydrogel (OEMOPI-CBP), which was then examined for color, phase separation, grittiness, and crystal formation.[107]

6.6 NANOPARTICLES-

Autoimmune diseases result from immune dysregulation, and antigen-specific immunotherapy can promote tolerance without affecting normal immunity. Tolerogenic dendritic cells are key but hard to generate in vivo. Nanoparticle-based delivery can improve antigen-specific tolerance, with their properties influencing therapeutic effectiveness[109] .In recent years, nanoparticles have been added to everyday products. Their ability to penetrate the skin depends on size, charge, and structure. Metal nanoparticles like palladium and platinum enhance enzyme activity and provide anti-inflammatory effects in UV-exposed HaCaT keratinocytes, while pretreatment with nano-platinum notably decreases the rate of cell apoptosis compared to untreated controls.[108]Nanocarrier systems, particularly lipid-based nanoparticles (LNPs), overcome major challenges in vitiligo therapy, including low drug solubility, quick degradation, and limited skin penetration. Additionally, LNPs provide controlled drug release, maintaining therapeutic levels at the target site for longer periods, enhancing treatment effectiveness, and reducing dosing frequency[88].

7. LIMITATIONS OF CONVENTIONAL TREATMENT-

Conventional therapies suffer from several drawbacks.

- Poor skin penetration of topical agents .
- Adverse local and systemic effects.
- Recurrence upon discontinuation .
- Long treatment duration and patient non-complaince.
- Inefficient targeting of melanocytes.
  These limitation underscore the need for novel drug delivery system that ensure targeted , sustained release with minimal side effects.[110]

8. CONCLUSION- Vitiligo is a chronic, multifactorial skin disorder characterized by the loss of melanocytes, resulting in depigmented patches, primarily on sun-exposed areas. Its pathogenesis involves a combination of genetic susceptibility, autoimmune responses, oxidative stress, and environmental triggers, making the disease unpredictable and difficult to manage. Conventional therapies, including topical corticosteroids, calcineurin inhibitors, antioxidants, phototherapy, and surgical interventions, aim to halt disease progression and promote repigmentation. However, their efficacy is often limited due to poor drug penetration, systemic side effects, and inconsistent therapeutic outcomes.Advances in nanotechnology have

introduced promising strategies for improving vitiligo treatment. Nanogels and lipid-based nanoparticles, such as liposomes, niosomes, ethosomes, and transfersomes, enable targeted and controlled delivery of therapeutic agents directly to melanocytes. These nanoformulations enhance drug stability, solubility, and skin permeation while minimizing systemic exposure and adverse effects. Stimuli-responsive nanogels further offer site-specific drug release, optimizing therapeutic action. By integrating conventional treatments with nanocarrier-based delivery systems, it is possible to achieve more effective, safe, and patient-friendly therapy. Continued research and clinical evaluation of these nanotechnologies hold significant potential to transform vitiligo management and improve patient outcomes.

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