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RESEARCH ARTICLE

RECENT ADVANCES IN IMMUNOGENETICS AND SKIN BARRIER MECHANISMS IN PSORIASIS: AN INTEGRATED REVIEW OF TRANSDERMAL DELIVERY SYSTEMS

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Abstract

Psoriasis is a chronic inflammatory skin disease characterized by an immune system response, manifesting in various forms including plaques, flexural lesions, wounds, pustules, and erythroderma. This condition affects individuals of all genders and impacts approximately 60 million people worldwide. The pathophysiology of psoriasis involves complex interactions between keratinocytes, dendritic cells, and T cells, with the IL-23/Th17 axis playing a crucial role in keratinocyte proliferation, chronic inflammation, and immune activation. Despite the widespread use of treatments, none have proven to be completely effective and safe for patients. Current drug treatments primarily provide symptomatic relief rather than a cure, and existing medications often have limited skin penetration and efficacy. Consequently, there is a growing need to explore new drug delivery systems or molecular approaches that are both safe and effective, aiming to improve patient compliance with psoriasis treatment. Nanocarrier-based formulations may represent a promising solution due to their high skin penetration, low dosing frequency, reduced side effects, and lower dosage requirements. This review aims to explore recent advances in the immunogenetics and skin barrier mechanisms underlying psoriasis, investigate the interplay between immune cells and cytokines involved in its pathophysiology, evaluate current treatment options, and identify future psoriasis treatments. Additionally, it will assess the potential of transdermal drug delivery systems utilizing nanocarriers for future developments in anti-psoriatic therapies.

Introduction:-

About 2-3% of the world's population has psoriasis. It has red, scaly plaques that lower quality of life [1]. The term "psoriasis" is derived from the Greek word "Psora" meaning "itch"[2, 3].Skin is the body's biggest organ, with three

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layers: epidermis, dermis, and hypodermis. Epidermis keratinocytes protect the skin. The stratum corneum (SC) includes tightly packed corneocytes in a lipid-rich matrix to limit water loss and pathogen invasion. Tight junctions (TJs) between stratum granulosum (SG) keratinocytes prevent paracellular molecule transit. Keratinocyte proliferation and differentiation occur in deeper levels such the stratum spinosum (SS) and stratum basale(SB)[4, 5].

Pruritus (itching) is a critical symptom of psoriasis, and it frequently results in skin thickening (lichenification) as a result of the repeated clawing. The condition is further exacerbated by pro-inflammatory cytokines, such as IL-17 and IL-23, which enhance peripheral nerve sensitivity and contribute to an itch-scratch cycle, primarily driving this itch[6, 7]. In the clinical setting, pruritus has a detrimental impact on the quality of life of patients, resulting in sleep disturbances, anxiety, and melancholy. Scratching can lead to the exacerbation of psoriatic lesions and the development of secondary infections. Lichenification, which is distinguished by thickened, leathery skin, is the result of altered skin barrier function and increased keratinocyte proliferation. This thickening can exacerbate psoriasis by accumulating an increased number of inflammatory cells, which ultimately exacerbates symptoms and perpetuates the inflammation[8-10]. The efficacy of topical treatments can also be influenced by a compromised skin barrier, which can alter their pharmacokinetics.

A variety of treatment options are available, contingent upon the severity of the disease. Coal tar, vitamin D3, UVA radiation, retinoids, and corticosteroids are among the topical treatments that are primarily employed for milder cases. Systemic therapies, including cyclosporine, tacrolimus, and psoralen, may be administered orally or via injection in more severe cases[11-14]. The potential adverse effects of these treatments, which include injury to other organs, necessitate meticulous monitoring.

Recent advancements in nanotechnology have created new opportunities for the localized administration of antipsoriatic medications, providing encouraging treatment options. Therapeutics are developed in nanomedicine by employing materials that are between 1 and 100 nanometer in size. In order to achieve effective topical drug delivery at the nanoscale, it is necessary to optimize several parameters: (1) increasing the bioavailability and efficacy of hydrophobic drugs, (2) reducing the dosage while enhancing drug absorption through the skin barrier, (3) controlling drug release for precise dosing, and (4) improving drug solubility while preventing degradation[15, 16]. The progression of transdermal drug delivery systems from the first to the third generation is indicative of substantial improvements in drug penetration mechanisms. Small lipophilic medications were employed at low dosages in the first generation, while iontophoresis and non-cavitational ultrasound were employed in the second generation. The third generation emphasizes innovative methods, including thermal ablation,electroporation, and microneedles[17, 18]. These methods are presently under investigation for the delivery of hormones and vaccines. The potential impact of these novel delivery systems on transdermal drug delivery has garnered significant attention, particularly the improvements in these systems. The dermis, epidermis, and transfollicular pathways are the three primary routes for transdermal drug delivery[19]. Nevertheless, numerous aspects of nanodrug delivery are still in the research or clinical phase, necessitating additional assessment to satisfy future requirements. Other delivery technologies are also being actively investigated as a consequence of these nanotechnology advancements.

This review will examine the pathophysiology of psoriasis and recent developments in transdermal delivery systems as therapeutic options, with a forward-thinking perspective on prospective future developments.

Pathophysiology of Psoriasis

Immune-mediated psoriasis is characterized by keratinocyte hyperproliferation and aberrant differentiation, resulting in erythematous, scaly plaques. Pruritus is one of several psoriasis symptoms. Disrupting the skin barrier and lowering patient quality of life adds to the disease's etiology.

Pruritus is a well-known and distressing symptom of psoriasis that has a substantial impact on the well-being of patients. It plays a multifaceted and intricate function in the disruption of the epidermis barrier and the promotion of inflammation. The act of clawing to alleviate itching can result in physical injury to the skin, which can exacerbate barrier dysfunction and promote additional inflammation. This section investigates the mechanisms by which pruritus disrupts the skin barrier and induces immune responses in psoriasis.

Itch and Skin Barrier Disruption

Mechanical injury to the epidermis is a common consequence of scratching, a common response to alleviate itching. This compromises the barrier function of the stratum corneum by disrupting its integrity. Excoriations, erosions, and

additional skin thickening (lichenification) can be the result of repeated trauma from clawing, all of which exacerbate barrier dysfunction. Scratching disrupts the "brick and mortar" structure of the stratum corneum, resulting in more transepidermal water loss (TEWL) and skin dehydration. The itchiness of the skin increases as it becomes drier, resulting in a cycle of scratching and itching. Additionally, clawing enhances skin permeability, which enables allergens, pathogens, and other irritants to penetrate the epidermis and dermis at a deeper level. This disruption in barrier function is essential for the initiation and perpetuation of inflammatory responses in psoriasis[6, 7].

Pathophysiology of Neuroimmune system in Psoriasis

The interaction between the immune and nervous systems is especially pertinent in the context of psoriasis and pruritus. Scratching that is induced by itching not only disrupts the physical barrier but also affects the local immune environment through neuroimmune interactions[7, 20-22].

The onset of the itch sensation is correlated with the activation of peripheral sensory nerve fibers, specifically unmyelinated C-fibers and thinly myelinated Aδ-fibers, which innervate the epidermis. The functions of these fibers are distinct: C-fibers transmit itch sensations that are sluggish and more sustained, whereas Aδ-fibers are responsible for the quicker transmission of sharp, acute itch signals[23, 24]. In psoriatic skin, chronic inflammation results in the sensitization of both fiber types, which in turn increases the sensation of itching. The release of neuropeptides and other mediators by sensory neurons that mediate pruritus can directly interact with immune cells in the epidermis, including mast cells, dendritic cells, and T cells[25]. The immune response can be modulated by these interactions, which can lead to the development of psoriatic lesions and the enhancement of inflammation (Fig. 1).

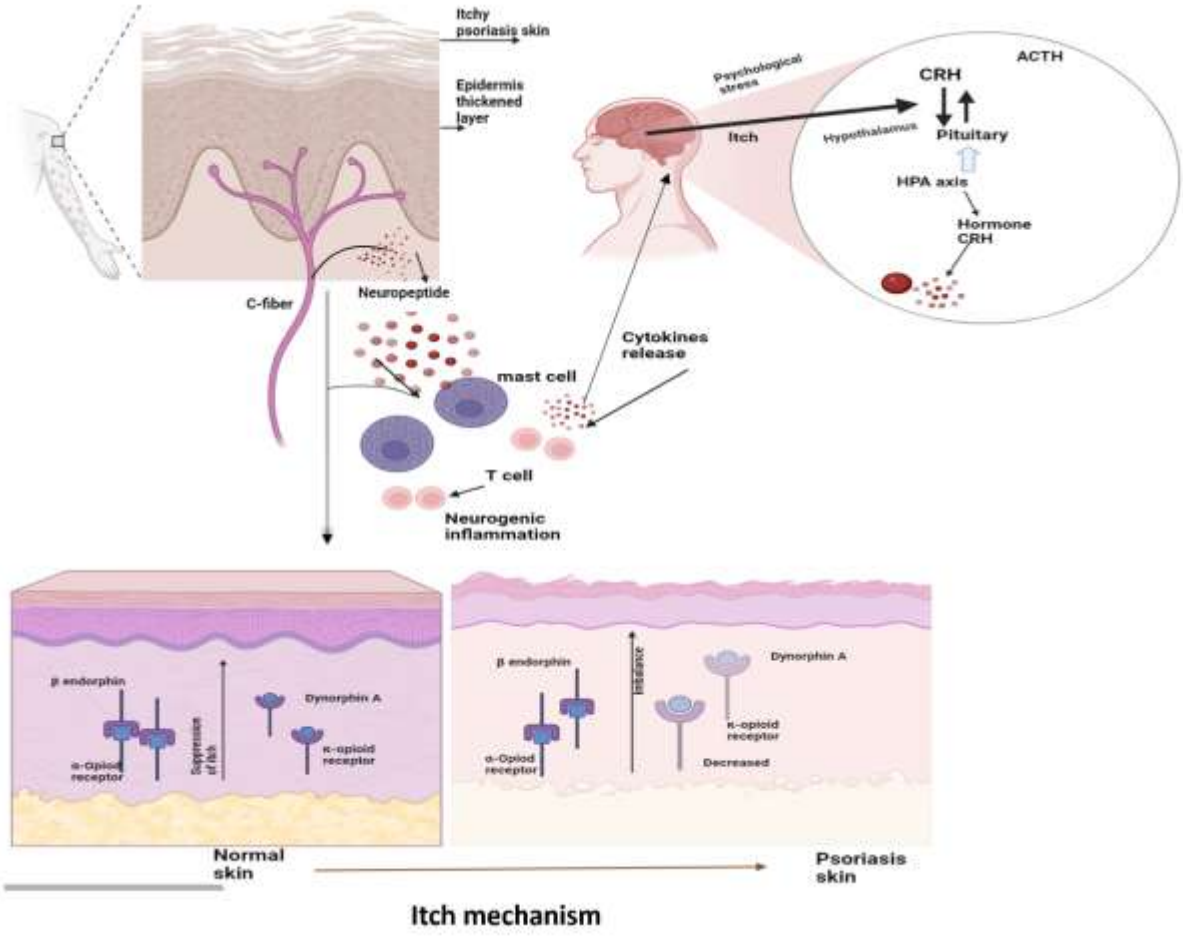

Fig.1:- Itch mechanismin psoriasis. Neuroimmune interactions are key in itch and psoriasis. Itch triggers scratching, which disrupts the skin barrier and affects immune responses. Peripheral nerve fibers, C-fibers and Aδ-fibers, transmit itch signals, with chronic inflammation in psoriatic skin heightening their sensitivity. These sensory

neurons release mediators that interact with immune cells, increasing inflammation and contributing to psoriatic lesions.

Substance P (SP) and Calcitonin Gene-Related Peptide (CGRP) neuropeptides transmit and amplify psoriasis itch sensations. SP, produced by sensory nerve terminals, attaches to NK-1 receptors (NK-1R) on immune cells and keratinocytes, releasing mast cell and immune cell histamine, proteases, and cytokines. SP directly activates sensory neurons, increasing skin-to-spinal cord itch impulses[21, 26, 27]. Neurogenic inflammation, where sensory neurons produce inflammatory mediators that attract immune cells to the site of inflammation, intensifies pruritus[22, 28].

Transient receptor potential (TRP) channels, especially TRPV1, are integral to the transmission of pruritic signals in conjunction with neuropeptides. TRPV1, a calcium-regulating ion channel, is significantly expressed in psoriatic lesions. The activation of TRPV1 by diverse itch-inducing stimuli, including cytokines and neuropeptides, leads to the depolarization of sensory neurons, hence commencing the transmission of itch-related signals. This channel is closely linked to the IL-23/IL-17 pathway, which is pivotal in psoriasis, therefore intensifying the inflammation and chronic itch often seen in the condition[29-31].

Cytokines, including IL-31, IL-17, and IL-23, also play a substantial role in the regulation of pruritus. IL-31, which is produced by Th2 and Th17 cells, binds to IL-31 receptors (IL-31RA) on sensory neurons, thereby facilitating the transmission of pruritus signals. IL-17 and IL-23, which are essential for the pathogenesis of psoriasis, indirectly contribute to itch by sensitizing peripheral nerves and promoting inflammation[32, 33]. The activation threshold for sensory neurons is reduced by the inflammatory environment generated by these cytokines, resulting in a hypersensitivity of the skin to stimuli that induce itching. This leads to a vicious cycle in which inflammation induces itching, which in turn exacerbates inflammation through scratching-induced skin injury.

The imbalance of opioid receptors and their ligands is another significant factor that contributes to the complexity of psoriatic pruritus. In psoriatic lesions, there is a dysregulation between μ-opioid receptors (MOR), which promote pruritus, and κ-opioid receptors (KOR), which inhibit it. MOR expression is upregulated in psoriatic skin, while KOR expression is reduced, resulting in increased pruritus sensitivity. The perception of pruritus is exacerbated by this imbalance in opioid receptor signaling, which is mediated by both central and peripheral pathways. Psoriasis also results in dysregulation of endogenous opioid peptides, including beta-endorphin, which are typically responsible for modulating these receptors[21, 34]. The intensity of the irritation is not the only effect of the altered equilibrium between MOR and KOR; it also increases its persistence.

Stress also worsens psoriasis pruritus via the hypothalamic-pituitary-adrenal (HPA) axis and Corticotropin-Releasing Hormone (CRH). Psychological stress releases CRH, which acts on sensory neurons, mast cells, and keratinocytes via CRH-R1 and CRH-R2. Psoriatic epidermis' high CRH levels cause mast cell degranulation, which releases pruritogenic substances that sensitize sensory neurons. CRH also activates the HPA axis, releasing cortisol. Chronic HPA axis dysregulation in psoriasis may prolong inflammation and pruritus, especially under stress, even though cortisol can control inflammation[35].Table 1 summarizes the critical function of a variety of irritating mediators in the development of psoriasis.

Table 1:- Mediator responsible for psoriasis itch.

System	Types	Mediator	Effects
Nervous system	Neuropeptide	SP	Skin lesions increase with blood serum percentage increase
		CGRP	The higher level of present in psoriatic skin causing severe itch
		NPY	Suppression of mechanical itch
		VIP/PACAP	The increase the percentage of the vascular adhesion protein
	Opioids	β-endorphin	The β-endorphin in serum level is higher with severe skin lesions
		Dynorphin-A	Percentage of Dynorphin –A suppressionof psoriatic lesion
	Neurotrophins	NGF	NGF percentage significantly higher in psoriasis patients' blood serum and skin

			lesions severe.
Immunesystem	Cytokines	IL-17	Induction of itch
		IL-21	Induction of itch
		IL-22	Itch with severe lesion
		IL-26	Induction of itch
		IL-31	Itch, severe lesion
		IL-2	Induction itch with inflammation
		IL-33	Induction of itch with aggravation of inflammation
		PGE2	Induction of histamine and serotonin inducing itch
Vascular		VEGF	Severe lesion
		ET-1/ E selectin	Induction itch
		VAP-1	Aggravation of itch
Endocrines and others		LCN2	Higher in blood serum of psoriasis patients having psoriasis arthritis's
		DPPIV	Induction of itch

Immune Cells in Psoriasis Pathophysiology

The inflammatory response that defines psoriasis is profoundly influenced by a complex interplay of immune cells, which is the foundation of the disease's pathophysiology (Fig. 2). T cells, dendritic cells, and keratinocytes are essential components of this process, each of which plays a unique yet interconnected function in the initiation and perpetuation of psoriatic inflammation. This disease is characterized by the chronic inflammation and hyperproliferation of keratinocytes, which are facilitated by a network of cytokines and chemokines that these cells communicate through. The comprehension of these interactions is essential for the development of targeted therapies that can effectively disrupt this pathogenic cycle and provide relief for patients with psoriasis. In psoriasis, pruritus is the result of a multifaceted interaction between neuropeptides and inflammatory cytokines. Tumor Necrosis Factor-alpha (TNF-α), Interleukin-17 (IL-17), and Interleukin-23 (IL-23) are inflammatory cytokines that are essential for the development of psoriasis and are also associated with the sensation of itching. These cytokines facilitate the release of pruritogenic mediators, including Interleukin-31 (IL-31), which directly induces pruritus by binding to its receptor on sensory neurons. Furthermore, IL-31 has the potential to increase the expression of nerve growth factor (NGF), which in turn further sensitizes nerve endings [6, 7, 24].

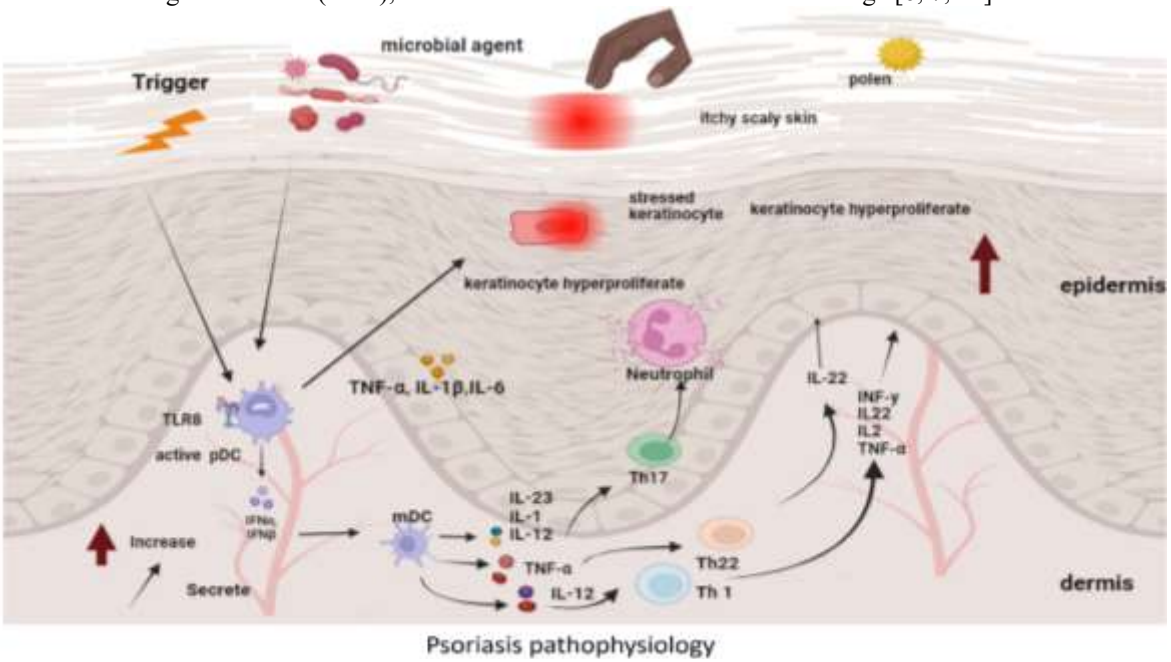

Fig.2:- Pathophysiology of psoriasis. The complex interaction of immune cells, including T cells, dendritic cells, and keratinocytes, is the primary cause of psoriasis. These cells sustain inflammation through the release of

cytokines and chemokines, which results in chronic inflammation and keratinocyte proliferation. Psoriasis pruritus is also characterized by the presence of inflammatory cytokines, such as TNF-α, IL-17, and IL-23, which contribute to the sensation of itching and inflammation. It is essential to comprehend these interactions to develop therapies that disrupt this cycle and alleviate symptoms.

T Cells

T cells, specifically CD4+ helper T cells (Th cells) and CD8+ cytotoxic T cells, are the primary components of the psoriatic immune response. Th1 and Th17 cells are particularly critical among CD4+ T cells. Th1 cells are predominantly responsible for initiating the inflammatory cascade and are heavily involved in the early phases of psoriasis. This cytokine, interferon-gamma (IFN-γ), is produced in significant quantities by these cells and has profound pro-inflammatory effects. IFN-γ activates macrophages and dendritic cells, which subsequently produce an increased amount of cytokines, including IL-12 and IL-23, thereby enhancing the immune response. This activation is crucial for the differentiation of Th1 cells and the enhancement of their pro-inflammatory activities, which are responsible for the erythema and edema characteristic of psoriatic lesions[36].

However, Th17 cells are the primary cause of chronic inflammation in psoriasis. The primary cell type in the epidermis, keratinocytes, are directly influenced by interleukin-17 (IL-17), a cytokine that is produced by these cells. IL-17 induces the proliferation of keratinocytes and the production of additional pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, as well as chemokines that attract neutrophils to the site of inflammation. The persistent thickening and scaling of the skin are the result of the continuous activation of keratinocytes by IL-17, which maintains the chronic nature of psoriasis. The survival and expansion of Th17 cells are substantially dependent on the cytokine IL-23, which is produced by dendritic cells and macrophages, which is essential for the maintenance of the inflammatory milieu in psoriasis[32, 37, 38].

CD8+ cytotoxic T cells, in addition to Th1 and Th17 cells, are also significant in the pathogenesis of psoriasis. Keratinocyte apoptosis can be directly induced by these cells, which recognize antigens presented by MHC class I molecules on keratinocytes. This cytotoxic activity not only induces the typical epidermal cell turnover but also releases inflammatory mediators from deceased keratinocytes, thereby exacerbating the inflammatory response[39]. Furthermore, CD8+ T cells generate pro-inflammatory cytokines, including TNF-α and IFN-γ, which contribute to the cytokine milieu that induces psoriatic lesions[37].

Dendritic Cells

Dendritic cells (DCs) are another important part of the psoriatic immune system. Antigen-presenting cells capture, process, and present antigens to T cells to start and sustain the immune response. The main dendritic cell subtypes involved in psoriasis are plasmacytoid and myeloid [36, 37, 40-42].

Plasmacytoid dendritic cells (pDCs) are notably significant during the initial phases of psoriasis. These cells are recognized for their capacity to generate substantial quantities of interferon-alpha (IFN-α) in response to viral infections. However, in psoriasis, they are stimulated by DNA and RNA released from stressed or decaying keratinocytes. Upon activation, pDCs emit IFN-α, which not only functions as an antiviral response but also acts as a potent stimulator of myeloid dendritic cells (mDCs). The activation of mDCs by IFN-α is a critical phase in the development of psoriasis, as mDCs are the primary producers of IL-12 and IL-23, cytokines that are essential for the differentiation and maintenance of Th1 and Th17 cells, individually. This results in a feed-forward cycle in which the inflammatory environment that promotes psoriasis is maintained by the continuous activation of the surrounding immune cells and pDCs and mDCs.

After activation, myeloid dendritic cells (mDCs) move to the lymph nodes and expose antigens to naïve T cells, which differentiate into Th1 and Th17 cells. IL-12 and IL-23 are generated by mDCs and are necessary for Th1 and Th17 cell development and maintenance. In psoriatic epidermis, mDCs directly interact with T cells, boosting local inflammation. Additionally, mDCs produce several cytokines and chemokines, such as TNF-α and CCL20, which recruit more immune cells to the epidermis, escalating the inflammatory cycle.

Keratinocytes

Keratinocytes, the epidermis' main cell type, are considered immune response passive targets in psoriasis. However, new evidence shows that keratinocytes initiate and maintain psoriatic inflammation[7, 25, 33, 39]. Keratinocytes generate several pro-inflammatory mediators in response to immune cell cytokines, such as IL-17 and TNF-α.

Antimicrobial peptides like LL-37 and cytokines like IL-1β, IL-6, and IL-8 are examples. These compounds contribute to local inflammation and attract more immune cells to the epidermis, boosting the reaction.

Keratinocytes affect psoriatic epidermis structure. Keratinocytes undergo hyperproliferation when exposed to cytokines like TNF-α and IL-17, leading to scale development and epidermal thickening. This fast turnover of keratinocytes is a hallmark of psoriasis and contributes to skin barrier dysfunction[25, 32]. Furthermore, the inflammatory process is perpetuated by a feedback cycle that is established by the production of antimicrobial peptides by keratinocytes, which in turn activates dendritic cells[6].

Additionally, keratinocytes have been demonstrated to express receptors for cytokines and chemokines that are engaged in the immune response, including IL-17 receptors and TNF receptors[37]. This enables keratinocytes to directly respond to the inflammatory signals in the epidermis, further emphasizing their active involvement in the disease. The pathophysiology of psoriasis is significantly influenced by the cross-talk between keratinocytes and immune cells, as keratinocytes serve as both responders to and amplifiers of the inflammatory response.

Therapeutic Approaches for Psoriasis

Psoriasis, a chronic inflammatory dermatological disorder, necessitates several treatment approaches to manage inflammation, regulate keratinocyte hyperproliferation, and relieve symptoms, especially pruritus. Treatments are classified into topical treatments, phototherapy, systemic drugs, and biologic therapies, each addressing unique facets of the condition.

Topical Treatments

Topical therapies are usually used for moderate to severe psoriasis. This group relies on corticosteroids' powerful anti-inflammatory capabilities. They work by binding to glucocorticoid receptors and blocking pro-inflammatory pathways, such as the NF-κB signaling cascade.They may cause skin atrophy and tolerance, thus use should be monitored[13, 43]. A commonly utilized category comprises vitamin D analogs such as calcipotriene. These drugs modulate keratinocyte proliferation and promote differentiation through interaction with vitamin D receptors. They further inhibit T-cell activation, hence diminishing the generation of inflammatory cytokines. To improve efficacy, vitamin D analogs are frequently utilized in conjunction with corticosteroids[44, 45].Topical retinoids, including tazarotene, function by influencing keratinocyte differentiation and proliferation through retinoic acid receptors, offering anti-inflammatory and anti-proliferative advantages. Nevertheless, they may induce irritation and are often employed in conjunction with corticosteroids to enhance tolerance[46]. Calcineurin inhibitors, such as tacrolimus, impede T-cell activation and cytokine secretion, rendering them especially effective for managing sensitive skin regions susceptible to irritation[47].

Phototherapy

For patients with moderate to severe psoriasis unresponsive to topicals, phototherapy is a key option, particularly narrow-band UVB light (311-313 nm), which reduces inflammation and cell turnover by inducing T-cell apoptosis and modulating cytokine levels. An alternative form, PUVA (psoralen plus UVA) therapy, uses a photosensitizing agent to enhance UVA absorption, cross-linking DNA in proliferative keratinocytes and T-cells to induce apoptosis[48]. PUVA is highly effective, though it has potential long-term side effects, such as photoaging and an elevated risk of skin cancer[49].

Systemic Treatments

Systemic treatments are advised for moderate to severe psoriasis, especially when topical and phototherapy methods prove inadequate. These therapies aim at immunological regulation and keratinocyte proliferation on a wider spectrum.

Methotrexate is among the most often recommended systemic therapies. It inhibits dihydrofolate reductase, so obstructing nucleotide synthesis and T-cell proliferation, in addition to diminishing inflammatory cytokine production. Continuous monitoring is essential owing to possible adverse effects, such as hepatotoxicity and bone marrow suppression.[1, 50]. Cyclosporine, another systemic option, inhibits calcineurin and blocks T-cell activation, rapidly reducing psoriatic inflammation but with risks such as nephrotoxicity and hypertension[51]. Additionally, acitretin, an oral retinoid, normalizes keratinocyte differentiation and is especially beneficial for pustular psoriasis, though it has teratogenic effects and can cause mucocutaneous side effects[19, 52].

Biologic Agents

Biologic therapies have revolutionized the treatment of moderate to severe psoriasis, especially in individuals with psoriatic arthritis or refractory to systemic therapy. TNF-α inhibitors, such etanercept, infliximab, and adalimumab, decrease this pro-inflammatory cytokine in psoriasis. This inhibits immune cell invasion and keratinocyte overproduction. Due to immunosuppression, these medications are successful but require constant infection surveillance[53]. Another biologic class targets IL-12/23 pathways. Ustekinumab modulates Th1 and Th17 immune responses to reduce inflammation by targeting the common p40 component of IL-12 and IL-23. These therapies are usually safe. Secukinumab, ixekizumab, and brodalumab suppress IL-17 or its receptor, lowering keratinocyte activation and immune cell migration. This reduces plaque and symptoms but may cause Candida infections and inflammatory bowel disease[53, 54]. Guselkumab and risankizumab target the IL-23p19 subunit, which maintains Th17 cells. These medicines indirectly reduce IL-17 by blocking IL-23, providing persistent relief with good safety[54, 55].

Transdermal Drug Delivery System

Topical corticosteroids, biologics, and systemic agents are among the numerous treatments available for psoriasis, as previously mentioned. Nevertheless, their efficacy is frequently restricted by the necessity for frequent applications, potential adverse effects, and inadequate epidermis penetration. A promising approach to enhancing psoriasis treatment is presented by transdermal drug delivery systems (TDDS), which enable for controlled drug release, increase patient compliance, and improve skin penetration. In this section, we examine the various forms of TDDS that are currently in use or under investigation for the treatment of psoriasis, with an emphasis on their mechanisms, benefits, and prospective applications.

Microneedle

A microneedle device is a hybrid of a hypodermic needle and a transdermal patch. It delivers an adequate amount of medication to the appropriate stratum of the epidermis by arranging hundreds of small, micron-sized needles on a small patch. The application of microneedles results in the rapid penetration of the SC layer through minimally invasive, minute punctures in the underlying epidermis. Various types of microneedles, including solid, coated, disintegrating, hollow, and hydrogel microneedles, have been developed contingent upon their precise purpose and functionality. Solid microneedles are frequently employed to enhance skin permeability in general prior to the administration of medication[56].

The drug-coating layer of coated microneedles is intended to be on the needles' surface, where it will quickly and directly come into touch with skin. Nontoxic polymers used to make dissolving microneedles enclose medications that eventually dissolve in skin. Regarding hollow microneedles, the hollow bores allow for the passive or active injection of a liquefied medication while also serving as a space and protective shield for the loaded pharmaceuticals[57].

Cross-linked, swelling hydrogels are used to make the unique microneedles. Hydrogel microneedles assimilate water and keep hydrogel's hydrophilic qualities, unlike other variations. Therapeutic materials for transdermal drug administration may be supplied via a reservoir connected to hydrogel microneedles or directly included into their manufacturing. Integrating hydrogel with microneedles improves drug-loading capacity, tunable drug release rate, biocompatibility, and biodegradability[58]. Microneedles are non-invasive and innocuous because their microstructure prevents them from penetrating deeply enough into the skin to interact with or activate dermal pain receptors. Pharmaceuticals are injected with needles, but microneedles need no training or staff. They are single-use to reduce medication cross-contamination and promote patient compliance[59, 60]. Dissolvable microneedles are chosen by patients for their convenience. A microneedle patch produced by Du et al. dissolves hyaluronic acid and has excellent mechanical, biocompatibility, biodegradability, and water solubility. It reduced psoriasis-like skin irritation more than MTX taken orally at the same dose in microneedles[61].

Microneedles have been engineered to facilitate the simultaneous delivery of many drugs. Wan et al. developed a dissolving microneedle patch including glucocorticoid sensitizers to address insufficient responses to topical or systemic glucocorticoid therapies due to glucocorticoid resistance[62]. The dissolvable microneedle patch was motivated by NLRP3's ability to increase glucocorticoid resistance. By precisely targeting and destroying NLRP3 in subcutaneous keratinocytes and immune cells, CRISPR-Cas9 allows transdermal co-delivery of glucocorticoids and NLRP3 antagonists. In murine models of psoriatic IMQ-induced psoriasis, the microneedles reduced severity and deleterious effects by 70% after one week[62]. Microneedle approaches are preferred for transdermal co-delivery of

medicines in psoriatic arthritis, an inflammatory arthritis accompanied with skin psoriasis, to treat both the arthritis and the skin lesions. The Yu et al. layered dissolving microneedle incorporated the topical immunosuppressant TAC in its inter-layer, which was administered into the skin at a depth of around 100 μm. The microneedle tip can administer diclofenac sodium, a commonly used drug, up to 300 μm into the articular cavity[63]. Microneedle tips might break if maintained in the skin due to their small size. Due to skin irritation and allergic responses on delicate skin, microneedles should be used sparingly. Development of this technology focuses on selecting sophisticated materials such dissolvable polymers to overcome these restrictions[64].

Iontophoresis

Iontophoresis (IP) is a non-invasive drug delivery method that uses low-intensity electric current (0.3–0.5 mA/cm2) to transport ionic drug molecules[2]. IP helps two electrodes work together to regulate delivery rate. Return electrode next to active electrode completes circuit, whereas active electrode contains drug system. IP efficiency depends on current density, pH, drug concentration, molecular size, and current application method (continuous or pulsed)[65]. Emerging experimental evidence suggests that drugs are transported iontophoretically via appendageal and intercellular routes through two primary mechanisms: (1) an ion flux induced by an electric potential across the skin; and (2) electroosmotic or convective flow occurring in the "anode-cathode" direction due to the skin's net electrical charge[66, 67]. It was specifically noted that IP induces Ca2+ influx into skin cells and consequent intracellular signal activations, which in turn cause a reduction in the expression of the gap junction protein connexin 43 and the de-polymerization of tight junction-associated polymerized actin, which weakens intercellular connections[65].

IP-mediated drug delivery allows intradermally injected medicines to gradually enter the systemic circulation and maintain a predetermined level[65]. In practical applications, proteins, peptides, antibodies, and oligonucleotides, normally delivered subcutaneously or intravenously by needles, have been validated for intradermal delivery. In a rat model of psoriasis produced by IMQ, Fukuta et al. found that noninvasive iontophoresis can deliver antibodies or the anti-TNF-α fusion protein ETA transdermally[2].

Fluorescein isothiocyanate (FITC) labeling may transfer up to 80% of antibodies, big molecules with high hydrophilicity, into skin tissue by intraperitoneal injection. IP ETA reduced psoriatic epidermal hyperplasia and stopped invasive damage better than needle injection. To confirm the results, hydrophilic macromolecular therapies such CpG oligo DNA (M. W. 6,600) and siRNA (M. W. 12,000) were administered intradermally (IP). In vivo, these medicines perform their biological functions[65]. Despite nanoparticles improving topical medication effectiveness, arthritis and nail psoriasis treatment remained unsatisfactory. Iontophoresis (IP) increases drug penetration 37-fold over passive formulations for nail fungus and onychomycosis. A retrospective research [68],found that 81% of nail psoriasis patients who received weekly dexamethasone IP for three months had nail improvement. IP's remarkable transdermal effectiveness suggests a unique role in treating arthritic psoriasis. The increased use of biologic treatment for psoriasis makes intraperitoneal biological macromolecular medicines beneficial in reducing inflammation and tissue damage from needle injections. IP mostly interacts with small, charged molecules and certain macromolecules up to several thousand Daltons without affecting skin structure. Thus, big compounds' transdermal effects are limited. IP effectiveness depends on present uses, which are limited by IP battery capacities, since medicinal dose varies with skin charge [69].

Nanocarrier-Based Systems

Nanocarrier systems, such as nanoparticles, liposomes, and niosomes, are non-invasive TDDS that encapsulate drugs to improve their stability, solubility, and skin penetration. Their small size allows them to pass through intercellular spaces in the stratum corneum, enhancing drug delivery to targeted sites within or beneath the skin. Nanocarriers enable controlled drug release and minimize systemic side effects, making them particularly effective for topical psoriasis treatment.

Here, we will discuss the mechanisms of transdermal drug penetration, the different types of nanocarriers, their applications in psoriasis treatment, and their limitations. The current status of nanocarrier-based system development for psoriasis treatment is summarized in Table 2.

Mechanism of Drug Penetration with Nanocarriers

The skin, covering approximately 15% of an adult’s total body mass, serves as a protective barrier against pathogens, water and electrolyte loss, and environmental stressors, while also providing UV protection and

thermoregulation. The outermost layer of the skin, the stratum corneum (10-20 µm thick), prevents the penetration of larger drug molecules (over 500 Da) due to its "brick-and-mortar" structure composed of dead keratinocytes and a ceramide-rich lipid layer. This layer contains three main components—natural moisturizing factors (NMF), corneodesmosomes, and lipids—that form a critical skin barrier alongside fatty acids, cholesterol, and ceramides[17].

In transdermal drug delivery systems, drugs are absorbed into the skin and can enter the bloodstream via skin blood vessels. This route is advantageous due to its ease of administration, high patient compliance, and suitability for both hydrophilic and lipophilic drugs at lower doses, which has attracted significant research interest.Lipid-based nanocarriers adhere well to the skin, enhancing the penetration of active compounds into the stratum corneum (SC). Polymer-based nanocarriers further support controlled drug release and maintain physical stability[18, 65].

Drugs penetrate the skin through two main pathways: transepidermal and transappendageal (Fig. 3). The transepidermal route allows drugs to pass either between or through cells in the SC, depending on their solubility in lipids. Lipophilic drugs penetrate more readily via the transcellular route, while hydrophilic drugs diffuse through intercellular spaces, reaching dermal capillaries based on their solubility in both lipid and water phases. The transappendageal route, which involves drug delivery via hair follicles or sweat glands, is suited for larger or polar molecules[16, 17].

While no single route optimally achieves transdermal delivery on its own, researchers are working to enhance drug absorption by adjusting drug formulations or modifying SC structure. The small surface-to-volume ratio of nanoparticles helps them navigate the skin barrier more effectively, increasing drug penetration. Compared to conventional topical treatments, nanocarrier-based drugs, whether topical or systemic, show improved penetration and drug concentration at psoriatic patches, reducing toxicity and enhancing therapeutic effects[70].

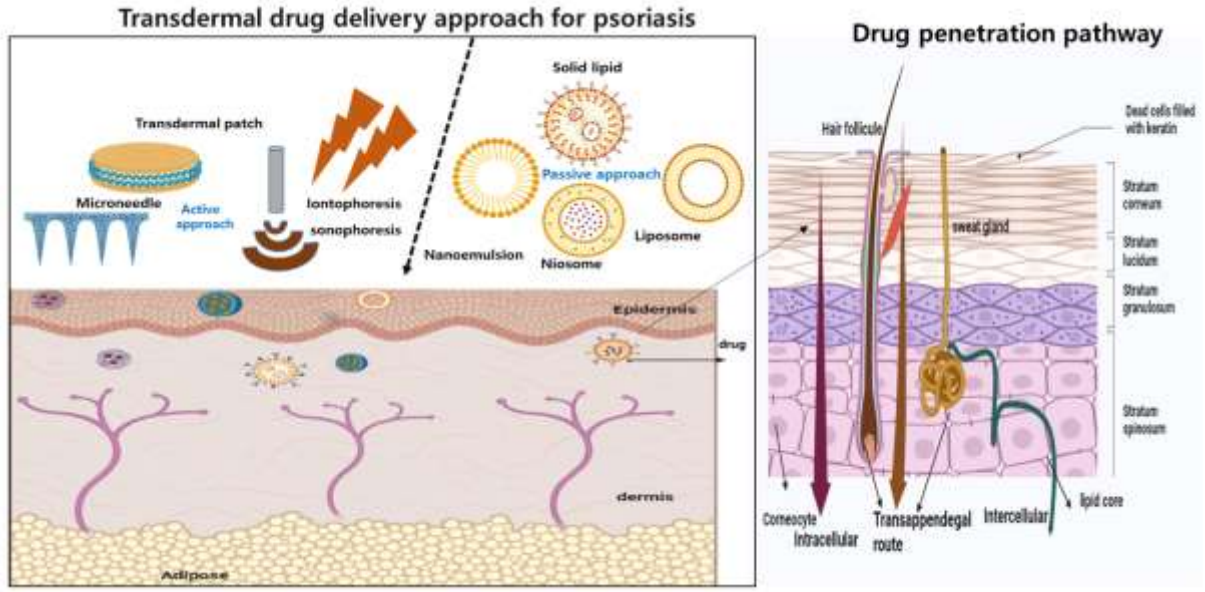

Fig.3:- Nano drug penetration mechanism. Transdermal drug delivery enables non-invasive absorption of drugs through the skin into the bloodstream, suitable for both hydrophilic and lipophilic agents. Lipid- and polymer-based nanocarriers enhance penetration and stability. Drugs enter the skin via transepidermal (through or between cells) and transappendageal (through hair follicles and sweat glands) pathways, with lipophilic drugs favoring transcellular diffusion and hydrophilic drugs migrating through intercellular spaces.

Lipid-based Nanocaarriers

Lipids, originating from keratinocytes and sebum, are essential components of the skin, playing a key role in maintaining skin integrity, moisture, and health. Due to their composition, which closely resembles that of epidermal lipids, lipid-based nanocarriers are excellent candidates for psoriasis treatment. Currently, nanocarriers like solid lipid nanoparticles, nanoemulsions, liposomes, and niosomes are popular drug carriers for psoriasis, as they enhance

drug penetration into the deeper layers of the stratum corneum [15, 71]. Consequently, lipid-based nanocarriers are considered one of the safest options for topical psoriasis treatment, supported by recent research and experiments.

Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are an advanced drug delivery system in which lipid molecules (such as Compritol 888, cetyl palmitate, steroids, fatty acids, and glycerides) form submicron particles immersed in a surfactant (e.g., Tween 80, Span 80). First developed by Gasco and Muller in 1991, these small, spherical particles remain solid at room temperature. Depending on the drug's characteristics and lipid properties, SLNs can be prepared through methods such as hot or cold homogenization, ultra-sonication, and microemulsion techniques. SLNs demonstrate higher drug loading capacity, entrapment efficiency, controlled release, and protection of active ingredients compared to conventional liposomes[72].

SLNs were developed to address drawbacks associated with polymeric nanoparticles and liposomes, such as polymer degradation, drug leakage, and cytotoxicity[73]. SLNs use either ionic or non-ionic surfactants, or sometimes co-surfactants, to reduce particle size. They also exhibit greater stability than other nanoparticles, with the potential to be stored in aqueous form for over three years[74]. The crystal structure of SLNs, often described as a "brick wall," allows drugs to be embedded within similar lipid compartments, enabling controlled release even after administration[75].

Recent dermatopharmacokinetic studies have shown that API-loaded SLNs achieve twice the drug penetration in the epidermis and five times higher penetration in the dermis compared to free drugs[76]. Additionally, studies have demonstrated that noscapine-loaded SLNs significantly improve psoriatic skin conditions in vivo compared to control drugs[77].

Nanoemulsion

A nanoemulsion is a heterogeneous system consisting of two immiscible liquids—water in oil (W/O), oil in water (O/W), or double emulsions (O/W/O and W/O/W)—stabilized by surfactants [78]. Nanoemulsions serve as delivery vehicles for lipophilic active compounds, essential oils, and natural bioactive compounds. Surfactants reduce the interfacial tension between these liquids, with common options including Tween 80, Span 80, phospholipids, and polymers. Non-ionic surfactants are preferred as they cause less local irritation and have a lower critical micelle concentration (CMC), making them more stable for drug delivery systems[79, 80]. Co-surfactants, such as C3-C8 chain alcohols, further stabilize the colloidal system and improve drug stability.In an O/W nanoemulsion, the inner layer contains oil, which solubilizes hydrophobic drug molecules, while the outer layer is water, with surfactants stabilizing both media[81]. The oil phase may consist of long-chain triglycerides (LCT), medium-chain triglycerides (MCT), or short-chain triglycerides (SCT), which enhance drug bioavailability and offer therapeutic effects[82]. However, nanoemulsions are sensitive to parameters such as pH and temperature, which can lead to instability issues like coalescence and flocculation[83]. Optimizing the manufacturing process is essential to avoid these problems.

Nanoemulsions are created through both high- and low-energy methods. High-energy methods commonly use high-pressure ultrasonication to break droplets mechanically, while phase inversion composition (PIC) and phase inversion temperature (PIT) methods are more energy-efficient and maintain constant temperature. For effective formulation, drug solubility, surfactant concentration, and processing time must be carefully established, and further optimization helps prevent formulation instability.Recent research showed that a nanoemulsion containing hymoquine, fulvic acid, and kalonji oil had a greater therapeutic effect on psoriatic skin in BALB/c mice compared to the free drug[84]. Another study found that MTX tablets combined with olive oil had higher penetration and drug-loading efficiency, leading to a 91% reduction in PASI scores in a rat model of imiquimod-induced psoriasis[85]. Nanoemulsions are highly recommended for incorporating natural substances that are not water-soluble, such as curcumin, resveratrol, and thymoquinone, which are beneficial for psoriasis therapy. These compounds, when combined with oleic acid and surfactants, improved psoriasis lesions in a mouse model by enhancing drug penetration[86].

Liposomes

Liposomes are multilayer vesicles that are colloidal, nano- or microsized, and typically have a diameter of 50 to 1000 nm. They are composed of an outer lipid bilayer and an interior aqueous layer. They can take on multilayered, unilamellar, or multivesicular forms[87, 88]. Thin-film hydration, solvent evaporation, detergent dialysis, reverse-

phase evaporation, high-pressure homogenization, and ultrasonication are frequently employed to prepare liposomes[87]. These vesicles are appropriate for use as topical therapies for a variety of skin conditions due to their non-toxic, biodegradable nature, which enhances drug absorption, permeability, and the stability of bioactive compounds[89].

Liposomes are not without their disadvantages, such as the potential for drug leakage, high manufacturing costs, brief half-life, and solubility issues[90]. Depending on factors such as liposome size, low concentration, presence of oxidizing agents, and fatty acid chain modification, the phospholipid layer of liposomes can endure hydrolysis and oxidation. The stability of the liposome is significantly influenced by the size of the liposome. The use of cationic lipids for gene delivery in liposome formulation has seen promising results in the treatment of psoriatic skin in recent modifications[91]. In a recent study, it was shown that a cationic liposomal gel reduced cutaneous lesions in an imiquimod-induced psoriatic plaque model and decreased critical cytokine levels, such as tumor necrosis factor-α, IL-17, and IL-22[92].

Niosomes

Niosomes serve as an alternative to liposomes, aimed at resolving challenges related to liposome stability and cost-effectiveness. Niosomes possess a liposome-like architecture, consisting of a non-ionic surfactant and a lipid bilayer, exhibiting biocompatible characteristics[93]. Preparation methods include reverse-phase evaporation, thin-film hydration, and microfluidization. Maintaining a hydrophilic-lipophilic balance (HLB) between 4 and 8 is essential for the formulation of stable niosomes[94]. Niosomes demonstrate superior chemical stability and improved drug penetration relative to liposomes; nevertheless, they have not attained Generally Recognized As Safe (GRAS) status, necessitating additional research [95].

A recent study investigated imiquimod-induced psoriasis in mice treated with clobetasol propionate-loaded niosomes. The findings indicated an improvement in the PASI index, a fivefold increase in drug deposition, and greater efficacy compared to a commercial cream[96].

Table 2:- Nanocarrier-based system for psoriasis treatment.

Lipid carrier	Anti-psoriatic agent	Method	Comment	Reference
Solid lipid nanocarriers (SLNs)	Methotrexate andetanercept	Hot Ultrasonication	No toxicity to human fibroblasts and keratinocytes and extended drug release in vitro.	[97]
	Cyclosporine	Micro-emulsion	Reduced side effects and systemic absorption while raising skin layer concentration in vitro.	[98]
	Thymoquinone (Nigellasativa extract)	Melt-emulsification andultrasonication	Reduced erythematous, oedematous, and thickening PASI score symptoms and a low skin irritation score	[99]
	Tacrolimus	Emulsification and low temperaturesolidification	Enhanced in vivo skin layer penetration and increased ex vivo skin penetration value	[100]
Nanostructured lipid carriers (NLCs)	Methotrexate	Solvent diffusion	Significantly increased drug deposition and trapping efficiency were observed, although no erythema was detected at the principal skin irritation index.	[101]
	Mometasone furoate	Micro emulsion	Increased skin deposition, minimal	[102]

			initial skin irritation index, and overall in vivo clearance of parakeratosis	
	Dithranol	Hot melt homogenization	Reduction in symptoms as shown by the PASI score and an enzyme-linked immunosorbent assay, accompanied with reduced disease severity and decreased levels of cytokines such as TNF-a, IL-17, IL-22, and IL-23.	[103]
	Methotrexate	Solvent diffusion	Reduction in PASI score, oxidative stress, inflammatory cytokines including TNF-a, IL-1b, and IL-6, and IMQ-induced histopathological alterations in murine ear models; enhanced therapeutic response and reduced local adverse effects in vivo	[104]
Liposomes	Cyclosporine	Thin-film hydration	displayed a safe profile when administered to patients with persistent plaque psoriasis	[105]
	Psoralen	Cationic liposomes by thin-film hydration method	A multiple-fold gain in the reduction of psoriasis plaque symptoms and psoriatic cytokine levels (TNF-a, IL-17, and IL-22) was demonstrated in skin penetration research.	[106]
	Cyclosporine	Cationic liposomes byethanol injection method	Decreased psoriatic cytokine levels (TNF-a, IL-17, and IL-22) and plaque symptoms, as well as exhibited shear-thinning behavior.	[92]
	Zedoary turmeric oil	Ethanol injection	Significant psoriasis that is drug-dependent in vivo and exhibits high drug penetration and retention in vitro	[107]
	trans-Retinoic acid andbetamethasone	Thin-film hydration	A cellular uptake on HaCaT cells that is time-dependent and simultaneously reduces in vivo cytokine levels (IL-6 and TNF-a) and epidermal thickness	[108]
	Liposomal spherical nucleic acids (L-SNA)	IL-17A receptor targeting	Decreased markedly in the PASI score and	[109]

			epidermal thickness on imiquimod (IMQ)-treated mouse skin, as well as in the expressions of TNF-a, phosphoinositide 3-kinase (PI3K), defensin, beta 4 (DEFB4), IL17RA, and IL-17C in psoriatic 3D rafts	
	Bexarotene (retinoid Xreceptor)	Thin-film hydration	Significantly decreased the PASI score and epidermal thickness on imiquimod (IMQ)-treated rat skin. There were also changes in the levels of TNF-a, PI3K, DEFB4, IL17RA, and IL-17C in psoriatic 3D rafts.	[110]
Niosomes	Diacerein	Thin-film hydration	Notable skin penetration in the dermal and epidermal layers in vitro, which was shown to be stable at low temperatures	[111]
	Acitretin	Thin-film hydration	Enhanced ex vivo permeability test and pharmaceutical deposition in HaCaT cells	[112]
	Celastrol	Thin-film hydration	Decreased erythema and in vivo desquamation of psoriatic manifestations	[113]
Nanoemulsions	Cyclosporine	Phase inversioncomposition	Elevated efficacy in vitro and improved skin hydration in vivo	[114]
	Tacrolimus	Spontaneousemulsification	The prolonged-release pattern and skin absorption were enhanced in vitro, while there was a reduction in blood cytokines and an amelioration of psoriasis symptoms in vivo.	[115]
	Methotrexate	Low energy emulsification	Augmented anti-psoriatic efficacy, proficient skin retention, and reduced serum and tissue accumulation in vivo, along with enhanced skin permeability and retention in deeper dermal layers ex vivo	[116]
	Curcumin (naturalcompound)	Low energy emulsification	Enhanced dermal absorption significantly and expedited recovery	[117]

			in psoriatic conditions.	
	Imiquimod and curcumin	Low energy emulsification	Skin permeability was enhanced, and psoriatic activity rapidly resolved.	[118]

Current Treatment challenges

The effectiveness of the drug delivery system is a critical consideration in formulating psoriasis treatments, particularly in ensuring that therapeutic agents reach the affected areas beneath the cuticle and epidermis. Psoriatic skin exhibits reduced levels of free fatty acids, moisture, and overall water content in comparison to healthy skin. The abnormal thickening of the stratum corneum (SC) resulting from keratinocyte proliferation presents a considerable obstacle to drug penetration. Ensuring that therapeutic agents achieve effective concentrations at the target site for an extended duration is a significant challenge for conventional formulations.

Conclusion:-

Psoriasis is a persistent disorder; nevertheless, the quality of life for sufferers can be markedly enhanced via proficient care of its symptoms. Considering the difficulties of medication penetration, it is essential to optimize epidermal absorption while reducing systemic absorption to prevent unwanted effects. The hyperkeratinized, thicker epidermis in psoriatic skin complicates targeted medication distribution. Innovative drug carriers, including liposomes, solid lipid nanoparticles (SLN), and niosomes, have demonstrated potential in surmounting formulation obstacles and improving therapeutic effectiveness.

The integration of SLN with sophisticated nanodevices may be a feasible treatment approach for patients with psoriasis, enabling appropriate management of their illness. Recent studies indicate that nanocarriers provide encouraging outcomes in various treatment stages, enabling a more individualized strategy for psoriasis therapy with increasing use. Consequently, nanocarrier-based approaches may soon provide a significant remedy for this problem.

CRediT authorship contribution statement

Esrat Jahan Rupa: Conceptualization,Formal analysis, Writing – original draft. Soo Jung Park, Ji Yong Jang, Hana Cho, Il-Joo Jo: Methodology, Validation, Formal analysis. Hyung-Jin Kim: Conceptualization, Writing – original draft, Writing-review & editing, Supervision. Gabsik Yang: Conceptualization, Writing-review & editing, Supervision, Funding acquisition. All authors read and approved of the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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