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Nano-Based Drug Delivery System for Psoriasis Management: A Comprehensive Review

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Abstract

Psoriasis is an autoimmune and inflammatory conditions and characterized by red, inflammatory plaques and macules that develop due to poor differentiation and increased proliferation of keratin-produced by epidermal cells. Pathophysiology, including as immune cells, genetic predisposition, antimicrobial peptides, and non-coding RNAs. The traditional prescription drugs are not enough to control the condition because they have many drawbacks. They are link to large dosage of drugs and the potential for toxicity and the adverse effects, which can result in long-term poor patient compliance. Nanotechnology-based approaches aiming at a greater therapeutic effect in order to get beyond the aforementioned restrictions and allow tailored pharmaceuticals treatments for psoriasis and reduced toxicity in psoriasis topical treatment. This comprehensive review included the type, onset of disease and pathophysiology of psoriasis, conventional treatment, the need for nano based drug delivery systems for the treatment of psoriasis and also described the nanobased drug delivery approaches such as lipid based nanocarriers: - nanoemulsion, liposomes, ethosomes, transferosomes, cerosomes, NLC, SLN and polymer based nannocarriers such as: - hydrogels, nanosphere nanocapsules, dendrimers and also metallic nanocarriers: - gold and silver nanoparticles. The review was prepared through literature search using the databases ScienceDirect, PubMed, and Google Scholar. The review article offered information on the utilization of nano carriers while talking about the drawbacks of traditional psoriasis treatment. Throughout the skin's penetration and permeation process, the biodegradable nanoformulations usually result in targeted drug administrations. Additionally, it controls drug release, avoids toxicity, and protects labile compounds from degradation.

Keywords: Psoriasis, Nanotechnology, Traditional medicines, Nanocarriers

1. Introduction:

Psoriasis is a common autoimmune and inflammatory condition and characterized by red, inflammatory plaques and macules that develop due to poor differentiation and increased proliferation of keratin-produced by epidermal cells. These plagues are frequently accompanied by silvery scale.[1] Psoriasis prevalence varies ranging from 0.27% to 11.4% depending on hereditary variables, sex, age, environment, ethnicity and region. Globally, it impacts about 64.6 million people.[2] This immune- mediated disease results in persistent inflammation that affects not just the skin but also the kidney, blood vessels, joints, and metabolic syndrome. About ≥ 40% of psoriasis patients may have psoriatic arthritis, which can cause joint degeneration and deformities that significantly impair physical performance and quality of life. For possible patient care, early diagnosis and therapy actions are essential. Chronic relapse is associated with a greater physical and psychological burden, which results in depression and a lower quality of life.[3]

Numerous elements are involved in its pathophysiology, including immune cells, genetic predisposition, antimicrobial peptides, and non-coding RNAs. T lymphocyte activation is a hallmark of psoriasis, an immune-driven illness. By producing interleukin-23 (IL-23), dendritic cells, which trigger the activation T helper 1 (Th17) and Th17 cells. Th17 cells produce IL-22, IL-17A, and IL-17F, Th1 cells produce interferon-ϒ (IFN-ϒ) and tumor necrosis factor–α (TNF-α). The proliferation of keratinocytes is significantly stimulated by these inflammatory cytokines. Increased infiltration cells are specifically caused by TNF-α.[4]

Psoriasis is currently managed with the goals of reducing symptoms, enhancing quality of life, and halting the disease's progression.[5] This method included systemic drugs, topical treatments, phototherapy, and biologic medicines that target particular immune pathways. Psoriasis treatments have advanced however, there are still a number of issues and unmet demands.

The broad usage and effectiveness of several medicines are restricted by side effects, treatment resistance, long-term safety concerns, and expensive prices. The requirement for the individualized and customized techniques in the management of psoriasis is highlighted by the variation in treatment responses among individuals.[6] Psoriasis is a complex condition; traditional prescription drugs are not enough to control the condition.[7] They have many drawbacks. They are linked to large dosages of drugs and the potential for toxicity and adverse effects, which can result in long-term poor patient compliance. Additionally, there are few treatments accessible because of inadequate drug penetration and absorption and they are typically are unable to fully treat the disease. Although, immunosuppressants and biological agents with immunosuppressive properties work well as systemic therapies for moderate to severe psoriasis, these drugs have limits when used orally because they are linked to a rise in infection and detrimental consequences on the liver and heart Therefore, there is a need for innovative therapeutic approaches.[8]

Formulation based on nanotechnology is now becoming more useful in the field of dermatology. Due to improved surface area, nano formulations generally vary in small size from 10 to 100 nm; the smaller-sized formulation increases the bioavailability and solubility of drug delivery and has been recommended as the best drug delivery method because it offer a safe, targeted, and controlled release dosage form while also assisting in resolving the problems with conventional dosage forms.[9] Now all the studies have focused on nanotechnology-based approaches aiming at a greater therapeutic effect in order to get beyond the aforementioned restrictions and allow tailored pharmaceuticals treatments for psoriasis and reduced toxicity in psoriasis topical treatment. The review article offered information on the utilization of nanotechnology while discussing the limitations of conventional psoriasis management. The biodegradable nanoformulations typically lead to targeted medication administrations throughout the skin's penetration and permeation process. That also prevents toxicity, regulates medication release, and shields labile materials from deterioration.[10]

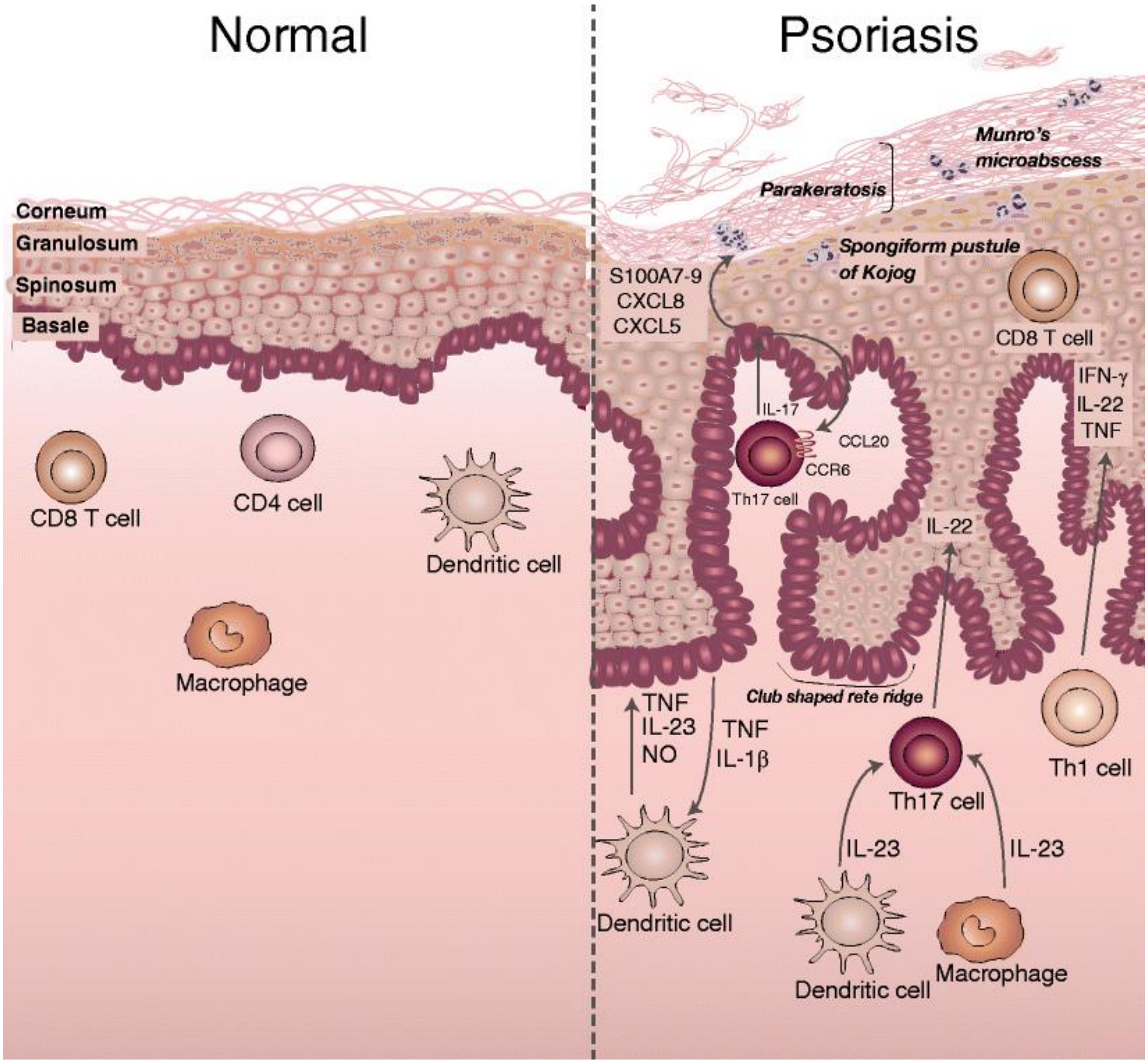

Figure 1: Comparison between normal skin and psoriasis skin. [111]

1.1 Types of psoriasis: Psoriasis is clinically classified into two groups:

1.1.1Non-pustular psoriasis:

1.1.1.1 Psoriasis vulgaris: Psoriasis vulgaris, the most common clinical form of psoriasis, accounts for around 85-90% of cases.[11] It is identified by the development of skin plaques. These plaques typically show up as red swollen spots on the knee, nails, elbow, etc. Over these plaques, silvery-white scales appear, which are made up of dead tissue. Plaque shedding, inflammation, dryness, and discomfort are among the symptoms. Additionally, it involved increased keratinocyte accumulation and aberrant differentiation.[12]

1.1.1.2 Guttate psoriasis: ''Guttate'' means ''drop'' in Latin. Small, red scale-like, tear-shaped droplets with silvery scales that occur on the arms, legs, and midsection of the body are the hallmark of guttate psoriasis. It typically affects those under 30. It usually follows an acute tonsil or pharyngeal β haemolytic

G.

Figure 2: A: Psoriasis vulgaris, **B:** Guttate Psoriasis, **C:** Inverse Psoriasis, **D:** Erythrodermic Psoriasis, **E:** Palmoplantar psoriasis, **F:** Psoriatic arthritis, **G:** Generalised Pustular Psoriasis.[110]

1.1.1.3 Inverse Psoriasis: arthritis Flexural psoriasis, also known as inverse psoriasis. Bright red, glossy lesions that develop in the skin folds like the armpit, groin area, and beneath the breast are its defining feature. Sweat and friction exacerbate the illness, which is also susceptible to fungal infection.[13]

1.1.1.4 Erythrodermic Psoriasis: This type of psoriasis affects around 80% of the body's surface.[11] This is a highly uncommon form of psoriasis that impacts just 3% of those who have the condition. It can manifest in two ways: the first is progressive chronic plaque psoriasis, which can become widespread and merged, and the second is erythroderma, which may disrupt the body's ability to regulate temperature, resulting in hypothermia and extensive inflammation across the skin.[13]

1.1.1.5 Palmoplantar psoriasis: Typically, this form of psoriasis symmetrically affects the palms of the hands and the soles of the feet, with the region being impacted more often than the hyposthenia region. While erythema is not always present, when it does occur, it manifests as a pinkish-yellow patch. The primary lesions are squamae. The presence of thick squamae can resemble keratoderma. The phenomena are negative.[14]

1.1.1.6 Psoriatic arthritis (PsA): It is a chronic inflammatory joint condition linked to psoriasis. The clinical characteristics consist of both skin and synovial inflammation, immune cell infiltration, and hyperplasia of the synovium, resulting in discomfort, tenderness in the joints, and swelling.[15] This illness is also a significant contributor to cardiovascular disease, particularly prevalent among elderly individuals[16]. TNF-α inhibitors are the most effective treatment option available for this condition. Additional treatment alternatives include anti- inflammatory drugs and disease-modifying antirheumatic drugs.[17]

1.1.2 Pustular Psoriasis: It is marked by elevated lesions containing non-contagious pus, or pustules. These pustules may be localized often on the hands and feet, or they can appear more broadly with scattered patches across various areas of the body.[11]

1.1.2.1 Generalized Pustular Psoriasis: This is a rarely encountered type of psoriasis characterized by the presence of pustules. It most commonly affects younger individuals. It can occur on its own or as a complication of psoriasis vulgaris. Particularly after sudden withdrawal from systemic steroid treatment, exposure to triggering factors, hypocalcemia, or aggressive treatment, the onset is abrupt and occurs on a red background, accompanied by general symptoms like high fever, fatigue, and joint pain.[18]

1.1.2.2 Impetigo herpetiformis: This is a less commonly observed form of psoriasis, also referred to as generalized pustular psoriasis of pregnancy. It is defined by red, inflamed patches that are covered with pustules, which emerge and spread from the flexural areas and tend to cluster together.

1.1.2.3 Localised pustular psoriasis: Palmoplantar pustulosis consists of two types: Barber's pustular psoriasis and Acrodermatitis continua of Hallopeau.[18]

- Pustular psoriasis of the Barber variety: It is a long-lasting and recurring condition that is more commonly found in women. It typically presents as pustules measuring 2-4 cm that are localized on the palms and soles, particularly in the reddish area of the thenar and hypothenar regions.[19]
- Pustular Acrodermatitis continua: Also known as Hallopeau disease, is a skin condition that progressively worsens from the proximal areas. It is marked by sterile pustular lesions on the fingers and toes, which can lead to the loss of nails and the distal phalange in more severe instances.[20]

1.2 Onset of disease

The psoriasis is triggered by the various factors:

1.2.1 Trauma: Psoriasis can be triggered by different types of physical, chemical, and inflammatory disruptions to the skin. Such disruption included abrasions, cuts, frictions, shaving, etc.[21]

1.2.2 Infection: Certain toxins, like those from bacteria that stimulate T-cells, often lead to the expression of cutaneous lymphocyte antigens, resulting in the development of psoriatic lesions. The prevalence of disease caused by infections varied between 15% and 76%.[22]

1.2.3 Obesity: Certain research studies have indicated that obesity may be a contributing factor to disease. Additionally, some research suggests that the proliferation of adipocytes and the release of pro-inflammatory cytokines are linked to psoriasis. A survey carried out by the Nurse Health study Found a significant correlation between psoriasis and a rise in body mass index.[23]

1.2.4 Stress: It has been suggested that stress contributes to the illness. Typically, there is less than a month between the start of the illness and a stressful event. The process behind this can be linked to the alteration that takes place during the management of stress and catecholamine.[24]

1.2.5 Smoking: Dose- response relationships show that smokers have a higher incidence of the disease. Women are more likely than men to have the illness. The risk is 1.7 times higher for men and 2.5 times higher for women than for non-smokers.[25]

1.2.6 Endocrine factor: Psoriasis is known to be directly impacted by a number of hormones, including thyroid hormones, prolactin, and androgen. Menopause and puberty are the two main stages of disease onset.[26] According to a study roughly 65 women, 40% of pregnancies are unaffected by the disease.[27]

1.3 Pathophysiology:

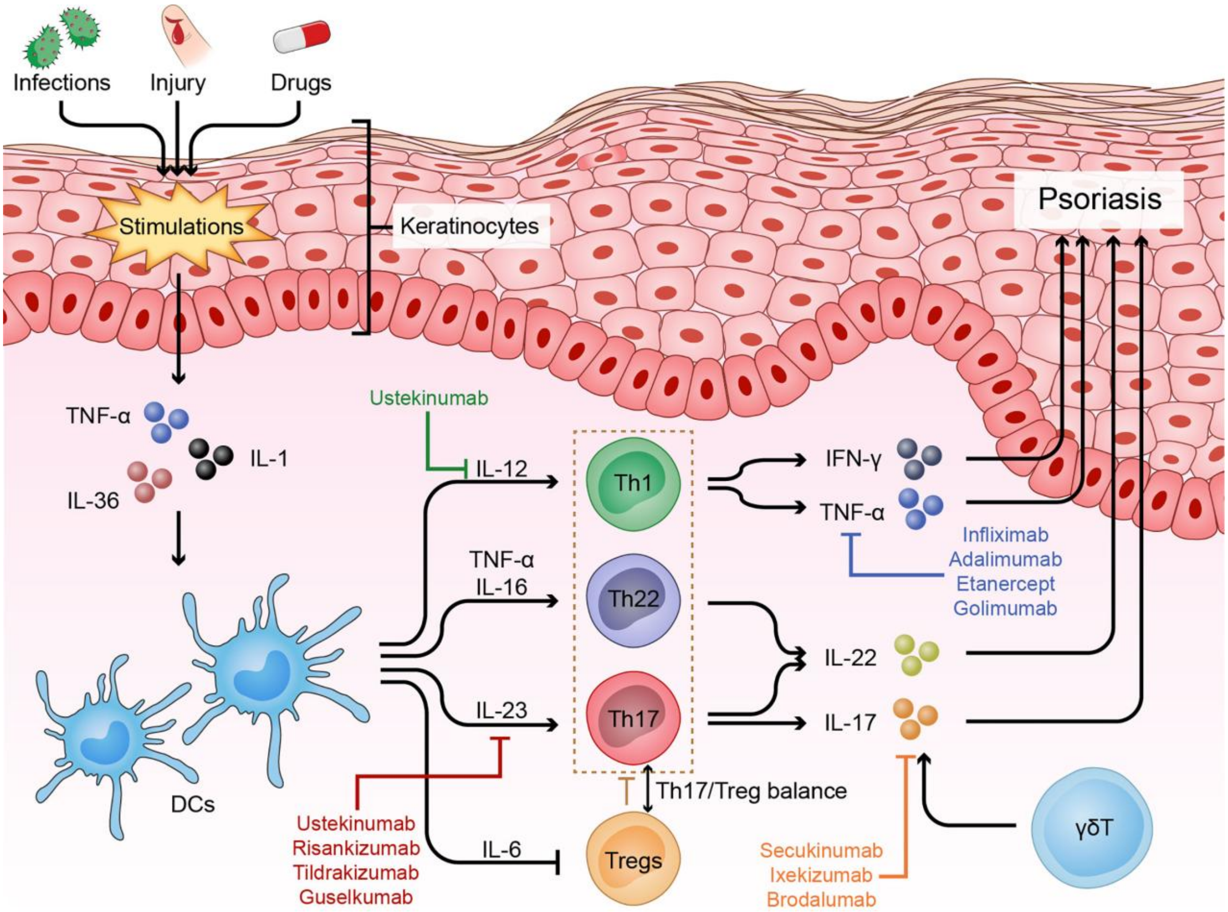

Figure 3: Pathophysiology of Psoriasis.[112]

1.3.1 Cell signaling pathway:

The development of psoriasis is associated with T cell immunity. The disease begins when antigen-presenting cells (APCs) in the skin, such as dendritic cell in the dermis and Langerhans cell in the epidermis, are activated by external and internal stimuli, which can include skin trauma or infection. Once activated, these APCs travel from the skin to adjacent lymph nodes, where they present antigens to naive CD45Ra + T cells marking the start of T cell activation. Subsequently, T cells move into the affected skin and secrete cytokines that trigger keratinocyte overproduction, disrupt normal cellular differentiation, and maintain inflammatory responses through positive feedback mechanisms in cell signaling. This sequence of events leads to the persistent development of psoriatic skin lesions.[28]

1.3.1.1 The IL-23/T Helper Cell (Th17) Axis:

In response to pathogenic signals, myeloid dendritic cells (DCs) activate and release a high number of inflammatory cytokines, including TFN-α and IL-6. Theses cytokines subsequently enhance the production of IL-12 and IL-23.[29] In response to II-23, Th17 cells generate elevated amount of IL-17, which influence keratinocytes, resulting in increased epidermal growth, activation of innate immune reaction, recruitment of leukocytes to the skin, and enhanced the production of cytokines like IL-1β, IL-6, and IL-8.[29] Inhibiting IL-17 can interrupt this detrimental cycle, thereby effectively diminishing inflammation and improving the clinical symptoms of psoriasis[30].

1.3.1.2 Macrophage Inflammatory Protein 3 Alpha/Chemokine (C-C Motif) Ligand 20-C-C Chemokine Receptor 6 (MIP-3α/CCL20-CCR6) Pathway:

The CCL20/CCR6 pathway has been recognised for its role in inflammation for a long time. CCL20, also referred to as MIP-3α, serves as a chemotactic agent that is essential for the movement of IL-17A- producing T cells from the bloodstream to the skin through its interaction with the CCR6 receptor during the development of psoriasis.[31] In psoriasis skin lesions, the activation of keratinocytes results in the increased expression of CCL20, which enhances its binding to CCR6. This heightened interaction draws in additional Th17 cells to the affected area, which secrete cytokines such as IL-17, further fueling the IL-23/Th17 pathways and sustaining the inflammation response in psoriasis.[32]

1.3.1.3: Nuclear Kappa-B (NF-κB) Signalling Pathway:

Moreover, the Caspase Recruitment Domain 14 (CARD14) gene, also referred to as CARMA2, is found to be highly expressed in the skin affected by psoriasis and has been demonstrated to interact specifically with BCL10, a protein that is known to enhances apoptosis and NF-κB activation. When introduced into cells, CARD14 triggers NF-κB activation and promotes the phosphorylation of BCL10.[33]

1.3.1.4 JAK/STAT Signaling Pathway:

STAT3 plays a crucial role in controlling cell proliferation and programmed cell death, and it is vital for the differentiation of Th17 cells, which are a subset of T cells that produce IL-17.[34] Tyrosine kinase 2 (TYK2) is an important regulatory protein that has gained attention as a potential therapeutic target due to its crucial involvement in facilitating pro- inflammatory and immune activating signaling cascades triggered by cytokines such as IL-12, IL-23/IL-17, and type interferon. To prevent unintended effects on other members of the JAK family, scientists are concentrating on TYK2's regulatory domains. By employing small-molecule ligands to target this specific domain, it becomes feasible to selectively block TYK2 signaling while leaving other JAK pathways unaffected.[35]

1.3.1.5 P13K/AKT Signaling Pathway:

The P13K/AKT pathway is crucial for inflammatory skin disorders, especially regarding its downstream target, mTOR, which is vital to several prevalent inflammatory skin diseases. The activation of mTOR leads to an increase in keratinocyte proliferation and a reduction in their differentiation, which contributes to the symptoms observed in psoriasis. Conversely, the activation of FoxO may serve as a potential prognostic marker for the progression of psoriasis in patients. Among the FoxO family, FoxO3, which is extensively expressed in various human organs and tissues, appears to be a promising therapeutic target. [36,37]

2. Current Therapy for the Treatment of Psoriasis

Psoriasis can be managed through different traditional methods, including topical treatment, oral medications, biologic therapies, and injectable options. Additionally, phototherapy has been utilized to offer symptomatic relief.

2.1 Topical treatment: Topical management is essential in the treatment of psoriasis. Approximately 70 to 80% of individuals with mild to moderate psoriasis can achieve effective control with topical therapies. A global survey indicates that 75% of patients with moderate to severe psoriasis were undergoing topical treatment.[38]

Table 1: Topical Agents with their mechanisms and Adverse effects

Drug	Mechanism	Adverse Effect	Ref.
Corticosteroids	Corticosteroids exhibit vasoconstrictive, antiproliferative, and anti-inflammatory properties. They attach to the intracellular corticosteroid receptor and influence the transcription of various genes, especially those that encode for proinflammatory cytokines. e.g. *betamethasone dipropionate, momentasone furoate, clobetasol propionate.*	Skin atrophy striae, telangiectasia, or secondary infection	39
Vitamin D analogues	These analogues prevent cell growth and promote differentiation. Furthermore, vitamin D analogs reduce the production of inflammatory cytokines in lesions associated with psoriasis. e.g. *calcitriol, calcipotriol*	Skin irritation and do not apply on eyes, nose, and mouth.	40,13
Dianthrol	Anthracyclines disrupt mitochondrial function by damaging their structure, which leads to apoptosis.	Skin irritation and also have stain properties.	41
Retinoid	A potential mechanism involves blocking the excessive growth and maturation of keratinocytes. *e.g. tretinoin.*	Scaling, burning, and erythema.	42
Tacrolimus	It inhibits its phosphate activity and lead to the suppression of T-lymphocyte activation.	Minor skin irritation	43
Keratolytic Agents:	It is acts by desquamation to corneocyte e.g. *salicylic acid, uboutrea, olive oil.*	Skin irritation, burning	44

2.2 Oral Systemic Treatments: Oral medication frequently utilized for managing the moderate to severe plaques psoriasis. The oral treatments choices for plaque psoriasis consist of MTX, apremilast, acitretin, and cyclosporine.[45] The side effects associated with oral therapies are greater as compared to topical treatments. While systemic treatments can help in treating psoriasis, but a considerable lot of the medication can cause genuine reactions.

Table 2: Oral systemic agents with their mechanisms and adverse effects

Drug	Mechanism	Adverse Events	Ref.
Methotrexate	It is an inhibitor of dihydrofolate reductase, which is found to be necessary for the synthesis of purine and pyrimidine in DNA production. It also works as an anti-proliferative and immunosuppressive drug.	Side effects include hepatotoxicity, nausea, diarrhoea, and vomiting	46, 47
Cyclosporine	Cyclosporine is a calcineurin inhibitor that acts as an immunosuppressant by suppressing T cells, and it is utilized for patients with moderate to severe psoriasis.	It can cause kidney problems, high blood pressure, and high cholesterol.	48,13
Apremilast	Apremilast is an oral inhibitor of phosphodiesterase 4 (PDE4). PDE4 acts as a T-cell inhibitor, reducing the synthesis of inflammatory cytokines.	Side effects include nausea, vomiting, and headache.	49
Acitretin	It functions by regulating the growth and development of skin cells while also decreasing inflammation.	Typical side effects may include chapped lips and skin, hair loss, and elevated liver enzyme levels.	50, 51
Fumaric Acid Esters	These exert anti-inflammatory antioxidative, and antiproliferative effects.	The rare side effects noted during the treatment consist of swelling in the lower limbs, headache, and esters in the management of psoriasis	52

2.3 Biologics and Parenteral Treatments: In the past few years, the development and authorization of biological therapies for managing moderate to severe psoriasis and psoriatic arthritis have garnered considerable interest. There are four categories of biologic therapies available for psoriasis treatment: IL-12 /23 inhibitors, TNF blockers, IL-23 inhibitors, and IL-17 inhibitors.[53] Biologics consist of designed monoclonal antibodies and fusion proteins that can inhibit particular cytokines and their receptors linked to psoriatic inflammation. These substances function by targeting and neutralizing proinflammatory cytokines associated with psoriasis. One more function is that biologic therapies need only four injections annually during the maintenance stage of treatment. [54]

Table 3: Biological Treatment for psoriasis management[55]

Class	Drug	Description
IL-17/IL-23 Inhibitor	Ustekinumab	It is used to treat plaque psoriasis and psoriatic arthritis by acting against both IL-23 and IL-12. Its dosage is determined by weight.
IL-17 Inhibitors	Secukinumab	It is an IgG monoclonal antibody that is usually used for psoriatic arthritis and severe scalp psoriasis. People with inflammatory bowel disease should not use it.
	Ixekizumab	It is used to treat psoriatic arthritis and plaque psoriasis by preventing cytokines from interacting with their target receptor.
	Brodalumab	It is recommended for psoriasis with plaque. It is frequently linked to suicidal tendencies.
TNF-α Inhibitors	Etanercept	It is used to treat children's chronic plaque psoriasis and adult plaque psoriasis. It should not be used if you have heart failure.
	Adalimumab	This antibody is monoclonal. It is used to treat plaque psoriasis, psoriatic arthritis, and nail psoriasis by interacting with the host ligand and preventing interaction with the TNF receptor.
	Infiximab	Additionally, it is a monoclonal antibody used to treat persistent plaque psoriasis and psoriatic arthritis. It is linked to the risk of cancer and infection.
	Certolizumabpegol	It is PEGylated TNF-α antibody that is used to treat psoriatic arthritis and moderate to severe plaque psoriasis.
Selective IL-23 Inhibitors	Guselkumab	It is used to treat plaque psoriasis and psoriatic arthritis by acting against both IL-23 and IL-12. Its dosage is determined by weight.

2.4 Phototherapy: Phototherapy is an age-old technique that uses artificial sources to apply controlled and repeated UV light exposure to the skin. Dermatosis and other skin conditions are treated by the endogenous skin chromophore, which absorbs this ray. UV-A and UV-B.[56] Moderate to severe psoriasis has been treated with phototherapy, which includes PUVA, broadband UV-B, and narrowband UV-B is more effective and has a better safety profile than broadband UV-B, it is chosen. Because UV-B phototherapy inhibits DNA synthesis, keratinocytes undergo apoptosis and produce fewer pro-inflammatory cytokines.

2.4.1 PUVA (psoralen + UVA radiation): Applying UVA radiation with a wavelength between 320 and 400 nm is deemed ineffectual since it does not aid in the treatment of dermatosis. When a photosensitizing drug and radiation are combined, such as psoralen and UVA (PUVA) radiation, psoriasis can be effectively treated. As a result, cytokine release is suppressed and epidermal proliferation is decreased.

2.4.2 UVB Radiation: When compared to UVA radiation, UVB light with a wavelength between 290 and 320 nm exhibits broadband or narrowband beams for phototherapy; these radiation treatments influence cellular processes. When compared to broadband UVB radiation, narrowband radiation is more effective and causes less cutaneous symptoms like burns and erythema.[57]

3. Nanotechnology-Based Drug Delivery System:

Psoriasis is a chronic inflammatory skin illness characterized by erythematous plaque, immune cell infiltration, and hyperproliferation of keratinocytes. It is extremely difficult to treat psoriasis effectively. The fact that traditional drug do not work highlights the need for more advanced therapeutic methods. Frequently have short half-lives, poor skin penetration, low drug bioavailability, and systemic side effects. Using nanocarrier technologies, which reduce systemic exposure while delivering tailored medication directly to the affected skin layers, is one possible strategy in the area. In a preclinical animal model of psoriasis, these nanoscale carriers have been extensively investigated.[58] There has been a lot of scientific interest in the topical delivery of antipsoriatic medications employing nanocarriers such as liposomes, niosomes, and polymeric nanoparticles.[59] This section provides a comprehensive assessment of the main types of nanocarrier system being studied for the treatment of psoriasis, with focus a on their advantages, mechanism of action, and outcomes from animal trials.[6]

3.1 Lipid-Based Nanocarriers: Lipid-based nanoparticles are a very versatile family of nanocarriers that are widely used in pharmacology and medical research.[60] They might encompass a variety of therapeutic agents such as monoclonal antibodies, tiny compound, and nucleic acids.[61] Lipid nanoparticles of the second generation are called nanostructured lipid carriers. Their nanoscale size allows them to penetrate deeper into the skin layer.[62] The medicinal molecule can be shielded by NLCs from the deterioration processes that are dependent on the external environment, such as oxidative, chemical, or physical degradation.[63]

3.1.1 Nanoemulsion: A nanoemulsion is an isotropic heterogeneous system that appears translucent or transparent. It is made up of two immiscible liquids (oil and water) with droplet sizes between 20 and 400 nm that are stabilized by a surfactant interfacial layer. According to the report, there are three different kinds of nanoemulsion: bicontinuous, water-in-oil, and oil-in-water.[64] Compared to traditional formulations and even some cutting-edge delivery technologies like microemulsion, it provides a number of advantages. These benefits include ultrafine droplet size with a large surface area, high loading capacity and entrapment efficacy for lipophilic drugs, kinetic stability, the ability to solubilize hydrophilic and lipophilic drugs, a high skin penetration rate, prolonged drug release, and targeting the site of action.[65] Khan *et al.* suggested a combined treatment using TQ and FA, incorporating kalonji as the oil phase and tween 80 as a surfactant, which provides efficient absorption through the skin FTQ-NEG improved psoriasis symptoms. This approach offered a personalized and appropriate safety profile, with good patient compliance. Long-term therapy is probably possible because of the reduced risk for irritation from the formulation. This promotes the formula's potential for future use and commercialization.[66]

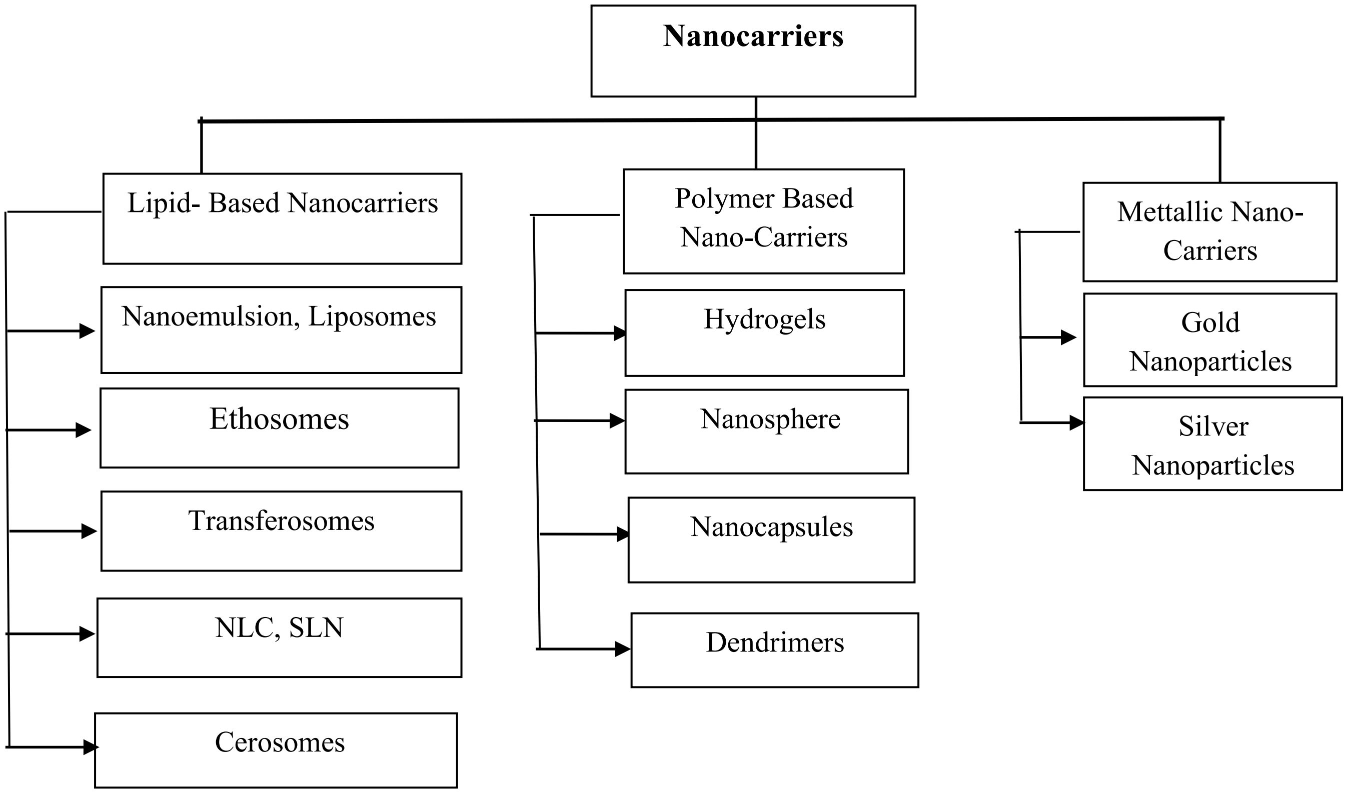

Figure 4: Classification of Nano-Carriers.

Rashid *et al.* reported a topical methotrexate-loaded almond oil-based nanoemulsion formulation for the treatment of psoriasis. Methotrexate-loaded almond oil nanoemulsion possesses high skin penetration, and drug entrapment effectiveness, and reduces skin irritation. These results imply that the MTX NE formulation is useful in treating psoriasis and may reduce psoriasis symptoms.[67] Bhardwaj *et al.* developed a topical nanoemulgel formulation containing methoxsalen and babchi oil that significantly enhanced the effect of imiquimod-induced psoriasis in rats. The nanoemulgel formulation enabled the medication to permeate deeper into the skin tissue in a controlled manner. It also minimized the side effects associated with oral and systemic administration.[68] Alam *et al* formulated babchi oil nanoemulsion-based hydrogel for topical psoriasis treatment that was made utilizing biosurfactant via a low-energy emulsification technique. The oil worked best for treating the skin's epidermal layer. It determined that the Babchi oil nanoemulgel formulation is a good substitute for conventional formulations and has better permeable capabilities for topical transdermal drug delivery.[69] Singh *et al* formulated the mometasone furoate loaded nanoemulsion-based in situ gel for improve solubility, permeability and also for the treatment of psoriasis. The results indicated that the nanoemulsion formulated in-situ gel is a promising method for enhancing the bioavailability and topical administration of mometasone furoate and is safe for topical use with low irritation potential, and it could support long -term therapy.[70]

3.1.2 Liposomes: Liposomes, functioning as nano-vesicular systems for drug delivery, haveb demonstrated considerable effectiveness in targeting specific disease sites.[71] Conventional liposomes consist of lipid bilayers formed from phospholipid, cholesterol, and stabilizers that encompass an aqueous core. The lipid bilayer and the surrounding aqueous space are capable of encapsulating compounds with varying physicochemical characteristics. Liposomes are further categorized based on their surface charge and the quantity of lipid bilayers present within the vesicles.[72] Additionally, utilizing liposomal formulation has improved skin retention, drug penetration, and local availability by overcoming the skin barrier. This has been verified by demonstrating drug penetration to the dermis using either appropriate cell culture or ex vivo skin.[73]. Zhang *et al* formulated the hyaluronic acid-modified liposomes and encapsulated methotrexate for targeted psoriasis management. The HA modification further enhanced the absorption of liposomes by HaCaT cells after exposure to TNF-α treatment. In vivo research additionally showed the increased effectiveness of Lips-HA@MTX against psoriasis, as evidenced by improvement in skin pain rating, symptoms, pathological skin characteristics, and cytokine mRNA expression level.[74] Wang *et al.* reported trans-retinoic acid and betamethasone were successfully co-loaded into flexible liposomes. According to the study, flexible liposomes had sustained drug release behaviors, high drug encapsulation efficacy, and nano-sized particles. The drug's skin penetration and retention were significantly enhanced by flexible liposomes. According to *in vivo* research, topical application of TRA and BT dual-loaded liposomal gel was most effective in reducing epidermal thickness and cytokine level (TNF-α and IL-6), which significantly reduced psoriasis symptoms.[75] Nakamura *et al.* formulated the tacrolimus-encapsulated liposomes and iontophoresis. The combination of FK-Lipo and ItP demonstrated anti-psoriatic efficacy, leading to both improved histological characteristics of psoriatic skin as well as decreased TNF-α and IL-6 level.[76] Chen *et al.* developed a topical drug delivery method that combines liposomal gel filled with tretinoin and zedoary turmeric oil for the management of psoriasis. According to an *in-vitro* investigation, liposome formulation could considerably increase drug penetration and retain more medications and anti-psoriatic efficacy in the skin.[77]

3.1.3 Ethosmoes: Ethosomes are non- invasive delivery systems made up of phospholipids, elevated levels of ethanol, and water, which aid in transporting drugs deeply into the skin or into systemic circulation. However, typical transdermal delivery systems often struggle with inadequate skin penetration, mainly due to the stratum corneum, which is the outer barrier of the skin. Developed to overcome this limitation, ethosomes contain 20-50% ethanol. Ethanol serves as a potent permeation enhancer by interacting with the lipid molecule within the stratum corneum, lowering its melting point, and improving cell membrane permeability. Hence, compared to standard liposomes and hydroalcoholic solutions, ethosome systems exhibit greater effectiveness in delivering substances through the skin. Halluru *et al.* formulated the film-forming gel loaded with thymoquinone ethosomes for treating psoriasis. The formulation showed regulated release both in vitro and ex vivo, with improved skin penetration, increased stability, and greater drug loading, indicating efficient localized delivery and minimized systemic exposure.[78] Mohan *et al* formulated the methotrexate ethosomal gel for psoriasis management. Ethosomes loaded with methotrexate (ME2) demonstrate extended effects, improve vesicle stability and drug incorporation, facilitate skin absorption, and manage psoriasis by suppressing skin cell growth.[79]

3.1.4. Transferosomes: Transferosomes are vesicular drug delivery systems that resemble liposomes in structure, but they are more stable and have higher skin penetration capabilities, allowing the medication to reach deeper skin tissues. Transferosomes are superior medication delivery vehicles because of their ultra-deformable structure.[80] Motwani *et al* reported the nano-transferosome of vitamin E and aloe vera for the management of psoriasis. The product formulation was shown to be very effective, showed extended drug release, and showed no sign of skin irritation. The vitamin-E-loaded nano transferosomes aloe vera gel formulation works well and shows promise for delivering the medication to the skin's deeper layers.[81] Prakash *et al.* formulated the transfersomal carrier's system of tacrolimus for the dermal management of psoriasis. The effects on particle size, entrapment efficiency, and flow were investigated by varying the amount of the drug, phosphatidylcholine, and sodium desoxycholat. Pharmacokinetics and pharmacodynamic research findings demonstrated that transfersomes were considerably better in terms of drug penetration. Transfersome was used to treat psoriasis because they have shown anti-psoriatic properties.[82]

3.1.5 Nanostructure lipid carriers: Nanostructure lipid carriers (NLC) have drawn interest because they successfully solve importance issues related to other nanocarriers. NLC is a second generation of surfactant-stabilized solid lipid non-compartments contained within a spatially incompatible solid lipid matrix. NLCs are typically between 200 and 400 nm in size. They improve drug loading by preventing the drug's poor crystal structure from causing an early release of the encapsulated molecule. Additionally, NLCs enhance skin penetration and emollience when applied topically by giving the skin deeper moisture.[83] Furthermore, NLCs have the ability to encapsulate medication in their molecular form or as amorphous clusters. They also stick to the skin well and produce thin film that reduces transepidermal water loss by creating an occlusive effect.[84] Rani *et al* formulated the nanostructure lipid carrier gel of hesperidin for an effective treatment of psoriasis. The optimized HPD-NLC displayed a spherical morphology with a particle size measuring 125.7 nm, a polydispersity index (PDI) of 0.36, and an entrapment efficiency of 52.26% w/w. In the vivo examination, the group treated with HPD-NLC-Gel exhibited normal skin characteristics with minimal keratosis, whereas the group receiving the drug-loaded gel showed indication of hyperkeratosis and parakeratosis. It was concluded that the HPD-NLC represents a promising advancement of psoriasis through nanotechnology.[85] Biswasroy *et al.* developed botulin-loaded nanostructured lipid carriers for the management of imiquimod-induced psoriasis. The optimized H Betulin (BE) is a naturally occurring pentacyclic triterpene known for its anti-inflammatory, anti-psoriatic, anti-proliferative, and cytotoxic properties and its acceptable level of toxicity. An extensive experimental investigation has shown that BE-NLCs in the nanosized range exhibited superior entrapment efficiency, enhanced drug loading capacity, and greater skin permeability.[86] Singh *et al* formulated nanostructured lipid carriers' gel for enhanced topical delivery of roflumilast in psoriasis management. The NLC-based gel that encapsulates the PDE4 inhibitor roflumilast was created to improves topical delivery. The resulting gel was uniform, white, and clear, maintaining a dermally compatible pH (5.36-5.85), optimal viscosity (3.5-14.5), and good spreadability (4.3-7.2 g/cm/s) and a high encapsulation efficiency of 90.38 ± 2.91%. The roflumilast-NLC gel appeared to be a promising topical treatment for psoriasis, featuring controlled release and improved skin retention.[87]

3.1.6 Solid-lipid nanoparticles: SLNs were the first type of lipid nanocarrier system developed in the 1990s.

They serve as sophisticated drug delivery vehicles consisting of submicron particles that range from 40 to 1000 nm in size. Solid lipid nanoparticles represent a novel type a combination of physiological lipids and surfactants.[88] SLNs possess distinct features such as their compact size, substantial drug loading capability, extensive surface area, and extended drug release profile due to the gradual degradation of lipid matrices. The small size of SLNs facilitates close interaction between the nanocarrier and the stratum corneum, thereby enhancing penetration into the skin.[89] Mahajan *et al* formulated solid lipid nanoparticles as carriers to increase local bioavailability of acitretin after topical administration in psoriasis management. The optimized formulation achieved an encapsulation efficacy of 89.86 ± 1.8%, with a PDI of 0.488 and a zeta potential of – 17.2 mV, indicating stability. The findings suggest that the SLN-based gel formulation developed is an effective and safe option for the topical delivery of acitretin, showing no potential for skin irritation, enhanced skin deposition, and serving as an alternative to oral therapy.[90] Maiti *et al* formulated the solid-lipid nanoparticles of methotrexate for the anti-psoriatic activity. The result indicated that the MTX in the formulation was gradually released and fully (80.36%) absorbed through the skin. The SLN-MTX formulation exhibits a dose-dependent suppression of keratinocyte growth, with the cytotoxic concentration (CTC50) identified.[91]

3.1.7 Cerosomes: Cerosomes are vesicles that are tabulated and enclosed by ceramide, formulated with various surfactants and phospholipids for use in pharmaceuticals. These carriers facilitate effective incorporation and dissolution of ceramide. They also provide excellent skin tolerability, permeability, and enhanced drug bioavailability when used topically. The incorporation of surfactant in the formulation contributes to the formulation of highly stable, non-aggregated vesicles made from a double lipidic mixture of phosphatidylcholine and ceramide.[92] Elhabal *et al* formulated cerosomes for co-delivery of cyclosporine and dithranol for topical psoriasis management. Cerosomes exhibited an average particle size of 222.36 nm ± 0.36, a polydispersity index of 0.415 ± 0.04, an entrapment efficiency of 96.91%± 0.56, and a zeta potential of 29.36±0.38mV. The results demonstrate that cerosome improved skin penetration, decreased the psoriasis area and severity index, and lowered the level of pro-inflammatory cytokines. [93] Yang *et al* developed a novel niosome based on ceramide (cerosomes) to co-deliver MTX and nicotinamide (NIC), i.e., MTX/NIC cerosomes, for topically treating psoriasis with improving effectiveness and minimizing toxicity. Cerosomes notably increased drug penetration and retention within the skin and demonstrated a robust anti-proliferative effect.[94]

3.2 Polymer-based nanocarriers: Polymeric nanoparticles (NPs) exhibit outstanding biodegradability, capable of protecting drugs from degradation while accommodating both hydrophobic and hydrophilic substances. Polymers-based nanocarriers typically consist of hydrogel, nanocapsules, tyrospheres, and dendrimers.[95]

3.2.1 Hydrogel: A three-dimensional network of hydrophilic polymers makes up the special material known as hydrogel. Large volumes of water or other aqueous fluid can be absorbed and retained by them without totally dissolving. Functional groups, including hydroxylic, amidic, carboxylic, sulfonic, and primary amidic groups that are bonded to the polymer backbone, are responsible for hydrogel's ability to hold water. These groups are very attracted to water. Hydrogels are adaptable materials for a range of applications because of their softness, high efficiency, and capacity to hold ingredients.[96] Rapalli *et al* reported an embedded hydrogel formulation of aprimilast-loaded lyotropic liquid crystalline nanoparticles was developed to improve efficacy while minimizing the side effects associated with oral therapy for psoriasis treatment. The chosen formulation demonstrated a particle size of 173.25 ± 2.192 nm with a polydispersity of 0.273 ± 0.008 and an entrapment efficiency of 75.028 ± 0.235%. Research involving animals demonstrated improved skin absorption and retention of apremilast in comparison to traditional gel formulation.[97] Asad *et al* formulated the polymeric-loaded nanoparticle hydrogel for the management of psoriasis. MTX-NPs were designed to improve skin deposition and solubility in order to maximize the therapeutic effects of MTX for the treatment of psoriasis. The particle size of MTX-NOPs was 256.4 ± 2.17 nm, and their encapsulation efficiency was 86 ± 0.003%. In 48 hours, the hydrogel loaded with MTX-NPs showed a 73 ± 1.21% sustained drug release. According to an ex vivo penetrated study, only 19.95 ± 1.04 μg/cm^2 of the medication penetration the skin in 24 hours, but the epidermis retained 81.33% of the drug. Therefore, this is a better way to increase the topical efficacy of MTX for the treatment of psoriasis.[98] Saxena *et al* formulated quercetin phytosome-infused hydrogel for improved skin penetration in the management of psoriasis. The hydrogel formulation considerably enhanced the delivery and effectiveness of quercetin for topical use, boosting antioxidant activity and promoting greater skin penetration, while also attaining the highest entrapment efficacy and therapeutic effect.[99]

3.2.2 Nanosphere: Nanospheres consist of a uniform distribution of the drug within their polymer matrix structure. The primary goals of nanospheres, which can be biodegradable based on the materials used in their production, are to increase solubility, boost absorption, and regulate drug release.[100] Kumar *et al* reported a cyclodextrin nanosponge-loaded hydrogel with clobetasol was developed to reduce the previously mentioned side effect and to regulate drug release. The formulation demonstrated an entrapment efficiency of 56.33 ± 0.94 %, a particle size of 194.27 ± 49.24 nm, a polydispersity index of 0.498 ± 0.095, a surface charge of -21.83 ± 0.95 mV, and a drug release rate of 86.25 ± 0.28. The prepared formulation was utilized in the topical management of psoriasis, leading to enhanced patient compliance.[101]

3.2.3 Nanocapsule: Polymeric nanocapsules (NC) represent a promising approach for delivering drugs topically. They not only reduce the negative effect associated with some medication but also have the ability to enhance drug absorption through the skin. Furthermore, these nanostructures improve the adhesive properties of formulations, allowing for extended contact with the targeted area. Nevertheless, the low viscosity of liquid formulations containing NC makes their topical application challenging. The highlights of integrating the NC into hydrogel for use in topical treatments, including bioadhesive polymers like Carbopol, chitosan, hydroxypropyl methylcellulose, and more recent options.[102] Kumar *et al* reported the release profile of sulfasalazine-loaded nanosponges indicated a sustained release effect showing 22.98 ± 2.24% in 3 h. The effectiveness of the SLZ-NS4-loaded hydrogel for managing psoriasis was demonstrated by a reduction in PASI of 81.68 ± 3.61 and 84.86 ± 5.74 for concentrations of 1 and 2 w/v of SLS-NS-HG. These results underscore the significant potential of the developed delivery system as a viable topical treatment for psoriasis.[103]

3.2.4 Dendrimers: Dendrimers have become a significant category of nanostructured carriers in the advancement of nanomedicine for treating various illnesses. Due to their structural variety and flexibility, dendrimers have been utilized to deliver both drugs and genes in numerous ways. For example, dendrimers that feature a hydrophobic core along with a hydrophilic exterior can act like unimolecular micelles; they have been employed to solubilize hydrophobic drugs by trapping them within the intramolecular cavity.[104] Yu *et al* formulated a new type of photo-responsive dendritic mesoporous silica nanoparticle carrier to deliver erianin, which enhanced its bioavailability and provided sustained-release effects. Transmission electron microscopy revealed that the blank DMSN@FSP nanoparticles are spherical in shape and consist of dendritic channels, exhibiting a consistent particle size ranging from 98 to 130 nm. Dynamic light scattering (DLS) confirmed that DMSN@FSP maintains good stability in phosphate-buffered saline. The result from BET analysis indicated that DMSN@FSP possesses a significant capacity for drug loading and also achieved more effective psoriasis treatment.[105]

3.3 Metallic Nano-carriers: Metallic nanoparticles are small metal particles that have dimensions (length, width, thickness) ranging from 1 to 100 nm. Faraday was the first to explore the presence of metallic nanoparticles in solution in 1857. In 1908, Mie provided a quantitative explanation for their color. Nowadays, these nanomaterials can be attached to antibodies, ligands, and drugs. Metallic nanoparticles offer a wide range of applications in the fields of therapy, biotechnology, and as carriers for gene and drug delivery.[106] It also included the gold and silver nanoparticles, which are synthesized through various techniques and utilized in numerous domains such as drug delivery, sensing, and detection. Their broad range applications can be attributed to their exceptional chemical and physical properties, large surface area, adjustable optical characteristics, stability, small size, and non-toxic nature. Silver and gold nanoparticles that are functionalized with diverse biomolecules, including proteins, DNA, amino acids, and carboxylic acids, have been employed in cancer treatment and offer an excellent system for delivering drugs.[107] Telange *et al* reported that green synthesis of silver nanoparticles utilizing pongamia pinnata seed extract incorporated with nanogel formulation (AgNPs CUD NG) aimed to enhance the retention, accumulation, and penetration of AgNPs into the epidermal layer of psoriasis. The entrapment efficiency of AgNPs was approximately 79.35%. The formulation exhibited non- Newtonian characteristics, improved spreadability, and superior extrudability, highlighting its appropriateness for transdermal applications.[108] Hadi *et al* reported that the research assessed the efficacy of gold nanoparticles derived from Syzygium aromaticum (SaAuNPs) in the treatment of psoriasis. The result indicated that SaAuNPs exhibited a notable $P \leq 0.05$ anti-inflammatory impact, with the group receiving 0.003% and 0.005%. SaAuNPs demonstrated a significant decrease in symptoms associated with psoriasis.[109]

Conclusion:

Psoriasis is a complicated skin condition that has profound effects on a person's body. In this review article, the studies concluded that there is significant potential for nanotechnology-based drug delivery systems for the management of psoriasis. Due to the low benefit-to-risk ratio, decreased treatment efficacy, and local and systemic toxicity, current traditional therapy is insufficient for treating psoriasis. So, according to these studies, nanotechnology is considered a highly promising and revolutionary frontier for psoriasis treatment, which has a lot of potential to develop novel treatments and reduce the high dosage frequency with low patient compliance. The solid-lipid nanoparticles, nanostructured lipid carriers, liposomes, polymeric nanoparticles, nanoemulsions, ethosomes, and other nano-carriers are becoming a popular strategy to manage psoriasis. These nanocarriers can improve efficacy, safety, and patient acceptance; improve skin penetration; extend drug retention; enable controlled and sustained release; and lower the systemic toxicity when compared to conventional therapies. Overall, nanotechnology provides a safer, more effective, and patient-friendly approach to managing psoriasis, with significant promise for future clinical use.

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