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REVIEW ON NANO CARRIER SYSTEMS IN PSORIASIS TREATMENT: BENEFITS, CHALLENGES, AND FUTURE DIRECTIONS

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ABSTRACT

This review looks at new developments in the treatment of psoriasis, with an emphasis on methods based on nanotechnology. It talks about the drawbacks of conventional remedies, like UVB treatments, which can have serious adverse consequences. The potential for improving drug delivery and reducing side effects being investigated for nanocarriers, including liposomes, niosomes, and metal-based nanoparticles (such as gold and silver). The analysis also highlights the potential of different nanocarrier systems to improve psoriasis treatment outcomes by summarising their advantages and disadvantages. But there are drawbacks, such as high production costs and scaling problems, which emphasise the necessity of more study to maximise these cutting-edge therapeutic approaches.

KEYWORDS: Nanocarriers, Drug delivery systems, Targeted therapy, Nanoparticles, Liposomes.

1. INTRODUCTION

Over 125 million people worldwide suffer with psoriasis, a chronic inflammatory skin disorder with prevalences ranging from 0.1 to 8% depending on the region.[1–3] The complicated aetiology of psoriasis was caused by a multitude of intrinsic and external factors. Several genetic risk factors were identified, including genes linked to cytokine signalling (IL12B, IL23R), interferon signalling, NF-κB signalling (TNFAIP3, NFKBIA, NFKBIZ, TNIP1, and RELA), and antigen presentation (HLA-Cw6). (Sieminska, Isabela et al., 2024).[3,4-6] Raised, well-defined, erythematous oval plaques with attached silvery scales are the disease's typical manifestation. Premature keratinocyte (KC) maturation and hyperproliferative epidermis are the causes of the scales. The epidermis's granular layer is either completely absent or significantly diminished in psoriatic lesions. Consequently, partial cornified KCs with nucleus retention (parakeratosis) created the stratum-corneum (J., & Van Gele, M. et. Al. (2017).[7] Psoriatic skin that is hyperproliferative resembles malignant disease in that it causes unchecked growth.[8] PsO's precise cause is unknown, however it has been linked to a number of environmental and genetic factors, such as prolonged stress, trauma, infections, alcohol, and excessive smoking. Skin and immune cells are involved in the pathogenesis of PsO. Increased ROS production, compromised antioxidant system performance, and oxidative damage may potentially be part of its aetiology.[9]

1.2 The pathophysiology and clinical categorisation of psoriasis[10]

1.2.1 Classification in Clinical Practice

Schäkel, K., and Rendon, A., et al. (2019). Although there were various forms of psoriasis, the most prevalent type was psoriasis vulgaris, also referred to as plaque-type psoriasis. Although the terms psoriasis and psoriasis vulgaris were used interchangeably in scholarly literature, they differed significantly. Psoriasis vulgaris, commonly referred to as plaque type, was one of the various clinical subtypes of psoriasis (see Figure 1).[10]

(Figure 1.)

1.2.2 Psoriasis Vulgaris

About 90% of all psoriasis cases were of the traditional clinical chronic plaque-type variety. The classic clinical signs were erythematous, itchy, sharply defined plaques coated in silvery scales. A large area of skin could be covered by the plaques clumping together. Typical sites included the scalp, the trunk, and the extensor surfaces of the limbs. (Nestle, F. O. et al., and A. 2013).[11,12] The symptoms were brightly delineated, itchy, erythematous plaques with silvery scales covering them. A large area of skin could be covered by the plaques clumping together. Typical sites included the scalp, the trunk, and the extensor surfaces of the limbs.[11,13]

1.2.3 Inverse Psoriasis

Clinically, it was characterised by slightly erosive erythematous plaques and patches. Mildly erosive erythematous plaques and patches that affected intertriginous tissues were the clinical hallmark of flexural psoriasis, another name for inverse psoriasis.[10]

1.2.4 Guttate Psoriasis

Guttate psoriasis was one form that was defined by abrupt appearances of small erythematous plaques. Usually affecting children or adolescents, tonsil infections brought on by group-A streptococci were the main cause. Plaque psoriasis developed in about one-third of people with guttate psoriasis.[13,14]

1.2.5 Pustular psoriasis

Acrodermatitis continuous of Hallopeau and pustulosa palmoplantaris (PPP) affected both the hands and the feet; PPP was restricted to the palms and soles, whereas ACS was more widely distributed at the tips. A characteristic of pustular psoriasis was the accumulation of many sterile pustules. It was possible to develop both localised and widespread pustular psoriasis. Two distinct localised symptoms were identified: acrodermatitis continua of Hallopeau and psoriasis pustulosa palmoplantaris (PPP). The acute condition known as erythrodermic psoriasis caused erythematous and inflamed skin covering more than 90% of the body. Erythroderma could develop from any kind of psoriasis and required immediate treatment (Figure 2). Erythrodermic psoriasis was an acute condition in which over 90% of the body's surface was erythematous and inflamed. Erythroderma could develop from any kind of psoriasis and required immediate treatment (Figure 2).[10]

Figure 2. Erythrodermic psoriasis.[10]

1.2.6 Comorbidities in Psoriasis: P11

(M. L., Zurakowski et. Al.2006) In oligoarticular or polyarticular patterns, it manifests clinically as enthesitis and dactylitis. Nail involvement is commonly linked to the polyarticular type.[15] Psoriatic inflammation can also affect the specialised dermal appendages known as nails. More than half of psoriasis patients are said to have nail psoriasis, and 5–10% of patients may have it as their sole psoriasis symptom.[16] The inflammatory process's effect on the structure dictated how nail psoriasis manifested clinically. It was estimated that 15% of psoriasis patients had undiagnosed PsA[17], and nail matrix involvement showed up as pitting, leukonychia, and psoriasis (Gelfand, J. M. 2013).[18–24] Clinically, it showed up as dactylitis and enthesitis in oligoarticular or polyarticular patterns. Polyarticular variance was frequently associated with nail involvement.[15] Psoriatic inflammation could affect the nails, which are specialist dermal appendages. Five to ten percent of people may have had nail psoriasis as their only psoriasis symptom, and over half of psoriasis patients were reported to have it (in Proniewicz, A.et al. 2003).[16] The clinical manifestation of nail psoriasis was established by the structure affected by the inflammatory process. While oil-drop colouration, splinter haemorrhages, and onycholysis indicated inflammation of the nail bed, pitting, leukonychia, and onychodystrophy indicated involvement of the nail matrix (Figure 3).[25] Nail involvement was associated with joint involvement, and nail symptoms were present in up to 80% of psoriatic arthritis patients.[26, 27]

Figure 3: Onycholysis and oil drop signs in nails affected by psoriasis.[10]

1.3.1 Immune Response in Psoriasis

In 2019, Ohtsuki M. et al. Psoriasis was characterised by a dysregulated cytokine network with many self-amplifying feedback loops that accelerated pathogenic processes. Psoriatic inflammation may have been brought on by environmental contaminants, sun exposure, medications, diseases, immunisations, or mechanical stress (Koebner phenomena) in predisposed people.[28] In 2019, psoriasis was responsible for 6.84% of all new cases of immune-mediated inflammatory diseases, which were becoming more prevalent worldwide.[29] Immune cells were the most prevalent of the five main elements that made up the epithelial immune microenvironment: barriers, immune cells, microbiota, and peripheral nerve terminals.[30] Immune cell activation and aberrant keratinocyte differentiation were the causes of psoriasis.[31] For example, elevated T helper 17 (Th17) cell expression and interleukin (IL)-17A release both contributed to the development of psoriasis. It had been demonstrated that immune mediators of the IL-17 pathway caused anomalies in the differentiation and proliferation of epidermal keratinocytes, which resulted in psoriasis. IL-17 and IL-17A-targeting therapies had shown great promise and were authorised for clinical usage.[32] The necessity to identify additional immune cells linked to psoriasis in order to better treat its negative consequences was highlighted by the fact that not all psoriasis patients had clinical benefits from IL-17 pathway immunotherapies. Furthermore, due to insufficient sample sizes, subpar study designs, and confounding variables that were outside the scope of present research, we still don't fully understand the relationship between psoriasis and immunological inflammation. Mendelian randomisation (MR) is an analytical technique that is mostly used in epidemiology to use genetic data to determine the aetiology of diseases. MR investigations aimed to determine whether individuals with specific genetic variations were more likely to develop diseases than those without these alterations by "randomising" genes depending on one or more alleles that influenced risk variables (Kerner, H., & Kalish, R. S. et. al.[33]

1.3.2 The connection between psoriasis and site-specific cancers is still uncertain

(J. G. Krueger and others, 2014) The immune system-mediated inflammatory skin condition known as psoriasis affected about 3% of the population.[34] Cancer was one of the leading causes of death for people with psoriasis[35], but the relationship between psoriasis and the risk of site-specific cancers remained still unclear. In a meta-analysis of cohort and case-control studies, psoriasis was associated with an elevated risk of 11 site-specific malignancies, including non-Hodgkin lymphoma, esophageal, colon, colorectal, kidney, laryngeal, liver, lymphoma, keratinocyte, oral cavity, and pancreatic.[36] There was also a strong genetic factor to psoriasis.[37] Although polygenic risk score (PRS) and Mendelian randomisation (MR) analyses were helpful methods for investigating causal impacts on outcomes[38,39], many MR research had produced conflicting results on the causal relationship between psoriasis and cancer.[39–42]

1.3.3 Air Pollution Exposure, Genetic Predisposition, and Psoriasis

(J. E., Ward, N. L., and others, 2022). Psoriasis, a common autoinflammatory disease that can result in physical deformity and decreased job capability, was characterised by symptoms such as skin redness, discomfort, itching, and bleeding.[43–46] Numerous cardiac issues, arthritis, and even a greater death rate had been associated with the sickness.[46–49] There was currently no known cure for psoriasis, and the medicines that were available could only control the condition for lengthy periods of time or without flare-ups, which caused financial losses and a significant strain on healthcare systems.[46,50] The prevalence of psoriasis has increased since the early 21st century, particularly in affluent countries, and it is becoming a major public health issue.[51,52] However, the complex interaction between genetic and environmental factors rendered effective prevention nearly impossible, and the exact aetiology of psoriasis remained unknown. This led to concerns about public health.

1.3.4 Prevalence and trends of contact sensitization in psoriasis patients in Lithuania

(Offidani, A., & Radi, G. et al. 2021). Psoriasis and allergic contact dermatitis (ACD) are common inflammatory skin diseases that are marked by abnormalities of the epithelium and changes in T cell immunity.[53] Distinct, variable-sized erythematous plaques that were caused by dysregulated immune cell activation in the dermis and epidermis, as well as abnormal keratinocyte differentiation and proliferation, were the primary characteristics of psoriasis.[54] However, the main symptoms of ACD were vesicles, papules, and erythema, which were followed by scaling. This occurred as a result of keratinocytes going through apoptosis due to type IV hypersensitivity.[53,55] The immune system was becoming more dysregulated in the population, leading to an increase in autoimmune illnesses. According to a number of studies, psoriasis prevalence varies globally based on factors such as gender, age, area, and ethnicity, with Caucasians having the highest frequency of the disorder.[56] Psoriasis may develop or worsen as people age, even though it was less frequent in children.[57]

Characteristics of the cohort: The average age of the 85 patients was 50.68 ± 15.30 years, their mean body mass index was 28.69 ± 6.53, and 31 (36.5%) of them were men and 54 (63.5%) were women. The PASI score was 9.50 ± 6.17, and the Dermatology Life Quality Index score was 8.86 ± 6.34. The general characteristics of psoriatic lesions were compiled in Table I. Two individuals showed the highest sensitivity to eight allergens, and the patch test was positive in 43.5% (n = 37) of cases. Skin sensitisation was more common in women than in men (75.7% vs. 24.3%, P = 0.041). At the time of the study, fourteen patients were receiving methotrexate, whereas three patients were getting biological therapy (Table 1).[58]

Table 1

Characteristic	Value
Total number of patients	85
Gender	Female: 54 (63.5%) Male: 31 (36.5%)
Mean age	50.68 ± 15.298
Mean body mass index (BMI)	28.69 ± 6.53
Mean PASI (Psoriasis Area and Severity Index)	9.50 ± 6.17
Mean Dermatology Life Quality Index (DLQI)	8.86 ± 6.34
Positive patch test results (percentage)	43.5% (n = 37)
Maximum sensitivity to 8 allergens	2 patients
Skin sensitization prevalence (female vs male)	Female: 75.7% Male: 24.3% (P = 0.041)
Biological therapy treatment	3 patients
Methotrexate treatment	14 patients

2. Treatment

(E. Guttman-Yassky and colleagues, 2018) People with mild to moderate psoriasis were usually treated with topical steroids or oral glucocorticoids, including dexamethasone. However, it was crucial to be mindful of their side effects, which included hormone-dependent dermatitis, telangiectasia, skin shrinkage, pigmentation changes, and rashes resembling acne.[59] In traditional Chinese medicine, psoriasis was referred to as "Bai Bi" (White Boil) because to the distinctive appearance of psoriatic plaques. It was believed that the pathological causes of psoriasis, particularly persistent cases, were blood heat, blood stasis, and dry skin. In Chinese medicine, psoriasis was often treated with herbs that cooled the blood and eliminated heat, such as Moutan Cortex, Rhinoceros Unicornis, Rehmanniae Radix, and Phellodendri Chinensis Cortex, as well as those that emptied wind and alleviated itching, such as Dictamni Cortex. In recent years, Wang et al. developed a Chinese herbal formula called the Inflammation Skin Disease Formula (ISDF) to treat a range of inflammatory illnesses. The well-known prescription known as ISDF was created by Prof. Zhi-Xiu Lin, a licensed Chinese medicine practitioner in Hong Kong.[60]

2.1 Standard treatment for psoriasis

(Zhou, Y., Huang, C., et al. 2005). Topical treatment remained the most common way to treat psoriasis. These therapies included calcineurin inhibitors, topical retinoids, vitamin D analogues, and topical corticosteroids.[61,62] The calcineurin inhibitor tacrolimus, the topical retinoid tazarotene, and the vitamin D analogues calcitriol and calcipotriol (or calcipotriene) were among the examples. Systemic treatment may be explored if topical medications did not work, the patient suffered extreme discomfort, or the size and severity of lesions increased. The most often utilised systemic medication in these circumstances was methotrexate, which had been used to treat psoriasis for over 50 years.[63] Competitive inhibition was used to ascertain the mode of action of ciprofolate reductase, a folic acid analogue. By preventing the synthesis of cofactors required for the synthesis of nucleic acids, this eventually hampered the production of T lymphocytes and keratinocytes. Initially used as an immunosuppressant to prevent organ transplant rejection, cyclosporin has also been demonstrated to be a successful antipsoriatic. Its therapeutic impact was due to the reduction of calcineurin, which inhibited T lymphocyte activation and the production of inflammatory cytokines.[64] Because ciclosporin may cause nephrotoxicity, hypertension, and increased immunosuppression, close observation was required.[65] (Kanwar et al., 2013; Jain et al., 2013) Individuals with kidney failure, uncontrolled, unstable hypertension, or cancer should not have used cyclosporin. It also shouldn't have been taken with other drugs that were metabolised by cytochrome P450. Acitrim was the only systemic retinoid approved for the treatment of psoriasis, and it was particularly effective for erythrodermic and pustular forms. It worked by controlling the differentiation and growth of the epidermis. At the start of treatment, a modest dose was often given and increased gradually. Despite its contraindications for pregnant women and women of reproductive potential, as well as its side effects, which included xerosis, nail and hair breakage, and dose-dependent reactions, acitretin remained the most commonly used treatment for severe instances of psoriasis. Phototherapy was a long-standing method of treating dermatoses that entailed carefully and repeatedly exposing patients to ultraviolet (UV) light from artificial sources. This radiation was absorbed by the skin's inherent chromophores. One could make use of UVA or UVB rays. UVA (320–400 nm) radiation was ineffective by itself, but it was highly effective when combined with topical or systemic photosensitising medications (such psoralen). This combined treatment was called PUVA (psoralen + UVA radiation). PUVA treatment reduced epidermal growth and prevented cytokine release. UVB light (290–320 nm) had a more significant biological impact and had an effect on cellular functions. Narrowband UVB beams were believed to be more effective than broadband UVB emissions, resulting in longer periods of remission and less skin reactions (such burns and erythema). These treatments, like PUVA and UVB, could be used in conjunction with other topical or systemic medications to enhance treatment outcomes and maximise efficacy. The need for more effective and less harmful alternative therapies, such as those based on nanotechnology, was highlighted by the severe side effects of these commonly utilised therapeutic alternatives.

3. Topical psoriasis treatments using nanotechnology-based strategies

Veiga, F., & Paiva-Santos, A. C. et al. 2022). Nanocarriers, which are typically smaller than 100 nm, were a unique class of strategies that had been studied for the treatment of skin conditions. These nano-based formulations' primary benefit was their ability to reduce the negative effects of traditional treatments while also enhancing drug penetration and providing more controlled drug release to reach the desired therapeutic target. However, there were still certain shortcomings that needed to be addressed. F. Mascarenhas-Melo et al. specifically looked at the nanotechnology-based methods being investigated for topical treatment of psoriasis (Fig. 4). Table 2 offered a clear and practical summary of their primary advantages and disadvantages.[58]

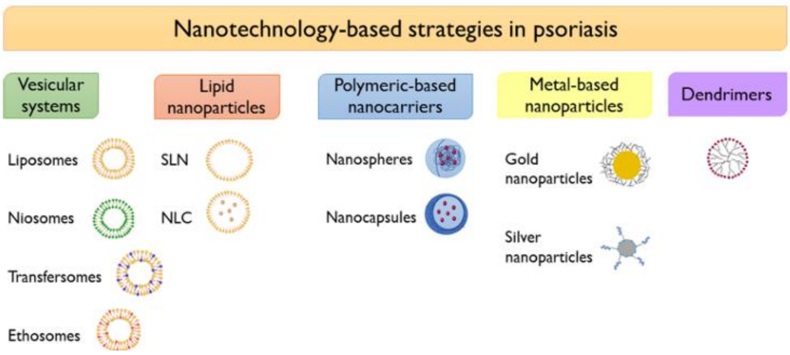


Fig. 4

Table: 2
Key advantages and disadvantages of various nanocarriers used in the topical treatment of psoriasis

Nanocarrier-based Strategies	Advantages	Disadvantages	References
LIPs (Liposomes)	Ability to deliver both lipophilic and hydrophilic drugs through the skin; Better drug release; Increased drug deposition into skin layers	Difficulty in large-scale production; High production costs; Need for phospholipid purification	[66,67]
NIOs (Niosomes)	Higher stability; Lower-cost production; Reduced transepidermal water loss	Lower skin permeation compared to liposomes; Difficult high-scale production	[66]
TRAs (Transfersomes)	Delivery of both high and low weight drugs to the skin; Ultra-deformability capacity	Difficult high-scale production; High-cost production	[66]
ETOs (Ethosomes)	Malleability; Encapsulation of both lipophilic and hydrophilic molecules	Predisposition to degradation; High-cost production	[68]
SLNs (Solid Lipid Nanoparticles)	Reduced skin irritation; Biocompatibility and tolerability	Lower skin penetration than NLCs; Limited drug encapsulation	[69]
NLCs (Nanostructured Lipid Carriers)	Better adhesion to the skin; Higher entrapment efficiency	Low viscosity; Not suitable for transdermal use	[66,69]
NSs (Nanostructured Systems)	Better skin permeation of lipophilic drugs; Biocompatible and biodegradable	Difficulty in scale-up processes	[66,70]
NCs (Nanocapsules)	Higher cutaneous penetration; Protect against premature degradation	Difficulty in scale-up processes; High-cost production	[71,72]

AuNPs (Gold Nanoparticles)	Minimized irritation effect; Increased permeation through the skin; Biocompatible and biodegradable	Difficulty in scale-up processes	[72,73]
AgNPs (Silver Nanoparticles)	Biocompatibility; Antimicrobial activity; Increased skin permeation	High-cost production	[72,73]
Dendrimers	Ability to be synthesized from chemical and organic materials; Biocompatibility	High-cost production	[72,74]

This table maintains the key details and structures it more clearly for easier comparison across the different nanocarrier-based strategies.

3.1 Lipid-based nanocarriers

3.2 Vesicular systems

3.2.1 Liposomes (LIPs)

Meng, X., Teng, Y., and others (2019) Liposomes, also known as LIPs, were small, unilamellar or multilamellar vesicles composed of phospholipids, cholesterol, and long-chain fatty acids.[75] Originally developed to treat inflammatory diseases like psoriasis, LIPs' moisturising properties enhanced the absorption of medications. Their use has been shown to improve drug penetration and permeation through the skin, and they could encapsulate both hydrophilic and lipophilic substances.[76,77]

3.2.2 Niosomes (NIOs)

Fessi, H., and A. Eliaissari et al. (2018) When non-ionic surfactants, cholesterol, and other lipids were hydrated, structures known as niosomes (NIOs) were formed. Both hydrophilic and hydrophobic drugs may be present in these NIO vesicles. According to their size, NIOs were separated into three groups: small unilamellar vesicles (SUVs, 0.025–0.05 µm), multilamellar vesicles (MLVs, 0.05 µm), and large unilamellar vesicles (LUVs, 0.10 µm). Similar to liposomes, NIOs may be used topically or in other ways to enhance drug release and skin penetration. They didn't require specific storage conditions because they were biodegradable, biocompatible, and osmotically active.[77]

3.2.3 Transfersomes. (TRAs)

(Fraceto, L. F., & de Araujo, D. R. et. al. 2020). Their flexibility allowed them to flow through smaller pores, which was one of their main advantages. The trapping of hydrophilic pharmaceuticals in the aqueous core and lipophilic drugs in the bilayer membrane was made possible by electrostatic and hydrophobic interactions.

3.2.4 Ethosomes. (ETOs)

Ethersomes (ETOs) were mostly composed of phospholipids, water, and alcohol. These nanosystems may range in size from a few microns to 30 nm. ETO-based formulations, like TRAs, were incredibly flexible and could fit through pores smaller than their diameter. They were commonly called elastic vesicles.

3.3.1 Lipid nanoparticles

(Su, Y. H., Saraf, S., & others, 2008-2018) As lipid nanoparticles, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) were both categorised. Particularly relevant to topical medication administration were SLNs, which were colloidal systems. Surfactants and physiological lipids were combined to make them. The combination of liquid and solid lipids, however, produced a novel type of lipid nanoparticle known as NLCs. Because of their enhanced compatibility and versatility, they were perfect for delivering medications in a range of ways.[78, 79] et al. Mascarenhas-Melo, F.

3.4.1. Polymeric-based nanocarriers

3.4.1.1 Nanospheres

Michniak, B., & Kohn, J. et al. (2008). The drug was uniformly distributed across a polymer matrix to create nanospheres (NSs), which were particles smaller than 1 µm. Polymers that are both biodegradable and non-biodegradable could be used. In addition to improved absorption, NSs also improved stability, solubility, and control over drug release.[80]

3.4.1.2. Nanocapsules

Nanocapsules (NCs) were colloidal particles smaller than 1 µm, similar to NSs. Unlike NSs, NCs had a reservoir system where the drug was encased in a polymeric membrane and contained within a core. NCs were prized for use in dermatological applications due to their remarkable skin penetration, which prevented the drug from degrading.[78]

3.5 Metal-based nanoparticles

(Adel-Mottaleb, M. M., et al. 2020; Arafa, M. G. There has been a lot of interest in using metallic nanoparticles for drug delivery for skin disorders because of their small size, ease of customisation, and high reactivity with living cells. The majority of their research has focused on treating tumours, but more recently, interest in their potential as anti-inflammatory medications to treat dermatological conditions has grown.[73]

3.5.1 Gold nanoparticles

(Fratoddi, I. et al., 2016; Pelacani, G.) AuNPs loaded with MTX were used to treat psoriasis. Sodium 3-mercapto-1-propane sulfonate (Au-3MPS) was utilised to enhance stability and distribution, and a hydrophilic coating was applied to further stabilise the AuNPs. The thiol-based layer maintained MTX activity while improving formulation stability. The MTX-AuNP treatment performed better than MTX alone, according to the results. Additionally, it was proposed that this treatment might be a topical remedy for psoriasis that is safe, non-toxic, and effective.[81]

3.5.2 Silver nanoparticles

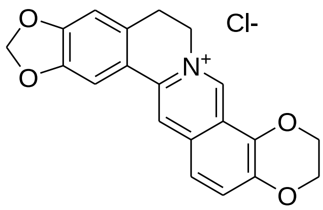
(E. Fischer-Fodor and G. A. Filip et al., 2014) Silver nanoparticles (AgNPs) have been successfully investigated as possible antipsoriatic therapy for psoriasis, despite their major use in cancer treatment and diagnosis. AgNPs loaded with a blackberry fruit extract were created in order to test their anti-inflammatory properties in psoriatic lesions.[82] AgNPs[73], which were known for their antibacterial[82] and biocompatible[72] qualities, were made from both chemical and organic components. However, it was still difficult to scale up their production for large-scale applications.[72]

3.6 Dendrimers

Yag, K., et al., and Maeda, I. (2003) Dendrimers assisted get around a number of resistance mechanisms and enhanced the dispersion of the active ingredient by conjugating or encapsulating drugs. Ocular, pulmonary, transdermal, oral, and intravenous routes were all viable ways to give drugs because of these properties.[83] These benefits were complemented by improved solubility, improved control over drug release, and the potential to produce pro-drugs or drug-polymer conjugates thanks to dendrimers. Dendrimers were a very effective delivery mechanism for anti-psoriatic drugs because of these features.[83]

4. Topical treatment berberine

Dhull, D. K., and R. Pottabathini et al. (2015) Berberine was applied topically to BALB/c mice to reduce imiquimod-induced psoriasis-like dermatitis by blocking the JAK1/STAT1 signalling pathway.[84] The alkaloid compound berberine, which was found in Berberis vulgaris, showed potent anti-inflammatory qualities. Its crystalline structure was distinctly yellow, and it was largely insoluble in water. According to Figure 7, Table 3, berberine decreased pro-inflammatory cytokine levels in plaque psoriasis, including interleukins (IL-23, IL-12, and IL-23), tumour necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). It also inhibited the JAK-STAT pathway.[85,86]



Berberine hydrochloride

Pharmacology of Berbbarine: p16

Table: 3

Pharmacokinetic Process	Description	Reference
Absorption	The oral bioavailability of berberine is very low, largely due to PG-glycoprotein, which mediates efflux from the intestine and liver. PG-glycoprotein reduces the transport of berberine by approximately 90%, causing it to be retained in the intestine. However, when taken with PG-glycoprotein inhibitors, such as cyclosporin A or verapamil, absorption is significantly enhanced.	[87]
Distribution	Animal studies indicate that berberine is rapidly distributed across various tissues, including the liver, kidneys, heart, brain, lungs, muscles, pancreas, and fat. There are currently no human studies available on the distribution of berberine.	[88]
Metabolism	Berberine is primarily metabolized in the liver. The cytochrome P450 enzyme CYP2D6 plays a key role in the metabolism of berberine, followed by CYP1A2, CYP3A4, CYP2E1, and CYP2C19. CYP2D6 is responsible for producing key metabolites, M1 and M2. Following phase I demethylation, these metabolites undergo conjugation with glucuronic and sulfuric acids, forming polar phase II metabolites that are easily excreted.	[89]
Excretion	While there are no human studies on the excretion of berberine, animal studies in rats show that 22.83% of berberine is recovered. The primary route of excretion for berberine metabolites, including thalifendine (M1) and berberine (M2), is through bile and urine, with fecal excretion being the main pathway.	[88], [89]

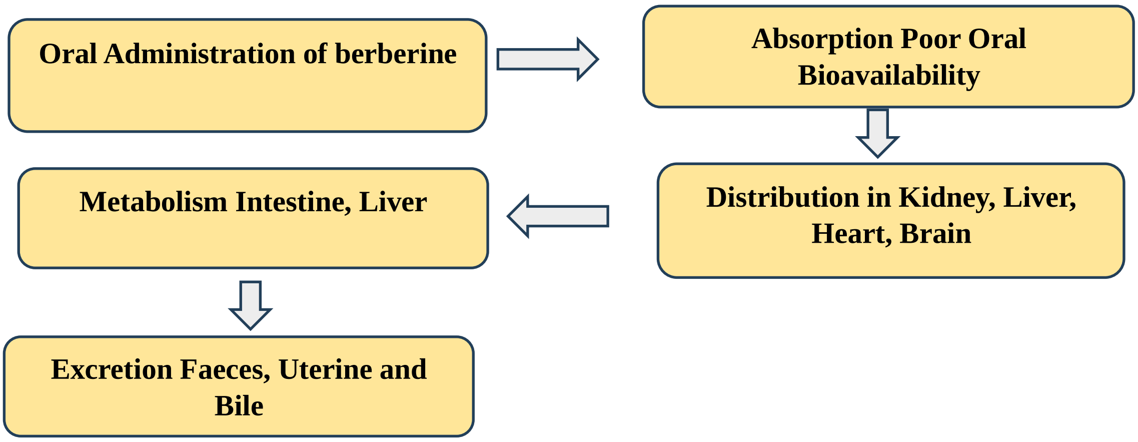


Figure: 5 Pharmacology of Berberine.[87]

(Wu, L., Li, X., Zhang, J., et al., 2024) Prior to the official experiment, a pre-experiment was conducted to assess the skin safety of Vehicle cream and Berberine creams at concentrations of 0.5%, 1%, 2%, and 4% for topical administration over a 6-day period. As seen in Figs. S1A and B, the mice's dorsal skins in the Vehicle, 0.5%, and 1% Berberine groups looked normal, just like the Control group. Mice in the 2% and 4% Berberine groups displayed aberrant epidermal thickening, indicating a considerable degree of skin irritation, in contrast to the Control group. Thus, 0.5% and 1% Berberine creams were utilised for the study. Both concentrations were prepared using the methods mentioned above, and they were optimised using a multi-factor orthogonal test. Topical application of either berberine cream or halometasone cream significantly reduced the IMQ-induced skin lesions, including erythema, scaling, and thickness. These treatments also significantly reduced the cumulative score ($P < 0.05$, $P < 0.01$, $P < 0.001$) as compared to the IMQ and Vehicle groups.

Fig. 6. Topical application of berberine improved skin lesions induced by IMQ.[84]

Bbr Protects Against Imq-Induced Psoriasis-Like Skin Lesion: [p14]

In 2019, Tian, F., Cui, J., and Zou, Y. et al. The therapeutic advantages of BBR were evaluated in vivo using the IMQ-induced mouse model. Five days of IMQ treatment significantly enhanced ear and epidermal thickness in comparison to the control group (Fig. 7a–f). Ear and epidermal thickness significantly decreased in the group treated with both IMQ and BBR compared to the IMQ-only group (Fig. 7a–f). Additionally, BBR treatment dramatically decreased the epidermis's expression of the proliferation marker Ki67 (Fig. 7g). BBR may have blocked JAK1/2 translation, as (Sun et al. 2019) found that BBR treatment had no effect on JAK1/2 transcription or protein degradation. Target genes are regulated post-transcriptionally by small noncoding RNA molecules called microRNAs (miRNAs), which have remained conserved throughout evolution. A number of miRNAs were dysregulated in psoriasis; several of these were known to govern keratinocyte differentiation and proliferation, as well as T-cell-mediated immunological dysfunction. Recent studies have shown that BBR's pharmacological benefits, such as its anti-inflammatory and anti-cancer qualities, are produced by regulating miRNAs. IMQ treatment significantly increased the expression of p-STAT3 and CDC6 in the epidermis (Fig. 7h, i). Co-administration of BBR, however, lessened this impact (Fig. 7h, i).

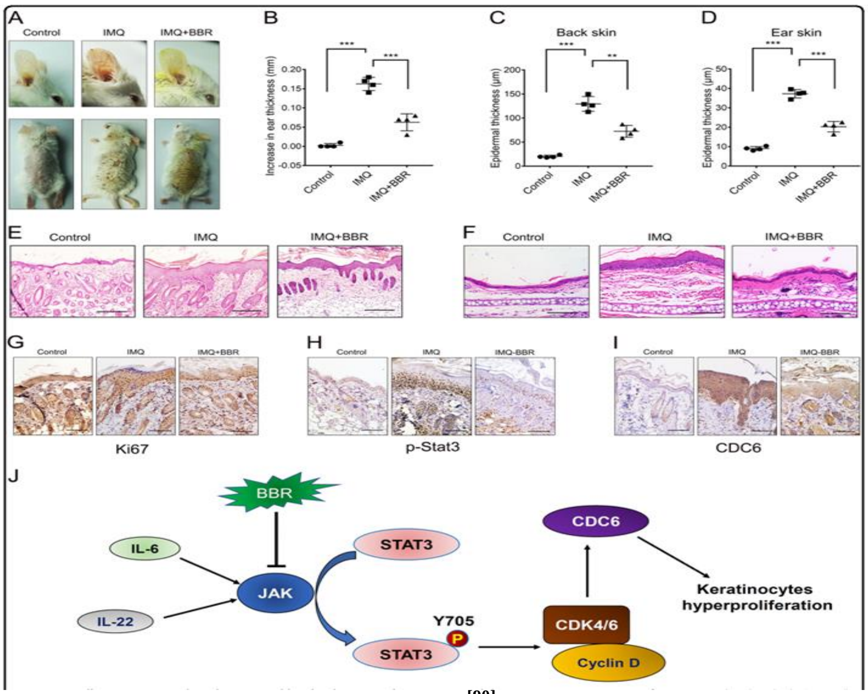


Figure:7[90]

4.1 Limitations of berberine usage: P16

Marek, R., and J. Dostál et al. (2007) According to records, just 0.5% of the berberine was absorbed in the small intestine, and once it was in the bloodstream, this level drastically dropped. Several clinical studies suggested using emulsifier enhancers to boost berberine's absorption rate and maximise its therapeutic effects. Clinical studies looked into several FDA-approved food additives, such as Quillaja extract and TPGS. However, it was thought that the best way to increase absorption was to use nano-formulations.[91]

Magnetic nanoparticles as berberine nanocarriers

(M. M. Lu and W. F. Dong et al., 2017) In the presence of a magnetic field, magnetic nanoparticles demonstrated potential for targeted and regulated drug delivery. Numerous formulations of iron oxide nanoparticles have been shown in research to enhance the effectiveness of medications and regulate the progression of psoriasis in model organisms. For delivering active compounds to specific locations, iron oxide nanoparticles were thought to be the best choice. To find out if the infection has cleared up, a compound of iron oxide nanoparticles and berberine (Fe OBBR) was injected into the back legs of mice that were solidly infected. Magnetic field orientation performed effectively when the Fe OBBR complex was also given orally in different mice. Histopathological studies of apoptosis revealed that these biocompatible nano-drug combinations did not affect the neighbouring healthy cells.[92] Drug-loaded magnetic nanoparticles prepared by the co-precipitation approach effectively co-delivered anti-psoriatic drugs and magnetic particles. In Prostatic Psoriasis DU145 4 Cell 4 models, this successfully halted the proliferation of psoriasis cells. Gene expression investigations, such as comet assays and QRT-PCR, revealed a mechanistic link between changes in Bax and Bcl expression levels and the activation of caspase activity, which triggered apoptosis.[92, 93]

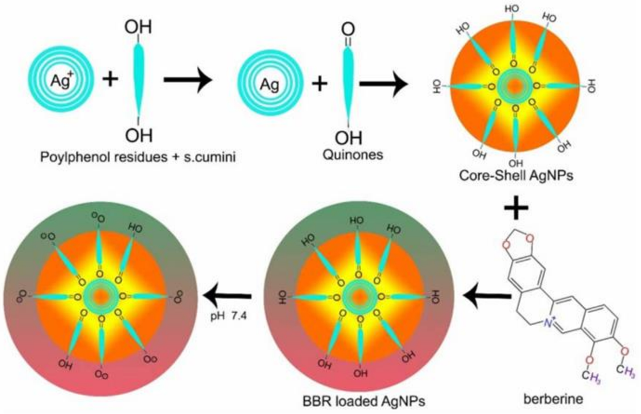


Fig. 8: Synthesis of berberine-loaded silver nanoparticles.[94]

Treatment of Psoriasis: P17

(G. G. Krueger and C. Griffiths et al., 2005) Eliminating psoriatic lesions and preventing their recurrence were the objectives of psoriasis treatment regimens. Many therapeutic approaches were effective in resolving lesions, but preventing recurrence was more challenging. There wasn't a permanent solution. If the disease did not reappear after therapy ended, it might have been due to a natural remission rather than the effectiveness of the medication.

Table 4: Adjunctive, Topical, and Systemic Therapies for Psoriasis.

Therapeutic Approach	Details	Notes/Considerations	Reference
Adjunctive Therapy	1. **Lubricating Oils** – Added to bath water to help lubricate psoriatic plaques and facilitate scale removal. 2. **Emollients/Ointments** – Hydrate skin and relieve itching. Selection should avoid volatile oils or perfumes that can worsen condition. 3. **Rest and Nutrition** – Important for overall health and well-being. 4. **Antianxiety Agents** – May help reduce anxiety related to psoriasis. 5. **Trauma Prevention** – Skin trauma can worsen psoriasis.	Use with caution; avoid irritating ingredients in skincare products.	[95]
Topical Therapy	**Common Agents** – Glucocorticosteroids, keratolytics (salicylic acid, sulfur), anthralin, and coal tar. Topical therapy is often the first line of treatment. Combination therapy is common due to different mechanisms of action.	Tailored to lesion type and severity. **Combination therapy** may enhance effectiveness.	[96]
Glucocorticosteroids	Used to reduce epidermal keratinocyte mitosis via anti-inflammatory effects. Available in sprays, ointments, lotions, and creams. May require occlusive dressings for better absorption.	**Potency**: Higher potency steroids (fluorinated compounds) used for resistant lesions. Prolonged use can lead to **dermal atrophy** and **systemic absorption** risks.	[97]
Keratolytics	Salicylic acid (1-20%), sulfur, and resorcinol used to aid plaque removal. Salicylic acid is the most effective and least toxic. May cause systemic toxicity in large doses.	Start with low concentrations to minimize irritation.	[98]
Anthralin	Reduces mitotic rate of epidermis. Applied as a paste (0.2-0.8%) on quiescent lesions, often after UV exposure or coal-tar bath (Ingram technique). **Irritant**: Can stain skin, should avoid normal or inflamed skin.	Reserved for **resistant cases**; requires specialized application.	[99]
Coal Tar	Used for its astringent, antiseptic, and keratoplastic properties. Combined with UV light in Goeckerman regimen for improved efficacy.	Can cause **folliculitis**, **photosensitization**, and **dermatitis**. Side effects lessened by gradual concentration increase.	[100]
Systemic Therapy	For severe, resistant psoriasis cases. Includes cytotoxic agents, corticosteroids, and psoralens with UV light.	Used when topical therapies fail. Requires careful monitoring due to potential **systemic side effects**.	[101]
Cytotoxic Agents	**Methotrexate** – Widely used for severe psoriasis. Folic acid antagonist that halts mitosis. Risks include liver toxicity and leukopenia. **Azaribine** – Formerly used	**Methotrexate** requires baseline tests and periodic monitoring for toxicity.	[102]

	but withdrawn due to risks.		
Corticosteroids (Systemic)	Used for life-threatening conditions like **pustular psoriasis** or rapidly progressing psoriasis. Can cause side effects such as osteoporosis, psychoses, and infection susceptibility.	Long-term use can lead to **flare-ups** and **progression** to pustular psoriasis.	[103]
Psoralens & UV Light (PUVA)	Psoralens (e.g., methoxsalen, trioxsalen) combined with UV light (320-400 nm) to treat psoriasis. Psoralens bind to DNA, inhibiting cell replication under UV light.	Effective but may increase risk of **skin cancer** and **cataracts**. Requires **informed consent** and careful monitoring.	[104]
Modified PUVA	Variants of PUVA, including the addition of topical corticosteroids or methoxsalen, aim to enhance efficacy and reduce treatment time.	May reduce patient exposure to UV light and improve outcomes.	[105]
Oral Retinoids with Radiation	Experimental approach involving **oral retinoids** combined with UV light to treat psoriasis.	Under investigation for potential efficacy and long-term safety.	[106]

Challenges In Topical Delivery of Drugs in Psoriatic Skin

Hadgraft, J. & Spuls, P. I. (2008, 1996) pointed out that new studies showed the stratum corneum (SC) was not an inert barrier but rather a "active wall" that stopped foreign substances (xenobiotics) from entering. This layer allowed for a certain amount of material penetration, but no molecule could easily and completely penetrate it. The primary means of penetration into the SC was through the intercellular lipids. Additionally, the degree of moisture of the SC was a significant factor influencing the rate of medication absorption within the skin. The SC's ability to "bind" water and the difference in water concentration between the skin's surface and dermis determined this level of hydration.[109] Various obstacles to transporting solutes via the skin were listed in Table 5.

Table 5: Challenges for Topical Drug Delivery.

Challenge	Details/Description
Variability in Percutaneous Absorption	Absorption rates can vary based on factors such as the site of application, the specific disease being treated, and the age of the patient.
Skin "First-Pass" Metabolic Effect	Drugs applied topically may undergo significant metabolism in the skin before reaching systemic circulation, altering their efficacy.
Reservoir Capacity of the Skin	The skin can act as a reservoir, storing drugs in its layers, which can affect the duration and extent of drug release.
Irritation Potential and Other Toxicities Due to Drug	Topical drugs can cause skin irritation, allergic reactions, or other toxicities depending on the drug formulation and the sensitivity of the skin.
Heterogeneity and Inducibility of the Skin in Turnover and Metabolism	Skin's characteristics (e.g., turnover rate, metabolic enzyme activity) can vary across individuals and conditions, affecting drug absorption and efficacy.
Inadequate Definition of Bioequivalence Criteria	There is a lack of standardized criteria for defining bioequivalence in topical drug products, leading to challenges in assessing their interchangeability and effectiveness.
Incomplete Understanding of Technologies to Facilitate/Reduce Percutaneous Absorption	A limited understanding of how to manipulate drug delivery technologies (e.g., nanocarriers, chemical enhancers) to improve or reduce percutaneous absorption effectively.

CONCLUSION

An important development in dermatological care is the application of nanotechnology to the treatment of psoriasis. Liposomes, niosomes, and metal-based nanoparticles like gold and silver are examples of nanocarriers that offer promising methods for boosting drug delivery, increasing therapeutic efficacy, and reducing the negative effects of conventional therapies. Even though these cutting-edge methods show promise in controlling psoriatic lesions and avoiding recurrence, issues including cost-effectiveness and production scalability still exist. To maximise these nanotechnology-based treatments and eventually provide safer and more efficient treatment alternatives for psoriasis sufferers, more research and development in this area is crucial. As medical knowledge of nanotechnology advances, it has the potential to revolutionise psoriasis treatment and enhance patient outcomes.

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