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Review

Beyond The Surface: Insights Into Psoriasis Pathophysiology and Therapy

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ABSTRACT

The autoimmune disease known as psoriasis affects 2-3 percent of all people worldwide while remaining as a continuous skin disorder. The clinical expressions from psoriasis adversely affect both physical health alongside mental wellness of patients. Pathogenesis arises via immune dysregulation that mostly affects keratinocyte proliferation through IL-23/Th17 axis activation. Genetic inheritances work together with environmental triggers as well as immune system responses to start and drive the development of diseases and progression. Medical professionals provide patients with mild psoriatic symptoms topical remedies yet systemic biologic drugs fight inflammatory cytokines in serious situations. A promising development emerges from JAK inhibitors and IL-23 antagonists which have become new therapeutic options. The study examines both the disease mechanism and medical approaches and new strategies for treating psoriasis.

Keywords: Inflammation; chronic skin disease; IL-23/Th17 axis; Chronic inflammatory diseases; Personalized therapeutics

INTRODUCTION

A chronic skin illness that is characterized by an immune response is referred to as psoriasis and is essentially categorized by a high rate of skin cell proliferation that translates to the formation of areas of skin with a thick silvery or red scale. It is a very disabling disease which reduces patients' quality of life and occurs in approximately 2-3% of the world's population. There are numerous comorbidities associated with psoriasis and some of them include psoriatic arthritis, metabolic syndrome, and cardiovascular diseases. It is an illness which results from stress, some infections, some drugs and most importantly genetics which predispose one to an over active or weak immune system. As an end result of immunological response, skin cells multiply at a higher rate, T cells are over-activated and cytokines are released. Anti-proteinase creams, PUVA treatment, systemic drugs, and biological agents comprise the treatment modalities that aims at decreasing inflammation and the formation of the new skin cells. Therefore, the disease process is slowly being unraveled, and personal treatments are being developed to improve the patient's outcomes and care even further.

Research on psoriasis identifies immune system dysregulation, genetic vulnerability (e.g., PSORS1), and a variety of clinical morphologies (plaque, guttate, pustular). For moderate to severe cases, treatment options include systemic medicines and biologics that target specific cytokines, as well as topical medications and phototherapy. New developments in personalised medicine using proteomics and genomes, as well as small molecule inhibitors (PDE4, JAK), present intriguing paths for more effective and precise treatment.

Long-term psoriasis is an inflammatory skin condition; it can also result in psoriatic arthritis, an inflammatory joint condition. It is characterized by the rapid skin cell growth that builds up to develop highly itchy, dry, red patches and thick, silvery scales. The mechanism through which psoriasis occurs remains a mystery to this date, though current research suggests that it has something to do with the immune system's T cells and another type of white blood cell known as a neutrophil.(1)

Pathogenesis

The root of psoriasis lies in the immune system not working right. T cells and dendritic cells play key parts in this. When someone's genes make them more likely to get psoriasis, and something in their

environment sets it off, it starts inflammatory processes. These processes involve interleukin-17 (IL-17) and interleukin-23 (IL-23). This leads to skin cells growing too fast and long-lasting inflammation.

Statistics Related to Psoriasis in the US: About 2-3% of people in the US have psoriasis. It costs a lot to treat and affects both physical and mental health. Because of this, we need good ways to manage it.

- **Biologics and Biosimilars in Psoriasis Treatment:** Biologics that target tumor necrosis inducing factor-alpha (TNF-α), IL-12/23, IL-17, and IL-23 have caused a revolution in how we treat psoriasis. These treatments give patients way better skin clearance and boost their quality of life. Biosimilars are cheaper options that help more people get these advanced treatments.
- **The Microbiome and Psoriasis:** New studies show that changes in skin and gut microbiome might perform part in explaining how psoriasis starts and gets worse. Getting a handle on how these tiny organisms affect psoriasis could open doors to new ways to treat it by tweaking the microbiome.
- **Psoriasis and Heart Problems:** People with psoriasis have a higher chance of getting heart issues because of long-term swelling in their body. Taking good care of psoriasis might help lower this risk. This means doctors need to come up with plans that look after both skin and overall health.
- **Psoriasis and Mental Wellbeing:** Psoriasis has a huge impact on people's emotions. Folks with this condition tend to feel down, anxious, or even think about self-harm more often. To support those dealing with psoriasis, it's crucial to look after their mental health as well. Psoriasis and Mental Wellbeing: Psoriasis has a huge impact on people's emotions. Folks with this condition tend to feel down, anxious, or even think about self-harm more often. To support those dealing with psoriasis, it's crucial to look after their mental health as well. This shows that doctors need to think about everything when treating psoriasis.
- **Genomic and Epigenetic Insights into Psoriasis:** Scientists have found many genes and control systems that play a part in psoriasis by studying DNA and how it works. This knowledge is key to create personal treatments and new ways to target the disease. This might lead to more specific ways to help folks with psoriasis.
- **Role of (IL-17 and IL-23.) Pathways in Psoriasis:** The (IL-17 and IL-23,) paths have a big impact on how psoriasis happens. They cause inflammation and make skin cells grow too .Using special drugs to block these paths has shown to work well. This proves how big a deal these paths are when it comes to treating psoriasis.
- **JAK Inhibitors to Treat Psoriasis:** Janus kinase (JAK) inhibitors are new oral meds that show promise for psoriasis. They give patients another choice besides biologics. People might like them better because they're easier to take and stick with.(2)
- **How Food and Lifestyle Affect Psoriasis Care:** Changing what you eat and how you live can help manage psoriasis. Losing weight, eating foods that fight inflammation, and quitting smoking can make the disease less severe. These changes are good for your overall health too.
- **New Stuff in Creams for Psoriasis:** People have come up with better creams and ways to put them on for psoriasis. These new treatments work better and patients use them more. They're a good option for mild or moderate psoriasis that doesn't need shots or pills.
- **Phototherapy in Psoriasis:** Phototherapy still plays a big role in treating psoriasis that's not too mild or too severe. This includes using UV-B (ultraviolet B) and puva (psoralen plus ultraviolet A) light. It's a good option to treat psoriasis for people who don't want to take medicine that affects their entire body.
- **Conventional Systemic Agents for Psoriasis:** Conventional Systemic Agents for Psoriasis: Doctors still count on old-school meds like methotrexate, cyclosporine, and acitretin to control psoriasis. These drugs help patients with severe psoriasis or when new treatments are not effective. They're a key part of treating this skin problem.(3)

To sum up, this review shows how complex psoriasis is and stresses the need to handle it in a complete way. This means using new discoveries about the disease and how to treat it. It's not just about one thing, but many parts working together to help people with psoriasis.

Classification of Psoriasis

Psoriasis is a chronic inflammatory dermatosis that develops in 1–3% of the total population(4). Current treatment plans would predict that only 20–30% of patients with plain psoriatic skin lesions should require topical treatments only. The lesions in the remaining group are more severe, which calls for the application of more complex therapeutic processes. Morbi ken originates from the Maori words meaning 'seat' or 'elbow' and the lesions commonly occur on the elbows, knees, scalp, umbilicus, and lumbar area. Psoriatic lesions are less frequent and present and may be seen on the face (49% of patients), nails (23–27%), palms and soles (12–16%), and intertriginous regions (21–30%)(5). Psoriasis is a condition that can affect both sexes, but it is more common in women and if one has a history of it in the family, it is likely to affect him/her at a younger age. It has an early onset pattern with the incidence rate ratios significantly higher in females at 10 years earlier and males at 30–39 and 60–69 years older. Experts believe psoriasis has an impact on 60 million people worldwide; its prevalence differs from country to country, with rates as low as 0.05% in Taiwan and as high as 1.88% in Australia.(6)

Psoriasis is classified as (Psoriasis Vulgaris, Inverse Psoriasis, Guttate Psoriasis, Pustular psoriasis) which can be discussed as Psoriasis Vulgaris can be described as the chronic plaque type makes up about 90% of psoriasis cases. You'll see red itchy well-defined plaques with silvery scales on top. These plaques can join together to cover big areas of skin. You'll often find them on the scalp, the outer parts of the arms and legs, and the body's main part. (7)Inverse Psoriasis in this condition shows up as reddened worn-down patches of skin in areas where skin rubs together. Guttate Psoriasis is a type that shows up as small red patches appearing out of nowhere. Kids or teenagers get it because of throat infections caused by group A strep bacteria.(8,9). Pustular psoriasis is the hallmark of pustular psoriasis is a cluster of sterile pustules that merge together.(10)

Mechanism of development of Psoriasis

Mechanism of Psoriasis can be explained in the following manner Keratinocytes, pDCs, mDCs, Th1 Cells, Th17 Cells, Th22 Cells, Neutrophils.

Keratinocytes

Keratinocytes are the principal cells that form the skin's outer layer or the epidermis. It forms a physical structure and also have significant function for initiating, maintaining and modulating skin immunity. Hypo keratotic layer's keratinocytes constantly transform into spiny as well as granular layers. Thus, in the end, the nucleus of all the cells evaporates and turn into the stratum corneum. Abnormal proliferation of the cells is well observed in psoriasis lesions and the maturation - bad final differentiation of the keratinocytes. When cells divide excessively it results to the situation where some of the keratinocytes are only partially transformed into pen cladding. This keeps the nucleus intact in epidermal keratinocytes causing a condition doctors call parakeratosis.(11) Dendritic cells (DCs), T cells, and keratinocytes interact as psoriasis develops. Activated keratinocytes release various cytokines when stimulated by germs or medications. At the same time, these keratinocytes produce antimicrobial peptides (AMPs), including LL37.These AMPs form with DNA or RNA in order to from complexes. Recent studies have revealed that the epidermis melanocytes' protein ADAMTSL5 also performs the function of autoantigen in psoriasis. It also activates CD8+ cells once it has been identified as a protein. Rodriguez et al have pointed out that this molecule is an antigen that triggers production of IFN-α/γ by plasmacytoid DCs by forming a complex with LL-37 and nucleic acid. This release also changes the myeloid DCs into mature DCs. In addition to presenting antigens to T cells and stimulating naive T cells to differentiate into Th17, Th1 and Th22 effector T cells, mature DCs migrate to draining LNs and express skin-trophic receptors CCR4 CCR6 and CCR10. Arising from this, these receptors go to other areas in skin tissue where they can exert an impact on the immune system.(12)

pDCs

pDCs are found in the non-lesional and lesional skin of patients with psoriasis whereas such cells are not found in healthy individuals' skin. Moreover, they found out that patients with psoriasis have higher levels of pDCs in their skin. In imiquimod induced psoriasis model, pDCs which are responsible for synthesis of IFN-α/β lead to skin inflammation mimicking psoriasis(13). pDCs remain refractive to DNA or RNA from stressed or dying cell when homeostasis remains intact. In psoriatic inflammatory conditions, AMP form complexes with nucleic acids and these complex structures are considered to be autoantigens. TLR9/TLR7 agonist was found in this autoantigen and through the activation of pDCs producing type I interferon leading to activation of T cells and development of psoriasis. A research conducted with the help of a xenograft mouse model showed that inhibition of type I interferon signaling or prevention of pDCs from producing IFN-α also affected the T cell proliferation and activation as well as psoriasis development (14).

mDCs

We observed a significant increase of mDCs in psoriatic lesions. Zaba et al identified that psoriatic lesional skin contained approximately 3 × 10^3 CD11c+ mDCs as compared to the non-lesional skin of psoriasis patients and normal subject's skin. The sharp increase in the number of mDCs infiltrating skin lesions confirms the hypothesis that mDCs are involved in the development of psoriasis(15). IFN-α and IL-6 pro-inflammatory cytokines that pDCs produce, has the ability to activate mDCs of macrophage derived CD8 cells in lesions corresponding to psoriasis. The nucleic acid-LL-37 complex also engage TLR8 on mDCs that provokes TNF-α and IL-6 production as well as mDC maturation. When mature, mDCs transform into -formed antigen-presenting cells and secrete number of cytokines which influence and activates the Naïve T cells such as (,IL-12, IL-23, IFN-γ TNF-α, IL-1β, and IL-6,). Specific cytokine signals encourage the naive T-cells to transform into specific subgroups such as (,Th-1, Th-17 and Th -22,)(16). There are also ordinarily DCs but additionally an inflammatory specified subpopulation in psoriatic skin has also been identified. This inflammatory group is heterogeneous and synthesizes numerous cytokines(17).

Th1 cells

Th1 CD4+ T cells produce TNF-α, IL-2 & CD4+ T cells that clumps together is known as Th1 cells makes TNF-α, Il-2, and Inf γ. IL-12 makes the T naive T-cells to differentiate into Th1 cells and leads to the enhancement of IFN-γ production(18). African and his team found that individuals with active psoriasis had higher amounts of IFN-gamma, TNF-alpha, and IL-twelve in their blood, which linked to how severe their condition was. Studies also showed psoriatic lesions had many more Th1 cells. IFN-γ from Th1 cells makes antigen-presenting cells create and release CCL20, a chemokine, and activates these cells in psoriasis(19).Therefore, CCL20 recruits IL-17Aplus T cells to the damaged site increasing skin-local inflammation. It also enhances the body's immune response in synergy with IL-17A by promoting increased production of key antimicrobial peptides by keratinocytes. Activated keratinocytes releasing Interleukin 1-family cytokines, such as interleukin-18 and interleukin IL-1β are crucial for Th1 dependent functionalities and for initiation of Th17 differentiation. Lin et al demonstrated that Th1 cell increase affects the initiation of the disease in psoriasis(20).

Th17 cells

Th17 cell plays a key part in how psoriasis starts & gets worse. Th(17) cell, a type of CD4plus T cell make IL-17A. These cells need the RORγt transcription factor to grow. When naive T cells get signals from cytokines like IL-23, IL-6,TGF-β, and IL-23 IL-1β, they start to make RORγt and become active(21). This leads to the creation of Th17 cells. Most Th17 cells found in psoriasis patches cause harm and directly affect how psoriasis begins and worsens. Th17 cells have a major influence on people with psoriasis and animals used in psoriasis studies. When you put imiquimod on skin, it lead to symptoms like (psoriasis) in mice that scientists use to study this condition. It has been suggested that this process is mediated by the Th-17 axis/IL-23. Neutralizing IL-17 antibodies or depletion of either IL-23 or IL-17A has been noted to alleviate features of psoriasis and decrease the severity of psoriatic disorder(22). Proof suggest that Th17 cell contribute to the development of psoriasis in clinical trials and in mice. Moreover, Fujishima also demonstrated that lesional skin of psoriatics had a significantly higher density of CD4plus T cells, which were producing IL-17A, comparing with normal skin and Carlo et al(23).

Th22 cells

Th-twenty-two cells produce IL-twentytwo, a cytokine that causes keratinocytes to grow. Luan and colleagues found that psoriasis patients with great severe symptoms also had higher levels of Th22 cells and IL-22 in their blood. Too much IL-22 makes the skin release chemicals that attract neutrophils (CXCL8, CXCL5, and CXCL1) and antimicrobial proteins (S100A9, S100A8, S100A7)(24). These overproduced molecules help psoriasis to develop. What's more, IL-22 blocks the simple differentiation of keratinocytes & slows down the skin's ability to heal(25). Ekman and colleagues found that IL-twenty two has a direct impact on keratinocytes encouraging cell stemness and excessive growth. Zheng and colleagues found that IL-twenty two leads to epidermal thickening and psoriatic skin inflammation by setting off the STAT3-controlled IL-23 signaling pathway. A lack of IL-22 reduces skin inflammation and overgrowth of the epidermis caused by IL-23. When active psoriasis is present Th22 cells in the epidermis produce more IL-twenty two, which produces keratinocytes resulting in thickening of the skin. On top of that even after six years without symptoms, Th-twenty-two cell in the epidermis of cured (psoriatic skin) keep releasing IL-twenty two. This suggests that Th22 might play a part in psoriasis coming back.

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Psoriasis has a strong link to neutrophils. A recent study concluded that people with psoriasis had a much higher neutrophil-to-lymphocyte ratio, which was tied to how bad their psoriasis was. Also, when patients got treatment for psoriasis, this ratio went down. This gives us more proof that neutrophils play a big part in how psoriasis gets worse(26). The skin lesion in psoriatic model (mice) show high levels of neutrophil chemokine), including CXCL2, CXCL1, and IL-8/CXCL8. Neutrophils are then recruited to the stratum corneum of the epidermis in the Lesions of psoriasis in response to these chemokines. Such buildup forms Munro's micro abscess the essential histological characteristic of psoriasis(27). Other than chemokines, neutrophils secrete other inflammatory mediators such as protease 3 which enhances the maturation of psoriasis. Protease 3 cleaves pro-IL-36 into mature IL-36 cytokine that enhances mDC response together with TNF-α and IFN-γ. Altogether, once psoriatic inflammation commences, neutrophils and Th17 cells 'interact' with one another. It is identified that Th 17 cells release IL-17A and IL- 17F within psoriatic tissues and that this cytokine stimulates neutrophils and is involved in chemotaxis connecting innate and adaptive immunity(28).Neutrophils are involved in the first line of defense in the human immune system. These cells fight germs in two ways: In that case they create extracellular bactericidal networks (NETs) or else they gobble up the microbes. NETs are nets of DNA which are coated with zit killing boast. Such matter involves histones MPO, cathepsin G high mobility group protein B1, germ-killing proteins as well as LL-37. Research shows that NETs relate to how bad psoriasis is. People with psoriasis have more NETs in their blood than others. Scientists have found more NETs not just in blood, but also in psoriasis skin patches. They saw this by looking for DNA and a protein called neutrophil elastase(29). Proteins that come from NETs may cause tissue damage in psoriasis and act as self-antigens. Studies have also shown that NETs might play a part in creating extracellular DNA in the epidermis. This process helps form nucleic acid-antimicrobial peptide complexes and could add to the underlying mechanisms of psoriasis.

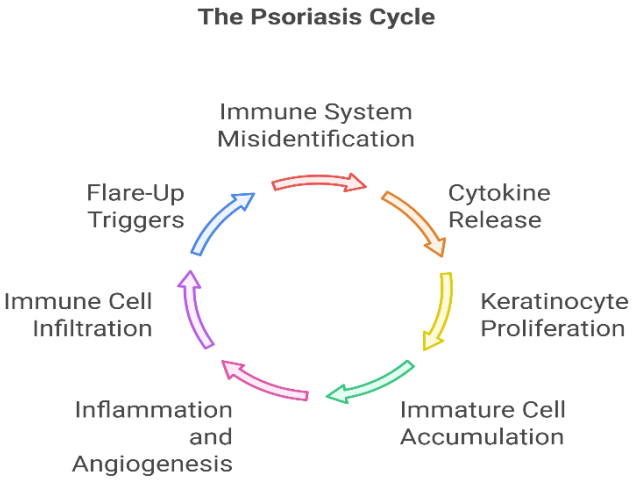

Fig (1): Development of Psoriasis

Herbal nanotherapeutics in psoriasis

The therapeutic potential of natural solutions makes them effective for psoriasis management since they demonstrate high efficaciousness with low toxicity risks. Historical people throughout China, India, Rome, Egypt, Greek territory and Syria engaged in scientific plant studies until they created Herbal Pharmacopoeias. Traditional books like Charak Samhita and Sushruta Samhita emerged from India and attract high professional recognition. The Food and Drug Administration in America classifies herbal medicines as insignificant or possibly dangerous to human health. The origins of medical discoveries rely on plant-based compounds despite the current classification of herbal medicines by FDA. Many natural compounds with their synthetic derivative versions underwent testing in experimental models throughout the past 15 years(30). Multiple experimental research models have been used to understand whether these substances have antipsoriatic properties. The botanical components provide the source for most natural compounds discovered.

Table 1: Different herbal nanotherapeutics in psoriasis

Name of the plant with important characteristics	Mechanism of Action	Type of drug delivery systems for psoriasis treatment	Reference
Aloe-emodin, Barbaloin	Certain cell proliferation enzymes become inhibited within this phytochemical application. Inflammation occurs along with the blocking of redox reactions that causes mitochondrial damage. The research demonstrated that psoriatic inflammation can harm mitochondria and destroy psoriatic epidermal membrane lipids. epidermal membrane lipids, etc.	Aloe emodin loaded chitin Nanogel, Barbaloin Gel, Emulgel, Hydrophilic cream	(31), (32)
Curcumin	The disintegrated cell nuclei population increased while Mitochondria released cytochrome c to stimulate caspase-9 and caspase-8 and blocked NF-κB activity as well as inhibited protein kinase B and extracellular regulated kinases 1/2. Additionally, Rhizoma anemarrhenae reduces Akt and ERK phosphorylation levels in cells and decreases the expression of IL-17A, 22, 17F, 6, 1 and TNF-α mRNA and protein while increasing the levels of involucrin and filaggrin in HaCaT cells and enhancing TRAIL- R1/R2 expression and reducing TNF-α induced IL-6 /IL-8 production.	Liquid crystalline systems, Liposomal gel, Turmeric Microemulgel, Curcumin Nanoparticles, Nanoparticle containing porous collagen patches, Curcumin-Loaded Hyaluronan Modified Ethosomes, Nanoemulsion gel, Liposphere gel, Nanosponge loaded topical gel, Polymeric Hydrogel, Nanoemugel,	(33), (34)
Capsaicin	Reduction of substance P from the terminals of native sensory nerve. Substance P functions as a neuropeptide because it produces effective vasodilator effects. The vasodilating activities of capsaicin potentially experience inhibition.	Cubosomes, Nanomiemgel, Capsaicin-loaded nanolipoidal carriers, capsaicin-loaded albumin nanoparticles	(35)
Kaempferol, Quercetin	The compound quercetin prevents the activation of both IFN-γ triggered STAT-1 in BV-2 microglia cells and LPS-governed NF-kB in addition to blocking STAT-1 and iNOS expression and stopping UV light from producing IL-1, IL-6, IL-8, IL-10 and TNF-α in human keratinocytes. Studies show that the intake of Kaempferol diminished psoriasis symptoms including erythema and scaling and thickness while lowering PASI scores and blocking murine Th17 development and reducing mRNA levels of IL-17A, 6 and TNF- but simultaneously enhanced FoxP3 and IL-10 gene expressions and psoriasis CD4 + FoxP3 + Tregs formation. The compound Kaempferol blocks the signaling pathways involving NF-B in psoriatic conditions and limits T-cell proliferation and mTOR signaling mechanisms.	Quercetin Loaded Liposphere Gel, Commiphora mukul	(36)
Amentoflavone (AMF)	The expression of mRNA blocker reduced M5-treated HaCaT cells skinfold thickness while decreasing cell reproduction and enhancing cell death and blocking the production of cyclin D1 & E tab3, IL-17A, and 22. The AMF treatment regulated proliferation of NFKB proteins including p65 NFKB in people with psoriasis.	Amentoflavone-loaded TPGS/soluplus mixed nanomicelles	(37)
Apigenin	The substance Flavone blocks NF-kB activity to minimize expression of E-selectin and IL-8. Apigenin's plays the role in generation of inflammatory cytokines (IL-6 & 8, TNF-α, GM-CSF) in human mast cells (HMC-1).	Cream, Ointment	(38)
Artesunate	The application inhibits cell proliferation as well as differentiation while triggering apoptosis and regulates immune responses and limits epidermal tissue thickness.	Cream	(39),(40)
Madecassoside and Asiaticoside	It inhibits keratinocyte replication.	Silver nanoparticles, Aqueous extract	(41)
Luteolin, Astilbin	The combination of reduced HaCaT activation through TNF-stimulation with enhanced keratinocytic proliferation along with elevated IFN-α and IL-2, 6, 17A, and TNF-α levels in CD4, CD81 T cells was reported by (138). Also, Astilbin controls the path of Th17 cell differentiation and isolated T cell IL-17 secretion while stopping signaling through Jak/Stat3 in Th17 cells.	Liposomes, Microemulsion	(42,43)
Corytuberine, columbamine, jatrorrhizine, oxyberberine, Berberine	The substance Berberine inhibits keratinocyte growth inhibitor while suppressing cell development through DNA intercalation and prevents the proliferation of autoreactive Th1 and Th17 cells and reduces T cell infiltration in both epidermis and dermis tissues.	Ointment, herbal gel	(44)(45)
Embelin	The substance reduces both IL-1 and TNF-α synthesis with simultaneous control of neutrophil-mediated myeloperoxidase	Extract	

	activity while it also affects pro-inflammatory cytokines which causes skin thickness and weight decrease.		
Toddacoumalone	The compound shows a moderate ability to inhibit PDE4 activity. Furthermore, it works to block inflammatory cytokines (TNF-α and IL-6) production in LPS-stimulated RAW264.7 cells.	Ointment	(46,47)

Co-morbid conditions related to psoriasis

Comorbidities come in two forms: Both psychological and physical. Onumah et al. noted that there are closer associations to such comorbidities among the patients with moderate to severe skin disease. This can go hand with disease aetiologies and or disease-causing pathways that the two are part of. Such comorbidities are likely to develop if there is high intensity of psoriatic skin disease.

Psoriasis has links to many mental health problems. These include poor self-image, sex issues, worry, sadness, and thoughts of suicide—up to 67% in one study. This makes sense, as mental health problems, along with drinking and smoking too much tend to happen more with any long-lasting condition one people can see(48). Many studies show that people with psoriasis shy away from social events always fear their symptoms coming back, and feel awkward, sad, or bothered by their shedding skin. People who get psoriasis when they're older might not face as much judgment as younger folks do(49). Doctors should use psychological and behaviour therapy to tackle this part of the disease. Psoriasis has big impact on a person social life and mental health. These mental health problems can make treatments less effective and can trigger or worsen the disease. Kimball and his team discovered that people with psoriasis had a much higher chance of developing mental health issues compared to those without the condition. Depression and anxiety were common. Other research has shown that up to 45% of psoriasis patients deal with anxiety, with women being more likely to experience it(50).

Metabolic syndrome

The relationship between the said syndrome and psoriasis exists. This syndrome comprises of obesity, high triglycerides, low high density lipoprotein cholesterol, is, and high blood pressure. It matters because this puts patient at higher risk of developing heart diseases. It estimated that Belly fat was more common among psoriasis patient as compare to low HDL cholesterol and high triglyceride level. Some diseases affected the women than men, and one of them is psoriasis. Overweight status when taken independently can cause psoriasis. Sterry and his team identify that compared to normal, overweight had more chances of having bad psoriasis, 3 of which involved more than 20% body surface area. Adipose tissue around the connection between the organ and the metabolic syndrome(51). Atherogenic dyslipidemia, with Lp(a), VLDL, total cholesterol, triglycerides, LDL and ApoB-II raised and HDL and ApoA-I low, has been associated with psoriasis, by a number of investigations(52). Females who have psoriasis increase their chances of getting diabetes at some point in their lifetime by 63 percent without psoriasis. Studies reveal, distinct relation between psoriasis and diabetes and high blood pressure. Researchers also found relationships between psoriasis and high blood pressure and elevated blood sugar in metabolic syndrome. This is particularly so because obese persons are always experiencing low-level inflammation, which might be a reason why obesity may cause psoriasis. The recent studies present the psoriasis severity's relationship with obesity using different parameters(53).

Cardiovascular disease (CVD)

Today's data regarding the connection between (psoriasis and cardiovascular disease) (CVD), where it is possible to associate psoriasis with an increased risk of CVD, in particular, if the patient has been a hospitalization or is on systemic treatment for a long time. It can also be noted that the prevalence of CV risk factors might be higher and, therefore, the risk of atherosclerosis and myocardial infarction connected with it. Psoriasis is a independent risk factor for myocardial infarction, among the young patients with severe psoriasis, the relative risk is the highest. Peripheral vascular diseases, other cerebrovascular illness, TIA, stroke and ischemic heart disease, angina, and MI are some of the diseases that are associated with psoriasis. Thus, it is common to find people with psoriasis developing these CV diseases that include pulmonary hypertension, structural cardiac abnormalities and arrhythmia occasionally. Imt, AS, and CAC are subclinical changes in the CV system that have a direct relation with (psoriasis)(54). The probability of developing (myocardial infarction) in cases of psoriasis where TNF-α inhibitors were given was significantly lower than when topical treatments were used with the incidence rate reduced by. Secondly, contrary to oral medication or phototherapy, TNF-alpha inhibitors for psoriasis was reported to have a non-significant decrease in

myocardial infarction incidence risk. Analyzing the risk and incidence rate of MI to that of using TNF-alpha inhibitors for psoriasis, the questionees observed that the former was lower than the outcome achieved from the topical therapy. Furthermore, analysis of the myocardial infarction incidence risk of both TNF-alpha inhibitors for treating psoriasis and oral medication or phototherapy showed a non-statically significant negative correlation between the former treatment and the former risk.(55).

Non-alcoholic fatty liver disease (NAFLD)

The most frequent symptom affecting obese people without evident reason is (Non-alcoholic fatty liver disease) (NAFLD). It includes diseases from nonalcoholic steatohepatitis NASH, cirrhosis fibrosis and hepatocarcinoma right up to simple fatty liver. Meta analysis of current opinion now regard NAFLD as the manifestation of metabolic syndrome in the liver. Besides, it affects endothelial function, which results in CV disease. NAFLD was significantly more prevalent in psoriatic patients who had higher blood IL-six & (C-reactive protein) (CRP), lower serum adiponectin and higher prevalence of metabolic syndrome than that of (Psoriasis). Individuals with psoriasis and NAFLD NASH are dangerous to liver by methotrexate (MTX) compared to other individuals with psoriasis or those NAFDL NASH(56). In the current study, both the metabolic syndrome and diabetes were found higher among NAFLD patient's group compared to psoriasis only. This was taken longer in the previous group where the disease of psoriasis and arthritis were presented. It was also found that patients with NAFLD who had (psoriasis) were of more advanced ill health. The mean steatosis, NASH, and fibrosis scores were significantly higher in the psoriasis patients and knew fewer NAFLD controls(57). A cross-sectional study by Binus et al. has suggested that major comorbidity related to the organization of psoriasis and IBD are significantly associated with higher rates of diabetes hepatitis autoimmune thyroiditis and seronegative arthritis. According to the authors, patients with IBD and those with psoriasis have other comorbidities, and some of them more frequent than in patients with psoriasis only. The psoriasis and CD inflammatory illnesses are mainly carried by Th-one cells that produce cytokines such as TNF-alpha and IFN-gamma. Concerning the genetic influences, which has a clear effect on the occurrence of Crohn's disease & Psoriasis, the families of the patient bear the brunt suffering from both diseases more frequently(58).

Cancer

Psoriasis is a skin condition that if its sufferers are prone to getting cancer then they will definitely get it. Patients who received whole-body treatment are most likely to be diagnosed with blood cancer other than melanoma and skin cancer other than melanoma. These patients are also predisposed to (non-melanoma) skin cancers while those receiving PUVA light therapy and this predisposition lasts up to fifteen years after ceasing (PUVA)(59). This does not hold true when it comes to bath PUVA. People as young as 18-years-old, isolated with very slight form of psoriasis face a high risk of developing cancer. Patients who are sixty-five years of age and above and who have psoriasis run a three-fold risk of developing lymphomas. Chinese people with psoriasis have higher chances of developing throat, lung/liver, mouth, pancreatic, esophageal, skin (Squamous cell carcinoma), bladder, kidney, breast (women) male genital, and blood cancer particularly in men(60). The general lifestyle risk factors for patients have also been established and it was found out that patients with a psoriasis age of 65 years and above have 3 folds risk of developing lymphomas. Some among them include mouth and throat, esophageal, lung, liver, pancreas, skin- squamous cell carcinoma, genital in males, kidney, female breast, bladder, and mycosis fungoides in males a are common among people with psoriasis(60). Psoriasis sufferers are at risk than the general population of getting some specific types of cancer(61).

Chronic obstructive pulmonary disease (COPD)

Psoriasis patients have a higher risk of Chronic obstructive pulmonary disease (COPD). A study conducted among the people of Taiwan revealed that for those with Psoriasis, the chances of staying out of the COPD were way lesser than other persons. They were also more likely to get COPD than the non-Asian NH White patients(62). In a large population study of case-control a more frequent coexistence of COPD in patients with psoriasis was identified (5. 7 % vs 3. 6 %, $P < 0.001$; OR = 1. 63). The researchers' claim that skin doctors treating the psoriasis condition should be aware of this connection. Lung specialists as well as regular physicians should offer them advice or maybe a diagnosis. They also should advise patients to stop smoking and reducing other COPD risks factors: Consequently(63).

A typical feature of spondyloarthropathies involves eye inflammation uveitis. When uveitis relates to psoriasis inflammatory bowel disease, or undifferentiated spondyloarthropathy, it might appear less. In these cases, it tends to affect the posterior pole more often, occur in both eyes, and last longer. Lima

and colleagues found that keratoconjunctivitis sicca was the most common eye condition linked to PsA(64).

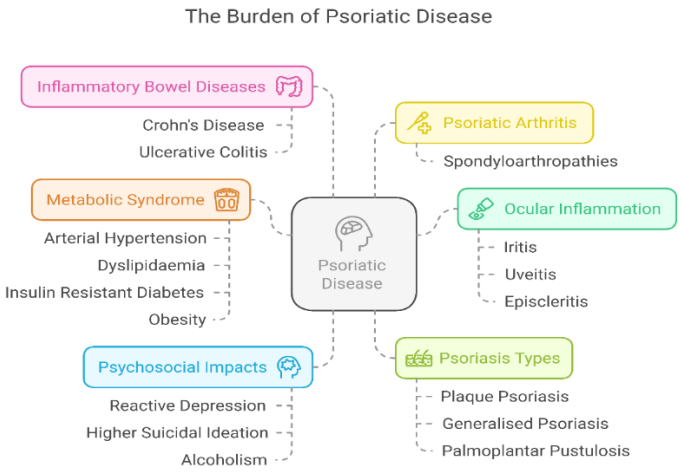

Fig (2): Comorbid conditions associated with psoriasis

Conventional treatment of Psoriasis

Fractional ablative lasers can boost topical drug delivery to the skin by making sized tiny ablation zones (MAZs). Now, it's possible to cross the skin barrier and improve drug delivery(65). Several studies have looked into topical methotrexate. Methotrexate is a folic acid analog. Its mechanism of action involves stopping the ribonucleotide transformylase of 5-aminoimidazole-4-carboxamide, which boosts intracellular and extracellular adenosine and has an anti-inflammatory effect. Doctors have used methotrexate as a systemic treatment for psoriatic arthritis and psoriasis for many years. In both cases, unlike its use in cancer treatment, methotrexate is given once a week in small doses (7.5-25 mg) by mouth, under the skin, or into a vein. However possible methotrexate side effects limit systemic treatment options(66).

Foams are colloids made up of two or three different phases: a gaseous dispersion phase scattered throughout a hydrophilic liquid continuous phase containing a foaming ingredient, and occasionally a third hydrophobic dispersed phase. Three transition stages are frequently seen in pharmaceutical aerosol foams: liquid in the can, propellant/aerosol when it exits the can, and foam on the patient's skin(67). Betamethasone dipropionate and calipotriol are available as a fixed combination that has been found to be superior to betamethasone ointment. A homogenous suspension of micronized betamethasone dipropionate is simple to achieve. However, cacipotriol presents a more difficult task and must be dissolved in a properly chosen vehicle component in order to guarantee uniform distribution. The product is made up of an emollient vehicle basis in which dimethyl ether and butane are combined to dissolve betamethasone and calcipotriol. Additionally, dimethyl ether functions as a solvent to improve the active compounds' solubility and enable full dissolution. This anti-psoriatic foam formulation has been shown to be more effective than systemic methotrexate or acitretin at week 12, and as systemic apremilast as determined by the PASI75 response, it is more effective at week 16(68).

Curcumin derived from the plant source is an anti-inflammatory which has been checked for possible application in topical psoriasis therapy. One of the most promising biocompatible biomaterials endowed with outstanding mechanical and film-forming properties is cellulose nanofiber (CNF). Five-hundred nanometers diameter fibres were; curcumin loaded and implanted in shea butter and Capmul MCM EP. A variety of analysis was also adopted in the study which included the Fourier transform infrared spectroscopy also known as the FTIR analysis as well as the scanning and transmission electron microscopy. Besides, atomic force microscopy was used to evaluate curcumin-CSF's local properties that could be related to the local characteristics. The similar analyses revealed that the curcumin deposition was found twice higher in the case of imiquimod induced psoriasis like dermatitis in mice as compared to the films without lipid component. By the action of curcumin-CNF, in dermatitis in vivo there was decrease in the pro-inflammatory cytokines which was near the range that was achieved by the common commercial topical corticosteroid. The films

also influenced the skins health and caused it to hydrate(69).

NLC

The next generation of solid lipid nanoparticles are NLCs which are prepared with a mixture of liquid and solid lipids. This leads to an order that is less coherent which hinders the capability of recrystallisation as well as increases the space of drug accommodation(70). Approximately 0. The above mentioned 1–30% w/w of solid lipids are dispersed in an aqueous phase to prepare SLNs. On the other hand, alcoves employ liquid lipids to exchange part of the solid lipid in NLCs and then employ both liquid and solid lipids at a proportion of 70:30 up to 99:1. 9:0. 1. Higher O/W ratio contributes to stability and therefore surfactants of certain ranges of concentration between 0. 5 and 5%(71).

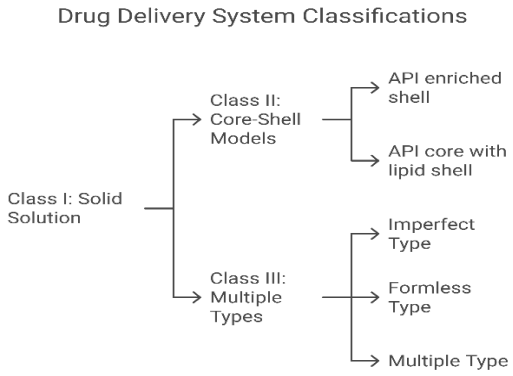

Fig (3): NLCs drug delivery system classification

It also shows the numerous advantages of NLCs over other nanocarriers such as polymeric nanoparticles, liposomes and SLNs(72).

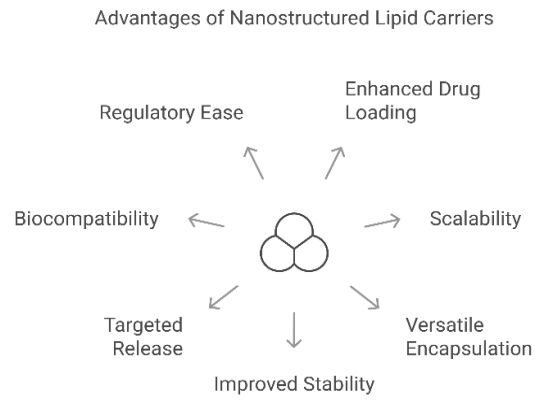

Fig (4): Advantages of NLCs

The lipids used to prepare NLCs are closer to SC lipids and their combined effect with SC lipids resulting in the establishing a depot which subsequently prolongs the stay of the drug in the skin. Moreover, oleic acid that is a liquid lipid can solubilise skin lipids and modify their arrangement of lamellae, which in turn enhances drug permeation and accumulation(73). Surfactants incorporated in NLCs enhance skin permeability, therefore increasing skin penetration, this is due to their ability to reduce skin lipids and increasing membrane fluidisation. The concern is to establish a lower particle size cut off of less than 200 nm in NLCs which offers a large surface area and good interaction with the stratum corneum thus enhancing the penetration of the drug. NLCs are known to be smaller in size and contain more lipid and therefore the product sticks on the skin surface almost fully. It is, therefore, coated on the SC in an even film. From the formulations of NLCs, an opaque look and an excellent skin feel are realized due to the non-transparent character, the presence of oil lipids, and the absence of thickening agents(74,75).

With little systemic escape, NLCs improve the therapeutic concentration and solubility of medications in the targeted tissues. There are a number of mechanisms that can account for the distribution of lipophilic medicines, as outlined by Pradhan et al. and Kilfoyle et al. First, there is an increase in the drug's improved solubility in lipid components, which heightens the concentration gradient at the skin's surface. The lipophilic medication can stay in its intercellular component as a depot and can penetrate the lower epidermal layers where psoriasis first appears more slowly due to the lipoid milieu of the stratum corneum. The lipophilic drug's partitioning is thus limited by the dermis layer's higher hydrophilicity. Additionally, psoriatic skin exhibits increased deposition because to its higher permeability than normal skin(76,77).

The transport of hydrophilic medications, like methotrexate, from NLCs has been studied by Lin et al. According to research, surfactants and derivatives of saturated and unsaturated fatty acids, which are utilised as a source of lipids, lower the functional barrier of SC and improve hydrophilic moieties' ability to penetrate.

Patent Information

In the past few years, a great deal of research on NLC-based formulations has been conducted and is patented under a number of organisations. Here, we have identified the seven most pertinent patents released on NLC-based formulations for the treatment of psoriasis after conducting a targeted patent search on the World Intellectual Property Organisation (WIPO) and Google patent search databases.

Table 2: Patent Information

Sr no	Title of Patent	Name of Inventors	Patent Grant No./ Application No.	Summary of Invention
1	A Method of Preparation of Triamcinolone Acetonide-Encapsulated Nanostructured Lipid Gamers For Psoriasis Treatment	Pradhan, M, Sahu KK Singh, D Singh, M.R., Yadav, K	A2021106678	• Triamcinolone acetonide loaded NLCS (TA-NLCs) were fabricated by melt dispersion technique for the treatment of psoriasis. • Docosahexaenoic acid (DHA) was incorporated to serve a dual role as an excipient as well as offer anti inflammatory activity. • Omega-3 fatty acid was used to enhance trans epidermal delivery. • Further, the NLCs were incorporated into the hydrogel matrix (TA-NLC hydrogel) for ease of application, proper spreading, and longer contact time. • The optimized TA NICs showed PS, PDI, ZP EE, and Di of 168.9 mm, 0.247, -26.6 mV, 01 12%, and 21.61%, respectively. • TA-NI. Cs and hydrogels followed the Korsmeyer Peppas and Higuchi kinetic model with R2 values of 0.9528 and 0.9063 respectively.
2	Nanostructured Lipid Carriers Containing Tazarotene and Pharmaceutical Formulations Containing Said Particles	Parmar, M. Patel, LD Rathod, L. Pankh, K	IN201921023616	• Cutina GMS, Cremophor EL, polyvinyl alcohol, and water were used as the solid lipid, liquid lipid, surfactant, and water, respectively. • TAZ-NLCS exhibited an average diameter of nearly 160-250 nm and a Z 130 mV • TAZ NLCs were further added in carbopol gel for topical application • Tazarotene-loaded NLCS (TAZ-NLCs) were formulated by melt emulsification and probe sonication methods
3	Antipsoriatic Effects of Clobetasol-Loaded Nanostructured Lipid Carriers on Imiquimod-Induced Psoriasis	Kudamada, R.R. Saggala, V S Veeram, J. R Palagali S	IN202141009486	• Clobetasol-17-propionate-loaded NLOS (CLB-NLCs) were formulated by melt emulsification and ultra-sonication technique lyophilized using 29% w/v mannose as a cryoprotectant. • CLB-NLCs with lipid: drug ratio of 7.5:1 and surfactant (Tween 20). et 1.5% w/v showed lesser PS, PDI, and greater EE of 81.3%. • CLB-NLCs were further poured into a gel using gel 1% w/w carbopol 934 • The ointment wears formulated by melt dispersion method by melting paraffin wax and stearyl alcohol under heating, followed by the addition of BHT and clobetasol. • Percent release of CLEB from ointment and gel system was found to be slower, ie, 35.1% and 74.6%, respectively after 24 h as compared to its solution form, which showed laster release of 94.5% within 7 h. • Epidermal thickness was greatly reduced in CLB-NLC gel-treated mice as compared to IMQ-treated mice. • CP-loaded NLCs gel showed a greater decline of IL-17, IL-22, und IL-23 levels ie, 529, 72.2, and 74.9% respectively as compared to ointment and negative control, and positive control groups. • TNF-a levels were found to be decreased by 51.2. 36. 8, and 49.2% in CLB-NLCs, ointment, and positive control treated groups respectively.

4	Clobetasol-Loaded Solid Lipid Nanoparticies and Nanostructured Lipid Carriers for Topical Treatment of Psoriasis	Kudamala, R.R Shaik, CB, Veeram, JR Medarametia KB Anna. B. Challe M.C Chiruthanur, G Ponnaleh, B.R.K Rangerietham, VP Palagali, S	IN202141046638	• A drug-lipid (Compritol) ratio of 14 and surfactant (Tween 80 (3%)) were used for the formulation of SLNS. • CLB-loaded NLCS were formulated by emulsification and sonication methods. • CLB-NLCs with drug lipid ratio (CLB to Compritol and oleic acid) of 17.5 showed significantly lower PS (even lower than SLNS). • Sodium azide (0.02%) was added to NICs to prevent microbial growth. • At lower drug loading, NLCs displayed faster drug release than SNLS. • At high drug loading, no noteworthy difference in drug release from SLNs and NLCS was observed. • The study demonstrated CLB loaded NLC gel had higher efficacy compared to SLNs and marketed formulations in psoratic management.
5	Topical Composition	Shah, M., Panigrahi, L: Patravale, V Kakade P	IN201921019828	• Apremilast or its pharmaceutically acceptable salt, ester, or prodrug was formulated using a li composition in various forms such as NLCS SLNS, liposomes, noisome, Ethosomes, transferosomes, etc. • NLCs consisted of solid lipid, liquid lipid, surfactant, co-surfactant, and water. Development of NLCS involved the following steps. • (A) Drug in the co-surfactant system: drug was solubilized in an optimized co-surfactant system. (B) Lipid phase: solid lipid and liqued lipid were added in the above system and melted in a water bath at nearly 60 °C. (C) Aqueous surfactant phase: surfactant was added in pre-heated water at 50-80 °C. (D)Emulsification step lipid and aqueous surfactant phases were mixed using a cyclomixer or overhead stirrer at a speed of 1000 rpm to obtain microemulsion, that was further dispersed in water under stiming at -3000 rpm

Association of CARD14 Single-Nucleotide Polymorphism With Psoriasis

Identification and Selection of nsSNPs

A full set of data from the CARD14 SNPs was obtained from the Ensemble genome browser platform. The research concentrated on missense or nonsynonymous SNPs (nsSNPs) because these variations can possibly alter protein structure. The genetic region contains 7311 nsSNPs. We applied various computational tools to organize deleterious nsSNPs which potentially alter CARD14 protein structure because of their potential association with the disease. The research evaluated six techniques to classify deleterious nsSNPs including SIFT, Polyphen2, Reval, CADD, MetaLR and mutation assessor(78)(79). The main function of SIFT is to identify nsSNPs into two binary categories: deleterious and tolerated. Among the 3331 nsSNPs SIFT labeled deleterious yet all other nsSNPs received either tolerated or less deleterious classification. Polyphen2 evaluates protein function and structure alterations by analyzing evolutionary data between different species. The evaluation assigns substitutions to three classification groups that include probably damaging alongside possibly damaging and benign outcomes. Polyphen2 classified 2984 nsSNPs found in the CARD14 gene as probably and possibly damaging through its analysis. The tool differentiates substitutions between three distinct groups which include probably damaging and possibly damaging and benign. Polyphen2 analyzed 2984 nsSNPs in the CARD14 gene and determined them to be probably and possibly damaging. The bioinformatics tools CADD and MetaLR and Revel organized nsSNPs according to their deleterious and benign status. Three other analysis methods showed a reduced number of substitutions as harmful in comparison to SIFT and Polyphen2. The assessment

of disease-related nsSNPs by CADD, Revel and MetaLR predicted 61 while Revel predicted 159 and MetaLR predicted 16 nsSNPs. The mutation assessor predicted 24 nsSNPs as highly damaging according to its evaluation(80).

Genotyping of CARD14 in Diseased and Control Samples:

Sanger sequencing sequenced all regions containing the selected nsSNPs of the CARD14 gene. Analyses of sequencing data enabled investigators to detect which nucleotides existed or not at the chosen positions between diseased patients and healthy control specimens. The observed allele frequencies among samples served to calculate odds ratios at 95% significance levels for determining the psoriasis-related associations between SNPs. Between eighteen predicted SNPs two of them rs2066964 and rs34367357 proved associative to psoriasis. An odds ratio evaluation showed that both rs2066964 (R547S) and rs34367357 (V585I) nsSNPs exhibited 1.01 and 1.49 values respectively. Our study population did not connect any of the new nsSNPs discovered through computational algorithms with psoriasis. An analysis was performed to check for rs2066964 and rs34367357 correlations with BMI, psoriasis severity scores and the occurrence of joint pain. Most psoriatic patients from all BMI categories carried heterozygous results. The G homozygous genotype existed in every BMI category apart from the underweight patient group. Most of the diseased individuals demonstrated no presence of homozygous G genotypes in the analysis of rs34367357. The heterozygous state in rs34367357 seems to offer possible disease resistance to affected individuals. The homozygosity and heterozygosity distribution patterns were measured in psoriatic patients who experienced joint pain as well as those who did not experience this symptom(81). The research showed that heterozygous genotype was dominating among patients who experienced joint pain alongside the G-homozygous genotype as the most frequent in patients suffering from pains.

Conclusion

Psoriasis is a common recapitulative nonsyndromic skin disease with prevalence of 1-3% impacting the global population with multifactorial genetic immuno-inflammatory root cause. The disease interacts with different immune cells such as keratinocytes, dendritic cells, and T cells, Th1, Th17 and Th22; revealing an inflammation process and excessive skin cell production. Neutrophils actually worsen the situation and also involved in the formation of the lesion. Psoriasis has skin expressions in the form of plaques, commonly observed in skin sites like the elbow, knee, and the scalp and; has depressive symptoms like, depression, anxiety, and social isolation. Also, patients experienced higher rates of comorbid with cardiovascular disease, metabolic syndrome, non-alcoholic fatty liver disease, as well as ophthalmologic complications uveitis. The interventions also include topical medication for mild manifestations to the systemic therapies including methotrexate and biologic agents for moderate to severe manifestations. New drugs are in development including JAK inhibitors and Nano structured lipid carriers (NLCs) which present better options especially when it comes to improving drug permeation in the skin. Formulations based on NLCs which improve the drug dissolution rate and its concentration in the skin have shown higher efficacy than the systemic treatment involving methotrexate for acne-vulnerable skin conditions. Curcumin encapsulated in cellulose nanofibers are as well exhibiting anti-inflammatory properties for cutaneous application. The new advances in formulations of anti-psoriatic foams have been described as a step up in the treatment management. Likewise, counselling has not lost its importance in the treatment of psoriasis since this condition does have a tendency of impacting the psychological well-being of the patient. In the last analysis, genetic and immunological studies on psoriasis along with development of drug delivery system further define the future perspective. In this context, the comprehensive and sided approach including the physical and psychological treatment is required for the further management of this complicated disease.

Future Prospects

The future prospects of psoriasis treatment focus on innovative therapies, personalized medicine, and integrated care**.** Promising new treatments include JAK inhibitors and microbiota-based therapies**,** which have shown positive clinical trial results, particularly for patients unresponsive to conventional treatments. Genomic research is paving the way for precision medicine, allowing targeted therapies based on a patient's genetic profile, enhancing treatment efficacy, and reducing trial-and-error approaches. Additionally, addressing co-morbidities such as cardiovascular disease, metabolic syndrome, and mental health issues is crucial, promoting a multidisciplinary approach involving dermatologists, cardiologists, and mental health professionals. Future research also highlights advancements in topical treatments, such as fractional ablative laser technology and curcumin-based formulations,

improving drug penetration and patient compliance. The globalization of clinical trials and data integration across populations will refine treatment strategies, ensuring more effective, inclusive, and personalized care for psoriasis patients worldwide.

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