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The treatment of psoriasis via herbal formulation and nano-polyherbal formulation: A new approach

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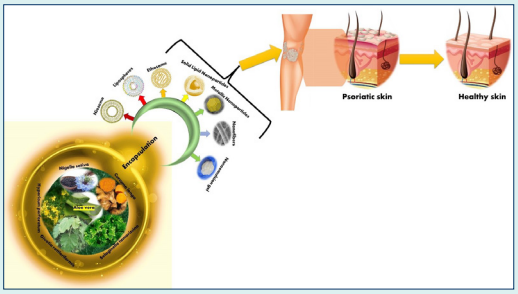
Abstract



Psoriasis is a chronic condition that can strike at any age. This sickness is associated with inflammatory problems that impact all humans in the world. Psoriasis is more common in Scandinavians than in Asian and African populations due to a combination of factors such as age, gender, geographic location, ethnicity, genetic and environmental factors. Immune stimulation, genetic contribution, antimicrobial peptides, and other significant triggers such as medicines, immunizations, infections, trauma, stress, obesity, alcohol intake, smoking, air pollution, sun exposure, and particular disorders cause psoriasis. Numerous clinical research investigations are now underway, and therapeutic alternatives are available. However, these therapies only improve symptoms and do not accomplish a complete cure; they also have dangerous and undesirable side effects. Natural products have gained popularity recently due to their great effectiveness, safety, and low toxicity. Natural formulations of various nanocarriers like liposomes, lipospheres, nanogels, emulgel, nanostructured lipid carriers, nanosponge, nanofibers, niosomes, nanomiemgel, nanoemulsions, nanospheres, cubosomes, microneedles, nanomicelles, ethosomes, nanocrystals, and foams, have significantly contributed and encouraged advancement in psoriasis disease treatment. These phytochemical-loaded new nanoformulations address several issues associated with natural products in conventional dosage forms, such as instability, poor solubility, and limited bioavailability. This article reviews some of the intriguing phytochemicals, as well as their possible molecular target locations and mechanisms of action, which may assist in the development of more specific and selective antipsoriatic medicines. Exploring and understanding phytochemicals' functions will allow for more site-specific psoriasis treatment techniques. This review concluded the psoriasis disease with phytoconstituent loaded herbal or polyherbal nanocarriers and their mechanistic approach.

Introduction

An immune-arbitrated inflammatory disease with autoimmunistic pathogenic features, psoriasis affects the scalp, skin, lower back, and joints (elbows and knees) and is chronic, painful, disfiguring, noncommunicable, and debilitating, with no treatment. It may develop at any age, although the majority of cases occur between the ages of 50 and 69. Psoriasis affects at least 100 million people globally, with prevalence estimates ranging from 0.09 percent to 11.43 percent. This makes psoriasis an important global health issue.[1] Worldwide, between 2 and 4% of the population suffer from the condition, which is more prevalent among Scandinavians than in Asian and African populations. This variance is due to a combination of variables such as age and sex as well as geographic location, ethnicity, genetic and environmental factors. Plaques of varying sizes and colors are seen in patients with psoriasis because of the unusual production and differentiation of keratinocytes.[2] Most psoriasis sufferers have silver-white scales covering their chronic erythematous plaques on their knees, elbows, scalps, umbilicuses, and lower back.[3] Diabetes, metabolic

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syndrome, cardiovascular disease, psoriatic arthritis, and type 2 diabetes are only a few of the conditions that have been linked to the illness. In addition, sadness, anxiety, and suicidality are all on the rise.[4] Psoriasis is caused by a variety of conditions, all of which hurt a patient's life qualities and create a significant physical, mental, and societal obligation. Psoriasis sufferers and their families are mentally devastated by social rejection, prejudice, and stigma.[5] With an average age of 33, men and women alike are affected by psoriasis, which is more common in women. Early beginning, at the age of > 40 years (75 percent of cases), and late-onset, beyond the age of 40 years (25 percent of cases) are two distinct subgroups based on genetic and immunological characteristics. Light-skinned persons are more susceptible to this illness, whereas blacks are less susceptible (Table 1, Fig. 1).

Epidemiology of psoriasis

The disease is most prevalent in high-income countries like Australasia, central Europe, western Europe, and North America. The most significant adult populations impacted by psoriasis were found in the US, India, and China, with Germany, Brazil, France, and the UK following closely behind. Among adults, the occurrence of psoriasis ranged from 30.3 per 100 000 person years (95% confidence interval 26.6 to 34.1) in Taiwan to 321.0 per 100 000 person-years in Italy. Psoriasis rates ranged from 0.14% (95% uncertainty interval 0.05% to 0.40%) in East Asia to 1.99% (0.64% to 6.60%) in Australasia. Psoriasis rates were notably elevated in various regions including Western Europe, central Europe, North America, and high-income southern Latin America. The occurrence and frequency of psoriasis were closely linked to age, with the disease being less common in children and more prevalent in adults.[19]

Psoriasis etiology

In the last 30 years, psoriasis has been identified as a non-curable illness that incorporates immunological stimulation, genetic contribution, antimicrobial peptides (AMP), and other significant causes.[17,20]

Pathogenesis mediated by immune stimulation.

Psoriasis is a T-cell-mediated autoimmune illness that is characterized by a strong interplay between innate immune cells (macrophages, DCs, neutrophils), adaptive immune cells (T and B cells), and resident skin cells (e.g. melanocytes, keratinocytes, and endothelial cells), all of which contribute to the production of cytokines. It seems that these interactions increase and maintain chronic inflammation. APCs, such as DCs, are critical in the beginning stages of the disease because of their role as professional antigen-presenting cells.[2] Myeloid dendritic (MD) cells release IL-12 and 23 following cytokine activation. Native T cells are induced to become TH1 cells by IL-12. The endurance and multiplication of TH 17 and 22 cells are dependent on IL-23. IFN-gamma (IFN-gamma) and TNF-gamma (TNF-gamma) are produced by TH1 cells; IL-22 is generated by TH22 cells; and TNF-gamma is compounded by TH17 cells. The TH17 pathway, activated by IL-23, is regarded to be the most important of these routes.[21] These cytokines are responsible for the stimulation of keratinocyte proliferation, increases in angiogenic mediator and endothelial adhesion molecule synthesis, as well as immune cell infiltration into lesional skin and dermal blood vessels.[10,22]

Pathogenesis mediated by genetic contribution.

In certain cases, psoriasis might be caused by a hereditary predisposition. HLA genes, together with psoriasis susceptibility 1 (PSORS1) on chromosome 6p21.3, PSOR2 on chromosome 17q, PSORS3, PSORS4 on chromosome 1cenq21, PSORS5 on chromosome 3q21, PSORS6 on chromosome19p, and PSORS9 on chromosome 4q31, are considered to be essential. As a result of the chemotactic effects of their products on T lymphocytes, NK cells, and monocytes, the CX3CL1 (fractalkine) and CX3CR1 (receptor) genes may be responsible for psoriasis outbreaks. CARD14 (also called CARMA2), a part of the Caspase recruitment family, has been the subject of a recent study. This scaffold protein mediates TNF receptor-associated factor 2 (TRAF2) related stimulation of NF-B signaling. MALT1 inhibitors have recently been shown to target moieties that may prevent CARD14-mediated mutations, according to new research.[23]

Pathogenesis mediated by antimicrobial peptides.

Mammals, insects, and plants have antimicrobial peptides. AMPs are made up of 12–50 amino acids and destroy pathogens including bacteria, protozoa, fungus, and viruses. Many variables, including chemotactic factors, angiogenesis factors, and cell cycle regulators, influence inflammatory responses. Psoriatic lesions express b-defensins, S100 proteins, and cathelicidin.[24-26] These AMPs may contribute significantly to psoriasis, according to some research. Triple disulfide bonds within the molecule are found in the defensin peptides, which are cationic and divided into three groups: namely α, β, and θ. Human neutrophil peptides (HNP) 1 to 6 are six kinds of α-defensins, of which HNP 1–3 is found in the levels of psoriatic lacerations. Human b-defensins (hBD) 1–4 are four kinds of β-defensins. TNF-a and IFN-c activate hBD 2–3 in keratinocytes, which are extremely conveyed in psoriatic dimensions. The IL-17A and IL-22 induction of hBD 2 is also seen. Individual β-defensin copy counts are linked to genetic impacts on psoriasis susceptibility.[27-31] S100 proteins are low molecular weight (9 to 13 kDa) proteins with two calcium binding sites in helix–loop–helix patterns. The epidermis of both healthy and psoriatic individuals expresses 13 different S100

Table 1. Clinical Classification of Psoriasis with some important manifestations

Type of psoriasis	Unique characteristics & manifestations	Reference
Psoriasis vulgaris or plaque psoriasis	• Most prevalent type (85% to 90% patients) • Inflammatory red, raised, erythematous, dry, and irregularly shaped scaly plaques frequently coated in silvery or white scales and the skin around a psoriatic plaque may show *Woronoff's ring*, which looks like a white color blanching ring. • The most frequent areas affected are the scalp and behind the ears, the forearm/knee joint extensor surfaces (particularly the elbow and knee joints), and the skin of your face, palms, soles, and gluteal fold. • Plaques may develop various shapes and sizes including: Wavy or curvy linear patterns are more prevalent in this type called Psoriasis gyrate. Ring-shaped lesions, known as annuli in psoriasis, form around the disease's clearing in the center called annular psoriasis. Small, scaly papules line the openings of pilosebaceous follicles called Psoriasis follicularis. • Plaque psoriasis has distinct morphological subtypes referred to as rupioid and ostraceous.	5-9
Inverse psoriasis or flexural psoriasis or intertriginous psoriasis	• Affects between 12-26% of all instances of psoriasis. • Characterised by flat, strongly delineated, moist patches or plaques that are deep red or white and lack scales, and may be mistaken for candidal, intertrigo, or dermatophyte infections. This disease mostly affects the body folds, like axillae, antecubital fossae, infra- and sub-acromial creases and umbilicus; the groyne; the gluteal cleft; the popliteal fossa; and other areas of the body.	5,6,10
Guttate psoriasis or droplet psoriasis	• 20% affected by this among all psoriasis type. • Usually affects the children and adolescents and Characterized by many tiny scaly reddish plaques, drop shape papules and plaques, typically affecting the legs, trunk, and arms. Onset is related with streptococcal infection of the UTI (tonsils or pharynx) and preceding skin traits. Guttate psoriasis is converting into the plaque psoriasis in the adulthood of a third of individuals.	3,6,9,11,12
Pustular psoriasis	• Multiple, consolidating sterile pustules and erythema with non-infectious pus are the hallmarks of this condition. Categorized in two phenotypes 1. Generalized pustular psoriasis (GPP) or von Zumbush psoriasis • It's quite rare, yet it might be fatal. The hallmarks of this disease are the Inflammation of the stratum spinosum (spongiform pustules of Kogoj) and sterilized eruptions on the skin, which is characterised by episodic, extensive skin redness, diffuse erythema, and systemic inflammation. • Impetigo herpetiformis, the medical term for widespread pustular psoriasis during pregnancy, is another name for this condition. Red, pustular lesions that spread outward from the flexures and tend to cluster together are a hallmark of this condition. 2. Localized pustular psoriasis or Palmoplantar pustulosis psoriasis (PPP) • Erythema and scaling accompany the sterile yellow pustules that characterise palmoplantar puptulosis. This is categorized into two forms. **a.** Barber's pustular psoriasis: This is more seen in females and individuals those have family history of this type of psoriasis condition. This condition is identifying by the 2 to 4 mm-sized pustules on the palmoplantar area, particularly the thenar and hypothenar regions, which are erythematous. **b.** Acrodermatitis continua of Hallopeau: Sterile pustular eruptions on the skin of hands and feet causes substantial nail and distal phalanx loss; severe instances may even result in amputations.	7,8,11-13
Erythrodermic psoriasis	• Affects between 0.4%-7% of all cases of psoriasis. • There is an intense redness and peeling of the maximum surface of the skin (more than 75%) and is characterised by diffuse form of erythema with or without skin's scaling. • It is the highly dangerous form of the disease, causing hypothermia, iron deficiency, vitamin B_{12} and folate deficiency, electrolyte imbalances and high-output heart failure.	5,7,8,13
Psoriatic arthritis (PsA)	• There are many types of PsA, which is a musculoskeletal disease with inflammation that affects nails, skin, and joints with cardiovascular disease, uveitis, Osteoporosis, and subclinical intestinal inflammation. • Normal incidence of Psoriatic arthritis is between 0.02-0.1%, but its prevalence varies between 5.4-7.0% in psoriatic patients. Prevalence of PsA increases to 30–40% in situations of severe skin involvement, notably pustular psoriasis. • Five distinct clinical subgroups of psoriatic arthritis have been identified by Moll and Wright. 1. Classical PsA: (Nearly 10% people affected by this).It affects the distal interphalangeal joints of the feet and hands with nails. 2. Asymmetric oligoarticular arthritis: This is the highly common kind of joint involvement. Distal and proximal interphalangeal, metatarsophalangeal, and metacarpophalangeal joints are also asymmetrically damaged, with the knee joint. 3. Symmetric poliarticular form: Rheumatoid arthritis (RA) like symptoms is present. When correlate to RA, distal interphalangeal joints are generally impacted, and joints have a propensity to become ankylosed. 4. Arthritis mutilans: Osteolysis of the bones includes phalangeal and metacarpal is a hallmark of this disease. Sacroiliitis is commonly a contributing factor. For the most part, hands and wrists are included in this definition; but, feet might also be included. 5. Spondylitic form: Isolated spondylitis occurs in just 2% to 4% of the population. In most cases, it is linked to a condition known as peripheral arthritis. Asymmetric or symmetric sacroiliac joint involvement is present in this variant of ankylosing spondylitis.	13-15

Table 1. Continued.

Type of psoriasis	Unique characteristics & manifestations	Reference
Nail psoriasis	• Capillaries underneath the nail, whitening of nails and a pinhead sized depression, cracking of nail and subungual hyperkeratosis are all signs of a nail infection with yellow or brownish patches at below the nails. • The chances of nail psoriasis are more with patients of plaque psoriasis, which can manifest by small pits on nails, nail plate separation from the nail bed (onycholysis), oil spots/salmon spots or even nail plate crumbling (dystrophy).	16,17
Scalp psoriasis or sebopsoriasis	• Scalp is affected, seborrhoeic portions of the face (eg, eyebrows and nasolabial folds), and the postauricular and presternal regions. • Flakes that resemble dandruff, Sleek, and silvery white scales with itching and burning sensations cause that temporary baldness.	17,18

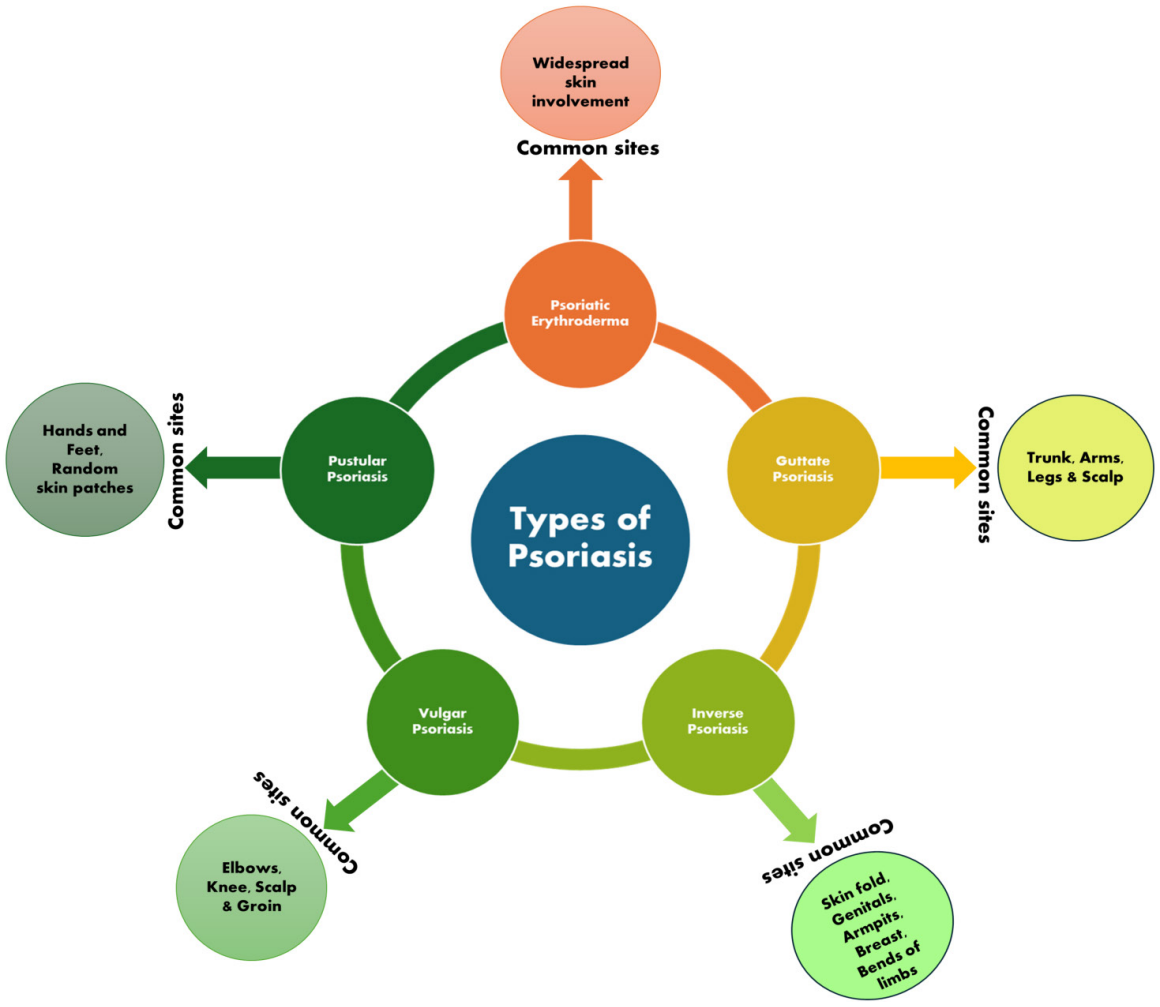

Fig. 1. Types of psoriasis disease.

proteins. S100A7 (psoriasin), S100A8 (calgranulin A), Psoriatic lesions are characterized by an increase in the levels of S100A9 (calgranulin B), S100A12 (calgranulin C), and S100A15 in the blood. Treatment of keratinocytes with interleukin-22, interleukin-17A, and interleukin-17F revealed increased S100A9 and S100A7 and S100A8 expression. S100A7 may be chemotactic in psoriasis.[32-34] It has been shown that the cathelicidin LL-37, which is AMP as well, is linked to the onset of psoriasis. As the LL-37 produced in the psoriasis skin is capable of enabling plasmacytoid DCs to identify self-DNA through TLR9.68, It's possible that it might have a role in inflammation in Fig. 2. DNA stimulation and LL-37 both activate type I IFN, which is significantly stated in psoriatic skin.[35-37]

Other important causes

Among known triggers of psoriasis, there are Air pollutants & sun exposure, vaccination, drugs, infections, physical trauma, obesity, diabetes mellitus, dyslipidemia, hypertension, smoking, alcohol, and stress.

Drugs

Some medications, such as imiquimod, an antiviral and

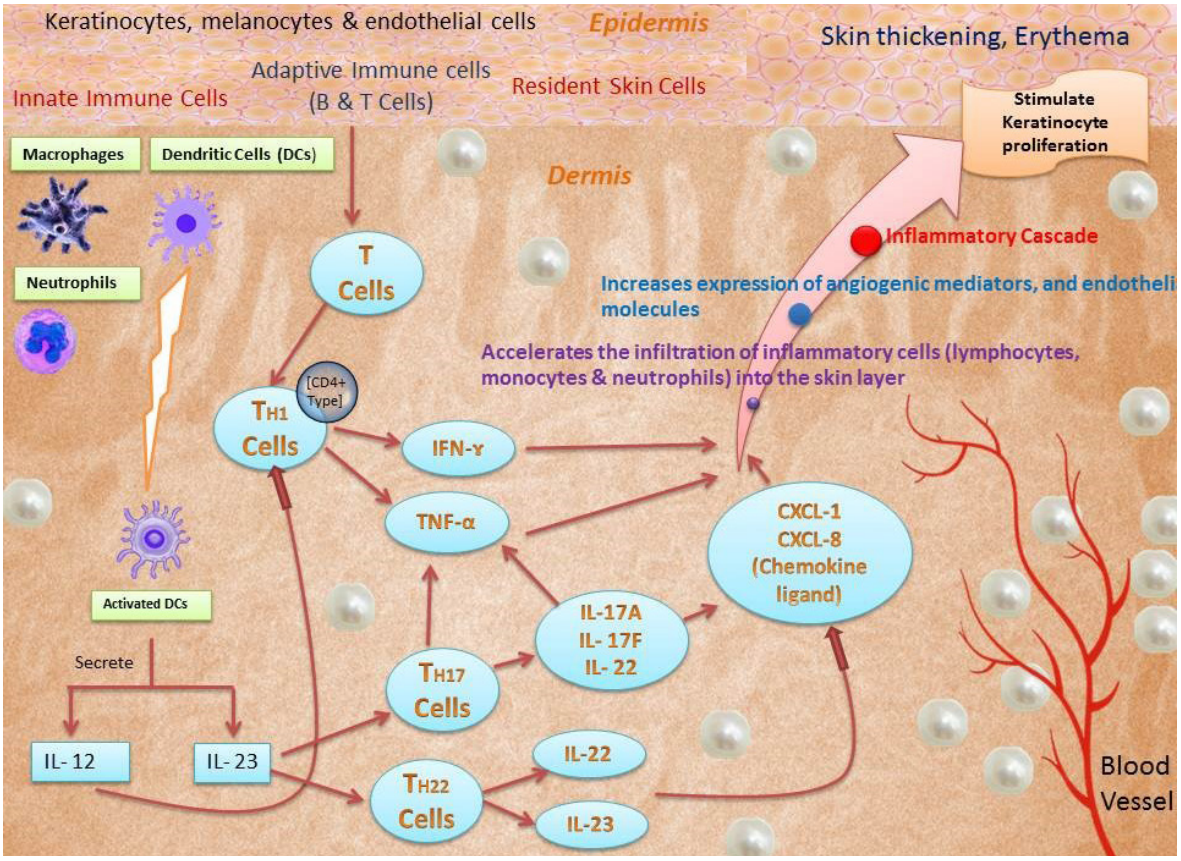

Fig. 2. Pathophysiology of psoriasis.

anti-proliferative drug, lithium, an antihypertensive (beta blockers), IFNs, and anti-cytokine treatments for psoriasis (anti-TNF antibodies), have been clinically related to the onset, aggravation, and exacerbation of the condition.[38] As one of the most well-studied psoriasis triggers to date, imiquimod promotes the type I interferon signaling pathway and is often employable in the therapy of warts and other nonmelanoma skin cancers in genital areas.[39-40]

Infections

Psoriasis, and more specifically guttate psoriasis, has been associated to a history of streptococcal throat infection, and similar T-cell clones have been identified in tonsils and skin lesions of individuals with plaque psoriasis.[41-43] The yeast Candida albicans is the more common kind of *Candida* that causes illness, and its colonization increases anti-fungal immunity, which may be involved in the etiology of psoriasis.[44]

Trauma

The Koebner phenomenon is caused by tattoos and surgical incisions, and psoriasis plaques form at the location of the trauma.[45]

Stress, obesity, alcohol and smoking

Despite several research showing a connection between psoriasis, stress, obesity, and smoking.[46-48] Many psoriasis sufferers and doctors feel that emotional stress exacerbates their condition, and this is a widely held belief. As shown by the Dermatology Life Quality Index scales, the connection in emotional distress and psoriasis is not straightforward. Stress-related illness was reported by 46 percent of patients in a comprehensive evaluation of 39 researches (32,537 individuals) that included 39 trials.[49] Psoriasis has been linked to smoking, drinking, and other risk factors. A comprehensive evaluation and meta-analysis found that patients with psoriasis were more likely to be existing or early smokers. Psoriasis is more likely to develop in those who smoke. Smoking has also been linked to pustular psoriasis lesions.[46,50-51] Several different types of drug-related psoriasis may occur, such as plaque, nail, palmoplantar, scalp, erythrodermic, and pustular.[38] Psoriasis development and aggravation are closely linked to obesity.[52-54] Another study that linked BMI with psoriasis looked at a much larger prospective cohort.[55]

Air pollutants and sun exposure

Ozone, Polycyclic aromatic hydrocarbons, oxides, volatile organic compounds, particles, heavy metals, and ultraviolet light (UV) are only some of the air pollutants that cause oxidative stress and harm to the skin.[56] A component of psoriasis' pathogenesis is cadmium, an air contaminant. Cadmium levels were greater in those suffering from psoriasis than those who did not have it.[57]

Vaccination

Vaccination may potentially cause psoriasis. Psoriasis may be triggered by influenza vaccination.[58] Bladder

cancer patients have received BCG injections as a kind of local immunotherapy, and one patient developed an erythrodermic pustular skin rash after receiving this treatment.[59] Adenovirus vaccination was linked to an enhanced risk of psoriasis, according to a retrospective analysis.[60] Other vaccinations, such as the tetanus-diphtheria and pneumococcal polysaccharide vaccines, may also cause psoriasis.[61,62]

Diabetes Mellitus (DM)

Psoriasis and diabetes mellitus have been linked in different meta-analyses.[63-65]

Dyslipidemia

Patients who have psoriasis have a greater prevalence of dyslipidemia, and the severity of their psoriasis is likely to cause their dyslipidemia to become even more severe. Previous research that included 70 people with psoriasis found that dyslipidemia was present in 62.85 percent of patients.[66-69]

Hypertension

Patients diagnosed with psoriasis had a higher overall frequency and incidence of hypertension, according to a meta-analysis. The results of this meta-analysis also demonstrated a correlation between serious psoriasis and an enhanced risk of hypertension development.[70] Those who suffer from psoriasis are more prone than the general population to have hypertension, as shown by multicenter, noninterventional research including 2210 participants with the disease, in which 26% of the participants had hypertension.[60]

Recently available treatments for psoriasis

Due to the very complicated pathophysiology of the Psoriasis illness, the treatment for this prevalent disease that cannot be cured currently primarily focuses on treating the symptoms rather than addressing the underlying cause. The choice of therapy is influenced by the severity of the psoriasis, as well as its location and any coexisting conditions. The body severity index (BSI), age, psoriasis with concurrent disorders, and psoriatic arthritis are among factors that are considered while developing a therapy strategy for psoriasis.[71] Local therapy, phototherapies, immunosuppressant medication, and other systemic treatment options are commonly included in the therapeutic choices for the control of psoriasis. These treatment opportunities are applied differently according to the various features of the psoriasis.[20] Psoriasis may be mild, moderate, or severe depending on symptoms. Mild to severe symptoms are commonly treated locally with corticosteroids, vitamin D, and its analogues. If local treatment fails or the condition worsens, phototherapy and systemic therapies should be tried. UVB and UVA phototherapies are combined with local therapy to boost effectiveness. Patients with photosensitivity, cataracts, or liver/kidney disease should not utilize phototherapy. When local and phototherapy fail, try systemic treatment with oral retinoids (acitretin), cyclosporine, Apremilast, methotrexate, Adalimumab, Etanercept, etc.[72] To be sure, long-term systemic therapy with synthetic medications may lead to hepatotoxicity and renal failure that can lead to fatalities as well as side effects, as well as undesirable consequences like high blood pressure or high cholesterol.[73,74] As a result, herbal therapy from nature is the greatest option for decreasing undesired effects, while innovative medication delivery technologies are a second option for modifying dose form.[75]

Herbal formulations for the psoriasis treatment

Natural solutions provide the potential to treat psoriasis safely and effectively since they have a high level of efficacy despite their relatively low level of toxicity. People from ancient civilizations in various places, such as China, India, Rome, Egypt, Greek, and Syria, conducted methodical and scientific research on plants, which eventually led to the development of Herbal Pharmacopoeias. Charak Samhita and Sushruta Samhita are two examples from India that are considered to be classical. Some regulatory agencies, such as the FDA in the USA, consider herbal medicines to be either inconsequential or possibly hazardous. This is even though the discoveries that led to the development of medicine were based on plant-based compounds.[76] Over the last 15 years, several natural compounds and their synthetic counterparts have been tested in a variety of experimental models to determine whether they possess antipsoriatic properties in Table 2. The majority of these natural compounds come from the components of plants.[77]

Herbal and polyherbal nanoformulations for the treatment of psoriasis disease

Traditional dosage forms like gels, ointments, creams, tinctures and lotions have poor or acceptable therapeutic efficacy for natural drug products due to the loss of skin ceramide and barrier functions that result in poor water absorption and hydration capacity when the skin is affected by the psoriasis. As a result, in order to get the most therapeutic benefit from natural medicines for treating psoriasis, the medications themselves must have the desired level of permeability and water holding capacity. Moreover, novel drug delivery systems such as liposomes, lipospheres, nanostructured lipid carriers, NE, crystals, and spheres niosomes, ethosomes, microneedles, and foams can be used to improve skin penetrability, possess hydration power, and target specific inflammatory cells or cytokines by natural drug products.

Improve skin permeability

Liposomes

Vesicular liposome delivery techniques are well-known in the cosmetics industry. Increased moisturization,

Table 2. Antipsoriatic activity of natural products from plant source

Name of the plant with important characteristics	Mechanism of Action	Type of drug delivery systems for psoriasis treatment	Reference
Aloe Vera Phytochemical *Aloe-emodin, Barbaloin*	Inhibition of certain enzymes involved in cell proliferation, inflammation, interference with redox reactions leading to damage of mitochondria, breakdown of psoriatic epidermal membrane lipids, etc.	Hydrophillic cream, Barbaloin Gel, Aloe emodin loaded chitin Nanogel, Emulgel	78-85
Curcuma longa Phytochemical Curcumin	The number of disintegrated cell nuclei increased Mitochondria discharges cytochrome c, Stimulation of caspase-9 and caspase-8, Block the NF-κB activity, and protein kinase B and also Inhibit the extracellular regulated kinases 1/2. Reduce the phosphorylation levels of Akt and ERK, Reduce the levels of IL-17A, 22, 17F, 6, 1, and TNF-α mRNA, TNF-α, and IFN- γ, whereas increase the involucrin and filaggrin, In HaCaT cells, increase the expression of TRAIL- R1/R2 whereas suppress the production of TNF-α induced IL-6/IL-8	Liquid crystalline systems, Liposomal gel, Nanoparticle containing porous collagen patches, Curcumin-Loaded Hyaluronan Modified Ethosomes, Nanostructured lipid carriers (NLC), Nanosponge loaded topical gel, Polymeric Hydrogel, Nanoemugel, Cellulose nanofiber (CNF), Nanogel, Silk fibroin hydrogel with polymeric nanoparticles, Nanoemulsion gel, Liposphere gel, Turmeric Microemulgel, Curumin Nanoparticles	86-106
Capsaicin annum Phytochemical Capsaicin	Reduction of substance P from the terminals of native sensory nerve. Substance P is a neuropeptide that has potent vasodilator activities. Capsaicin's vasodilating activities may be inhibited.	Lipidic Nanoparticles, Capsaicin-loaded vesicular systems (liposomes, niosomes, emulsomes and carbopol gel), Capsaicin Loaded Silver Nanoparticles , Lipid-polymer hybrid nanoparticles, Cubosomes, Nanomiemgel, Capsaicin-loaded nanolipoidal carriers, capsaicin-loaded albumin nanoparticles,	107-116
Nigella sativa Phytochemical Kaempferol, Quercetin	Quercetin inhibits IFN-γ activated STAT-1 induction in BV-2 microglia, LPS-activated NF-kB, STAT-1, iNOS expression and UV-induced creation of IL-1, 6, 8, and TNF-α in human keratinocytes. Kaempferol reduced erythema, scaling, and thickness, PASI scores, murine Th17 development, IL-17A, 6, and TNF- mRNA levels while increasing FoxP3, IL-10 gene expressions and psoriasis CD4 + FoxP3 + Tregs. Kaempferol suppresses psoriatic NF-B signaling and hampers T-cell proliferation and mTOR signalling.	Commiphora mukul and Quercetin Loaded Liposphere Gel	117-120
Givotia rottleriformis Phytochemical Rutin, Luteolin, Kaempferol	Block the keratinocyte cell division	Rutin and Gallic Acid Loaded Herbal Gel	121,122
Selaginella tamariscina, Selaginella pachystachys, Selaginella nipponica and *Ginkgo biloba* Phytochemical Amentoflavone (AMF)	Blocking mRNA expression diminished skinfold thickening, and decreased cell proliferation, accelerated apoptosis, and suppressed cyclin D1 & E, IL-17A, and 22 productions in M5-treated HaCaT cells. AMF also suppressed p65 NF-KB upregulation in psoriasis.	Amentoflavone-loaded TPGS/soluplus mixed nanomicelles	123,124
Hypericum perforatum and *Matricaria chamomilla* Phytochemical Apigenin (Biapigenin), Flavonoids	Flavone inhibits NF-kB and downregulates 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).	Ointment, Cream	125-127
Artemisia annua, Artemisia capillaries Phytochemical Artesunate, Essential oils	Inhibit proliferative, differentiated, apoptotic, immune-regulatory processes and epidermal thickness.	Cream	128-130
Centella asiatica or *Hydrocotyl asiatica* Phytochemical Asiaticoside and Madecassoside	Keratinocyte replication should be inhibited.	Aqueous extract, Silver nanoparticles	131-134
Smilax glabra Phytochemical Astilbin, Luteolin	Decreased TNF-induced HaCaT activation, and increased keratinocytic proliferation, CD4, CD81 T cells produced more IFN-α, IL-2, 6, 17A, and TNF-α. (138), Astilbin inhibits differentiation of Th17 cell and secretion of IL-17 of isolated T cells and block Jak/Stat3 signalling in Th17 cells	Microemulsion, Liposomes	135-141

Table 2. Continued.

Name of the plant with important characteristics	Mechanism of Action	Type of drug delivery systems for psoriasis treatment	Reference
Scutellaria baicalensis Phytochemical Baicalin	Baicalein slowed keratinocytes cell growth and produced morphological differentiation, and raised keratin 1 and keratin 10 (K1/K10) expressions.		142
Mahonia aquifolium Phytochemical Berberine (isoquinoline alkaloid), oxyberberine, jatrorrhizine, columbamine, and corytuberine	Reduce T cell infiltration in the dermis & epidermis and inhibit keratinocyte growth inhibitor, Berberine suppresses cell development by intercalating into DNA, and cell proliferation, with inhibition of autoreactive Th1 and Th17 cells.	Herbal gel, ointment,	143-148
Boswellia serrate Phytochemical Boswellic acids (KBA or 11-keto-b-boswellic acid) and (AKBA or acetyl-11-keto-b-boswellic acid)	Prevention of leukotrienes production by the inhibition of 5-lipoxygenase (5-LO)	Extract (Bosexil(®), cream, Nano Gel	149-152
Camellia sinensis, *Coffea Arabica*, *Cola acuminate* Phytochemical Caffeine	Caffeine reduces the activity of inflammatory pathways and slows the evolution of psoriasis.	Nanosponge loaded topical gel, solid-lipid nanoparticles (SLNPs) and nanostructured lipid carriers (NLCs)	97,153,154
Camptotheca acuminate Phytochemical Camptothecin and isocamptothecin	Down regulation of telomerase function leads to keratinocyte and antiproliferative apoptotic action.	Ointment, Tincture and extract	155,156
Cannabis sativa Phytochemical Cannabinoids, (Δ9-Tetrahydrocannabinol), cannabinol, cannabidiol, cannabigerol)	Decreased the proliferation of hyper proliferating human keratinocytes (HPV-16 E6/E7 transformed human skin keratinocytes).	Ointment, hydrophilic gel and transdermal patch	157-160
Vaccinium sect. Cyanococcus (blue-berry) Phytochemical Delphinidin	Reduced psoriasiform lesion pathological indicators, infiltration of inflammatory cell, inflammatory cytokine mRNA and protein expression, PI3K/Akt and mTOR inhibition.	Solution	161-165
Embelia ribes Burm Phytochemical Embelin	Inhibits IL-1 and TNF-α production as well as neutrophil-mediated myeloperoxidase activity, Reduce skin thickness and weight due to direct effect on pro-inflammatory cytokines.	Extract	166
Toddalia asiatica (L.) Lam. (T. aculeata Pers.) Phytochemical Toddacoumalone	Inhibit PDE4 with moderate potency, Also inflammatory cytokines release (TNF-α and IL-6) is Inhibited in lipopolysaccharide stimulated RAW264.7 cells.	Ointment	167-169

restoration, biodegradability, biocompatibility, and longer and delayed dermal release are only a few of the benefits of liposome treatment on the skin. When compared to alternative distribution technologies, their resemblance to biological membranes permits them to pass through the epidermal barrier.[170] Liposomal medicines are spherical means hydrophilic as well as lipophilic drugs are encapsulated within the spherical shell. Since they're so tiny, they're capable of delivering medication to particular locations.[171] Liposomes can interact with epidermal keratinocytes and lipids, resulting in improved medication absorption through the skin's surface layer.

Severe, resistant psoriasis is routinely treated with PUVA (Psoralen plus ultraviolet A radiation). Psoralen's therapeutic impact in psoriasis is hampered, however, by its poor skin deposition and low skin permeability. Therefore, Doppalapudi et al[172] formulated liposomal nanocarriers with psoralen, which involves binding of nanocarrier with gels to increase capabilities of skin adhesion and capacity to hold the water. Although the solution of psoralen remained confined to the upper SC, liposomal gels were able to overcome the SC barrier. Intracellular lipids in SC may be incorporated into the liposome bilayer structure when it interacts with skin, increasing diffusion of liposomal molecules into skin cells while maintaining their multi-bilayer structure.[173]

Dithranol is encased in phospholipid liposomes in the liposomal dithranol formulation. This formulation has been proven in early trials to cause very little skin irritation and to leave very little discoloration on clothing or skin. 0.5 percent liposomal dithranol gel proved to be equally efficient in treating stable plaque psoriasis as 1.15 percent dithranol cream, and it had essentially no local side

effects. Dithranol lipogel is more acceptable by patients and clinicians than presently available formulations because of its minimal fabric and skin discoloration and ease of washing.[174]

Psoriasis mice treated with psoralen solution saw their PASI score drop to 1.5, while those treated with psoralen liposome gel had their PASI score drop to 1. For psoriasis, the liposome gel demonstrated greater effectiveness, which may be attributed to an improvement in permeability. This enables the medicine to reach the dermis, where it may lessen inflammation-inducing chemoattraction of cells related to inflammation (mononuclear and neutrophils) and the presentation of inflammatory factors (such as IL - 17 and 22).[175,176]

Ethosomes

Ethosomes are flexible vesicles made up of phospholipids (often with a concentration ranging from 0.5 to 10 %), water, and ethanol (typically with a concentration ranging from around 20 to 50 percent of ethanol content).[177] When compared to typical liposomes, Ethosomes target the deeper skin layers, with minor starting skin deposition but more long-term deposition.[178] The ethanol in the Ethosomes may form an ionic bond with the water-soluble functional group of the lecithin molecules in the skin; the melting point of the lipids is reduced in the subcutaneous layer (SC) and so enhancing their fluidity and their potential to pass across the cell membrane. Ethosomes produce high elasticity and deformability, so the Ethosomes may be able to fit through skin channels smaller than the diameter of the vesicle.[179]

Compared to tincture, skin deposition in psoralen-loaded ethosomes was 6.56 times larger, indicating improved skin penetration and deposition for reduced toxicity and better effectiveness over the long term. In comparison to a tincture, this formulation allowed for a higher medication concentration in the dermis.[179]

Solubility, medication retention, and penetration may be improved by using ethosomal vesicular systems. This is why Ethosomal gel containing thymoquinone (TQ) has shown promising results in psoriasis therapy.[180]

Considering that curcumin has low water solubility and for targeting the CD44 protein in inflamed epidermis, hyaluronic acid (HA) is a good organic ligand. HA Ethosomes have been developed as the latest topical delivery method to target the CD44 protein present in the inflamed epidermis. This has resulted in increased therapeutic action and decreased toxic effects in the psoriasis treatment.[181]

To increase the safety and efficacy of anthralin, ethosomal preparations loaded with anthralin were made using a simple process and then compared to liposomes. The anthralin ethosomal gel showed much more penetration across the abdomen skin of rats than the drug liposomal gel, according to ex-vivo permeability experiments. PASI scores suggested that ethosomes outperformed liposomes in terms of efficacy. Results from this study show that the anthralin ethosomal gel produced by the researchers in this study has the potential to improve the drug's effectiveness and safety in psoriasis patients.[182]

Curcumin-loaded glycyrrhetinic acid-D-α-tocopherol acid polyethylene glycol succinate (GA-TPGS)-modified multifunctional ethosomes (Cur@GA-TPGS-ES) were effectively created using the "modification-encapsulation" technique. Curcumin and glycyrrhetinic acid uptake and loading are increased by the use of multifunctionalized ethosomes as permeation enhancers and solubilizers. On HaCaT cells and mice stimulated with IL-6 in in-vivo and in-vitro tests, Cur@GA-TPGS-ES demonstrated modest anti-inflammatory and antioxidative effects. To sum up, multifunctionalized ethosomes based on the "modification-encapsulation" technique may be able to achieve the combination treatment of psoriasis, presenting a novel notion for therapies combining synergistic therapy, taking benefit of the effective co-delivery of Cur and glycyrrhetinic acid in the system.[183]

Niosomes

Niosomes are a special, vesicular drug delivery process that may be employed for the prolonged, regulated, and targeted distribution of pharmaceuticals. Niosomes were first discovered in the 1990s.[184] Because niosomes are composed of non-ionic surfactants, they are called niosomes and due to surfactant composition, they are non-toxic.[185] Cholesterol or its derivatives, as well as charged molecules, may be included in these surfactants. The charged molecule in cholesterol offers stability to the formulation by providing stiffness. There is a noisome-forming process when nonionic surface-active agents come together. They can load and distribute hydrophilic and hydrophobic medicines, according to their structure.[186,187] In comparison to traditional gels, Niosomal gel demonstrated deeper skin layer penetration, improving effectiveness while simultaneously reducing systemic absorption.[188] Niosome preparations utilizing a Box-Behnken design (3-factor, 3-level) have shown that tailored administration of diacerein might be obtained using topically applied niosomes for increased therapy of psoriasis, which may discard the negative side effects linked with systemic exposure.[189] Niosome encapsulation of celastrol resulted in an increase in both the polarity and penetration of celastrol into the mice's skin, resulting in a considerable enhancement in the drug's ability to treat psoriasis.[190] Incorporating acitretin into niosomes for topical administration provides an effective way for psoriasis treatment. This strategy would regulate the amount of medicine that would be absorbed via damaged skin.[191]

Lipospheres

A hydrophobic, solid lipid core is surrounded by a phospholipid layer to form a liposphere. Lipospheres

are self-assembled structures that are based on lipids. Lipospheres can penetrate deeper layers of skin, they gently release their contents, and they are compatible with skin. The antipsoriatic effectiveness of *Commiphora mukul* and Quercetin loaded liposphere gel formulation exhibited gradual release of both medicines, which is a positive characteristic of topical formulation. The skin of an imiquimod-induced psoriasis skin model was used for skin penetration research, and Franz diffusion tests were used to investigate the retention of both medications in the dermal layer. When compared to traditional cream, the results showed that *Commiphora mukul* and Quercetin loaded liposphere gel improved the retention of both medications in the dermal layer. These findings provide credence to the hypothesis that a liposphere gel containing a mixture of *Commiphora mukul* and Quercetin might be a successful and effective therapy for the psoriasis therapy.[192]

Despite its anti-psoriatic properties, thymoquinone (TMQ) is difficult to supply because of its hydrophobicity, low water solubility, and light or pH sensitivity. Lipospheres were considered as a possible solution to these delivery issues. Lipospheres, when applied topically, provide an excellent penetration method that is both stable and scalable. Particles less than 70 nm in diameter were used to make and test TMQ lipospheres. Deeper skin penetration, slower absorption, and skin compatibility were all made possible because of these lipospheres. Anti-inflammatory and anti-psoriatic properties have been shown by lipospheres in an in-vitro psoriasis model. IL-2, 6, 1, TNF-α and Nitric oxide levels were lowered in cell line investigations, although improvements in phenotypic and histological characteristics and lower levels of Interlukin-17 and TNF-α were shown in animal models with psoriatic skin.[193] Problems with tacrolimus and curcumin topical administration include low solubility, inability to penetrate skin and unpredictable absorption. Tacrolimus and curcumin lipospheres with a particle size of roughly 50 nm were produced and combined into a gel for topical administration to address these issues. With the entry of the liposphere gel into the epidermal layers, both the medicines and the shear thinning behaviour were seen. Liposphere gel loaded with Tacrolimus and Curcumin improves the phenotypic and histological characteristics of psoriasis.[194]

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)

Biodegradable lipids make up SLNs, which are nanocarriers that may break down in the body. Next-generation lipid nanoparticles (NLCs) are an attempt to address the drug seepage complications associated with SLNs by increasing their physical strength. If a monolayer appears after applying NLCs, it will block epidermal water loss and make the epidermis more hydrated. As a result, NLCs have a significant advantage over other treatments for psoriasis. An effective and safe technique for Acitretin administration via topical route, with no possibility for skin irritation and increased skin deposition, is the SLN-based gel formulation of Acitretin. This also provide a choice to its oral route treatment.[195] Using a psoriasis animal model, researchers have developed an ointment with lipidic nanoparticles (LNs) containing tetrahydrocurcumin (THC) inserted into the base. Because of this, the new THC-LNs ointment is a secure and efficient option to already used psoriasis treatments, and it also has de-pigmenting characteristics.[196]

Psoriasis patients who received Thymoquinone (TQ) lipid nanoparticles (NPs) demonstrated slower drug release (57.55% ± 5.38%) and higher cutaneous flux (5.77 μg/cm^2/h). It was discovered that the distinctive endothermic peak of TQ had vanished from the TEM picture, and this was corroborated by thermal analysis. It was discovered that the main irritation index score was (1.4), and the PASI score also demonstrated a decrease in all three of these symptoms in the psoriatic model of the toxic control group, both of which were found in the skin irritation investigation.[197] NLCs were created with particle sizes below 300 nm, 100% entrapment efficiency, and polydispersity index (PDI) < 0.3. The NLC gel was tested for drug release, staining, and effectiveness. Dithranol-loaded NLC gel improved psoriasis symptoms in an IMQ-induced model, as measured by PASI and ELISA. The created approach reduced illness, severity, and cytokines ILs-17, 22, 23, and TNF-α release compared to the negative control.[198]

Psoriasis is better treated with nanostructured lipid carriers containing curcumin and caffeine in a topical gel than with conventionally marketed formulations. A topical gel based on an enhanced NLC-based formulation provided a 12-hour-long sustained drug release. Ex-vivo permeation experiments and in-vivo research have shown that NLC-based gel can weaken psoriasis more than previously thought. Psoriasis sufferers may benefit from a gel containing NLC that might be used to offer an effective and improved local therapy.[199]

Nanoemulsions

Nanoemulsion (NE) includes two immiscible phases of liquids (oil and water) in conjunction with a surface-active agent with droplet sizes of 5 to 200 nm. Anti-psoriatic medications may be safely transported as NE since macroemulsions are prone to creaming, flocculation, sedimentation, and coalescence. These are ideal for skin via topical administration because they never irritate the skin, they are very permeable, and have a large capacity for drug loading.[200]

NE increases the curcumin solubility and penetrability via skin following topical administration due to its poor solubility and skin penetrability. Nano-emulgel healed psoriatic mice faster than curcumin and betamethasone-17-valerate gel. Curcumin nanoemugel showed promise

for long-term psoriasis therapy.[201] Alpinia galanga extract (AGE) containing non-aqueous nanoemulsion (NANE) was formulated by researchers. AGE NANE's effectiveness was tested in an imiquimod-induced mice model. Low and high dosages of AGE NANE improved psoriasis in mice ($P < 0.05$).[202]

Tacrolimus and Kalonji oil (a functional excipient) were combined in a nanoemulsion system to achieve synergistic antipsoriatic effectiveness. NE gel had good spreadability and a consistent release pattern (biphasic). An increase in dermal bioavailability (4.33-fold) went hand in hand with encouraging in vitro findings. In-vivo studies have shown that NE decrease in serum cytokines and improve psoriasis condition, demonstrating that the formulation was more effective than the commercial formulation (Tacroz Forte, Glenmark Pharmaceuticals Ltd, Maharashtra, India).[203] To combat psoriasis, a NE combining Curcumin, resveratrol, and thymoquinone was developed. An increased anti-psoriatic impact was shown in trials using Balb/c mice, indicating that the nanoemulgel formulation's triple natural bio-actives combination is useful for treating psoriasis.[103]

Nanospheres

The polymer matrix entraps or homogeneously disperses the medication, resulting in nanospheres. Polymers used might be either biodegradable or non-biodegradable in character, depending on their composition. The therapeutic moiety is better protected from chemical and physical degradation in nanospheres, drug absorption is enhanced, and the therapeutic agent is released gradually over time. Drug distribution to the skin has proven accomplished using nanospheres (tyrospheres).[204] To test the efficacy of E/DMSN on human immortalized keratinocyte (HaCaT) cells, researchers created dendritic mesoporous silica nanospheres (DMSNs) with pore sizes as small as 3.5 nm and as large as 4.6 nm (DMSN2). These E/DMSNs had a significantly stronger anti-proliferative and pro-tumor effect than free erianin (E).[205] Topical delivery applications may benefit from tyrosine-derived nanospheres because they help transfer lipophilic compounds into the skin via deeper layers.[206] Psoriasis is caused by an overgrowth of keratinocytes in the epidermis' deeper basal layer, and tyrospheric delivery of paclitaxel at concentrations more than 100 ng/cm2 of skin surface area and an increase in the cytotoxicity of paclitaxel (laden into tyrosphere) to keratinocytes may help treat it.[207]

Foams

As a colloidal solution, foam consists of a gas distributed in a liquid, solid, or gel substrate. With their minor potential for irritancy, consistent spreading, absence of residual oil, and non-sticky properties that make them ideal for innovative topical carriers, foams have a significant advantage over standard dosage forms (like ointments, creams, and gels). Foams have recently demonstrated definite results in psoriasis control.[208] It has been shown that the Cal/BD foam has a faster beginning of action and better effectiveness than foam vehicles, especially in individuals with more severe psoriasis that can be treated with topical therapies. This might help doctors better manage patient expectations and enhance patient adherence, which could lead to better overall topical therapy efficacy.[209] For the first time, the Cal/DB foam therapy was shown to be efficacious and safe over the long tenure in a study for the control of psoriasis in the PSO-LONG trial.[210] Psoriasis severity ranges from mild to severe, and Cal/BD aerosol foam is efficacious and well tolerated in all these patients. Patients prefer and accept this Cal/BD formulation since it has a faster impact on itch-related symptoms, as well as more efficacy than other preparations (including powerful/very potent corticosteroids). As a result, Cal/BD aerosol foam is an excellent first choice therapy for individuals with psoriasis, regardless of the severity.[211]

Nanohydrogel

Using an IMQ-induced psoriasis model, a nanohydrogel produced by the micellar Choline-Calix [4] arene (CALIX and CUR) and Curcumin (CUR) showed no toxicity and efficient activity against psoriasis. Because of the nanohydrogel's ability to solubilize and protect curcumin from fast decomposition, Study findings showed that curcumin retains its anti-inflammatory efficacy when curcumin is entrapped in the hydrogel based on calixarene. A novel delivery method for curcumin in the anti-psoriatic strategy improves patient pleasure while also boosting effectiveness and comfort when compared to traditional therapies may be found in its routine qualities, such as skin dispersibility, stickiness, and perforation.[212]

Nanogel

This work develops a topical nanogel of two different anti-psoriatic medicines (Acitretin (Act) and Aloe-emodin (AE)). Simple regeneration chemistry created Chitin Nanogel Systems (CNGs). All Nanogel (control chitin (CNGs), acitretin-loaded (ActCNGs), and aloe-emodin-loaded (AECNGs)) systems were blood-compatible in the in-vitro hemolysis experiment. Acidic pH increases system swelling and release. Fluorescent imaging and ex-vivo porcine skin penetration experiments showed increased system accumulation at epidermal and dermal layers. Acitretin and aloe-emodin were effective in Perry's mouse tail model and skin safety investigations of psoriasis.[84]

Liquid crystalline nanoreservoir

In this study, hydrotrope technique was used to generate Berberine oleate (Brb-OL) loaded Liquid Crystal Nanoparticles (LCNPs) (Brb-OL-LCNPs). Three times more Brb was collected in the skin of rats treated with Brb-OL-LCNPs than was the case with pure Brb. Psoriasis symptoms were decreased, and psoriatic inflammatory cytokines were lower when Brb-OL-LCNPs hydrogel was applied to the skin in an in-vitro model of the disease.[213]

Metallic nanoparticles

To control the skin-related inflammatory responses, researchers used nanoparticles of silver and gold

complexed with the plant extract Cornus mas (AgNPsCM, and AuNPsCM, respectively) on the skin. Pro-inflammatory macrophages produced NO, TNF-α, and IL-12 when exposed to nanoparticles, with AuNPsCM more effective than AgNPsCM. The varying effectiveness of Au-NPs (13-52 nm) in comparison to Ag-NPs (9-82 nm) may be due to their smaller size, which allows for greater cell penetration and activity.[214]

Improve skin hydration power

Microemulsion

A microemulsion containing salvianolic acid B lessened the severity of the condition, decreased the amount of acanthosis, and suppressed interleukin-23 and interleukin-17 cytokines. Additionally, microemulsion boosted epidermal proliferation and skin moisture. According to the findings of this research, salvianolic acid B has the potential to become an innovative new medication for psoriasis treatment. In addition to this, such a formulation has the potential to provide a high therapeutic effectiveness while also delivering enough hydration for dry skin.[215]

Improve the targeting ability

Nanofibres

Curcumin-laden nanostructured lipid carriers (NLCs) were hybridized along with cellulose nanofiber (CNF) film for topical medication delivery. Using solvent diffusion, ≈500-nm NLCs were made. In-vivo studies showed that Cur-loaded lipid@CNF films control psoriatic skin indicators in IMQ-induced mice, lowering cytokine levels nearly as well as a commercially available topical corticosteroid cream. These outcomes might be ascribed to CNF's target alteration and the films' skin-hydrating impact.[216]

Microemulsion gel

A hydrogel-based microemulsion method was created for the transdermic administration of indirubin to increase effectiveness and tailored action. To make the microemulsion more uniform, it was mixed with carbomer 934 hydrogels. IL-17, Ki67, and CD4 + T expression were shown to be decreased in patients with psoriasis when this treatment was tested via an imiquimod-induced mouse model of psoriasis.[217]

Nanoemulgel

In this work, Babchi oil is used to create a topical formulation of methoxsalen that may be applied to the skin for prolonged release and increased penetration, leading to better epidermal localization and greater anti-psoriatic efficacy. They have created nanoemulgels that combine synthetic methoxsalen and natural Babchi oil. Babchi oil was utilized as the oil phase, while Tween 80 was used as the surfactant, to develop four different nanoemulsion formulations using high-pressure homogenization. The optimised nanoemulsion formulation(s) were mixed into the carbopol gel base to produce a nanoemulgel based on characterization outcomes. In ex-vivo skin permeation, nanoemulgel (NG2) exhibited improved penetration and localized deposition of methoxsalen all over the skin compared with plain gel. In vivo hyperproliferative skin symptoms improved significantly, verifying ex vivo results. The promising findings indicate that nanoemulgel is an adequate carrier for topical methoxsalen–Babchi oil delivery.[218]

Sirbal (SIRB)-001 (novel herbal concoction)

Scientists in this study combined *Rheum palmatum* L., *Lonicera Japonica*, and *Rehmannia glutinosa* Libosch in a 1:1:3 ratio to create a novel aqueous polyherbal formulation (SIRB-001). SIRB-001 has shown encouraging results in psoriasis management. The anti-psoriatic activity of SIRB-001 in patients is supported by in-vitro data. In numerous ways, SIRB-001 acted as an anti-psoriatic agent in the cells (antiproliferative, pro-apoptotic, anti-inflammatory, and anti-angiogenic).[219]

Liposomal gel

In this study, zedoary turmeric oil (ZTO) and tretinoin (TRE)-loaded liposomal gel were used to create a topical medicine delivery technique. Single factor and orthogonal experiments optimized compound liposome encapsulation. In vitro studies showed that liposome formulations might maintain medicines in mice's hair follicles longer than gel formulations. Liposomal gel treated psoriasis better than regular gel in vivo and displayed a dose-dependent impact.[93]

Nanoemulsion gel

This drug-loaded nanoemulsion (DLNE) employs oleic acid as the oil phase and Tween 20 as the surfactant to deliver the weakly water-soluble medications thymoquinone (TQ), resveratrol (RS), and curcumin (CR) via the skin at the nano range size of NE. Investigator found that the transparent and uniform hydrogel produced by our texture analysis of an optimized NE formulation was preferable for topical delivery and demonstrated superior antipsoriatic effects when compared to the other groups; this was likely due to the gel's mucoadhesive nature, which improved drug retention in the skin, as was to be expected during treatment for psoriatic skin. DLNE gel is safe for topical use and nonirritating, allowing long-term treatment. Results demonstrate that DLNE gel is impervious and effective and might be used to treat topical psoriasis[103].

Mechanistic approaches of natural drugs present in herbal and polyherbal nanoformulations for psoriasis treatments

Psoralen (psoralen-loaded liposomal nanocarriers)

PUVA (psoralen liposomal nanocarriers with ultraviolet light A (UVA)) is effective in reducing psoriasis signs by shifting the autoimmune reaction away from the inflammatory Th1/Th17 axis and towards the counter regulatory Th2 axis,

which is the result of repealing the cytokine description commonly found in psoriasis. PUVA works by lowering IL17, IL-22, and TNF-α levels, which reduces inflammation and keratinocyte proliferation. Psoralen tends to act by intercalating DNA, and when exposed to UV-A, it develops monoadducts, which trigger apoptosis.[172]

Dithranol or anthralin (liposomal dithranol gel and anthralin ethosomal gel)

Dithranol slows the TCA cycle because it causes a drop in the C1 correlation group TCA intermediates citrate and malate. Glycolysis intermediate metabolite levels are altered by dithranol. Higher concentrations of dithranol (0.3-0.5 μg mL^{-1}) led to the buildup of glucose, glucose-6-phosphate, pyruvate, and lactate. Therefore, the presence of these metabolites strongly suggests that dithranol affects central metabolism in HaCaT cells. This suggests the medicine has entered the cells and is making its way to the mitochondria where it may perform its work. Also, cellular amino acid concentrations are affected by dithranol exposure.[220]

Diacerein (diacerein loaded cholesterol rich niosomes)

On primary human keratinocytes, inhibit the proinflammatory effects of IL-17A, IL-22, Oncostatin M, Interlukin-1A, and TNF-α.[221] Diacerein inhibits both skin inflammation and atherosclerosis caused by inflammation via reversing IL-1's pro-atherogenic and pro-inflammatory regulation of gene expression in endothelial cells and keratinocytes.[222]

Alpinia galanga (nanoemulsion)

Expression of CSF-1 mRNA transcripts and NF- κB (nuclear factor-κB) mRNA transcripts were both suppressed by Alpinia galanga, whereas expression of TNFAIP3 (the NF-κB gene) was boosted.[223]

Thymoquinone (TMQ) (lipospheres)

IL-2, IL1β, IL-6, IL-17 AND TNF-α levels are reduced by Thymoquinone.[193] The chemical structure of mentioned herbal plants with their biological origin are shown in Fig. 3.

Tacrolimus and curcumin (liposphere gel)

Reduce the cytokines like TNF-α, IL-17 and IL-22.[194]

Conclusion and future scope of natural drugs with nanoformulations or novel drug delivery systems

Natural medicines offer benefits in psoriasis therapy, particularly in combination with contemporary drug delivery technologies with the very least side effects. There are, however, certain issues that need to be addressed. When it comes to safety, there is a lot of room for argument. Drug absorption, accumulation, and circulation are considerably altered in psoriasis lesions compared to normal skin lesions. To have a more effective therapeutic impact, it is necessary to thoroughly evaluate the delivery capability, effectiveness, and safety of a novel drug delivery system. A single natural ingredient has been the mainstay of most natural psoriasis treatments up to this point. The synergistic effects of natural products with other biologic agents can therefore be used to treat more complicated conditions such as mild or serious psoriasis, but the combined mechanisms of action must be thoroughly investigated. Clinical trials have been stymied by the drawbacks of novel drug delivery systems, such as low drug loading and stability, physicochemical characteristics, encapsulation efficiency, and industrial production difficulties. As a result, additional research into these aspects is needed to help guide future psoriasis treatments. Preclinical studies on natural products and novel drug delivery systems for the current treatment of psoriasis are limited because most of these studies use

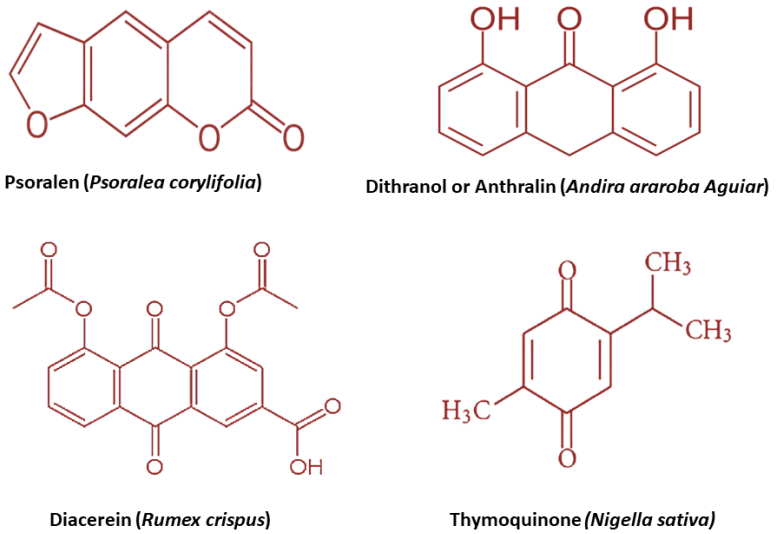

Fig. 3. Chemical structure and biological origin of some antipsoriatic herbs.

Table 3. Recent clinical studies for psoriasis treatment

NCT Number	Study phase with sponsor name	Type of Condition	Treatment	Reference
NCT05680740	Phase 4, Dermavant Sciences, Inc.	Plaque psoriasis	VTAMA® (tapinarof) Cream 1%	224, 225
NCT05701995	Phase 4, Bristol-Myers Squibb	Plaque psoriasis	Deucravacitinib	224, 226, 227
NCT05969223	Phase 4, AbbVie	Genital psoriasis, scalp psoriasis	Risankizumab	224, 228
NCT06336343	Phase 4, Icahn School of Medicine at Mount Sinai	Plaque psoriasis	Bimekizumab	224, 229-231
NCT05872256	Phase 4, Dermatology Consulting Services, PLLC	Scalp psoriasis	0.045% Tazarotene/0.01% Halobetasol Lotion	224
NCT06042647	Phase 4, Dermatology Consulting Services, PLLC	Psoriasis vulgaris	0.01% Halobetasol, 0.045% Tazarotene and 0.05% Clobetasol Propionate	224
NCT05684744	Phase 3 completed, Cairo University	Psoriasis	Roflumilast, Methotrexate	224,232,233
NCT05763082	Phase 3 completed, Padagis LLC	Plaque psoriasis	Roflumilast cream 0.3%, Zoryve	224,234
NCT05919082	Phase 3 completed, LEO Pharma	Stable plaque psoriasis	LEO 90100, Daivobet® ointment	224
NCT06084663	Phase 3 completed, Humanis Saglık Anonim Sirketi	Psoriasis and psoriatic arthritis	Apremilast 30 mg Tablets, Otezla 30 mg film-coated tablets	224,235

only a single animal model for preclinical testing. The treatments currently available are mainly for mild or moderate psoriasis not for severe one. A more stringent standard for psoriasis treatment is now necessary in the age of precision medicine. By targeting specific cells or genes, targeted therapy and precision medicine might one day become a reality for people with psoriasis. Some recent clinical studies for antipsoriatic action of different drugs in various psoriasis conditions are shown in Table 3.

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Review Highlights
What is the current knowledge?
- There is currently no complete review that summarizes the natural products along with all of their dosage forms for antipsoriatic benefits.

What is new here?
- We have compiled a comprehensive summary of several plant items, including all available dosage forms, mechanisms, and antipsoriatic activity.
- We have also provided a concise overview of the most recent herbal and polyherbal nanoformulations, focusing on their underlying mechanisms.

Competing Interests
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