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AN OVERVIEW OF PROMISING HERBAL MEDICINES FOR TREATMENT OF PSORIASIS

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ABSTRACT: Psoriasis is a skin disorder marked with inflammation. The development and progression of the disease are associated with a chronic inflammatory response, which is attributed to the dysregulated innate immune system. The dendritic cells and T cells secrete various cytokines leading to disturbances in the keratinocyte proliferation and differentiation. Several medications are available for the mitigation of psoriasis. The currently used anti-psoriatic medications are expensive; carry the threat of serious side-effects and frequent remission attacks of the disease. Exploring safer and effective anti-psoriatic drugs remains still a major concern. Natural products represent important treatment options for psoriasis. This review article discusses studies related to the topical formulations of anti-psoriatic plants and plant products. The pathogenesis and clinical symptoms of psoriasis include multiple immunological mechanisms and pro-inflammatory cytokines. The review aims to summarize the research done in this area and to explain the mechanism of action of herbal medicines. The review article is aimed at opening new medical approaches for treating psoriasis. All the findings suggested that various herbal constituents are responsible for anti-psoriatic activity. Herbal medicines can be used as promising anti-psoriatic agents. The anti-psoriatic effects of herbal medicines are through modulation of the signaling pathways of the cells. The phytoconstituents inhibit keratinocytes proliferation and differentiation by targeting different molecular targets. The results suggested the use of plants as a safe, effective, and inexpensive option for treating psoriasis.

INTRODUCTION: Psoriasis, a chronic inflammatory skin disease, poses a major burden on patients' quality of life. Recently psoriasis is being considered a systemic disease of immune dysfunction. The pathogenesis and clinical features of psoriasis include several environmental and genetic risk factors, various immunological mechanisms, and pro-inflammatory cytokines. Currently prescribed drugs are associated with serious side effects, high rates of remission, and resistance to drugs.

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The current treatment approaches have limitations, and the production of safer and more effective agents is strongly required [1, 2]. Medicinal plants have been used to treat skin disorders. It is a common human activity that lasted for centuries together [3]. Various plants from traditional Ayurveda, Siddha, Uighur, Thai, Korean, Chinese medicine are used for the management of various skin ailments, psoriasis, vitiligo, dermatitis, and leuco-derma. A large population uses complementary medicines for two reasons, namely, the limitations of synthetic drugs and the ability of the natural compounds to act on multiple targets [4]. The plants can pave the way for new therapeutic approaches to psoriasis treatment since they have significant preventive activity against psoriasis [5].

The goal of this paper is to indicate worthy prospects of Conventional therapeutic approaches

against psoriasis. We reviewed the literature related to herbal medicinal products that are capable of functioning against psoriasis. We addressed the pathophysiological issues of psoriasis and the role of plant products in the modulation of patho-physiology. The scientific data that supports the use of medicinal plants in psoriasis as well as their underlying mechanism of action, is summarized in the article.

METHODS: We conducted searches on PubMed from 2000–2019, SCOPUS, using keywords "anti-psoriatic herbal medicine" or synonyms, "anti-psoriatic plant," "anti-inflammatory natural," "inflammatory cytokines," "traditional anti-psoriatic medicine," "anti-psoriatic Chinese medicine," "anti-psoriatic Ayurvedic medicine." The articles, published in English, were only examined. The content of the full-text articles or abstracts were referred.

Dosage Forms Consisting of Herbal Medicine/s: Dosage forms that have been investigated for anti-psoriatic activity include topical herbal medicinal products. There are examples of herbal ointments or creams, herbal baths, and herbal steam showing anti-proliferative, anti-inflammatory, anti-pruritic activities. These herbal medicines are used as adjunct therapies for psoriasis. Simultaneous use of the topical herbal medicines along with conventional pharmacotherapy was beneficial since a short-term clinical improvement was observed. No serious adverse events were reported [6].

Treatment with drug-loaded silver nanoparticles, containing fruit extract of *Sambucus nigra*, showed decreased cytokines production in HaCaT cells. In vivo, drug-loaded silver nanoparticles showed a decrease in the paw edema and in the cytokines levels in the paw tissues in mice [7]. *Scutellaria baicalensis*, Chinese herbal medicine, contains a flavonoid baicalin. Application of topical cream, consisting of baicalin, on mouse tail, revealed thinning of the mouse tail and increased orthokeratosis in the granular layers. The topical cream exerted the keratinocytes differentiation and reduced the contact hypersensitivity response in mice [8]. Durr Derma (consisting of extracts of tea tree oil, black cumin, vitamin B12, cocoa butter, olive oil, and vitamin A) showed a significant reduction in PASI score in less than 12 weeks in 5 patients [9]. The topical nanogels consisting of acitretin, aloe-emodin, and chitin revealed spherical particles, desirable particle size range, and zeta potential. The *in-vitro* hemolysis assay indicated the compatibility of the nanogels with blood. The in vivo study confirmed the anti-psoriatic activity, whereas the skin toxicity study confirmed the safety of the nanogels [10].

Madecassoside is isolated from *Centella asiatica*. Madecassoside ointment lowered mRNA expression of IL-23, IL-22, IL-17A in ear skin of mice. It inhibited the growth of abnormal keratinocytes by regulating the IL-23/IL-17 axis [11]. Leaf extract of *Gynura pseudochina* was incorporated in an ointment and its efficacy was compared with marketed triamcinolone cream. The efficacy of the herbal ointment was similar to that of triamcinolone cream. The herbal ointment exerted minimum side effects [12]. A skin lotion consisting of olive fruit extract and tetramethoxyluteolin was applied in patients twice daily for 2 weeks. The results indicated improvement of the skin lesions. The anti-allergic and anti-inflammatory actions of flavonoid tetramethoxyluteolin were confirmed [13]. Nail bed balm, consisting of plant based essential oils and waxes, was prepared and used in patients (receiving the chemotherapy) for controlling the chemotherapy-related nail damage. The symptom score, recorded with the dermatology life quality questionnaire, was lowered after the nail bed balm treatment as compared to the pre-treatment [14]. IMQ-induced psoriasis-like inflammation was significantly inhibited by *Nigella sativa* (black seed) oil. IMQ induced epidermal and the dermal changes were relieved [15].

Ageing, psoriasis and atopic dermatitis is associated with deficiency or alteration in the ceramides, lipid component of stratum corneum. Depletion of ceramides leads to dry skin and weak skin barrier. Replenishing the native ceramides with exogenous ceramides such as oat ceramides is beneficial. However, oat ceramides are unable to overcome the stratum corneum barrier and penetrate deep into the lipid matrix below stratum corneum. Hence lecithin-based microemulsions and starch-based nanoparticles of oat ceramide were designed. The microemulsion and the nanoparticles were incorporated into the Carbopol® 980 gels. The results of skin permeation revealed better drug release as well as skin permeation of oat ceramide

from microemulsion than the microemulsion gel. The release of oat ceramide from the nanoparticles was retarded. The skin permeation from the nanoparticles gel was enhanced. Microemulsion enhanced the degree of permeation of oat ceramide into the deeper layer of the skin [16].

Apitherapy is the medical use of honey bee products namely, beeswax, bee venom, honey, royal jelly and propolis for relieving the diseases. Propolis, a traditional folk medicine, is derived from tree buds and plants and contains flavonoid rich essential oils. The ointment, consisting of propolis (50%) and *Aloe vera* (3%), was effective in patients with mild to moderate psoriasis [17].

Moisturizers are useful in both prevention and treatment of hand dermatitis. They protect the skin from the environment, improve the skin hydration, and repair the skin barrier. Natural oils are commonly used in moisturizers for their moisturizing and emollient properties. A study confirmed the safety and efficacy of a moisturizer, consisting of sweet almond oil and colloidal oatmeal, in patients suffering from moderate to severe hand dermatitis [18].

Venusia® Max's effectiveness and safety were tested in Indian patients with psoriasis. Venusia® Max is a plant-based butter moisturizing cream. Dry skin and PASI score were reduced significantly after 4 weeks of the topical application. No serious adverse effects or deaths have occurred [19].

A traditional Chinese medicine, *Qing Dai*, is used in the treatment of moderate psoriasis. It is usually prepared from *Naturalis indigo* and is applied on the skin. *Qing Dai* was made from aerial parts of *Strobilanthes cusia*. It revealed 3 novel indole alkaloids namely, indigodoles A, B and C, with 7 known compounds. IL-17 production by Th17 cells was significantly impaired by Indigodole C and tryptanthrin. Indigodole A and indirubin blocked dose-dependent gene expression of IL-17 without being cytotoxic towards Jurkat cells and Th17 cells [20].

Curcumin is a natural, safe, and cheap photo-sensitizer and is used in photodynamic treatment of mild to moderate psoriasis. The photosensitizer is administered orally or applied topically and irradiated with a particular wavelength. Subsequently, the reactive oxygen species (ROS), including singlet oxygen ($1O_2$) are produced. The ROS, mainly the singlet oxygen, is highly cytotoxic. They attack the substrates involved in cell cycles, leading to cell necrosis and apoptosis [21].

Anti-psoriatic Plants: The current perception about the cause of psoriasis is the changes in immune-related genes triggered by changes in the environment. This section describes the multi-focused actions of phytochemicals for the treatment of psoriasis.

Lu I *et al*., [22] reported that proliferation of keratinocytes was inhibited by oral and topical calcitriol whereas they induced differentiation of keratinocytes in terminal stage. Topical calcitriol decreased immune activation in psoriatic plaques by suppressing K-16 keratin expression. Topical vitamin D exerts anti-psoriatic effect through suppression of the immune system and activation of keratinocyte *in-situ*.

Aqueous extracts of *Psoralea corylifolia* and *Centella asiatica* inhibited SVK-14 keratinocyte growth before and after polyvinylpolypyrrolidone treatment of the extracts. The inhibitory effect produced by *Centella asiatica* was attributed to triterpenoid glycoside constituents namely, made-cassoside and asiaticoside [23].

Indigo naturalis treatment was followed by reduction in the number of keratinocytes. The plant treatment downregulated Proliferating Cell Nuclear Antigen (PCNA) and upregulated cytosolic involucrin. The changes in the PCNA and involucrin was attributed to the mRNA and protein modulations at cellular level by indirubin alone whereas the G(0)/G(1) phase was blocked by indirubin and indigo [24].

Indirubin is one of the components of Dang Gui Long Hui Wan, a traditional Chinese medicine. In zebrafish embryos, it interfered with the formation of the intersegmental blood vessels in a dose-dependent manner. It induced cell apoptosis, arrested the G0/G1 phase, and inhibited proliferation in HUVEC [25].

Quercetin was isolated from the methanol extract of *Smilax china* Linn. Quercetin showed ortho-

keratosis, higher anti-inflammatory, and anti-proliferant activity than extract [26]. The leaves of *Wrightia tinctoria* were extracted with a mixture of water and ethanol. The extract showed a significant degree of orthokeratosis and antioxidant activity [27]. In Siddha system of medicine, oily extract of *Wrightia tinctoria* R. Br. Fresh leaves is used as the analgesic, anti-inflammatory, anti-pyretic, for psoriasis and skin diseases treatment. The activity of the leaves and the pods were attributed to glycoflavones, iso-orientin, flavonoid, and phenolic acids [28].

Alcoholic extract of *Cassia tora* leaves contains flavonoids namely, formononetin-7-O-β-D-glucoside, luteolin-7-O-β-glucopyranoside and quercetin -3-*O*-β-D- glucuronide. *Givotia rottleriformis* bark extract, the phytochemicals, and leaf extract of *Cassia tora* were assessed for the anti-psoriatic activity. The histopathological examination revealed the elongation of rete ridges, absence of Munro's micro-abscesses, capillary loop dilation, and reduction in epidermal thickness in mice [29, 30].

Psoriasis is a condition mediated by dysregulated dendritic cells and T cells. The psoriasis symptoms were relieved by heme oxygenase-1 (HO-1) in the animal model. HO-1 enzyme is released in stress conditions. However, HO-1-based therapeutic agents are not used commonly due to unavailability of suitable HO-1 inducers. Curcumin and carnosol, the plant-based polyphenols, are potential HO-1 inducers. When human dendritic cells were treated with these polyphenols, the maturation of dendritic cells was prolonged, pro-inflammatory cytokine production was lessened, and allospecific T cell responses were prevented/ not induced. Curcumin, but not carnosol, reduced proliferation of T cells and cytokines' activity. It downregulated cytokines including IFNγ, IL-17, GM-CSF, and IL-22 [31].

Phyllanthus simplex (whole plant), Retz., *Crotolaria juncea* Linn. (seeds), *Leucas aspera* Linn. (aerial parts), and *Vitex glabrata* R.Br. (leaves) were extracted with ethanol and petroleum ether. In HaCaT cells, the extracts inhibited lipid peroxidation and NO production. This suggested that the antioxidant mechanism contributes to the anti-psoriatic activity of the extracts [32].

The aerial parts of *Polypodium leucotomos* L. diminished the formation of nitrogen species and reactive oxygen species. Besides, photoisomerization of trans-urocanic acid and UV radiation-induced apoptosis were prevented by the plant. In the presence of the plant, the genetic material from the keratinocytes, remained unaltered, and DNA repair was enhanced. It is photoprotective, non-mutagenic, and safe and may be used as a supportive agent in UVB phototherapy or in UVA with psoralens [33].

No significant difference in treatment efficacy was observed between the *Tripterygium wilfordii* Hook F and acitretin treated groups within 8 weeks. The treatment-related adverse events were lesser in the *Tripterygium wilfordii* Hook F group than acitretin group[34].

Woodfordia fruticosa flowers were extracted with ethanol, and the extract was incorporated in an ointment. The use of ointment was followed by decreased epidermal thickness and reduction in the severity of psoriatic lesions (redness, erythema, and scales) [35].

An essential oil from bitter apricot seeds (*Armeniacae amarum*) inhibited the HaCaT cell growth, activated caspases-3/8/9 and PARP, prompted apoptosis of HaCaT cells, and arrested G0/G1 cell cycle. Z-VAD-FMK inhibits many caspases and declines the cell apoptosis. Essential oil treatment elevated Bax levels and decreased Bcl-2 levels as well as Rel/NF-κB levels. The anti-proliferative effect of the phytoconstituent was mediated through the death receptor pathway, mitochondrial pathway, and NF-κB pathway [36].

Topical treatment with methanolic extract of *Andrographis nallamalayana* resulted in a reduction of psoriatic symptoms in male BALB mice. The anti-psoriatic action was attributed to the presence of flavones/flavanones and their glycosides, phytosterols, monostearin, chromones in the extract [37].

The flowers of *Woodfordia fructicosa* and the leaves of *Gardenia gummifera* were extracted with ethanol. The extracts were incorporated into a gel and suspension, respectively. The results of biochemical estimation, histological study, and the severity index showed that the gels and the suspensions exhibited considerable anti-psoriatic activity. The gels and the suspensions were safe at

1% w/w and 1000mg/kg dose of the extract, respectively [38].

The wound healing effect of the hydro-alcoholic, ethyl acetate, and petroleum ether extracts of *Dillenia indica* fruit was studied *in-vivo*. Topical application of the extracts on psoriasis-like wounds exhibited rapid wound healing. The extracts negated the features of lipid peroxidation *in-vitro*. The wound-healing effect was attributed to betulinic acid [39].

Kv1.3 is one of the therapeutic targets for the treatment of autoimmune diseases, such as psoriasis, asthma, type-1 diabetes, and multiple sclerosis. Inhibition of Kv1.3 by *Euphorbia peplus*, was attributed to its phytoconstituents, pepluacetal, pepluanol A, pepluanol B [40].

Brazilian population uses *Combretum leprosum* flowers for treating various skin disorders. The herbal folk medicine contains triterpene, 3β, 6β, 16β-Trihydroxylup-20(29)-ene, which reduced epidermal thickness and proliferating cell nuclear antigen expression. Triterpene prevented edema development and cellular infiltration in chronic and acute inflammatory skin models. It had caused cell apoptosis of HaCaT cells. The anti-proliferative function of the triterpene was attributed to stimulation of corticosteroid receptors. However, the corticosteroid-related cutaneous side effects were not shown by the triterpene [41].

Topical and oral administration of ethanolic extract of stems of *Solanum xanthocarpum*, (dashamula) an Ayurvedic medicine, depicted a potent anti-psoriatic activity. The effect was more prominent in topical route. Dashamula extract downregulated IL-6, IL-1β, IL-17, and TNF-α tissue concentration. The hyperkeratinisation was reduced by the extract [42]. Bergamot (*Citrus bergamia*) essential oil and juice are useful in ultraviolet B therapy of psoriasis [43].

Paeonia lactiflora Pallas root contains paeony glycosides. The findings of the clinical research showed that the number of patients showing 50% reduction in PASI score was higher for the combination of acitretin and paeony glycosides than for the placebo acitretin combination. The acitretin and paeony glycosides combination showed a lower rate of serum alanine amino-transferase levels than the placebo acitretin combination. The plant extract enhanced the anti-psoriatic efficacy of acitretin and reduced liver damage due to acitretin [44].

In Palestine, plants such as *Catharanthus roseus*, *Trigonella arabica*, *Aloe vera*, *Anthemis cotula* are used for the treatment of psoriasis by 54.4% of patients. The medicinal plants were used commonly by elderly patients and patients having lesser monthly income [45].

The aqueous extracts of *Rheum palmatum* L. (1 part), *Lonicera japonica* (1 part), and *Rehmannia glutinosa* Libosch (3 parts) were mixed. The polyherbal mixture reduced IL-17/IL-23 secretion, prevented HaCaT cell growth and triggered cell apoptosis. The pro-inflammatory markers (VEGF, NO, TNF- α, sPLA2, IL-6, IFN-γ,) were significantly downregulated. Various signaling markers (PRKCA, MAPK1, FLT3, AKT1, MAP2K) and Topoisomerase-II activity were inhibited by the herbal formulation [46].

An in-silico approach was employed for exploring the anti-arthritic effect of phytoconstituents. The in silico approach is important since it identifies the targets at a molecular and cellular level and explains the therapeutic action of natural compounds in a scientific manner [5].

Topical application of hydroalcoholic extract of *Malva sylvestris* reduced mouse ear edema, leukocyte migration (mono and polymorphonuclear cells) and keratinocyte hyperproliferation. The extract showed low toxicity in HaCaT cell line and reduced cell proliferation, induced cell apoptosis. The extract didn't exert the anti-inflammatory effect through glucocorticoid receptors [47].

The ethyl acetate extract of *Juniperus communis* fruits, European folk medicine, demonstrated anti-melanogenic activity. The extract was standardized, applied topically in melanin-possessing HRM-2 hairless mice. The reduction in the number of melanocytes and the skin-lightening effect in mice was attributed to the phytoconstituent hypolaetin-7-O-β-D-xylopyranoside. In B16 murine melanoma cells, the production of melanin was reduced through inhibition of protein expression for tyrosinase [48].

The PASI score and the epidermal thickness were reduced when *Artemisia capillaries* was applied topically on psoriasis-like lesions. Reduction in Ki-67 and intracellular adhesion molecule-1,L levels in excised skin tissues, was noticed. There was a substantially greater number of apoptotic cells in HaCaT cells. Cell cycle arrest results of assay confirmed the anti-proliferation activity of the plant [49].

The ointment containing dichloromethane and methanol extracts of fruits of *Vernonia anthelmintica*, showed significant anti-psoriatic activity in mice and in HaCaT cell line. Essential saturated and unsaturated fatty acids containing 12 to 18 carbon atoms were detected in the extracts [50].

Cancer, psoriasis, and rheumatoid arthritis reveal common feature angiogenesis. Angiogenic blood vessels secrete numerous cytokines, namely, GRO, MMP-1, bFGF, IGF-1, EGF, PLG, and ANG. *Picrasma quassioides* contains an alkaloid, 1-methoxycarbony-β-carboline. *In-vivo* study demonstrated restraining of formation of blood vessels in zebrafish caudal fin by the alkaloid. The alkaloid hampered the viability, migration, invasion, and tube formation of HUVECs *in-vitro*. The alkaloid treated HUVECs showed the downregulation of the angiogenic cytokines as well as of the membrane receptor proteins TIE-2 and uPAR[51].

Silver fir (*Abies alba*) bark extract contains a mixture of polyphenols. The bark extract hampered the expression of IL-1β cytokine *in-vitro*. The patients received an ointment with 2% of silver fir bark extract or placebo. Silver fir extract was well-tolerated by the patients. An improvement in PASI score and the psoriasis symptoms on the elbow was observed in patients receiving the ointment in comparison with placebo. However, a significant statistical difference was absent between placebo and active treatment with the extract from silver fir bark [52].

Plasmacytoid dendritic cells secret type I interferon. Treatment with Gold lotion, consisting of the peels of citrus fruits, inhibited the inflammatory cytokines, including type I interferon, from skin lesions. It efficiently lowered the number of T cells and of $CD4^+$ T cells/ neutrophils in lymph nodes and skin lesions and reduced the IL-17-/IL-22 levels [53].

Carthamus tinctorius L. (Safflower) is a flavoring and coloring agent. It is an Iranian folklore medicine and used for curing psoriasis and other diseases [54].

Clinical trials related to *Mahonia aquifolium*, reported significant improvement in symptoms of psoriasis with minimal side effects. The study reported efficacy *of Mahonia aquifolium*, a plant from United States, in the treatment of atopic dermatitis [55].

The petroleum ether extract of *Annona squamosa* seeds inhibited the proliferation of the keratinocytes in vitro (HaCaT cells). The growth inhibition was significantly higher for the plant extract than that was observed for clobetasol propionate, cortico-steroid. Lowering of erythema and ear edema of female Balb/C mice by the plant extract was similar to clobetasol propionate. The psoriatic lesions depicted increased levels of cytokines IL-6, GMCSF, TNF-α, INF-γ, IL-17and decreased infiltration of CD4-T cells. Acute toxicity and repeated topical application dermal toxicity studies confirmed the safety of the extract [56].

Males *et al*. reported the use of *Ginkgo biloba* L., *Phlebodium aureum* L., *Panax ginseng* C. A. Mey., *Podophyllum peltatum* L., *Rosmarinus officinalis* L., *Aloe vera* L., *Capsicum annuum* L., *Allium cepa* L., *Camellia sinensis* L. Kuntze, *Berberis aquifolium* Pursh in mitigation of psoriasis, genital warts, alopecia and vitiligo [3].

The traditional Korean treatment of psoriasis includes acupuncture, herbal medicine, probiotics. Traditional Korean treatment, in combination with phototherapy, was effective in the resolution of psoriasis [57].

Malassezia species, present on the human skin, cause skin infections or aggravate multiple skin disorders, including psoriasis. The herbal essential oils revealed antimicrobial activity against *Malassezia* species and are useful in the treatment of psoriasis [58].

Indigo naturalis (leaves and stems) is a component of traditional Chinese medicines. It stimulated IL-22 secretion from lymphocytes type-3 and promoted mucosal healing. Oral administration of *Indigo naturalis* showed severe adverse effects

such as pulmonary arterial hypertension and colitis and. Consequently, topical treatment is preferred [59].

Melissa officinalis L. (lemon balm) is widely used in Greece. Triterpene derivatives and polyphenolic compounds are present in aqueous decoction and organic extract of the plant. The decoction and the dichloromethane extract revealed significant anti-psoriatic and antioxidant activity. The dichloro-methane extract was a weaker antioxidant. The decoction decreased skin dryness and enhanced skin barrier function [60].

Dodonaea polyandra, a traditional medicinal plant from Cape York Peninsula Australia, contains polyandric acid A, the diterpenoid. Topical application of the phytochemical to the mouse ear showed inhibition of interleukin-1β production. It reduced the ear thickness and myeloperoxidase accumulation in chronic skin inflammation model. Pretreatment of neonatal human keratinocytes with polyandric acid A reduced production of IL-6 [61].

The extract and the phytoconstituents of *Psoraleae fructus*, traditional Chinese medicine, were admini-stered orally to rats, and the metabolic fate was studied. Psoraleae fructus extract produced 142 metabolites and showed different metabolic fate from the metabolic fate of single phytoconstituent. Interactions amongst phytoconstitutens have contributed to variation in metabolism. It suggested that the single phytoconstituent is not responsible for the plant's overall anti-psoriatic activity [62].

Signaling Pathways: Patients with psoriasis often use medicinal plants for the treatment of disease. Herbs exhibit anti-psoriatic activity through modulation of various cell signaling pathways.

Vitamin D Receptor (VDR) is regulated by the nuclear hormone, 1alpha, 25-dihydroxy vitamin D3 (VD). VD has a pivotal role in cell cycle regulation. VD binding with its receptor changes the conformation of VDR accompanied by an interaction between amino acid residues from the co-activator proteins and the ligand-dependent activation function 2 (AF-2) region. As a result, various VD-responsive genes were activated. By employing a limited protease digestion technique, 7 amino acid residues from the AF-2 region of VDR and different functional VDR conformations were identified.

The relative potency of VDR ligands was quantified. The study revealed the interaction between co-proteins having Phe-422 and Val-418 with all seven VDR ligands. The anti-psoriatic drug MC903 (VD analogue) interacted with the AF-2 region of VDR at more than seven points. This information suggested the use of synthetic VD analogues in the treatment of hyperproliferative diseases [63].

Camptothecin exerts anti-psoriatic effect through inhibition of topoisomerase I. Due to the serious side effects and toxicity, its clinical use is limited. Isocampethicin is a synthetic derivative of campto-thecin. Inhibition of keratinocytes proliferation varied directly with concentration of isocam-pethicin and time of exposure; a correlation was observed between cell apoptosis and concentration of isocampethicin. The cytotoxicity produced by isocampethicin was less than camptothecin. The telomerase activity was downregulated by iso-camptothecin at concentrations to induce apoptosis as well as concentration insufficient to induce apoptosis [64].

Gambogic acid is reported to inhibit angiogenesis. In human keratinocytes, cell proliferation was hampered by an O/W cream of the plant active. In HUVEC cell line, the bioactive inhibited the NF-κB signaling pathway by blocking receptors for TNF-α-. The topical treatment improved morpho-logical and histological features significantly in K14-VEGF transgenic mice. Adhesion molecules (ICAM-1 and E-selectin) expression was down-regulated, and inflammation of the blood vessels was suppressed. It blocked VEGFR2, p-VEGFR2 and of IL-17, IL-22 expression. As a result, angiogenesis was inhibited. The number of T lymphocytes was lowered [65].

Viola tricolor L. (heartsease) was extracted with water, and the bioactive components were determined using bioactivity-guided fractionation, and their effect on lymphocyte functions were evaluated. The aqueous extract, containing circular plant peptides cyclotides, inhibited the proliferation of activated lymphocytes. The bioactivity was attributed to downregulation of secretion of interleukin-2, production of interferon-γ and tumor necrosis factor-α. IL-2 receptor expression was unaffected [66].

Psoriasis is induced due to the absence of two late cornified envelope (LCE3) genes from a group of five (LCE) genes. Both 1, 25-dihydroxyvitamin D3 and cyaniding upregulated expression of all five LCE3 genes in primary human keratinocytes, cyanidin, being more potent than vitamin D3. Proanthocyanidins, cyaniding, natural compounds are useful in psoriasis [67].

Magnolia officinalis contains a biphenolic Neolignan, honokiol. The phytoconstituent significantly diminished the ratio of Th1/Th2 cells and the CD4(+) T cells and improved the histological and morphological characteristics of psoriasis. Honokiol treatment repressed the mRNA levels of IFN-γ and TNF-α, and blocked NF-κB initiation. It suppressed subsequent phosphorylated proteins (p-ERK1/2, p-VEGFR-2, p-p38, p-AKT) expression and VEGFR-2, nuclear p65 expression. Honokiol's anti-psoriatic activity was elucidated by VEGFR-2 and NF-κB inhibition [68].

Poly (I:C)-increases expression of both NLRP3, an important component of inflammasome, and of chemokines such as IL-8, CCL20, TNF-α, IL-6 in keratinocytes. It induces inflammasome activation. *Paeonia lactiflora* pallas extract significantly down-regulated NF-κB signaling pathway, reduced secretion of IL-1β, caspase-1, NLRP3, and poly (I:C)-induced cytokines resulting into inhibition of inflammasome activation [69].

In Southern Italy, *Artemisia arborescens*, *Inula viscosa*, *Achillea ligustica* (Asteraceae) and *Acanthus mollis* (Acanthaceae) are used in psoriasis treatment. Inhibition of 5-LOX and COX-1, by the methanol extracts of the plants was observed *in-vitro*. However, 12-LOX pathway was not impacted by the extracts adversely. The extracts indicated the presence of the free radical scavengers. All the extracts, except *Inula viscosa*, increased 15(S)-HETE biosynthesis. 15(S)-HETE is an anti-inflammatory eicosanoid. All the extracts, except *A. mollis*, blocked NF-κB activation [70].

When toll-like receptors (TLRs) are activated excessively, it results into psoriasis. Andrographolide was ineffective in both IL-23- induced psoriasis model and microtubule-associated protein 1 light chain 3 beta (MAP1LC3B) knockout mice. In imiquimod induced psoriasis model, it lowered interleukin-1β and interleukin-23 levels. In bone-marrow-derived dendritic cells (BMDCs) model, it reduced IL-1β, IL-6, IL-23, CD86, CD80 mRNA expressions. However, in case of BMDCs treated with lipopolysaccharide (LPS), the phytoconstituent interfered with IL-1β, IL-6, IL-23 mRNA expressions but not of CD80 and CD86. Andrographolide induced degradation of MyD88. Consequently, TRAF6 was not deposited in TLRs, leading to inhibition of TLRs. Andrographolide induced MyD88 degradation was reversed in the presence of NH4Cl or MAP1LC3B(-/-) BMDCs. Andrographolide relieves psoriasis in mice by inducing MyD88 autophagous proteolysis and modulating MyD88-dependent cytokines activation [71].

Bakuchiol, a meroterpene from *Psoralea corylifolia*, reduced A431 xenograft tumor development *in-vivo* model. It hampered the anchorage-independent growth of A431 human epithelial carcinoma cells. Bakuchiol restrained epidermal growth factor (EGF)-initiated changes in neoplastic cells. The kinases, namely, Hck, Blk and p38 mitogen activated protein kinase (MAPK) were blocked by bakuchiol and EGF-induced signaling pathways were hampered. Bakuchiol binds directly to each kinase in an ATP-competitive manner. Consequently, the AKT/p70S6K, p38 MAPK/ MSK1 and MEK/ERKs pathways were inhibited [72].

Cell proliferation, apoptosis, necrosis, and cell survival involve various immune and inflammatory responses. TNF-α is a major regulator of immune and inflammatory responses. The herbal extract was prepared from 10 herbs. The phytoconstituents exerted anti-inflammatory effect through inhibition of TNF-α [73].

Ayurveda describes the preventive role of *Curcuma longa, Tinospora cordifolia, Aloe vera,* and *Celastrus paniculatus* against psoriasis-like dermatitis. The herbal extracts were administered orally/topically to mice. Semi-quantitative reverse transcription analyses, histological examinations and phenotypical observations indicated that the extracts reduced the over-expressed cytokines. The efficacy in descending order was the combination of all the extracts < the *Curcuma longa* extract < *Celastrus paniculatus* extract < *Tinospora cordifolia* extract [74].

Dendritic cells (DCs), when stimulated by R848, revealed increased expression of IRAKM, MYD88, TLR8, TLR7, increased expression and secretion of IL-1β and IL-23 mRNA, increased expression of CD80, I-A/I-E, and CD86. R848 activated DCs and activated DCs modulate TLR7/8 pathway. Lithospermum contains β, β-dimethylacryloyl alkannin. The phytochemical inhibited all the effects of the TLR7/8 pathway activation by R848. It alleviated psoriasis-like skin lesions, decreased the number of CD11c+ cells in spleen and skin lesions [75].

A polyphenolic compound, isolated from *Terminalia chebula*, improved the erythema and PASI score, decreased epidermal, ear, skin thickness, decreased keratinocyte proliferation. In IMQ-treated mice, it decreased TBARS content and increased GSH content. TNFα, ROS, IL-23, IL-17A levels, and matrix metalloproteinase (MMP)-9 expression in M5-treated cells, were reduced by the phytoconstituent. Zinc protoporphyrin IX, a heme oxygenase (HO)-1 inhibitor, reverted the effects induced by the plant bioactive. The upregulation of p65 NF-x03BA; B was inhibited by the plant compound *in-vitro* whereas the plant induced inhibition of p65 NF-x03BA; B was suppressed by zinc protoporphyrin IX. It indicated that the plant bioactive exerted the anti-psoriatic effect through HO-1-mediated downregulation of NF-x03BA; B [76].

The glycoside 9, 19-cycloartenol was identified in the root extract of C. simplex. The phytochemical inhibited the immune responses by suppressing the differentiation of CD4+ cells and by suppressing the JAK/STAT signaling pathways. The glycosides inhibited the pro-inflammatory mediators and arrested the disease progression in IL-23-induced mouse ear model. The glycoside prolonged the maturation of DCs which induced differentiation of T cells *in-vitro*. As a result, Treg cells increased, and Th17 cells decreased. The glycoside suppressed the IL-17+RORγt+/IL-10+FoxP3+ ratio [77].

Dysregulated gene expression leading to the up-regulation of the interleukin (IL)-17 pathway was observed in psoriatic patients. *Indigo naturalis* ointment improved the PASI scores in patients with moderate plaque psoriasis. The phytoconstituent, tryptanthrin, demonstrated an *in-vitro* IL-17-inhibitory effect. *Indigo naturalis* treatment was led to the restoring of the genes expression to normal expression and down-regulation of the IL-17 pathway [78].

The drug-likeness of the oil prepared from *Wrightia tinctoria* leaves was examined. The oil showed the presence of 67 bioactive compounds capable of interacting with 238 protein targets. It indicated the involvement of bioactive compounds in various signaling pathways. Recovery of the disturbed signaling pathways may be ascribed to the synergistic action between the bioactive [79].

Natural compounds block the interaction between endosomal TLRs and their ligands. They inhibit TLRs activation by different mechanisms. The plant actives derived from *Antrodia cinnamomea* extract, curcumin, mustard seed, resveratrol, thiostrepton, andrographolide, and azithromycin are the antagonist of TLRs [80].

In the guinea pig, paeoniflorin, the total glucosides of paeony, mitigated the psoriatic lesions and reduced the Baker Score. Paeoniflorin substantially down-regulated the mRNA expression of IL-6, IL-17A, and IL-22 and suppressed IL-17A and IL-6 protein expression. The phosphorylation of p38 MAPK was inhibited by paeoniflorin leading to inhibition of the protein expression of IL-22 [81].

Quercetin, a dietary flavonoid, improved the histopathological features, reduced the temperature of the skin lesions and the PASI scores in IMQ-induced mice. It effectively reduced serum IL-17, TNF-α, IL-6 levels, decreased MDA accumulation in skin tissue, and increased activities of GSH, CAT, and SOD. Quercetin up-regulates TRAF3, whereas it down-regulates the NF-κB, IKKα, NIK pathways, and RelB expression [82].

Rhododendrin was isolated from *Rhododendron brachycarpum*, traditional Oriental medicine. In IMQ mouse model, skin hyperplasia, infiltration of inflammatory mononuclear cells, and the pro-inflammatory cytokines were lowered by rhododendron topical application. It inhibited the activation of the TLR-7/NF-κB and mitogen-activated protein kinase pathways in both IMQ-induced psoriasis-like skin inflammation in mice and in normal human epidermal keratinocytes treated with IMQ [83].

The effect of topical *Hypericum perforatum* on TNFα levels in psoriatic lesions was investigated. The results of the clinical trial revealed that TNFα concentrations in the dermis, endothelial cells, and dendrite cells were significantly reduced in drug-treated lesions. PASI scores of ointment treated lesions were significantly lower when compared to treatment with placebo [84].

The roots of *Euphorbia kansui* radix were extracted with methylene chloride. The symptoms of Th17-related inflammatory bowel disease were relieved by the plant components. *In-vitro* the extract impeded the production of IL-17A and interferon-γ. *In-vivo* the production of IL-12, IL-23, IL-22, IL-17, and RAR-related orphan receptor gamma t (RORγt) was hampered by the extract. The plant compounds significantly reduced acanthosis and the infiltration of inflammatory cells into the dermis. The activation of the dendritic cells was impacted adversely by the extract, whereas the keratinocytes remained unaffected. The plant elucidated anti-psoriatic activity through inhibition of Th17 differentiation and activation of dendritic cells [85].

Topical application of an ointment containing aqueous extract of *Actinidia arguta* (kiwifruit) reduced skin thickness and IL-17A level in lymph nodes. Psoriasis symptoms were relieved without causing any adverse effects. When cytokine-stimulated HaCaT cells were treated with the extract, it revealed suppression of cell hyper-proliferation, various chemokines and antimicrobial peptides, and neutrophil infiltration. NF-κB and signal transducer of activation (STAT) signaling pathways were impeded by the extract. The chemotaxis of neutrophils was abated *in-vitro* and *in-vivo* [1].

Baicalein caused morphological differentiation inhibited cell growth and increased expression of keratins 1 and 10 (K1/K10) in HaCaT cell line in lower dose. It showed no effect regarding apoptosis, ROS generation, and cytochrome c release. It arrested the G0/G1 phase, increased inflow of Ca(2+), activated TRPV4 receptor, produced phosphorylation of ERK, Akt, and p38 MAPK, but not of JNK. Baicalein-induced increase in K1/K10 expression, was not affected by the blockade of phosphorylation of Akt or p38 MAPK. However, the K1/K10 expression was inhibited by the blockade of phosphorylation of ERK. It confirmed the involvement of ERK in K1/K10 expression. The growth arrest was not affected by the removal of extracellular Ca(2+) or blockade of either Ca(2+) influx or of the TRPV4 receptor. However, removal of extracellular Ca(2+) downregulated baicalein-induced ERK phosphorylation. Baicalein treatment increased keratinocytes differentiation, which is Ca(2+) dependent, and decreased keratinocytes proliferation, which is Ca(2+) independent. Baicalein restored abnormal keratinocytes differentiation and multiplication, the common features of psoriasis and atopic dermatitis [86].

Dendritic cells (DCs) initiate the activation and differentiation of T cells and play a critical role in psoriasis and other inflammatory diseases. Diaryl-heptanoid, isolated from rhizomes of *Curcuma kwangsiensis*, exhibited an impact on the immunological functions of dendritic cells. It suppressed the uptake of FITC-labeled ovalbumin by DCs and delayed maturation of DCs as indicated by reduced levels of CD86, CD80, and MHCII. In lymphoid tissue, the DC expression of the chemokine receptor CCR7 as well as DC migration towards CCL21, the ligand for CCR7, was reduced by the phytocomponent. In imiquimod stimulated DCs, the plant active impeded the production of proinflammatory cytokines, including IL-1β, IL-6 and IL-12, and phosphorylation of p65-associated cell signaling pathway. Diarylheptanoid significantly inhibited T cell proliferation and differentiation in the coculture of OVA323-339 peptide-pulsed DCs and OVA-specific T cells from OT-II mice [87].

Aloe polysaccharide from *Aloe vera* greatly reduced the expression levels of pro-inflammatory cytokines, including TNF α., IL 12, IL 8. It hampered TNF α induced cell proliferation in HaCaT cell line in a dose dependent manner. Aloe polysaccharide treatment was followed by significant increase in IκBα protein expression levels and decrease in the mRNA and p65 protein expression levels. Aloe polysaccharide inhibited TNF-α induced proliferation of keratinocytes and overactivation of the NF κB signaling pathway [88].

Glabridin downregulated the production of pro-inflammatory cytokines and improved the anti-

oxidant status. It inhibited the production of nitric oxide (NO), NF-κB subunit p65, IL-6, and IL-1β in lipopolysaccharide (LPS)-stimulated HaCaT cells. It reduced the levels of IL-17A, IL-22, and IL-23 in TNF-α-stimulated-HaCaT cells. It improved the PASI scores and the histopathological features of psoriasis. The plant active lowered the mRNA expression of IL-17A, p65, IL-23, IL-1β, IL-22, and IL-6 [89].

Isogarcinol, isolated from *Garcinia mangostana* L., inhibited the gene expression of IL-23/ T-helper 17 axis, interferon-γ, IL-2, and TNF-α. It suppressed the differentiation of CD4+ T cells into Th17 cells and prevented the abnormal distribution of T cell types in the spleens of mice. The number of regulatory T cells in the spleen was enhanced by the bioactive compound. The IL-10 expression in the skin and serum IL-10 were enhanced by the phytochemical, whereas the serum IL-17 was reduced. Cyclosporine A exerted more adverse effects on the liver and kidneys of mice than isogarcinol. It caused more cell apotosis in HaCaT keratinocytes than cyclosporine A. It greatly impeded expression of inflammatory factors in lipopolysaccharide (LPS)-stimulated HaCaT cells [90].

Increased oxidative stress and T-cell abnormalities are observed in psoriasis. A higher concentration of reactive oxygen species results in aberrant cell proliferation and differentiation of Th17/Th1/Th22 cells. The anti-inflammatory activity of regulatory T (Treg) lymphocytes is also inhibited. As a result, inflammatory cytokines, such as TNF-alpha, IL-22, interferon-gamma, IL-17, and vascular endothelial growth factor are secreted, which stimulate keratinocytes proliferation and angiogenesis. The flavonoids from plants and fruits, proanthocyanidins, prevent the formation of reactive oxygen species, suppress cell proliferation, and regulate Th17/Treg cells [91].

Rhodomyrtone, from *Rhodomyrtus tomentosa*, lowered the expression of the inflammatory gene and the expression and secretion of inflammatory proteins. IL-17A/TNF induced changes in the 724/1587 transcripts of the primary keratinocytes. Rhodomyrtone treatment inhibited 724/1587 transcripts indicating modulation of MAP kinase and NF-κB signaling pathways by rhodomyrtone. It also inhibited TNF-induced phosphorylation of p38, NF-κBp65, JNK, and ERK. Rhodomyrtone reversed skin hyperplasia and epidermal thickening in imiquimod-induced mice [92].

Three compounds, namely sitosterol-3-O-β-d-glucoside, marumoside A, and niazirin were isolated from the seeds of *Moringa oleifera*. The phytochemicals suppressed the expression of Th17-relevant cytokines (IL-23 p19, IL-17A, IL-12/IL-23 p40, IL-22) in lipopolysaccharide-stimulated THP-1 cells. The plant compounds increased the expression of markers of keratinocyte differentiation, decreased mRNA expression of IL-17A and ameliorated psoriasis-like skin lesions *in-vivo* [93].

Naringin and sericin were isolated from *Citrus maxima* (Burm) and *Bombyx mori*, respectively. In psoriatic patients, naringin/sericin combination inhibited mRNA expression. Subsequently, the production of the pro-inflammatory cytokines (IL-12p40, IL-23, TNF-α, IL-6) was lowered. The combination exhibited a higher inhibitory response than naringin or sericin alone [2].

C57BL/6 mice model of imiquimod induced psoriasis was employed for studying the anti-psoriatic efficacy of the methanol extract of *Dictamnus dasycarpus* Turcz root bark. The extract treated lesions exhibited infiltration of the immune cells in the dermis, reduction in scaly skin and epidermal hyperplasia. The extract reduced interleukin IL-17 and interferon IFN-γ levels, the number of Th17 cells and γδT cells, and the size of the Th1 cells and STAT3 signals [94].

The mechanism of antipsoriatic action of *Datura metel* L. was determined in imiquimod-initiated psoriasis-like dermatitis C57BL/6 mice. The plant treatment showed a reduction in the PASI score, epidermal thickness in mice. The plant treatment diminished the recruitment of CD3+ cells in psoriatic lesions, lowered the higher levels of intercellular adhesion molecule 1 (ICAM-1) and inhibited the production of inflammatory cytokines (IL-2, IL-6, IL-1β, IL-12, IL-10, IL-17, IL-23, IL-22, monocyte chemotactic protein 1 (MCP-1), TNF-α and IFN-γ. Expression levels of IL-1β, the apoptosis-associated speck-like protein contained a caspase recruitment domain (ASC), MyD88, p-IKKα, TLR7, TLR8, NLRP3, TRAF6, p-IKBα, p-NF-κB, cysteinyl aspartate specific proteinase 1

(caspase-1) were lowered by the plant treatment. The anti-inflammatory response was elucidated through the inhibition of the TLR7/8-MyD88-NF-κb-NLRP3 inflammasome pathway [95].

A new class of Kv1.3 blockers is capable of functioning against psoriasis. The proliferation and activation of leukocytes is regulated by Kv1.3, a voltage-gated potassium channel. The role of T effector memory (TEM) cells is critical in the development of autoimmune diseases.

TEM cells become aggressive due to the differential expression of this channel. Blockade of Kv1.3 inhibits the reactivity of these cells and ameliorates symptoms of psoriasis in animal models with no side effects. The researchers are trying to enhance the selectivity of the blockers, thereby reducing their side effects [96].

Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl) chromen-4-one), natural isoflavone, impaired the activity of certain genes which are overexpressed in psoriasis. It stimulated the expression of other genes that are repressed in dermatosis in both skin specimens and peripheral blood cells of psoriatic patients [4].

Nephrotoxicity and infections are linked with the long term treatment of immunosuppressants. Kaempferol is a natural flavonol that occurs in different plants. Kaempferol treatment protected mice from developing psoriasis-like skin lesions in imodiaquin induced psoriasis model. It down-regulated the gene expression of proinflammatory cytokines (TNF-α, IL-17A, and IL-6), the recruitment of CD3+ T cells in the psoriatic skin lesion, and the NF-κB signaling in the skin. It increased the number of CD4+ forkhead box protein 3 (FoxP3)+ regulatory T cells in the spleen and lymph nodes, whereas it lowered the number of IL-17A+ CD4+ T cells. Owing to the loss of CD4+ CD25+ regulatory T cells, kaempferol lost the therapeutic efficacy. Kaempferol suppressed the mTOR signaling and T cell proliferation *in-vitro* [97].

Shikonin is a bioactive compound of *Leptospermum erythrorhizon*. It markedly reduced PASI Score and improved the histopathological symptoms of psoriasis. It inhibited cell proliferation and induced apoptosis in both LV-STAT3 HaCaT and HaCaT cells. Shikonin increased CEBPD expression in local skin lesions by suppressing the JAK/STAT3 signaling pathway [98].

Ethanolic extract of aerial parts of *Stellera chamaejasme* (Langdu) and its phytoconstituent, luteolin 7-O-glucoside, improved atopic dermatitis-like reaction in mice. The extract significantly reduced inflammatory cell infiltration. Serum IL-4 and IgE levels were lowered by Luteolin 7-O-glucoside. It increased skin hydration by reducing water loss through epidermis [99].

Ellagic acid, quercetin, and myricetin were identified from the ethanolic extract of *Woodfordia fruticosa* flowers. The bioactive compounds revealed the inhibition of heat shock protein (HSP70-1) and higher immunomodulatory activity than the marketed anti-psoriatic drug tretinoin during molecular docking. ADMET prediction revealed drug-likeness and efficacy of these ligands for HSPs. The gold nanoparticles, containing the extract were incorporated in Carbopol®934 gel. The gel was more effective in reducing the mean DAI score, epidermal thickness, epidermal cell proliferation, serum cytokines (IL-22, IL-23, and TNF-α,) levels and parakeratosis [100].

The role of ethanolic extracts of Thai medicinal herbs, namely *Curcuma longa, Annona squamosa* and *Alpinia galangal on* NF-κB signaling pathway was investigated in HaCaT cells. The plant extracts modulated the biomarkers involved in the NF-κB signaling pathway and downregulated 10 genes' expression of the NF-κB signaling network. Alpinia galanga extract increased the expression of TNFAIP3 and reduced the expression of CSF-1 and NF-kB2. *Curcuma longa* extract decreased the expression of CSF-1, IL-8, NF-kB2, NF-kB1, and RelA, while *Annona squamosa* extract lowered the expression of CD40 and NF-kB1 [101].

The cutaneous permeation of retinoic acid, tacrolimus, 5-aminolevulinic acid, and calcipotriol through psoriasis-like lesions was studied. The most hydrophilic molecule, 5-aminolevulinic acid, revealed the highest skin absorption through psoriatic lesions as compared to normal skin. Retinoic acid, the most lipophilic drug, showed higher permeation. The lipophilicity plays a crucial role in drug permeation through psoriatic lesions. However, drug permeation is independent of the molecular size [102].

A case study of the use of traditional Korean herbal medicine with acupuncture for the treatment of psoriasis is quoted. With this treatment, the symptoms completely disappeared in less than 14 months [103].

Curcumin inhibited cell proliferation, down-regulated the pro-inflammatory cytokines, IL-17, TNF-α, INF-γ, and IL-6 in imodiaquin treated HaCaT cells. Treatment with curcumin decreased the number of psoriatic-like cells, increased the number of apoptotic and dead cells. Curcumin improved the skin-barrier function by up-regulating involucrin and filaggrin, the regulators of epidermal skin barrier, namely [104].

Psoriatic-like animal models were employed in the study of anti-psoriatic drugs. However, the ethical issues and complexity involved in the animal models have interfered with the development of new anti-psoriatic drug entities. It is difficult to create an animal model that exactly simulates psoriasis. The xenotransplantation model involves all the genetic, phenotypic, and immunopathogenic aspects of psoriasis and is considered as a replica of psoriasis. The imiquimod (IMQ)-induced model is employed commonly due to its ease of use, convenience, and low cost [105].

CONCLUSION: The results support the claims of topical use of the plants as a bioactive therapeutic agent or an adjuvant therapeutic agent for treating psoriasis. The experimental models were imiquimod (IMQ), HaCaT cells, zebrafish caudal fin, IL-23-induced mouse ear model of skin disease, IL-23- induced psoriasis model and microtubule-associated protein 1 light chain 3 beta (MAP1LC3B) knockout mice, coculture of OVA323-339 peptide-pulsed DCs and OVA-specific T cells from OT-II mice, oxazolone-treated BALB/c mice, and 2,4-dinitrochlorobenzene-treated hairless mice. The herbal medicinal products exerted their activity either by blocking Kv1.3 or acting as VD analogs or by controlling various cell signaling pathways: death receptor pathway, mitochondrial pathway, NF-κB pathway, IL-23/IL-17 axis, TLR7/8-MyD88-NF-κb-NLRP3 inflammasome pathway, IKKα, NIK and RelB mediated upregulation of TRAF3, HO-1-mediated down-regulation of NF-x03BA; B. Statistical analysis showed no significant differences between treatment with the plants and placebo/ currently prescribed anti-psoriatic drugs. There was no significant difference in treatment efficacy between the medicinal plants and allopathic medicines, but there were fewer treatment-related adverse events in the medicinal plant's group.

The plants exert multiple effects such as antiproliferative, pro-apoptotic, anti-oxidant, anti-inflammatory, anti-angiogenic at the cellular level. Psoriasis involves interactions between epidermal keratinocytes, T lymphocytes, leukocytes, and vascular endothelium. The exacerbation of psoriasis is associated with enhanced leukocyte recruitment and elevated levels of growth factors, genetic factors, and cytokines, namely, interleukin (IL)-1β, IL-6, IL-17, IL-22, IL-23, tumour necrosis factor (TNF)-α, interferon (IFN)-γ, transforming growth factor (TGF)-β, toll-like receptor (TLR)-2, signal transducer and activator of transcription (STAT-3), 15-lipoxygenase (LOX)-2, coiled-coil alpha-helical rod protein 1 (CCHCR1), steroi-dogenic acute regulatory protein (StAR), vitamin D receptor (VDR), CEBPD, Heat shock proteins (HSPs). Randomized, double-blind clinical trials are required before the herbal medicinal products are used clinically. The results suggest that the plants have tremendous preventive/ treatment potential against psoriasis and are a safe and cheap alternative for psoriasis treatment.

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