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Nano phyto-pharmaceuticals: An alternative road to Psoriasis treatment

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Abstract: Nano phyto-pharmaceuticals are the current focused study for the psoriasis management in an alternative manner. Psoriasis is a skin disease that lasts for a long time. It is a multifactorial skin disease, making it impossible to provide a suitable solution to date. Since psoriasis is an autoimmune condition, proper treatment is more crucial than just providing medicine. Long therapy durations of exciting synthetic drugs are associated with a higher incidence of side effects. These side effects can be overcome by using alternative strategy is Nano phyto-pharmaceuticals. Many psoriasis patients find that taking vitamins, applying oils, extracts of herbals on skin, and food supplements will benefit them to soothe irritated skin and aid in skin clearing. The available electronic data analysis has been performed for the thorough assessment of widely used herbals for psoriasis. Herbal extracts, oils and active phyto constituents have shown to be useful in preclinical and clinical trials and are prescribed as a psoriasis auxiliary therapy. A few of herbal extracts or phyto constituents are available in a variety of dosage forms, including pills, capsules, soft gelatin capsules, liquids, gels, and powders to cure or relieve psoriasis. As a result, patients may be supplemented with single or mixture of herbals to improve their health. Although the herbals has similar potential effects as that of synthetic drugs has facing the challenges of insolubility, poor bioavailability and instability. To overcome these challenges novel approaches called nano phyto-pharmaceuticals are the alternative strategies for the safe and efficacious management of psoriasis.

Keywords: Nano phyto-pharmaceuticals, Psoriasis, herbal phyto constituents, novel drug delivery system, herbal extracts.

1. Introduction: Psoriasis is an autoimmune genetic skin disorder characterized by hyperproliferation of the skin cells (AlShobaili et al., 2010). Till date the etiology of psoriasis remains unclear. However, the condition is triggered by environmental factors such as stress, skin injury, infection, drugs and/or genetic mutation. In addition to these triggers, dysbiosis of skin microbiota was also observed in psoriatic patient's (Knackstedt, Knackstedt, & Gatherwright, 2020). The clinical diagnosis of red itchy patches with silvery white multi-layered flakes at body sites such as elbows, knees, scalp, back, umbilicus, nails, etc. are the features for confirmation of psoriasis (Wang et al., 2019). The disease severity and associated comorbidities like cardiovascular disorders, diabetes mellitus, psoriatic arthritis, anxiety, lymphoma, etc. shows a significant impact on the physical, emotional and psychological well-being of the patient (Wang et al., 2019). In most developed countries, the prevalence rate of psoriasis was reported to vary from 1.5 to 5 %. However, the prevalence rate in different countries covers between 0.09-11.4%. In north India, the prevalence rate was reported from 0.44 to 2.8% (Thappa & Munisamy, 2017) The prevalence rate of psoriasis is increasing day by day. According to National Psoriasis Day Consortium, global prevalence of psoriasis was estimated to be 125 million people (National psoriasis foundation). Despite of having such a high prevalence rate, the treatment option to provide complete relief is still limited.

Some of the treatment options for psoriasis are topical agents (calcineurin inhibitors, steroids, vitamin D3derivatives, retinoids, keratolytics), phototherapy(ultraviolet radiation), systemic drugs (Janus kinase

inhibitors, phosphodiesterase inhibitors, calcineurininhibitor, folic acid antagonist, fumaric acid esters), biologics (TNF-α, IL-23 and IL-17 inhibitors). Patients are not satisfied with existing medication due to itching and stinging (calcineurin inhibitors), burning and peeling of skin (Vit.D3 derivatives), dryness, redness and peeling of skin (retinoids), swelling, tenderness, redness (keratolytics) redness and irritation (dithranol), skin staining (coal tar), toxic effects (biologics), skin thinning, tuberculosis, and skin cancer (PUVA) (Huang, Lin, Alalaiwe, Yang, & Fang, 2019). Therefore, it is important to find an alternative therapy that can overcome above mentioned side effects as well as ensure safety and efficacy.

Significant research studies have been carried out using herbal extract and/or their isolated phytoconstituents. Ease of availability, affordable cost, fewer side effects and ability to act on multiple sites have shown increased demand in exploration of Phytomedicines (Herman & Herman, 2016). In this review, the various phytomedicines which are found to be effective in psoriasis has been discussed. The mechanism of action, preclinical and clinical studies of phytoconstituents that elicit antipsoriatic activity have been discussed in detail. Special emphasis has been provided to research activities carried out for phytoconstituent based novel nanocarriers that has shown better efficacy in treatment of psoriasis.

2. Pathogenesis of psoriasis

The exact cause of psoriasis is unclear, though certain factors trigger both innate and adaptive immune system. Some factors that trigger psoriasis are injury in the skin, drugs, trauma, stress, leaky gut, and skin infection caused by *Staphylococcus aureus, Corynebacterium, Propionibacterium, and Streptococcus aureus* which results in stimulation of innate immune system.

These stimuli create damages in the keratinocytes leads to the synthesis of antimicrobial peptides (LL37, β-defensins, and S100). Among these peptides, LL37 forms a complex with deoxyribonucleic acid (DNA) as well as ribonucleic acid (RNA) of the damaged cells. The LL37-DNA complex bind to the Toll-like receptors (TLR-9) on the plasmacytoid dendritic cells (DC).The activated plasmacytoidDC produces type-1 interferon (IFN)-α,β. Type-1 IFN activates myeloid dendritic cells (mDCs) to release IFN-γ.The activation of T-helper cell-1(Th-1), and Th-17 leads to production of interleukin (IL)-17,tumor necrosis factor-α (TNF-α), IL-1, and IL-6. When LL37complexes with RNA, it activates myeloid DCs and secretes more amount of TNF-α, IL-23, and IL-12.

The over expression of above mentioned cytokines cause inflammation and hyper proliferation of the keratinocytes. These initial psoriatic inflammatory process further stimulate the adaptive immune response through distinct T cells.Th-17 cells releases IL-17, IL-21 and IL-22 which stimulate keratinocyte proliferation in the epidermis.The most clinically significant signalling is stimulated by IL-17A and IL-17F, each of which acts via the same receptor but have diverse binding affinities. The recruitment of the ACT1 adaptor protein occurs when IL-17A binds to its trimeric receptor complex, which consists of two IL-17RA subunits and one IL-17RC subunit.

All extracellular signal-regulated kinase (ERK), p38 MAPK, TGF-beta-activated kinase 1 (TAK1), I-kappa B kinase (IKK), and glycogen synthase kinase 3 beta (GSK-3 beta) are activated when ACT1 interacts with the IL-17A receptor complex. All kinase facilitate the generation of chemokines, AMP and cytokines via nuclear factor kappa-light-chain-enhancer of activated B cells(NF-κB), AP-1 and C/EBP transcription process. On the other hand,γδT cells together with Th1 and Th17 releases IL-17 without involvement of stimulation of IL-23. Th1and Th2 helps in the stimulation of cytokines through the Janus kinase (JAK)-STAT signaling pathways. The released cytokines over activates the epidermis which leads to hyper proliferation of the keratinocytes (Rendon & Schakel, 2019; Wilsmann Theis et al., 2018). The sequences involved in the immune pathogenesis of psoriasis is illustrated in the Fig.1

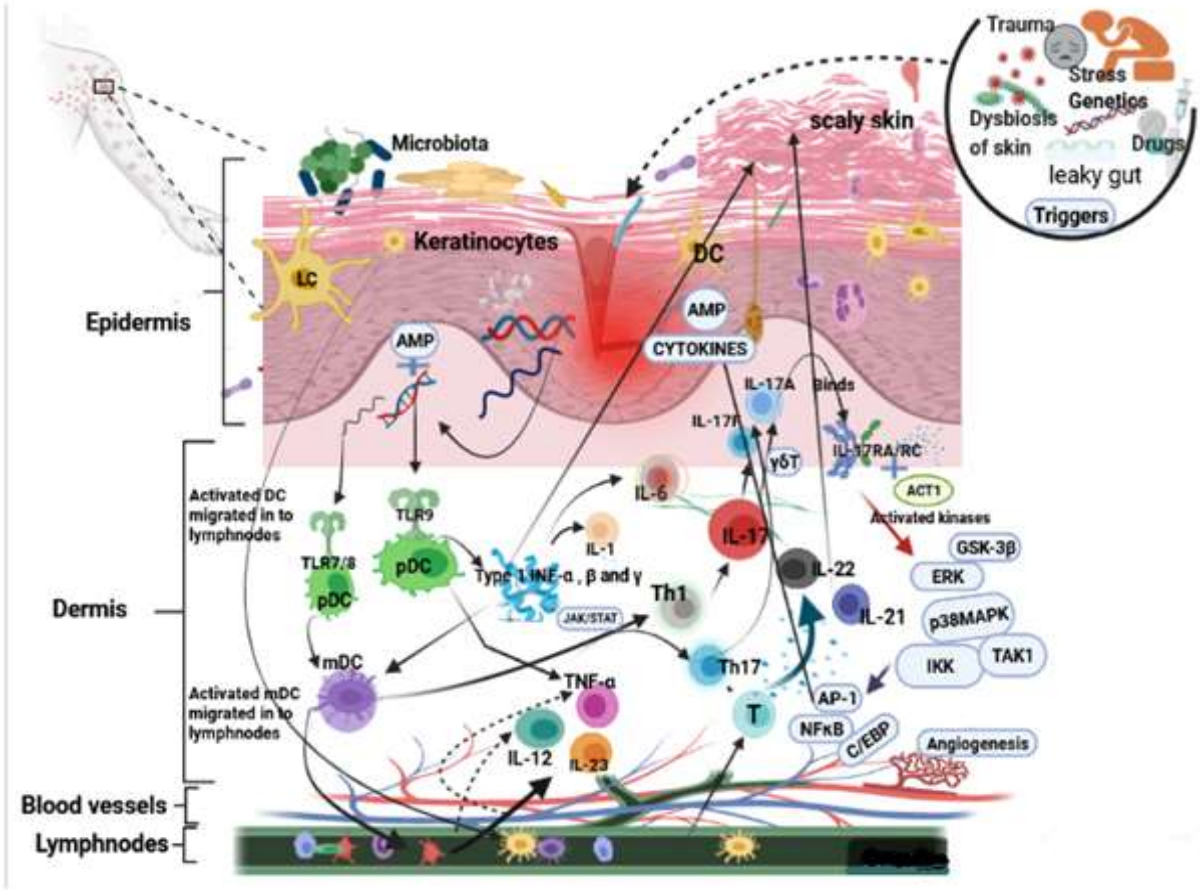

Fig:1 Sequences involved in the immune pathogenesis of psoriasis.

Abbreviations/legends: AMP: antimicrobial peptides **DC**: Dendritic cells **LC**: Langerhans cell **TLR7/8/9**: Toll like receptors 7, 8 and 9 **pDC**: plasmacytoid dendritic cells **mDC**: Myeloid dendritic cells **INF**: Interferon α, β and γ **TNF-α**:Tumor necrosis factor alfa **IL**:Interleukins-12/23/22/17A/17F/21/1 **Th1 and Th17**: T helper 1 and 17 cells **NFkB**: Nuclear factor kappa-light-chain-enhancer of activated B cells **ERK**: Extracellular signal-regulated kinase, **TAK1**: TGF-beta-activated kinase 1 **IKK**:I-kappa B kinase **GSK-3β**: Glycogen synthase kinase 3 beta **JAK/STAT**-Janus kinase-signal transducer and activator of transcription proteins signalling pathways**p38MAPK**:Mitogen activated protein kinase **C/EBP**: Protein family forms the transcription factor in controlling immune system responses **AP-1**: Activator protein 1 transcription factor **γδT**: Gama delta T-cells and **T**: T-cells

3. Conventional treatment with phytomedicine:

The extracts and secondary metabolites from the plant have the potential to treat chronic diseases due to their safety and synergistic activity. Phytomedicines can reduce the side effects of synthetic agents, such as atrophy, organ toxicity, immunosuppression, and carcinogenicity. The in vitro and in vivo studies carried out for few herbal extracts and isolated pure constituents has shown its potential role in effective management of psoriasis (Pang et al., 2018)

3.1 Herbal extracts

3.1.1 *BaiXuan Xia Ta Re Pian* (BXXR) extract: It is an ancient traditional uighur prescription medicine in China. Some of the phytoconstituents reported in the extract are *Euphorbiae Humifusae Herba, Chebula Fructus, Terminalia Belliricae Fructus, Chebulae Fructus Immaturus Aloe and Resina Scammoniae*. Xiaobo. Pang et al.2018 performed antipsoriatic activity on imiquimod (IMQ) induced psoriasis model. This study has shown the inhibitory effect of the extract on IL-17 signalling pathway and reduces inflammation (Pang et al., 2018)

3.1.2 *Tripterygiumwilfordii*Hook.f. (TwHf)root decoction and extract:

It is a Chinese vine plant belonging to the family Celastraceae. It mainly consists of triptolide, celastrol, and demethoxylzeylasteral as active ingredients, which are obtained from the root of TwHf. Yiru et al.2020 explored the antipsoriatic activity of TwHf decoction on IMQ induced psoriasis model. It was found to reduce the skin inflammation, inhibit the keratinocyte (KC) multiplication and increased the apoptosis factors. Subsequently it acts on the T-lymphocyte release, decreases the inflammatory response by decreasing the

level of IL-17A, IL-17F, IL-10, IL-22, IL-23, IFN-γ, and TNF-α. The TwHf extract was found to regulate proliferation and apoptosis in PAM212 cells (Ru et al., 2020)

3.1.3 *Punicagranatum L.* *Punicagranatum L* of Lythraceae family was reported to have some active components such as *Punicalagin, 2,3(S)-hexahydroxydiphenoyl-D-glucose, Punicalin*. Jacob et al. 2019 evaluated the in vitro anti-psoriatic activity of aqueous acetone extract of *Punicagranatum*fruitrind using thymidine phosphorylase inhibition assay. The isolated compounds showed the inhibitory activity against thymidine phosphorylase, but further in vivo evaluation required for confirmation of activity (Jacob et al., 2019)

3.1.4 *Wrightiatinctoria (Roxb*): It is a traditional system of Indian medicine used for the treatment of skin diseases which include psoriasis. It belongs to the family of Apocynaceae. The extract and oils prepared from the leaves of this plant has shown the anti psoriatic effect due to the presence of flavonoid, glycoflavones-iso-orientin and phenolic acids (Dhanabal, Priyanka Dwarampudi, Muruganantham, & Vadivelan, 2012;Dhanabal et al. 2012) evaluated the antipsoriatic activity of hydroalcholic leaves extract of *Wrightiatinctoria*in mouse tail method. (Dhanabal SP, 2012 ;Dhanabal, Priyanka Dwarampudi, Muruganantham, & Vadivelan, 2012) The study has reported reduction in orthokeratosis and antioxidant activity. Sundarrajan et al. 2017 investigated the mechanism of action of *Wrightiatinctoria* for curing psoriasis and its associated comorbidities. In the study, 67 compounds were reported and they have 238 target proteins.Among these potential proteins, mostly targeted proteins are apolipoproteinE APOE (T21), CAT (T46), IL12B (T123), and TP53 (T228). Some of the compounds suchas α-sitosterol and cholesterol controls APOE protein for the regulation of lipid metabolism. Tryptanthrin inhibits mutant p53 for the regulation of apoptosis and cell division. Benzoic acid, 3 –hydroxy1-methylpropyl ester (C27) are reported to directly inhibit IL-12 (T123). Pyrogallol directly acts on CAT (T46) enzyme for the suppression of humoral immune mediated responses. It also induces the activity of Caspase 3 (T43) and Caspase 8 (T44), thus activates apoptosis. The synergistic mechanism of these compounds suppresses the immune system and restores the disrupted apoptosis mechanism. This multi-targeted mechanism has shown its effect in treatment of psoriasis (Sundarrajan, Lulu, & Arumugam, 2017)

3.2 Isolated phyto constituents

3.2.1 *Luteolin:* *Luteolin* is a natural flavonoid obtained from the leaves of *Reseda luteola* belonging to Resedaceae family. In vitro studies on HaCaT cell line has reported reduction in IL-6, IL-8, vascular endothelial growth factor, and inhibited NFkB activation at transcriptional and translational levels. It also prevented keratinocyte proliferation without affecting ATP production. Therefore *luteolin* has shown its potential effects in the treatment of psoriasis (Weng, Patel, Vasiadi, Therianou, & Theoharides, 2014)

3.2.2 *Baicalin:* Baicalin is a flavonoid isolated from the roots of *Scutellaria baicalensis George* and *Scutellarialateriflora* belongs to Lamiaceae. It has shown pharmacological activities including antiapoptotic, anti-inflammatory and antioxidant effects. Topical application of baicalin on IMQ induced psoriasis model has shown anti-inflammatory activity. It was reported to block the activities of IL-17A, IL-22, IL-23, and TNF-α. Hence, reduction in acanthosis, neutrophil infiltration, hyperkeratosis, epidermal hyperplasia was observed showing its potential to treat psoriasis (Hung et al., 2018)

3.2.3 *Convallatoxin(*CNT*):* CNT, is a traditional Chinese medicine, is extracted from the leaves or flowers of the wild plant *Convallariamajalis*Linn (Asparagaceae). It is clinically used to treat acute and chronic congestive heart failure and paroxysmal tachycardia. Bo-Wen Jiang et al.2020 demonstrated potential activities of CNT via in vitro and in vivo studies. In vitro HaCaT cell line study confirmed necroptosis inhibition via ROS mediated mechanism. In vivo study on IMQ and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) induced psoriasis model demonstrated inhibitory effect of CNT to release cytokines such as IL-17A, IL-17F, IL-22, TNF-α and IFN –γfromTh1/Th17cells (Jiang et al., 2020)

3.2.4 *Rottelerin*: It is a poly-phenolic compound obtained from *Mallotus philipinens* is belonging to Euphorbiaceae family. Min M et al. 2017 has performed the in vitro and in vivo studies of *Rottelerin.* In vitro HaCaT cell line studies demonstrated the inhibition of keratinocyte proliferation via arresting NFkB signalling mechanism. In additions to this it induces apoptosis via autophagy mediated pathway. In IMQ induced psoriasis model it was reported to suppress chronic T cell dependent skin inflammation as well as inhibits TNF-α, IL-6, and IL-23. It also reduces skin thickening and angiogenesis (Min et al., 2017)

3.2.5 *PSORI-CM02*: It is Chinese herbal medicine formula, composed of *Rhizomacurcumae, Radix paeoniaerubra, sarcandra glabra, Rhizomasmilacisglabrae and Fructusmume.* Chen et al. 2018 conducted HaCaT cell line study which inhibited the cell proliferation at G1 phase. In IMQ induced psoriasis model study it has reported to inhibit the TNF-α, IL-6 and IL-17 levels via NFkB signalling pathway. This study also reported to control the oxidant/antioxidant status, alter the equilibrium between Th17 response and CD4+

FOXP3+ Treg generation.Yue L et al. 2019 investigated the effect of PSORI-CMO2. It induces the autophagy by suppressing the phospho-inositol-3 kinase (PI3K)/protein kinase B (Akt) and mammalian target of the rapamycin(mTOR) signal transduction pathway in the skin (Yue et al., 2019)

3.2.6 *Genistein:* Genistein is a flavonoid extracted from the *Prunus* and *soy bean* belonging to the family of Legumes. Wang et al. 2019 conducted in vivo study on IMQ induced psoriasis mouse model. The study has demonstrated to inhibit the inflammatory mediators, such as IL-1β, IL-6, IL-17, IL-23, TNF-α, chemokines ligand 2 (CCL2), via NFkB pathway (Wang et al., 2019)

4. Conventional herbal drug delivery system:

4.1 Fish oil soft-gelatin capsule: Bittiner et al. 1988 conducted 8-week clinical trial on 28 patients with the chronic stable psoriasis. The patients were grouped and subjected to treatment with fish oil capsules and placebo capsules daily along with a strict diet. A participant receiving fish oil therapy experienced a substantial reduction in scaling, erythema, and itching, while the placebo group experienced no improvement in psoriasis symptoms (Bittiner, Cartwright, Tucker, & Bleehen, 1988)

4.2 *Aloe vera(AV)*: To treat psoriasis, herbal shampoos, creams, gels, and organic extracts are available, which ensure water preservation in dry skin tissues, remove dead skin cells, and promote the development of healthy skin. Regular intake of AV juice is extremely beneficial because it serves as a digestive aid, internal cleanser, and anti-inflammatory agent (Tanweer A. Syed' & Afzal', 1996)

4.2.1 *Aloe vera cream*: Syed et al. 1996 performed a double-blind, placebo-controlled clinical trial to assess the acceptability and effectiveness of topically applied *Aloe vera* extract cream for 16 weeks. It was found that the cream was well tolerated by all the patients with reported no adverse reactions. The use of *Aloe vera* extract cream has shown significant improvement in the psoriatic plaque (Tanweer A. Syed' & Afzal', 1996)

4.2.2 *Aloe vera gel*: Dhanabal et al. 2012 tested a gel formulation of ethanolic extract of *Aloe Vera* for antipsoriatic effect in mouse tail model. They found that the extract caused similar epidermal changes similar to tazarotene (0.1 percent) standard gel. *Aloe vera* contains lignin that primarily penetrate into deep skin layers that helps to cure psoriasis (Dhanabal et al., 2012)

4.2.3 *Curcumin gel*: Sun et al. 2013 formulated the *curcumin* gel and evaluated the anti inflammatory activity on IMQ psoriasis model. *Curcumin*gel therapy greatly reduced the inflammatory cytokine interleukin-23 (IL-23)/IL-17A, which plays an essential role in psoriasis pathophysiology, as well as other inflammatory cytokines (Sun, Zhao, & Hu, 2013)

4.2.4 *Silymarin gel*: Khan et al. 2014 used Carbopol as a gelling agent to develop a topical gel of *Silymarin*. It was tested for physicochemical and in vitro drug release, and it was found to release 96.30 percent of the drug within 3 hours. It was studied for primary skin irritation test in healthy human volunteers after adequate in vitro parameters, and there was no sign of irritation at the end of 72 hours (Khan, Thube, & Rab, 2014)

4.2.5 *Nigella sativa* capsules and ointments: Jawad et al. 2014 performed a randomised clinical trial in 60 psoriatic patients to assess the effectiveness and safety of *Nigella sativa* (NS) when administered orally and topically. The outcomes of the study were evaluated using a PASI score and serum malondialdehyde (MDA) levels. Twenty patients were given a 10% w/w topical NS ointment, twenty patients were given a 500 mg oral capsule of pure NS powder, and the remaining twenty patients were given a mixture of ointment and capsule. When the PASI score was calculated, it was revealed that 65 percent of the ointment group had fully healed from psoriatic lesions, while 50 percent of the oral administration group had been healed. However, better results were obtained with the combination treatment where 85 percent lesions were healed. The Serum MDA levels were measured by thiobarbituric acid assay before and after 12 weeks of treatment. In patients using the ointment of (NS) (10 percent w/w) twice daily, 0.78±0.23 µmol/L baseline serum MDA level was observed. The mean baseline serum level of MDA in patients received with powder (NS) 500mg capsule was 1.09+0.37 µmol/L. The mean baseline serum level of MDA in patients with combination treatment was 1.2+0.37 µmole/L. The MDA levels of psoriatic patients decreased in all three categories as comparison to pretreatment levels; differences from the baseline were statistically significant in two groups of patients (ointment and combined groups), $p < 0.05$ (Ahmed Jawad, Ibraheem Azhar, & Al-Hamdi Khalil, 2014)

5. Nano phyto pharmaceuticals for psoriasis:

Phytomedicines are thought to be safe; however they show the similar physiochemical problems as synthetic drugs. Those are insolubility, instability and poor bioavailability. This physiochemical and physiological obstacles can be overcome using a variety of nanotechnologies (Sajid, Cameotra, Ahmad Khan, & Ahmad, 2019).It is the new system to deliver the drugs in the controlled manner, for a prolonged time. It reduces the dosing frequency, improves the bioavailability of the drug, minimizes drug degradation, controls the release of the drug from the dosage form, and achieves a therapeutic window at a sustained level. These systems overcome the adverse effects of conventional drug delivery systems. To deliver the drug to the specific target

site of the body, carrier-based delivery systems are used. These vehicles adhere to the skin effectively, maintain the sustained level of drug in the blood and prevent water loss from the skin. The use of various drug-delivery systems such as solid lipid nanoparticles (SLNs), Nanostructured lipid based carrier's(NLCs), liposomes, niosomes, ethosomes, polymeric nanoparticles, and metallic nanoparticles for successful delivery of phyto-medicines to their respective targets is covered in this section (Sajid, Cameotra, Ahmad Khan, & Ahmad, 2019; Damiani et al., 2019; Ramanunny et al., 2021).In addition to that a list of the currently, developed and evaluated numerous nano phyto-pharmaceuticals are tabulated in the Table:1

5.1 *Lipid-based Nano-carriers*

Lipid-based nanocarriers are prepared with physiological lipids which are free from toxicity, biodegradable, enhance stability, and economical. These nanocarriers comprise solid lipid nanoparticles (SLN) and nano structured lipid carriers (NLCs)

5.1.1 *Capsaicin* (*CAP*)loaded SLNs and NLCs: U. Agrawal et al. 2013 developed the lipid nanoparticles containing *CAP*. The in vitro, in vivo studies of SLNs and NLCs were performed for exploring the potential activity of *CAP* for enhancing the topical delivery. The *CAP* loaded NLCs was compared with the *CAP* loaded SLNs, NLCs exhibited higher drug loading, lower size with higher drug entrapment efficiency, higher skin permeation and no skin irritation. Depending upon the desired drug permeation profile and deposition of drug at target site NLCs are the better option for skin delivery. This report concluded that the NLCs are more suitable for topical delivery (Agrawal, Gupta, & Vyas, 2015)

Table 1: List of the currently developed and evaluated numerous nano phyto-pharmaceuticals

S.no	Phyto-drugs	Formulation	Mechanism of action	Evaluation	Results
1.	*Curcumin* (Filippone et al., 2020)	Nanohydrogel	Inhibits NF-KB$^{\Gamma}$ and MAPK$^{\Uparrow}$ pathways and the expression of TNF-α$^{\#}$,IL-1β$^{\infty}$,IL-6$^{\perp}$ and cyclin E	In vivo (IMQ) $^{\Pi}$	Nanohydrogel enhanced the water solubility of *Curcumin*, prevent the degradation of *Curcumin* and improved the penetration into the psoriatic skin
2.	*Celastrol* (Meng et al., 2019)	Niosomes	Inhibited the IL-23$^{\rho}$, IL-17$^{\sigma}$, IFN-α $^{\delta}$and IL-22$^{\eta}$ release	In vitro/In vivo (IMQ)	Enhanced in vitro permeation(465.3±84.1ng/cm^2) and alleviated scaling and erythematic lesions on mice skin.
3.	*Mangiferin* (Pleguezuelos-Villa et al., 2020)	Glycethosomes	It reduced the oxidation and inflammation	In vitro/ In vivo(TPA)$^{\Delta}$	Improved *Mangiferin* retention in the epidermis, reduced the oedema and inflammation
4.	*BerberineOleate* (May S Freag & Abdallah., 2019)	Liquid crystalline nanoparticulates	Anti-inflammatory actions, Inhibition of cyclooxygenase lipooxygenase, cytokines release TNF-α, IL-17A$^{\varepsilon}$, IL-23	In vitro, Ex vivo and In vivo (IMQ)	Increased skin penetration, skin deposition and Improved in vivo efficacy with inhibition of cytokines release
5.	*Curcumin* (Zhang et al., 2019)	Hyaluronan-Modified Ethosomes	Lowers TNF-α, IL-17A, IL-17F$^{\phi}$, IL-22 and IL-1β	In vitro HaCaT† /In vivo (IMQ)	Improved skin permeability and In vivo skin retention
6.	*Epigallocatechin-3-Gallate* (Chamcheu et al., 2018)	Chitosan-based polymeric nanoparticle	Reduced the skin thickness, erythema, scales, mastcells, proliferation, neutrophils, macrophages, CD4+ T cells and angiogenesis	In vitro/ In vivo (IMQ)	Improve bioavailability and stability

$^{\Gamma}$: Nuclear factor kappa light chain enhancer of activated B cells
$^{\Uparrow}$:Mitogen activated protein kinase
$^{\#}$: Tumor necrosis factor-α
$^{\infty}$:Interleukin 1β
$^{\perp}$:Interleukin 6
$^{\Pi}$:Imiquimod induced psoriasis model
$^{\rho}$:Interleukin 23
$^{\sigma}$:Interleukin 17
$^{\delta}$:interferon α
$^{\eta}$:Interleukin 22
$^{\Delta}$:12-O-tetradecanoyl phorbol-13 acetate treated mice

$^{\varepsilon}$:Interleukin 17A
$^{\phi}$:Interleukin 17F
† :Human epidermal keratinocyte cell line

7.	*Psoralen* (Doppalapudi, Jain, Chopra, & Khan, 2017)	Liposomes	Reduced the TNF-α, IL-17 and IL-22	Ex vivo/ In vitro/ In vivo (IMQ)	Enhanced skin permeation and skin deposition. It showed safety and efficacy
8.	*Berberisaristata Extract* (Nimisha, Rizvi, Fatima, Neema, & Kaur, 2017)	Transferosomes -gel	Anti- inflammatory action and anti- psoriatic effect	In vitro/In vivo on IMQ	Avoids first-pass effect, enhanced in vitro release, improved anti inflammatory activity
9.	*Ammonium Glycyrrhizinate* (Marianecci et al., 2014)	Niosomes	Reduced the inflammation, pain and oedema	In vitro/In vivo	Increased anti-inflammatory and anti-nociceptive responses
10.	*Psoralen* (Y. T. Zhang, Shen, Zhao, & Feng, 2014)	Ethosomes	Reduced the TNF-α, IL-17 and IL-22	In vitro/In vivo skin micro-dialysis	Skin deposition (6.56 folds), peak concentration and AUC‡ (3.37&2.34 times higher) was observed when compared with psoralen tincture. It reduced the toxicity and improved the efficacy

5.1.2 ***Mometasone furoate (MF)*** **NLCs:** MF is a prodrug, non-fluorinated synthetic corticosteroid that is primarily used topically to treat psoriasis and eczema. It inhibits the synthesis of cytokines including IL-1, IL-6, and TNF-α. The conventional drug delivery system of *Mometasone furoate* has been associated with a number of issues, which including low drug uptake due to the stratum corneum, swelling of hair follicles, systemic absorption, skin burning, and may cause skin atrophy if used for an extended time. NLCs have the ability to improve skin retention at the target site, it also lowering the risk of local and systemic side effects associated with topical corticosteroids. Kaur et al. 2018 loaded MF in to the NLCs, incorporated in to the carbopol 940 based hydrogel and evaluated the activity of optimized formulation. The drug permeation study

‡ : Area under curve

of NLCs based gel has shown the prolonged drug release when compared with the marketed product. In vivo study of MF –loaded NLCs on IMQ induced psoriatic skin mouse reduced the psoriatic lesions. It has been concluded as the use of NLCs based drug delivery system on topical administration could reduced the side effects and it can be inferred that formulas based on NLCs are efficient (Kaur, Sharma, & Bedi, 2018)

5.1.3 *Capsaicin*(CAP)loaded vesicular system: Gupta et al. 2016 developed and evaluated the *CAP* loaded liposomes, niosomes and emulsions for localized and controlled topical drug delivery. The vesicular system incorporated in to the gel form. The comparative study of percentage drug release, degree of entrapment, skin permeation study, amount of drug in the skin and draize test of 3 vesicular systems were evaluated. The skin retention study of *CAP* loaded emul-gel formulation showed the more accumulated drug in the skin. It has concluded that the emul-gel could be promising dosage form for delivering *CAP* to the skin for successful psoriasis treatment (Gupta, Gupta, Mangal, Agrawal, & Vyas, 2016)

5.2 *Babchi oil microemulsion gel:* Ali et al. 2008 investigated the oil contained in *Psoraleacorylifolia*, known as *babchi oil*, prepared as a micro-emulsion gel for psoriasis treatment. The in vitro and in vivo studies were performed for the evaluation of skin permeability and anti-inflammatory properties. A optimized microemulsion-based gel formulation increased *babchi oil* penetration in the skin and demonstrated excellent in vivo anti inflammatory activity in a foot pad oedema model (Ali, Akhtar, Sultana, Baboota, & Ahuja, 2008)

5.3 *Turmeric* microemulgel: Sarafian et al. 2015 formulated the microemulgel and performed 3-week clinical trials. It was given topically for mild to moderate plaque psoriasis patients for the identification of its safety and efficacy. The Dermatology Life Quality Index (DLQI) Questionnaire and Psoriasis area & severity index (PASI) was used to evaluate the microemulgel treated patients with the untreated population. It has been reported that PASI score and quality of life parameters in microemulgel treated patients improved ($P<0.05$) when compared with untreated population (Sarafian et al., 2015)

5.4 *Thymoquinone(TQ)* loaded ethosomes: TQ is a lipid-soluble benzoquinone, which is the primary active ingredient in *Nigella sativa's* volatile oil (NS). Negi et al. 2019 has developed the *TQ l*oaded ethosomes to overcome the problems of *TQ*, such as hydrophobicity, low aqueous solubility and photosensitivity. The formulated TQ ethosomes are loaded into hydrogel. The optimized formulation was evaluated for the anti-psoriatic activity by employing Swiss albino mouse tail model. The percentage anti psoriatic property of *TQ* loaded ethosomes, plain TQ, NS extract, marketed formulations was compared with each other in which TQ-loaded ethosomal gel has shown the better results. As a result of this research, potential possibilities for topical application of TQ in the form of ethosomal hydrogel has shown the better results (Negi et al., 2019)

5.5 Polymer based nano-carriers

Polymeric Nanoparticles are solid structures that can either encapsulate or absorb bioactive molecules**.** It has shown great promise in the delivery of drugs to specific locations for the treatment of a variety of diseases. They consist of nano-spheres, nano-capsules, and dendrimers. Polymeric nanoparticles are protects the drugs from oxidation, which also improves the solubility and bioavailability. Polymeric nanoparticles were created using a variety of biodegradable polymers. Polylactic acid, poly(lactide-co-glycolic acid) (PLGA), polyglycolic acid, and poly(cyanoacrylate) are used to create the hydrophobic zone (caprolactone). The hydrophilic element of PEG has been widely used (L. Sun et al., 2017)

5.5.1 PLGA-*Curcumin* nanoparticles: *Curcumin* (*CUR*) loaded PLGA nanoparticles (NPs) were developed and administered topically on IMQ induced psoriasis-like mouse model. It has increased the aqueous solubility and chemical stability of CUR. The *CUR* bioactivity was greatly improved by encapsulating lipophilic *CUR* in PLGA NPs in the mouse skin. The PLGA NPs system improved the drug dispersion, enhanced the drug penetration, more drug deposited in the skin and circulation along with sustained release (L. Sun et al., 2017)

5.5.2 Curcumin* polymeric nanopaticles based hydrogel*: Mao KL et al. 2017 formulated the *CUR* loaded Polymeric (RRR-a-tocopheryl succinate grafted e-polylysinconjuagate (VES-g-e-PLL) nanoparticles and incorporated in to the silk fibroin hydrogel for topical delivery. They evaluated the activity of *CUR* loaded nanoparticles and the *CUR* containing nanoparticles gel on imiquimod-induced psoriatic mice model. It revealed that *CUR*-NPs-gel had a more powerful skin-permeating capability and a more efficient anti-keratinization mechanism than *CUR*-NPs. As a result, *CUR*-NPs-gel was able to block the release of inflammatory cytokines TNF-α, NF-kB, and IL-6 more effectively. It has concluded, that the permeable nanoparticle-gel formulation could be used to incorporate lipophilic anti-psoriatic drugs for topical administration (Mao et al., 2017)

5.6 Metallic based Nano-Carriers: These are inorganic in nature and biocompatible, showing good stability, for a long period. They have the potential to target the site and exhibit cellular uptake. Mainly utilized for transdermal delivery but may cause toxic effects. Predominately they comprise silver and gold nanoparticles. The gold nanoparticles have a size, in the range of 0.8 -200nm. The polyphenolic extract of *Cornusmus* loaded

gold and silver nanoparticles were formulated and evaluated by the Crisan D et al. 2018. It has shown the anti inflammatory effects in bonemarrow derived murine macrophages by reducing the Nitrous oxide, TNF-α and IL-12 (Crisan et al., 2018)

5.6.1 *Hypoxis hemerocallidea* extract and *hypoxoside gold nanoparticles* (AuNPS*):*

Elbagory et al. 2019 synthesised the AuNPs from the extract of *H.hemerocallidea and hypoxoside* secondary metabolite. They conducted the immunomodulatory effect study of the aqueous extract of *H. hemerocallidea*, *hypoxoside*, AuNPs derived from the extract and *hypoxoside* using a solid phase sandwich ELISA technique. They measured cytokine levels in macrophages (IL-1, IL-6, and TNF-α) and NK cells (IFN-γ). The results recognized as *H. hemerocallidea* extract, *hypoxoside*, and their respective AuNPs can reduce pro-inflammatory cytokine levels in macrophages, but only *hypoxoside*-derived AuNPs can reduce cytokine responses in NK cells (Elbagory, Hussein, & Meyer, 2019)

6. Conclusion : To overcome the drawbacks of the synthetic agents, herbal extracts and phyto constituents are suitable. However herbals and phyto constituents are facing the insolubility, poor bioavailability and instability challenges. Nano phyto pharmaceuticals are the acceptable drug delivery system which will reduces the challenges and shows the good therapeutic range in effective manner. Mostly nanocarriers developed by lipids were shown the best improvement in the psoriasis, due to less toxicity, stable, compatibility and economical.

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