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# MANAGEMENT OF PSORIATIC ARTHRITIS: AN OVERVIEW OF SYNTHETIC, RECOMBINANT DNA, MONOCLONAL ANTIBODY AND NATURE-DERIVED AGENTS

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**Keywords:**

Psoriatic arthritis, Ustekinumab, Golimumab, Hederagenin, Gold sodium thiomalate

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**ABSTRACT:** Psoriatic arthritis is an inflammatory condition of the skin and musculoskeletal system with cutaneous psoriasis that leads to joint deformity and disability and is commonly seen in 40-50-year-old population. Clinically, TNF-α inhibitors and JAK inhibitors form the main line of treatment of this rare disorder. A systematic review was conducted via an electronic search of Google Scholar, PubMed, Science Direct, Wiley, Embase, and Cochrane databases till May 2020 using the following keywords: "Psoriatic arthritis", "Atrophic arthritis", "Rheumatoid arthritis". Published literature that explores the therapeutic methods of treating CSOM are included along with data of randomized control trials (RCTs), *in-vivo* studies and ELISA assays are collated in this review. 43 qualitative studies from 6 databases are included in this systematic review. Of these, 40 studies depict the efficacy of chemically synthesized, nature-derived, monoclonal antibody and recombinant DNA compounds (TNF-α inhibitors, T-cell suppressors, inhibitors of MAP kinase, and JAK) and 3 studies depict the benefits of alternative agents (ZSTK474, gold sodium thiomalate nanoparticles and whole body cryotherapy) in PsA. A critical analysis of the published literature indicates that filgotinib, golimumab, upadacitinib, etanercept, guselkumab, N, N-dimethylsphingosine, and hedera-genin are most effective in reducing arthritic pain (by 58 to 80%). This review aims to provide a comprehensive perspective on the role of diverse synthetic, recombinant DNA and nature-based agents in the modulation of inflammatory events and joint tenderness and swelling involved in the complex path physiology of PsA.

**INTRODUCTION:** Psoriatic arthritis (PsA) synonyms: rheumatoid arthritis, rheumatism, and atrophic arthritis is chronic inflammatory arthritis of the joints of the fingers and toes that frequently occurs in association with skin and nail psoriasis [1]. It is characterized by red, dry, itchy, and scaly skin patches and sausage-shaped swelling of the fingers and toes [2].

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The manifestations of PsA include peripheral arthritis, taxiospondylitis, dactylitis, enthesitis, asymmetric oligoarticular, symmetric polyarthritis, and distal inter-phalangeal, spondylitis, and arthritic mutilans [3].

It is commonly seen in people of 40-50 years of age, with about 10-30% of psoriasis patients developing psoriatic arthritis [4]. The CASPAR classification, developed by an international multicentre study, is widely used for PsA. The CASPAR criteria have a sensitivity of 90% and specificity of 98% [5]. The primary aim in the therapeutic management of PsA is to relieve the signs and symptoms of arthritis and target both the skin and joint features of the disease to cover the

entire landscape of this disease [6, 7]. This review presents an overview of current curative strategies used in PsA, providing relevant clinical study trial findings and *in-vitro* screening results supporting their efficacy **Fig. 1** represents arthritic person's hand associated with psoriasis of skin.


**FIG. 1: HAND OF A PATIENT SUFFERING FROM PSORIATIC ARTHRITIS**

**METHOD:** This systematic review includes 43 studies from 6 databases- Google Scholar, PubMed, Science Direct, Wiley, Embase, and Cochrane. We have included randomized control trials (RCTs), observational studies and ELISA assays in the collation and compilation of this review. We included only those studies that involved patients with a clinical diagnosis of PsA, one intervention, and its outcomes. We excluded studies wherein the diagnosis was unclear.

**Outcome:** In all these studies, the efficacy of treatment was assessed by change in swollen joints, tender joints, pro-inflammatory cytokine serum levels using Psoriatic Arthritis Severity Index (PASI), improvement in American College of Rheumatology (ACR) index, 28 Joint Disease Activity Score (DAS28) and ELISA assay.

**Search Methods for Identification of Studies:** The authors searched above mentioned 6 databases using keywords "Psoriatic arthritis", "Atrophic arthritis," and "Rheumatoid arthritis" till May 2020. All the data files were extracted with SciHub. The duplicate files were removed after a thorough screening, and full-text articles were screened for further inclusion. The process of study selection is depicted in **Fig. 2.**

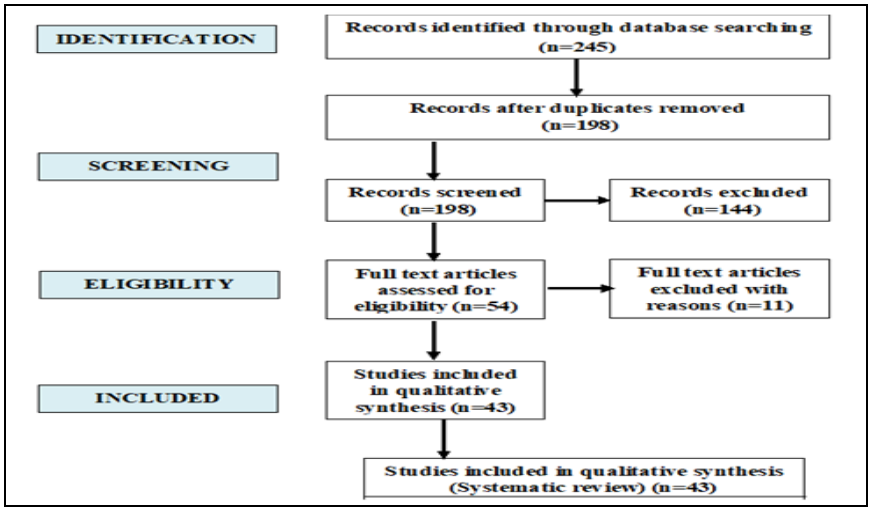


**FIG. 2: PROCESS OF STUDY SELECTION**

**RESULTS:** Therapeutic agents used in the treatment of PsA. The therapeutic agents used in the treatment of PsA can be classified based on the mechanism of action as follows. Tumor necrosis factor-alpha (TNF-α) and pro-inflammatory cytokines (IL-6, IL-17, IL-12 and IL-23) blockers**.** T-cell suppressors**.** Mitogen-activated protein kinase (MAP kinase) inhibitors.Janus activated kinase (JAK) inhibitors. Miscellaneous agents (ZSTK474, Gold sodium thiomalate, Whole body cryotherapy).

Over the last decade, TNF-α inhibitors along with DMARDs have been widely used for treating psoriasis and PsA that blocks inflammatory cascade that includes IL-17 and IL-23. The cytokines interplay in the pathophysiology of PsA as raised levels of cytokines are found in the joints of patients with PsA, as well as in psoriatic lesions. The modulation of the expression of inflammatory cytokines by TNF-α, MAP kinase, JAK inhibitors, and T-cell suppressors is depicted in **Table 1.**

**TABLE 1: TNF-A, MAP KINASE, JAK INHIBITORS AND T-CELL SUPPRESSORS USED IN PSA**

| S. no. | Name of Compound | Receptor/Mechanism Targeted | Cytokines Affected |
|---|---|---|---|
| **TNF-α Inhibitors and Pro-inflammatory Cytokine Blockers** | | | |
| | | **Synthetic Compounds** | |
| 1. | Apremilast[8] | PDE4 | ↓ TNF-α, IL-12, IL-17, IL-23, IFNγ |
| 2. | Aconibal[10] | TNF-α | ↓ IL-6, IL-1α, NO, MMP1, MMP3 |
| 3. | N,N-dimethylsphingosine[12] | Prevent conversion to sphingosine-1-phosphate | ↓ TNF-α, IL-12, MMP-9 |
| 4. | CR6086[14] | Prostaglandin E2 receptor 4 | ↓ IL-6, IL-17, IL-23 |
| 5. | BS-181,siRNA-CDK7[15] | CDK7, NF-KB,P65 | ↓ IL-17, IL-23 |
| | | **Phytoconstituents** | |
| 1. | Magnolol[16] | P13k, Akt, NF-kB | ↓ TNF-α, N0, COX-2, $PGE_2$, IL-6, MMP13 |
| 2. | Deacylcynaropicrin[17] | RANKl, JNK, Akt | ↓ TNF-α, IL-1β, IL-6 |
| 3. | Curcumin[18] | TNF expression | ↓ IL-1β, IL-6 |
| 4. | Esculetin[19] | Ikkα, p65, NF-kB | ↓ IL-16, IL-17A, IL-22, IL-23, TNF-α, IFNγ |
| 5. | Micheliolide[20] | NF-kB, p13k, Akt, p7056k | ↓ TNF-α, IL-1β, IL-6, IL-10, IFN-β |
| 6. | Etretinate [21] | RARα, RARβ, RARγ | ↑ IL-10, ↓ ROS |
| 7. | 5'-methoxyhydnocarpin[23] | TNF-α, 5-LOX | ↓ IL-8 |
| 8. | 1,25-Dihydroxyvitamin D3[24] | STAT3 | ↓ IL-17A |
| 9. | Ethyl caffeate[25] | NF-KB, Akt, kinase | ↓ TNF-α, IL-6, NO |
| | | **Monoclonal Antibodies** | |
| 1. | Golimumab[26] | TNF-α | ↓ IL-6 |
| 2. | Secukinumab[27] | IL-17 receptor | ↓ IL-17A |
| 3. | Rituximab[28] | IRF5 and IRF7, TYK2, STAT4 | ↓ IFN-1 |
| 4. | Ixekizumab[29] | IL-17 receptor | ↓ IL-17A |
| 5. | Adalimubab [30] | P55 and p75 cell surface TNF receptors | ↓ TNF-α |
| 6. | Bimekizumab [31] | IL-17 receptor | ↓ IL-17A, IL-17F |
| 7. | Brodalumab [32] | IL-17 receptor | ↓ IL-17A |
| 8. | Guselkumab [33] | IL-23 receptor | ↓ IL-23 |
| 9. | Certolizumab pegol [34] | TNF-α | ↓ IL-6 |
| | | **Recombinant Product** | |
| 1. | Etanercept [35] | TNF-α, TNF-β | ↓ TNF activity |
| | | **T-cell Suppressors** | |
| | | **Phytoconstituent** | |
| 1. | Paeoniflorin [36] | NF-kB, T-cell proliferation | ↓ IL-1β, IL-6, IL-8, IL-17, TNF |
| | | **Monoclonal Antibodies** | |
| 1. | Ustekinumab[37] | T-cell activation | ↓ IL-12, IL-23 |
| 2. | Neihulizumab [38] | CD162,induces apoptosis of late-stage activated T cells | ↓ IL-12, IL-23 |
| 3. | Efalizumab [39] | CD11a of LFA-1 | ↓ IL-17, IL-23 |
| | | **Recombinant DNA Product** | |
| 1. | Abatacept[40] | T-cell expression | ↓ IL-12, IL-17, IL-23 |
| | | **MAP Kinase Inhibitors** | |
| | | **Synthetic Compound** | |
| 1. | Diindolylmethane[41] | P38, JNK, MAPkinase, Akt | ↓ TNF-α, IL-1β, IL-6, IL-8 |
| | | Phytoconstituents | |
| 1. | Plumbagin[42] | RANKl, MAP kinase P38-kinase, NF-kB | ↓ IL-17 |
| 2. | Nitidine chloride[43] | NF-kB, MAP kinase, p65 | ↓ TNF-α, IL-1β, IL-6 |
| 3. | Astragalin[44] | P38, JNK, AP-1, C-Jun | ↓ TNF-α, IL-1β, IL-6, IL-8 |
| 4. | Sinomenine[45] | NF-kB, MAP kinase, p38 | ↓ TNF-α, IL-1β, IL-6, IL-8, COX-2, MMP-2, MMP-9 |
| 5. | Hederagenin[47] | NF-kB, ERK, JNK, p38 | ↓ TNF-α, IL-1β, IL-6, NO |
| | | **Janus Kinase Inhibitors** | |
| 1. | Baricitinib[48] | JAK1, JAK2 | ↓ IL-2, IL-4, IL-6, IL-15, IL-21, IFNγ |
| 2. | Tofacitinib[50] | JAK1 | ↓ IL-2, IL-4, IL-21 |
| 3. | Upadacitinib[51] | JAK1 | ↓ IL-2, IL-4, IL-15, IL-21 |
| 4. | Peficitinib[52] | JAK3 | ↓ JAK1/3-mediated cell proliferation |
| 5. | Filgotinib [53] | JAK1 | ↓ IL-1β, IL-2, IL-6, IL-12,IL-15, IL-17, IL-21, IL-23 |

**Abbreviations:** TNF-Tumor Necrosis Factor, IL-Interleukin, NO-Nitric oxide, IFN-Interferon, PDE-Phosphodiesterase, MMP-Matrix metalloproteinase, CDK-Cyclin dependent kinase, NF-kB-Nuclear factor kappa-light-chain-enhancer of activated B cells, P13k-Phosphoinositide 3-kinase, JNK-c-Jun N-terminal kinase, COX-Cycloxygenase, LOX-Lipoxygenase, Ikkα-IkB kinase alpha, IRF-Interferon regulatory factor, RANKl-Receptor activator of nuclear factor kappa-B ligand, TYK-Tyrosine kinase, STAT-Signal transducer and activator of transcription, JAK-Janus activated kinase, MAPkMitogen-activated protein kinase, PGE-Prostaglandin E.

**TNF-α Inhibitors and Pro-inflammatory Cytokine (IL-6, IL-17, IL-12, and IL-23) Blockers in PsA:** These agents inhibit cell proliferation, apoptosis, and angiogenesis, thereby down-regulating the inflammatory activities in the synovial fluid and peripheral joints. They are classified into synthetic compounds, phytoconstituents, monoclonal antibodies, and recombinant compounds.

**Synthetic Compounds:**

**Apremilast:** Apremilast is a phosphodiesterase-4 (PDE4) inhibitor that upregulates plasma cyclic adenosine monophosphate (cAMP) level and inhibits expression of TNF-α, IFNγ, IL-12, IL-17z and IL-23 in the synovial tissue.8A single-center, randomized clinical trial was reported by Abignano *et al.,* 2017 wherein 22 PsA patients were given 30 mg Apremilast orally twice daily for 4 months. The patients were evaluated for improvement in the tender and swollen joint counts using a 5-point Likert scale at an interval of 1 month. The results indicated that apremilast significantly (p=0.04) improved tender and swollen joint counts by 7% and 10%, respectively [9].

**Aconibal:** Aconibal decreases the expression of IL-6,IL-1α, chemokine ligand5, granulocyte-colony stimulating factor, nitric oxide synthase, cycloxyenase (COX) and matrix metalloproteinases (MMP1 and MMP3) in peripheral joints via MAP kinase pathway.10ELISA and western blotting assays were conducted by Park *et al.,* 2018 wherein LPS-stimulated raw 264.7 macrophage cells were cultured with aconibal at concentrations (10-1000 μg/ml).

The results of these assays indicated that1000 μg/ml aconibal significantly decreased the expression of IL-6 (550.80 to 113.66 pg/ml), IL-1 (42.77 to 5.19%), COX-2 (293.11 to 131.4%), MMP-1 (122.66 to 109.74 pg/ml) and MMP-3 (6.64 to 4.48 pg/ml) providing basis for further *in-vivo* studies to be conducted on aconibal [11].

**N, N-dimethylsphingosine:** N, N-dimethyl-sphingosine (DMS) blocks sphingosine kinase, thereby inhibiting the conversion of phosphorylate sphingosine into sphingosine-1-phosphate and suppresses TNF-α and IL-12, MMP-9 expression in PsA peripheral blood mononuclear cells [12]. ELISA and western blotting assays were conducted by Hu *et al.,* 2011 wherein paraformaldehyde-fixed PMA/PHA-stimulated jurkat-U937 were cultured with DMS at concentrations of1-10 μM.10 μM DMS significantly reduced the expression of TNF-α (893 to 200 pg/ml), IL-1 (224 to 100 pg/ml), IL-6 (245 to 28 pg/ml) and MMP-9 (203 to 83 ng/ml) indicating its potential in modulating the cytokines involved in the pathophysiology of PsA [13].

**CR6086:** CR6086 is a prostaglandin E2 receptor-4 antagonist that suppresses IL-6 and vascular endothelial growth factor (VEGF) expression in macrophages, IL-23 release from dendritic cells, and IL-17 release from Th-17 cells.Polymerase chain reaction (PCR) and ELISA assays were conducted by Caselli *et al.,* 2018 wherein LPS-stimulated human-embryonic kidney cells-293 (HEK293) were cultured withCR6086at concentrations of 0.1-10 μM. 1 μM of CR6086 significantly decreased the expression of IL-6 and IL-23 by 62% and 64% respectively and can be taken up as a potential lead in the development of new agents in the management of PsA [14].

**BS-181, siRNA-CDK7:** BS-181, siRNA-CDK7 are cyclin-dependent kinase7 (CDK7) inhibitors that prevent activation of NF-kB signaling; restrain p65 nuclear translocation and inhibit p65 phospho-rylation, thereby down-regulating the expression of IL-1β and IL-6 in peripheral joints. Polymerase chain reaction (PCR) and ELISA assays were conducted by Hong *et al.,* 2018 wherein LPS-stimulated human rheumatoid fibroblast-like synoviocytes MH7A cells were cultured with 80 nM BS-181, siRNA-CDK7.

BS-181, siRNA-CDK7significantly decreasedIL-1β (3.9 to 2 ng/ml) and IL-6 (6.1 to 4 ng/ml) levels [15].

**Phytoconstituents:**

**Magnolol:** Magnolol is a lignin constituent from *Magnolia Officinalis* that suppresses the activation of phosphoinositide 3-kinase (P13K), Akt/NF-kB pathway, thereby inhibiting the expression of NO,prostaglandin E2 (PGE2), COX-2, TNF-α, and IL-6 in the synovial tissue. ELISA, western blot and MTT assays were conducted by Wang *et al.,* 2012 wherein IL-1β stimulated fibroblast-like synoviocytes (1x106) cells were cultured with magnolol at concentrations of 0.25-25 μg/ml. The results of these assays indicated that 25 μg/ml magnolol significantly reduced the expression of IL-6 (163 to 62 ng/l), PGE-2 (62 to 17 ng/ml), MMP-1 (118 to 40 ng/ml), and MMP-13 (488 to 197 ng/ml) showing the scope of magnolol in the modulation of cytokines involved in PsA [16].

**Deacyl Cynaropicrin:** Deacyl cynaropicr ininhibits NF-kB ligand (RANKl), JNK, Akt pathway and suppresses the release of TNF-α, IL-1β and IL-6 in synovial fluid.

An ELISA assay was conducted by Li *et al.,* 2019 wherein primary bone-marrow-derived macrophage (BMM) cells were cultured with deacylcynaropicrin at concentrations of 2-10 μM. 10 μM deacylcy naropicrin significantly reduced the expression of TNF-α (268 to 89 pg/ml), IL-1β (177 to 78 pg/ml), and IL-6 (141 to 69 pg/ml), proving its utility as an agent worth exploring for the management of PsA [17].

**Curcumin:** Curcumin alters the expression of TNF-α that suppresses the release of IL-1β and IL-6, thereby decreasing PsA flares. A randomized clinical trial was reported by Nardo *et al.,* 2018 wherein 60 arthritic patients were treated with 500 mg curcumin capsule and 60 patients were treated with placebo capsules twice daily for 6 months.

The patients were clinically assessed for improvement in tenderness, pain, swelling, and stiffness using pain visual analogue score (PVAS) at 1-month interval for 6 months of the study. The results of this RCT indicated that curcumin significantly lowered the PVAS score to 2.9 compared to 3.92 in the placebo group, depicting the benefit of curcumin in PsA [18].

**Esculetin:** Esculetin inhibits the phosphorylation of IKKα, p65 that blocks NF-kB signaling, and decreases the proliferation and differentiation of keratinocytes, CD8+ T cells activation, subsequently suppressing the production of IL-16, IL-17A, IL-22, IL-23, TNF-α and IFNγ in peripheral joints and lymph nodes. An *in-vivo* study was conducted by Chen *et al.,* 2018 on 40 imiquimod-induced psoriatic BALB/c mice. The mice were administered 100 mg/kg/day esculetin for 1 week and evaluated daily for change in erythema, scaling, thickness and pain using psoriasis area and severity index (PASI). Esculetin significantly reduced the PASI score to 6.2 in comparison to 10.1 in the control group [19].

**Micheliolide:** Micheliolide is a sesquiterpene lactone that effectively decreases the lip polysaccharide (LPS) induced activation of NF-kB and p13k/Akt/p7056k pathways, thereby down-regulating the expression of cytokines IL-6,IL-1β,IFN-β, IL-10 and TNF-α.An *in-vivo* study was conducted by Xu *et al.,* 2014 on 40 collagen-induced arthritic DBA/1 mice. The mice were administered 30 mg/kg micheliolide at alternative of 1 day for period of 60 days. They were evaluated for change in swelling, redness and arthritic pain using arthritic scores at interval of each week. It was found that treatment with micheliolide significantly ($p<0.01$) reduced the arthritic score to (5.1), compared to (9.7) in the control group [20].

**Etretinate:** Etretinate, a vitamin A derivative, suppresses the differentiation of Th1/Th17 cells and production of reactive oxygen species that induces maturation of dendritic cells, production of IL-10 from macrophages. 21A randomized clinical study was reported by Miyabe *et al.,* 2012 wherein 15 PsA patients were given 50 mg etretinate orally once a day for 4 months. The patients were assessed for improvement in grip strength, Ritchie Joint index and pain at the 1-month interval for the entire duration of the study. Etretinate significantly reduced psoriasis by 19%, joint swelling by 22% and pain by 27%, showcasing its benefits in PsA [22].

**5'-Methoxyhydnocarpin:** 5'-methoxyhydnocarpin (5'-MHC), an active constituent of Mahonia oiwakensisis reported to inhibit TNF-α, NO, 5-lipoxygenase, growth of keratinocytes, thereby down-regulating IL-8production in peripheral

joints. An *in-vivo* study was conducted by Chao *et al.*, 2009 on 30 carrageenan-induced paw oedema mice. The mice were administered 500 mg/kg of ethanol extract of the roots of Mahonia oiwakensisorally for 2 weeks. They were assessed by writhing response and licking time of formalin test. Mahonia oiwakensis extract significantly decreased the number of writhing responses and licking time by 34.74% and 20.60% respectively [23].

**1, 25 - Dihydroxyvitamin D3:** 1, 25-Dihydroxy vitamin D3 downregulates the STAT3 phosphorylation, thereby suppressing IL-17A production in CD4+ T cells and Th17 differentiation in synovial fluid and lymph nodes. An open-label study was reported by Zhong *et al.*, 2019 wherein 10 PsA patients were administered 2μg/day of 1,25-Dihydroxyvitamin-D3 orally for 6 months. The patients were assessed for improvement in tenderness, grip strength using Arthritis Impact Measurement Scales (AIMS) at 2 weeks intervals for the duration of the study. 1, 25-dihydroxyvitamin D3 significantly decreased the AIMS score from 7.58 to 6.16 [24].

**Ethyl Caffeate:** Ethyl caffeate, an active constituent of Physalis alkekengi inhibits nuclear translocation of NF-kB, thereby modulating Akt and MAP kinase signaling pathways, subsequently down-regulating the expression of nitric oxide, TNF-α, IL-1β, and IL-6 in peripheral joints. An ELISA assay was conducted by Moniruzzaman *et al.*, 2016, wherein LPS-stimulated THP-1 cells were cultured with ethanol extract of Physalis alkekengiat concentrations of 25-100 μg/ml. The results indicated that 100 μg/ml Physalis alkekengi extract significantly reduced the expression of TNF-α (3.4 to 2.38 pg/ml), IL-1β (800 to 640 pg/ml), and IL-6 (260 to 234 pg/ml), warranting further explorative studies of this compound in PsA [25].

**Monoclonal Antibodies:**

**Golimumab:** Golimumab has a greater TNF binding capacity that decreases IL-6 expression, thereby preventing the progression of bone erosion in peripheral joints. A go-reveal study was reported by Urdaneta *et al.*, 2017 wherein 146 PsA patients were administered Golimumab 100 mg subcutaneously once in four weeks for a treatment period of 24 weeks. They were assessed for improvement in the swollen and tender joint count by ACR20, ACR50, and ACR70. The results indicated that golimumab significantly improved the scores of ACR20 (61%), ACR50 (38%), and ACR70 (21%) [26]. Results of anti-psoriatic effects of 100 mg golimumab are depicted in **Fig. 3.**

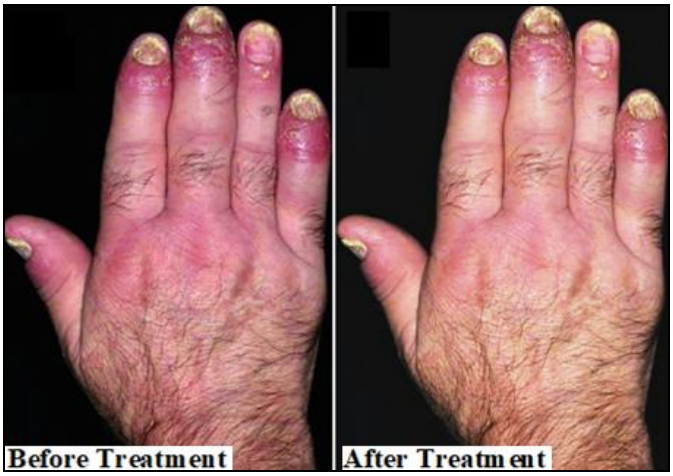


**FIG. 3: BEFORE AND AFTER EXAMPLE OF A PATIENT WITH PSORIATIC ARTHRITIS WHO UNDERWENT TREATMENT WITH 100 mg GOLIMUMAB**

**Legend:** The treatment with golimumab for 6 months effectively reduced about 50-55% redness of skin and swelling of the joints.

**Secukinumab:** Secukinumab is a human IgG1 monoclonal antibody that binds to the IL-17A cytokine and inhibits its interaction with IL-17 receptor; thereby reducing inflammation in PsA. A randomized, double-blind, placebo-controlled trial was reported by Jayaraman *et al.*, 2015 wherein 42 PsA patients were administered Secukinumab 150 mg subcutaneously once in four weeks for a treatment period of 24 weeks. They were assessed for improvement in the swollen and tender joint count by ACR20. Secukinumab significantly improved the ACR20 score (42%) in comparison to 16% in the placebo group [27].

**Rituximab:** Rituximab is a chimeric anti-CD20 monoclonal IgG1 antibody that inhibits NF-kB signaling and IFN1 pathways, suppresses IFN regulatory factors 5 and 7 (IRF5 and IRF7), tyrosine kinase 2 (TYK2), signal transducer, and activator of transcriptor4 (STAT4) in synovial joints. An open-label trial was conducted by Jimenez-Boj *et al.*, 2015 on 23 PsA patients. The patients were administered rituximab 1000 mg subcutaneously once a week for a treatment period

of 6 months. The patients were assessed by DAS28 and disease activity index for psoriatic arthritis. Rituximab significantly improved the DAS28 scores from 6.2 to 4.9 and disease activity index for psoriatic arthritis from 52 to 32.5 [28].

**Ixekizumab:** Ixekizumab is a humanized IgG4 monoclonal antibody that binds to the IL-17A cytokine and prevents interaction with the IL-17 receptor, thereby reducing the PsA inflammation. A randomized, double-blind, placebo-controlled study was reported by Haroon *et al.,* 2019 wherein 123 PsA patients were administered Ixekizumab 80 mg subcutaneously once in 2 weeks for a treatment period of 24 weeks. They were assessed using ACR20 and DAS28. Ixekizumab significantly improved the ACR20 and DAS28 scores (48% and 1.8) in comparison to (19% and 0.8) in the placebo group [29].

**Adalimubab:** Adalimubab is a humanized IgG1 monoclonal antibody that binds to TNF-α and inhibits its interaction with the p55 and p75 cell surface TNF receptors, thereby neutralizing the TNF-α activity and reduces joint inflammation and damage. An Italian real-life retrospective study was conducted by Angelo *et al.,* 2019 wherein 190 PsA patients were administered Adalimubab 80 mg subcutaneously for 12 months. They were assessed for improvement in swollen joints and tenders using Disease activity in PsA (DAPSA) and PASI. Adalimubab significantly improved the scores of DAPSA and PASI (25.5 to 11 and 5.3 to 2.7); it also significantly decreased the number of tenders from 7 to 2.3 and swollen joints from 2.7 to 0.4.30

**Bimekizumab:** Bimekizumab is a humanized IgG1 monoclonal antibody that binds to and neutralizes IL-17Aand IL-17F, preventing their interaction with IL-17 receptors expressed on keratinocytes, synoviocytes and osteoblasts.

A 48 weeks, randomized, double-blind, placebo-controlled, dose-ranging phase 2b trial was conducted by Ritchlin *et al.,* 2020, on 82 patients with PsA. Of these, 41 patients were treated with 160 mg bimekizumab, and the remaining 41 patients with placebo subcutaneously once in 4 weeks for a period of 12 weeks. The patients were assessed using ACR50 after each 4 weeks. The results indicated that treatment with bimekizumab significantly improved the ACR50 score by 8.1 in comparison to 2.2 in the placebo group [31].

**Brodalumab:** Brodalumab is a humanized IgG2 monoclonal antibody that binds to IL-17A cytokine and prevents interaction with IL-17 receptor, thereby reduces joint inflammation. 24-week phase III Amvison-1 and 2 trials were conducted by Mease et al., 2015 on 644 patients. 322 patients were treated with 210 mg brodalumab, and the remaining 322 patients were treated with placebo subcutaneously once in 4 weeks for 24 weeks. They were assessed using ACR20, ACR50, and ACR70. It was found that treatment with brodalumab significantly ($p<0.0001$) improved the scores of ACR20, ACR50, and ACR70 (55%, 37%, 21%) compared to (24%, 11%, 5%) in placebo group [32].

**Guselkumab:** Guselkumab is a human G1λ monoclonal antibody that selectively binds to p19 subunit of IL-23 in dendritic cells and keratinocytes and blocks its interaction with IL-23 receptor, thereby preventing the release of pro-inflammatory cytokines and chemokines via stimulation of Th17 cells. A randomized, double-blind, placebo-controlled, phase 2 study was conducted by Deodhar et al., 2018 on 149 patients. Of these, 100 patients were treated with 100 mg guselkumab, and remaining 49 patients were treated with placebo subcutaneously once in 4 weeks for 24 weeks. They were assessed using ACR20. Guselkumab significantly improved the ACR20 score by 58% in comparison to 18% of the placebo group [33].

**Certolizumab Pegol:** Certolizumab pegol (CZP) is a fully-humanized monoclonal antibody comprising of PEGylated Fab′ fragment and Fc-free protein. It binds to TNF-α, thereby preventing its interaction with TNF receptor and suppresses IL-6 expression leading to a reduction in joint inflammation.

A phase III, double-blind, randomized, placebo-controlled study was conducted by Mease *et al.*, 2014 on 368 patients. Of these, 208 patients were treated with 200 mg CZP, and the remaining 160 patients were treated with placebo once in 2 weeks for 24 weeks. They were assessed using ACR20. CZP significantly improved the ACR20 score by 58% in comparison to 24.3% of the placebo group [34].

**Recombinant DNA Product:**

**Etanercept:** Etanercept is a fully human recombinant molecule consisting of two soluble TNF receptor (p75) subunits fused to the Fc portion of human IgG1. It binds to TNF-α and TNF-β, preventing their interaction with TNF receptors and reduces TNF activity and subsequently joint pain. An open-label, placebo-controlled, randomized study was conducted by Mease *et al.*, 2004 on 205 patients. Of these, 125 patients were treated with 25 mg etanercept, and remaining 80 were treated with placebo subcutaneously twice week l for 24 weeks. They were assessed using ACR20. Etanercept significantly improved the ACR20 score by 59% in comparison to 15% of the placebo group [35].

**T-cell Suppressors in PsA:** These agents block T-cell activation, proliferation, and expression, thereby reducing inflammation in synovial fluid. We have classified these agents into phytoconstituents, monoclonal antibody, and recombinant DNA compounds.

**Phytoconstituent:**

**Paeoniflorin:** Paeoniflorin, a glucoside obtained from the leaves of Paeonialactiflora, suppresses T cell proliferation, thereby suppressing the production of IL-1β, TNF, IL-6, IL-17 and chemokines (IL-8, CC chemokine ligands 2 and 20) in synovial fluid. An ELISA assay was conducted by Tacconelli *et al.*, 2018 wherein spleens of collagen-induced arthritic mice were cultured with paeoniflorin (7.5 mg/kg). Paeoniflorin significantly suppressed the expression of TNF-α (61 to 42 pg/ml), IL-1β (281 to 37 pg/ml), and IL-6 (76 to 57 pg/ml) [36]. This opens up an entire range of plant-derived compounds, mainly secondary metabolites, that can be evaluated for potential benefits in PsA *via* modulation cytokine expression.

**Monoclonal Antibodies:**

**Ustekinumab:** Ustekinumab is an anti-IL12/IL23 monoclonal antibody that blocks T-cell activation, decreases IL-17 and IL-12 expression, thereby attenuating the inflammatory responses in peripheral joints. An open-label, double-blind, placebo-controlled trial was conducted by Savage et al., 2015 in 208 PsA patients. The patients were administered ustekinumab 90 mg subcutaneously once in 4 weeks for 24 weeks. They were assessed using ACR20 and PASI75. Ustekinumab significantly improved the ACR20 and PASI75 scores (49.5% and 60.8%) in comparison to (22.8% and 11%) of the control group [37].

**Neihulizumab:** Neihulizumab is a humanized monoclonal antibody that targets CD162 involved in the regulation of T cell homeostasis. It preferentially induces apoptosis of late-stage activated T cells. A phase-II open-label clinical study was conducted by AbGenomics International, 2016, wherein 20 patients received 9 mg/kg neihulizumab-subcutaneously for12 weeks. They were assessed using ACR2, ACRC50, and ACR70. Neihulizum ab-significantly improved the ACR20, ACR50 and ACR70 scores by 53.3%, 40%, and 13.3%, respectively at week 12 [38].

**Efalizumab:** Efalizumab is a humanized mono-clonal antibody that binds CD11a subunit of the lymphocyte function-associated antigen-1 (LFA-1) and inhibits activation of T cells. A phase-II randomized, double-blind, placebo-controlled multicenter study was conducted by Papp *et al.*, 2007 on 107 patients. Of these, 67 patients received 1 mg/kg efalizumab, and the remaining 40 patients received a placebo subcutaneously for 12 weeks. They were assessed using ACR20. Efalizumab significantly improved the ACR20 score by 28% in comparison to 19% of the placebo group [39].

**Recombinant DNA Product:**

**Abatacept:** Abatacept binds to CD80/86 on the surface of antigen cell and prevents binding of CD28 to CD80/86, decreasing T-cell activation and down-regulating IL-17, IL-12, IL-23, and characterization of Th17 cell levels in synovial fluid. An open-label ASTRAEA study was conducted by Noisette and Hochberg, 2018 in 424 PsA patients. The patients were administered Abatacept 125 mg subcutaneously once in 4 weeks for 24 weeks. They were assessed using ACR20, ACR50, ACR70, and PASI75. Abatacept significantly improved the ACR20, ACR50, ACR70 and PASI 75 scores (39.4%, 19.2%, 10.3% and 16.4%) in comparison to (22.3%, 12.3%, 6.6% and 10.1%) of the control group [40].

**MAP Kinase (MAPk) Inhibitors in PsA:** These agents inhibit cell proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis,

thereby down-regulating inflammatory activities in the synovial fluid and peripheral joints. These agents are classified into synthetic compounds and phytoconstituents.

**Synthetic Compound:**

**Diindolylmethane:** Diindolylmethane is an acid-catalyzed oligomerized product of indole-3-carbinol that blocks p38, JNK, MAPK, Akt signaling pathways, thereby down-regulating the expression of TNF-α, IL-6, IL-8, and IL-1β in the synovial fluid. An ELISA assay was conducted by Dong *et al.,* 2010 wherein collagen-induced fibroblast-like cells were cultured with diindolylmethane at concentrations of (5-50 mg/kg). 50 mg/kg of diindolylmethane significantly reduced the expression of TNF-α (46 to 34 pg/ml), IL-1β (57 to 42 pg/ml), and IL-6 (48 to 46 pg/ml) [41].

**Phytoconstituents:**

**Plumbagin:** Plumbagin, obtained from Plumbago zeylanica L, binds MET169 of JNK kinase and LYS138 and SER138 of p38 kinase and inhibits MAPk phosphorylation; downregulates the expressions of Th17 cells and T-reg cells, thereby suppressing IL-17 levels in synovium. An ELISA assay was conducted by Messeha et al., 2017 wherein collagen-induced mice left hind paws were cultured with plumbagin at concentrations (2.5-10 μM). 10 μM plumbagin significantly reduced the expression of TNF-α (57 to 19 pg/ml), IL-1β (432 to 173 pg/ml) and IL-17 (117 to 42 pg/ml) [42].

**Nitidine Chloride:** Nitidine chloride is a penta-cyclic alkaloid obtained from Zanthoxylum nitidum. It inhibits NF-kB, phosphorylation, MAPkinase and translocation of p65, thereby decreasing the production of TNF-α, IL-1β, and IL-6 in peripheral joints. An ELISA assay was conducted by Wang *et al.,* 2016 wherein LPS stimulated raw 264.7 cells were cultured with nitidine chloride at concentrations of 1-5 μM. 5 μM nitidine chloride significantly reduced the expression of TNF-α (4.4 to 1.9 ng/ml), IL-1β (0.86 to 0.34 ng/ml) and IL-6 (18.1 to 9.8 ng/ml) [43].

**Astragalin:** Astragalin, a flavonoid obtained from Cassia alatablocks phosphorylation of p38, JNK and activation of C-Jun/AP-1, thereby suppressing the production of TNF-α,IL-1β,IL-6, IL-8 and expression of MMP-1, MMP-3, and MMP-13 in synovial cells. ELISA and PCR analysis was conducted by Chighizola *et al.,* 2019 wherein TNF-α induced MH7A cells were cultured with astragalin at concentrations of 50-200 μM. 200 μM astragalin significantly reduced the expression of TNF-α (801 to 192 pg/ml), IL-1β (1754 to 334 pg/ml), IL-6 (736 to 329pg/ml), IL-8 (1053 to 262 pg/ml), MMP-1 (16364 to 7245 pg/ml), MMP-3 (12443 to 7505 pg/ml) and MMP-13 (7521 to 4211 pg/ml) [44].

**Sinomenine:** Sinomenine, obtained from Sabio japonica suppresses the expression of NF-kB and MAP kinase, COX-2, NO, GM-CSF, MMP-2, and MMP-9. It also decreases TNF-α, IL-6, IL-1β, IL-8, malondialdehyde levels in synovial fluid. 45AnELISA assay was conducted by Chen *et al.,* 2011 wherein LPS-stimulated raw 267.7 macrophage cells were cultured with sinomenine at concentrations of 10-50μg/ml. 50μg/ml sinomenine significantly reduced the expressions of TNF-α (681 to 362 pg/ml), IL-1β (260 to 78 pg/ml), IL-6 (116 to 64 pg/ml) and GM-CSF (141 to 52 pg/ml) [46].

**Hederagenin:** Hederagenin, a triterpene obtained from Clematis mandshurica ruprecht suppresses LPS-induced inducible nitric oxide synthase (iNOS),COX-2,NF-kB, and MAPK's (ERK, JNK and p38), thereby decreasing the expression of TNF-α, IL-1β, IL-6, NO and PGE2in synovium. AnELISA assay was conducted by Lee *et al.,* 2016 wherein LPS-stimulated raw 264.7 macrophages cells were cultured with hederagenin at concentrations of 10-100 μM. 100 μM hederagenin significantly reduced the expression of TNF-α (2702 to 989 pg/ml), IL-1β (136 to 61 pg/ml), IL-6 (1156 to 588 pg/ml), NO (24 to 2.5μM) and PGE2 (1607 to 187 pg/ml) [47].

**Janus Kinase (JAK) Inhibitors in PsA:** These agents block JAK enzyme, thereby suppressing the expression of pro-inflammatory cytokines and inflammation in the synovium.

**Baricitinib:** Baricitinib is a selective and reversible JAK1 and JAK2 inhibitor that blocks IL-2, IL-4, IL-15, IL-21, IFN-γ, and IL-6 expression in the synovial fluid.48A randomized, double-blind, placebo-controlled trial was conducted by Heijde *et al.,* 2018 in 271 PsA patients.

The patients were given baricitinib 10 mg orally once a day for 24 weeks. They were assessed using PASI50, PASI75 and PASI90. Baricitinib significantly improved the PASI50, PASI75 and PASI90 scores (76%, 54% and 36%) in comparison to (23%, 18% and 3%) of the control group [49].

**Tofacitinib:** Tofacitinib is a selective JAK1 inhibitor that blocks the activity of IL-2, IL-4 and IL-21 in synovium. An open-broaden clinical study was reported by Yamaoka, 2019 wherein 209 PsA patients were administered Tofacitinib 10 mg orally once a day for 24 weeks. They were assessed using PASI50, ACR20, ACR50 and ACR70. Tofacitinib significantly improved the PASI 50, ACR20, ACR50 and ACR70scores (44%, 61%, 40% and 14%) in comparison (15%, 33%, 10% and 5%) to the control group [50].

**Upadacitinib:** Upadacitinib is JAK1-selective inhibitor that decreases the expression of IL-2, IL-4, IL-15 and IL-21 in peripheral joints. A multi-centre, randomized, double-blind study was reported by Smolen *et al.*, 2019 wherein 243 PsA patients were administered Upadacitinib 30 mg orally once a day for 24 weeks. They were assessed using PASI75, ACR20, ACR50 and ACR70. Upadacitinib significantly improved the PASI75, ACR20, ACR50 and ACR70 scores (62%, 79%, 52% and 25%) in comparison to (21%, 36%, 13% and 2%) of the control group [51].

**Peficitinib:** Peficitinib is a JAK3 selective inhibitor that blocks the JAK1/3-mediated cell proliferation. A randomized, double-blind, placebo-controlled, parallel-group study was reported by Qiu *et al.*, 2019 wherein 507 PsA patients were administered Peficitinib 150 mg orally once a day for 52 weeks. They were assessed using ACR20, ACR50, and ACR70. Peficitinib significantly improved the ACR20, ACR50 and ACR70 scores (74.5%, 42.2% and 27.5%) in comparison to (30.7%, 8.9% and 1%) of the control group [52].

**Filgotinib:** Filgotinib is JAK1 inhibitor that downregulates the expression of IL-1β, IL-2, IL-6, IL-12, IL-15, IL-17, IL-21, and IL-23 in the peripheral joints. A randomized, placebo-controlled phase 2 trial was conducted by Mease *et al.,* 2018 in 131 patients. Of these, 65 patients were treated with 200 mg filgotinib, and the remaining 66 patients were treated with placebo orally once a day for 24 weeks. They were assessed using ACR20. Filgotinib significantly improved the ACR20 score by 80% in comparison to 33% of the placebo group [53]. Results of anti-psoriatic effects of 200 mg filgotinib are depicted in **Fig. 4.**


**FIG. 4: BEFORE AND AFTER EXAMPLE OF A PATIENT WITH PSORIATIC ARTHRITIS WHO UNDERWENT TREATMENT WITH 200 mg FILGOTINIB**

**Legend:** The treatment with filgotinib for 6 months effectively lightened the redness and flaky skin, reduced arthritic pain.

**Miscellaneous Therapies:** These agents inhibit the expression of pro-inflammatory cytokines and B-cell proliferation in synovial fibroblasts. The modulation of inflammatory cytokine expression by miscellaneous agents is depicted in **Table 2.**

**TABLE 2: MISCELLANEOUS THERAPIES FOR PSA**

| S. no. | Name of the Therapy | Mechanism Involved | Cytokine Affected |
|---|---|---|---|
| 1 | ZSTK474[54] | Inhibits proliferation of B-lymphocyte, synovial fibroblast | Reduce osteoclastogenesis |
| 2 | Gold sodium thiomalate[55] | NF-kB, 1-kappa B-kinase, MAP kinase | ↓ TNF-α, IL-1, IL-1β, IL-6 |
| 3 | Whole body cryotherapy[56] | Exposure at (-110 to -140) $^{o}$C for 2 min | ↓ TNF-α, IL-2, IL-6, IL-8 |

**Abbreviations:** TNF-Tumor necrosis factor, NF-kB-Nuclear factor kappa-light-chain-enhancer of activated B cells, IL-Interleukin.

**ZSTK474:** ZSTK474 is a phosphoinositide-3-kinase (Pi3K) inhibitor. It inhibits proliferation of B-lymphocytes and synovial fibroblasts; downregulates IL-17/IL-23 expression thereby decreasing osteoclast formation in joints. An *in-vivo* study was conducted by Okkenhaug *et al.*, 2015 on 12 collagen-induced arthritic DBA/1 mice. The mice were administered

an oral dose of 100 mg/kg ZSTK474 daily for 1 month and were evaluated using mean arthritis score. ZSTK474 significantly reduced the mean arthritis score to 2.4 in comparison to 6.8 of the placebo group [54].

**Gold Sodium Thiomalate:** Gold sodium thiomalate (GST) suppresses NF-kB, MAPkinase signaling and activation of 1-kappa B-kinase, decreasing the production of TNF-α,IL-1, IL-6 in the synovial fluid.A double-blind study was conducted by Davis, 1988 on 42 PsA patients. The patients were administered 50 mg GST intravenously once in 4 months for12 months. They were evaluated for change in swollen joints, tender joints mean arthritis index at end of treatment. GST significantly reduced swollen joints (8 to 3.6), tender joints (13 to 3.4) and arthritis index (56 to 9) [55].

**Whole Body Cryotherapy (WBC):** The arthritic patients are exposed to cold air temperature of -110°C to -140 °Cusing special temperature-controlled cryochambers for 3 minutes. This results in a decrease in TNF-α, IL-2, IL-6 and IL-8.A 2-week comparative study was conducted by Gizinska *et al.,* 2015 on 44 arthritic patients, wherein 24 patients were treated with WBC and remaining 20 patients were treated with traditional rehabilitation. They were evaluated using DAS28 score, change in serum TNF-α and IL-6 by ELISA assay.

The results indicated that WBC significantly improved DAS28 score (5.27) in comparison to traditional rehabilitation group (4.97); WBC significantly decreased the levels of TNF-α (11.77 to 4.46) and IL-6 (17.96 to 11.75), thereby establishing its serviceableness as a therapy value exploring for the management of PsA [56].

**DISCUSSION:** A critical analysis of clinical trials, randomized studies along with results of ELISA assays indicates that the most effective therapeutic agents in the management of PsA are

1) Filgotinib as it significantly improved ACR20 score by 80% [53].
2) Upadacitinib as it significantly improved the scores of ACR20, ACR50 and ACR70 by 79%, 52% and 25% [51].
3) Golimumab as it significantly improved the scores of ACR20, ACR50 and ACR70 by 61%, 38% and 21% [26].
4) Etanercept as it significantly improved ACR20 score by 59% [35].
5) Guselkumab as it significantly improved ACR20 score by 58% [33].
6) Hederagenin with overall 68% improvement in PsA condition, as it significantly reduced expression of TNF-α (2702 to 989 pg/ml), IL-1β (136 to 61 pg/ml), IL-6 (1156 to 588 pg/ml), NO (24 to 2.5 μM) and PGE2 (1607 to 187 pg/ml). [47]
7) N, N-dimethylsphingosine with overall 67% improvement in PsA condition, as it significantly ($p<0.05$) reduced expression of TNF-α (893 to 200 pg/ml), IL-1 (224 to 100 pg/ml), IL-6 (245 to 28 pg/ml) and MMP-9 (203 to 83 ng/ml) [13].

The limitations of this review are the lack of evidence-based studies on many of these agents, and most of the clinical evidence is derived from observational studies with low sample size and short length of trials, raising plausible questions regarding the long-term efficacy and safety of these agents. Given these limitations, there is immense scope of further research on these agents to validate the preliminary *in-vitro, in-vivo* and small base clinical trial results and subsequently translate them into large base clinical trials. This review hopes to garner the interest of the pharma and biologics industry into more basic and translational research avenues in PsA.

**CONCLUSION:** This review presents an insight into the complex pathophysiology of psoriatic arthritis, an achronic inflammatory arthritis condition associated with skin and nail psoriasis. The current therapeutic options for the management of PsA include TNF-α inhibitors, T-cell suppressors, MAP kinase inhibitors, and Janus kinase inhibitors. These agents function by down regulating pro-inflammatory cytokines and matrix metallo-proteinases and improve the psoriatic condition. Synthetic compounds such as apremilast, to facitinib and baricitinib are current gold standards in PsA however long-term exposure raises safety concerns (stomach upset, liver

dysfunction, blood problems). The results reported of plant-derived compounds have proved to be a viable alternative compared to synthetic compounds due to comparative efficacy and reduced side effects. There exists an unmet need of initiating high-quality blinded RCTs to explore the benefits of combination therapy in PsA, for example, (TNF-α inhibitors along with gold sodium thiomalate) or (plant-derived compounds possessing anti-rheumatoid activity along with whole body cryotherapy).

There is plenty of opportunities to work on molecular level studies and extensive exploration of the compounds used in PsA alone and versatile novel combinations for anticipated synergy and reduced side effects. Such studies will foster the development of new alternatives (both synthetic and plant-based compounds), combination therapies augmenting the current armamentarium of PsA therapeutics leading to more effective clinical outcomes in PsA.

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