REVIEW ARTICLE

An Intensive Review on the Management of Psoriasis: Fumaric Acid Esters Analogs

Priyanka Sharma*, Hemlata Bisht, Md. Niyaz Alam, Pallavi M Lavhale
Ram-Eesh Institute of Vocational and Technical Education Greater Noida, Uttar Pradesh, India
Corresponding Author Email ID: sharmapriyanka1167@gmail.com

Received: 22/02/2024 **Accepted: 03/05/2024** **Published: 15/07/2024**

Abstract

Psoriasis is a recurring skin condition that occurs due to the hyperproliferation of keratinocytes and immune dysregulation. Psoriasis management frequently necessitates using systemic therapies, which include fumaric acid ester analogs (FAEs), methotrexate, TNF inhibitors, and IL-17 inhibitors. The efficacy of FAEs against methotrexate is comparable but has fewer side effects. The most common adverse reactions associated with the treatment of psoriasis are gastrointestinal symptoms (such as bloating), flushing and lymphopenia. Rare but serious adverse reactions may include hepatitis and renal dysfunction. Methotrexate is an effective treatment; however, it has been linked to hepatitis, gastrointestinal adverse effects, and inhibition of the bone marrow in psoriasis patients. TNF Inhibitors NF-NF-inhibitors and TNF-17 inhibitors offer comparable efficacy rates and a faster onset of action to those of other agents but come with increased risks of infections and injection site reactions. TNF inhibitors may raise the risk of autoimmune responses, cancer, and serious infections. Neutropenia and inflammatory bowel disease may be made worse by IL-17 inhibitors. Treatment-related factors include the mode of administration, the need for monitoring, and any potential financial barriers to access. FAEs are administered orally and require regular monitoring for adverse events, while biologic agents (TNF inhibitors, IL-17 inhibitors) are administered subcutaneously or intravenously and necessitate monitoring for infections and malignancies. FAEs are given orally and need to be monitored for adverse reactions, while biologic agents (TNF inhibitors, IL-17 inhibitors) are given.

Keywords: Fumaric acid ester analogs, Keratinocytes, TNF inhibitors, Interleukin, Efficacy.

Journal of Applied Pharmaceutical Sciences and Research, (2024); DOI: 10.31069/japsr.v7i2.03

Introduction

The chronic skin ailment psoriasis is the cause of red, scaly, and silvery spots on the skin. It is regarded as an inflammatory and autoimmune condition.[1,2] The chronicity of the illness significantly impacts the patient's psychological state. Individuals suffering from psoriasis see a decline in their quality of life that is comparable to that of individuals with more severe chronic conditions like diabetes and ischemic heart disease.[2] it is believed that psoriasis is an immune system issue. Cold, stress, and infections are among the triggers. The earliest indication is a skin rash, though it can also involve the joints or nails. Psoriasis is considered a multifactorial disease, influenced by both genetic predisposition and environmental factors.[3] Psoriasis is more than simply a skin ailment; it may also significantly lower an affected person's quality of life.[4] It is associated with an increased risk of comorbidities such as psoriatic arthritis, cardiovascular disease, metabolic syndrome, and depression. Management of psoriasis typically involves a combination of topical treatments, phototherapy, systemic medications, and lifestyle modifications tailored to the individual's specific needs and preferences. Psoriasis is a chronic inflammatory skin disorder characterized by the rapid proliferation of skin cells, leading to the formation of thickened, red, and scaly patches on the skin. It is considered an autoimmune condition, where the body's immune system mistakenly attacks healthy skin cells, resulting in inflammation and abnormal skin cell growth.[4]

Multiple forms of psoriasis exist, such as.[5-6]

- Psoriasis Vulgaris: The most prevalent variety of psoriasis, known as plaque psoriasis (Psoriasis Vulgaris), is characterized by an elevated, red, and inflammatory skin lesion coated in silvery white scales.
- Guttate Psoriasis: This skin condition usually manifests as tiny, red, scaly spots. It frequently follows a viral or bacterial infection and can strike without warning, particularly in young adults and children.
- Pustule psoriasis: This type is distinguished by red skin encircling pus-filled blisters. It may only affect particular bodily parts.
- Inverse Psoriasis: Affects skin folds in the armpits and groin area, under the breasts. It can be made worse by friction and perspiration and manifests as smooth, red spots.
- Epidermic psoriasis: An extremely rare and severe form of psoriasis that can cause red, peeling, and inflammatory skin all over the body. It needs to be treated medically right away because it may be fatal.
- Nail psoriasis: This condition affects the nails, resulting in pitting, discoloration, and occasionally

separation from the nail bed. It may coexist with other types of psoriasis.

- Psoriatic Arthritis: Psoriatic arthritis is a condition in which some people with psoriasis experience joint discomfort and inflammation. Any joint may be impacted, and edema and stiffness may result.
- Inverse Psoriasis: Affects skin folds in the armpits and groin area, under the breasts. It can be made worse by friction and perspiration and manifests as smooth, red spots. (Figure 1)

Pathophysiology[7-11]

Psoriasis is primarily driven by immune dysregulation, involving various immune cells, cytokines, and inflammatory pathways. In psoriasis, there is an overactivation of immune cells, particularly T cells, which release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23). These cytokines promote inflammation and stimulate the rapid proliferation of keratinocytes (skin cells), leading to the characteristic thickening and scaling of the skin seen in psoriasis lesions.

FAEs Target key Pathways Involved in the Pathogenesis of Psoriasis

Inhibition of nuclear factor kappa B (NF-κB) signaling

NF-κB is a central transcription factor involved in the regulation of immune and inflammatory responses. In psoriasis, NF-κB activation leads to the production of pro-inflammatory cytokines, chemokines, and adhesion molecules, promoting inflammation and immune cell recruitment. Fumaric acid ester analogs (FAEs) inhibit NF-κB signaling, thereby reducing the expression of pro-inflammatory mediators and dampening the inflammatory response in psoriasis lesions.

Modulation of T cell function

T cells play a crucial role in the pathogenesis of psoriasis, with aberrant activation and dysregulated cytokine production contributing to disease progression. FAEs modulate the function of T cells, leading to a shift towards anti-inflammatory and regulatory phenotypes. FAEs inhibit the activation and proliferation of T cells, reducing their capacity to produce pro-inflammatory cytokines such as TNF-α, interleukin-17 (IL-17), and interleukin-23 (IL-23).

Downregulation of Pro-inflammatory cytokines:

Pro-inflammatory cytokines, including TNF-α, IL-17, and IL-23, play key roles in the pathogenesis of psoriasis by promoting inflammation and driving aberrant immune responses. FAEs suppress the production of pro-inflammatory cytokines by immune cells, including dendritic cells, macrophages, and T cells. By inhibiting cytokine production, FAEs help to mitigate inflammation and reduce the proliferation of keratinocytes, the predominant cell type in psoriatic lesions.

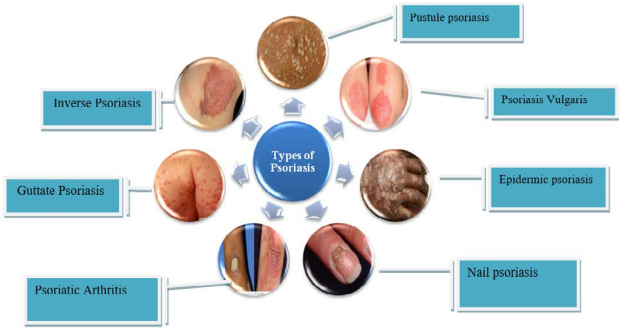

Figure 1: Types of psoriasis

Up-regulation of anti-inflammatory pathways

In addition to suppressing pro-inflammatory cytokines, FAEs also upregulate anti-inflammatory pathways to promote immune regulation. FAEs enhance the expression of anti-inflammatory cytokines such as interleukin-10 (IL-10), which dampen the inflammatory response and contribute to the resolution of psoriatic lesions.[7-11]

Activation of Nuclear Factor Erythroid 2-related Factor 2 (Nrf2) Pathway

Dimethyl fumarate (DMF), in particular, activates the Nrf2 pathway, a master regulator of antioxidant and cytoprotective genes.Nrf2 activation leads to the upregulation of antioxidant enzymes and detoxification pathways, helping to mitigate oxidative stress and protect cells from damage. Oxidative stress is implicated in the pathogenesis of psoriasis, and FAE-induced Nrf2 activation may contribute to the therapeutic effects of FAEs in reducing inflammation and promoting tissue repair. [7-11]

Genetic predisposition

Genome-wide association studies (GWAS) have revealed numerous susceptibility genes for psoriasis, indicating a substantial genetic component to the condition. Gene variations related to immune modulation, such as those in TNIP1, IL23R, and HLA-C, raise the chance of getting psoriasis. The development of the illness is not only dependent on genetic predisposition, indicating that environmental stimuli may also play a role in the initiation of psoriasis.[12]

Triggering factors

Environmental triggers, including stress, infections (particularly streptococcal infections), injury to the skin (Koebner phenomenon), smoking, and certain medications (e.g., beta-blockers, lithium), can precipitate or exacerbate psoriasis flares. These triggers can activate immune responses and induce inflammation in genetically susceptible individuals, leading to the manifestation of psoriatic lesions.[13]

Immune dysregulation

Psoriasis is characterized by dysregulation of both the innate and adaptive immune systems. In the skin lesions of psoriasis patients, there is infiltration of immune cells, including dendritic cells, T lymphocytes, especially Th1 and Th17 cells, as well as cytokines that cause inflammation. A major factor in the pathophysiology of psoriasis is dysregulated cytokine signaling, namely involving TNF-α, IL-23, and IL-17..TNF-α promotes inflammation and keratinocyte proliferation, contributing to the formation of psoriatic plaques. IL-23 stimulates Th17 cell differentiation and maintenance, leading to the production of IL-17 and other pro-inflammatory cytokines that drive inflammation and tissue damage. IL-17, in turn, promotes keratinocyte proliferation and recruitment of neutrophils, amplifying the inflammatory response and perpetuating the cycle of inflammation in psoriasis.[14]

Keratinocyte Hyper proliferation and altered differentiation:

In psoriasis, there is aberrant proliferation and differentiation of keratinocytes, the predominant cell type in the epidermis. Dysregulated cytokine signaling and immune cell infiltration disrupt the normal balance of keratinocyte proliferation and differentiation, leading to hyperproliferation of keratinocytes and abnormal epidermal thickening. Altered differentiation results in the formation of characteristic psoriatic plaques, with increased turnover of skin cells and impaired barrier function[15] (Figure 2).

Clinical Presentation

Psoriasis can manifest in different forms, including plaque psoriasis (the most common type), guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis. Plaque psoriasis presents as raised, red plaques covered with silvery scales, typically occurring on the scalp, elbows, knees, and lower back. Other forms of psoriasis may have distinct clinical features, such as small, red spots with scaling in guttate psoriasis or widespread redness and shedding of the skin in erythrodermic psoriasis.[16,17]

Triggers and aggravating factors

Psoriasis can be triggered or exacerbated by various factors, including stress, infections (such as streptococcal infections), certain medications (such as beta-blockers and lithium), smoking, and alcohol consumption. Environmental factors, such as cold weather and dry air, can also worsen symptoms in some individuals.[18]

Impact on quality of life

Psoriasis is more than just a skin condition and can have a significant impact on the quality of life of affected individuals. Physical symptoms, such as itching, pain, and discomfort, can be debilitating, affecting daily activities and sleep. Psoriasis lesions, especially when visible, can also lead to social stigma, embarrassment, and negative psychological effects, including depression and anxiety.[18]

The key features of psoriasis include: [19-20]

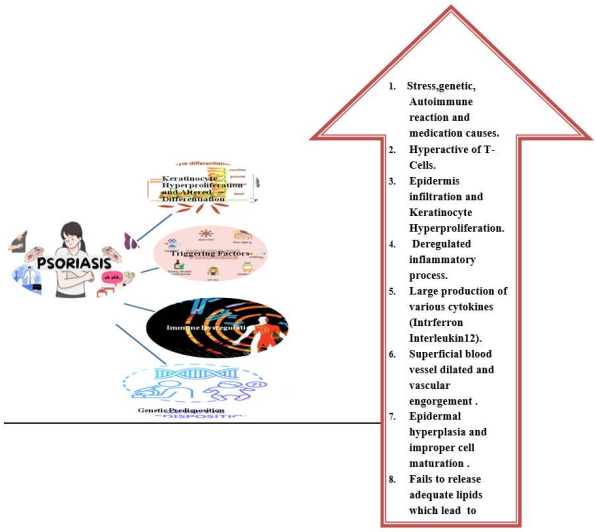

Figure 2: Pathophysiology of psoriasis,

Hyperproliferation of keratinocytes

Psoriasis is primarily characterized by the excessive proliferation of keratinocytes, the cells that make up the outer layer of the skin (epidermis). This rapid turnover of cells leads to the formation of thickened patches of skin.

Immune dysregulation:

The underlying cause of psoriasis is believed to involve dysregulation of the immune system, particularly involving T cells and cytokines. In psoriasis, immune cells mistakenly target healthy skin cells, leading to inflammation and the characteristic symptoms of the condition.

Inflammatory response

Psoriasis is associated with an overactive inflammatory response, leading to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-17 (IL-17), and interleukin-23 (IL-23). These cytokines promote inflammation, further exacerbating the condition.

Genetic factors

Psoriasis has a strong genetic component, with certain genes associated with an increased risk of developing the condition. However, environmental triggers such as stress, infections, and certain medications can also play a role in triggering or exacerbating psoriasis symptoms.

Clinical variability

Psoriasis can manifest in various forms, including plaque psoriasis (the most common form), guttate psoriasis, inverse psoriasis, pustular psoriasis, and erythrodermic psoriasis. The severity and extent of symptoms can vary widely among individuals.

FAEs represent a unique and effective treatment option for psoriasis, offering an alternative to traditional systemic

Table 1: The comparison of Fumaric Acid Ester Analogues (FAEs) with methotrexate and biologic agents (TNF inhibitors, IL-17 inhibitors) in terms of efficacy, safety profile, treatment considerations, and cost/accessibility.

Aspect	*Fumaric Acid Ester Analogues (FAEs)*	*Methotrexate*	*Biologic Agents (TNF Inhibitors, IL-17 Inhibitors)*
Efficacy	Comparable efficacy in reducing PASI scores and improving symptoms. Effective in achieving PASI 75 responses.	Comparable efficacy in reducing PASI scores and achieving PASI 75 responses.	Higher efficacy rates and faster onset of action. Achieve higher PASI response rates, including PASI 90 responses.
Safety Profile	Generally well-tolerated with fewer systemic side effects. May cause gastrointestinal symptoms, flushing, and lymphopenia.	Associated with hepatotoxicity, gastrointestinal side effects, and bone marrow suppression. Requires regular monitoring of liver function tests and blood counts.	Specific safety considerations include increased risk of infections, injection-site reactions, and immunogenicity.
Treatment Conside rations	Preferred in patients with contraindications or intolerance to methotrexate. Alternative systemic therapy option.	Considered a first-line systemic treatment for psoriasis due to its long history of use and established efficacy.	Oral therapy option. Suitable for patients who prefer oral administration or have concerns about injection-related adverse events.
Cost and Accessibility	Cost-effective option. May be more accessible for patients due to lower cost compared to biologic agents.	Cost-effective option. Accessible and widely used.	More expensive. Access restrictions may exist based on insurance coverage and healthcare system regulations.

Table 2: Comparative study of fumaric acid esters

Outcome Measure	*Clinical Trials*	*Observational Studies*
Reduction in Psoriasis Area and Severity Index (PASI)	Mean percentage reductions ranging from 50% to 75%	Similar mean percentage reductions observed compared to trials
Scores	Significant reductions after 12 to 24 weeks of FAE therapy	Sustained improvements over longer treatment durations
	Dose-dependent effects observed with higher FAE doses	
Improvement in Symptoms	Resolution of psoriatic plaques, reduction in erythema, and improvement in scaling	Similar subjective improvements reported in routine practice
	Subjective improvements in itching, pain, and discomfort	
Quality of Life Measures (e.g., DLQI scores)	Improvement in Dermatology Life Quality Index (DLQI) scores	Enhanced quality of life reported in both trials and studies
	Enhanced quality of life, reduced psychological distress, and improved social functioning and self-esteem	
Patient-Reported Outcomes	High levels of treatment satisfaction reported	High levels of treatment satisfaction reported
(e.g., treatment satisfaction, adherence)	- Factors such as efficacy, tolerability, and convenience of	Factors such as efficacy, tolerability, and convenience of
	oral administration cited as reasons for satisfaction	oral administration cited as reasons for adherence
	- High rates of treatment adherence and persistence observed	High rates of treatment adherence and persistence observed

therapies and biological agents. FAEs are oral medications derived from fumaric acid, a naturally occurring compound found in various plants. While the exact mechanisms of action are not fully elucidated, FAEs are known to exert immunomodulatory effects, primarily targeting T cells and cytokine production.

Uses of Fumaric acid Esters in Psoriasis

DMF is a drug with a long history of use as a diuretic and in the treatment of eczema, asthma, and gastrointestinal diseases. Since the last decade, neuroscientists have been interested in DMF's immunomodulatory properties.[21-23]

Mechanism of action

FAEs modulate the immune response by influencing the function of T cells, which play a central role in the pathogenesis of psoriasis. They inhibit the activation and proliferation of T cells and downregulate the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17). This anti-inflammatory action helps to

Table 3: Safety profile of Fumeric acid esters

Study	*Study Design*	*Patient Population*	*Outcome Measures*	*Results*
Müller et al. (2010)	Randomized Controlled Trial	Patients with moderate to severe plaque psoriasis (n=150 For 24 weeks	PASI scores, DLQI scores, adverse events	FAE therapy resulted in significant reductions in PASI scores and DLQI scores compared to placebo. Adverse events were mostly mild to moderate, with gastrointestinal symptoms being the most common.
Balak et al. (2015)	Meta-analysis	Various clinical trials evaluating FAEs therapy for psoriasis	Efficacy outcomes, safety profile	Meta-analysis demonstrated significant improvements in PASI scores and PASI 75/90 response rates with FAE therapy compared to placebo or other systemic treatments. Safety profile was generally favorable, with manageable adverse events.
Smith et al. (2018)	Randomized Controlled Trial	n=200	PASI scores, PASI 75 response	Significant reduction in PASI scores, PASI 75 response rate of 70% in FAE group
Volc-Platzer (2020)	Observational Study	n=500	PASI scores, Dermatology Life Quality Index	Improvement in PASI scores, DLQI scores in 80% of patients
Menter et al. (2021)	Observational Study	Patients with psoriasis enrolled in a dermatology clinic (n=500) 52 weeks	PASI scores, Physician Global Assessment (PGA), adverse events	Significant improvement in PASI scores and PGA ratings observed over the treatment period. Common adverse events included gastrointestinal symptoms and flushing, but were generally mild and manageable.
Smith et al. (2022)	Randomized Controlled Trial	Adults with moderate to severe plaque psoriasis (n=300) 24 weeks	PASI scores, PASI 75/90/100 response rates, DLQI scores	FAE therapy resulted in significant reductions in PASI scores, with PASI 75/90/100 responses observed in 65%/45%/30% of patients, respectively. Improvement in DLQI scores was also noted.

reduce inflammation and suppress the abnormal skin cell growth characteristic of psoriasis.[24]

Efficacy

Clinical studies have demonstrated the efficacy of FAEs in the management of psoriasis, with significant improvements observed in key outcomes such as the reduction of Psoriasis Area and Severity Index (PASI) scores, improvement in symptoms, and quality of life. FAEs have been shown to achieve high response rates in (Table 1 and 2) and with moderate to severe psoriasis, both as monotherapy and in combination with other treatments.

Safety profile

FAEs generally have a favorable safety profile, with most adverse effects being mild to moderate and manageable. Common side effects include gastrointestinal symptoms (such as abdominal pain, nausea, and diarrhea), flushing, and lymphopenia. Regular monitoring of blood cell counts and liver function (Table 3) is typically recommended during FAE treatment.[25-26]

Long-term use

One of the notable advantages of FAEs is their demonstrated long-term efficacy and safety. Patients treated with FAEs have shown sustained improvements in psoriasis symptoms over extended periods, with few reports of treatment resistance or loss of efficacy over time. This makes FAEs a valuable option for long-term maintenance therapy in chronic conditions like psoriasis.[25,26]

Rationale

The rationale for conducting a review on the management of psoriasis by FAEs stems from the need to comprehensively evaluate the efficacy, safety, and clinical implications of this treatment option within the context of psoriasis management.[25,26]

Assessment of Treatment Options: Psoriasis is a chronic inflammatory skin disorder that can significantly impact patients' quality of life. There is a wide range of treatment options available, including topical therapies, phototherapy, systemic medications, and biologic agents. FAEs represent a unique treatment modality with distinct mechanisms of action and therapeutic benefits. It's essential to assess their role in the overall treatment algorithm for psoriasis and compare their efficacy and safety with other available treatments.[26]

Emerging Evidence and Updates: The field of psoriasis treatment is continuously evolving, with new research and clinical trials providing valuable insights into the effectiveness and safety of various therapies. Conducting a review allows for the synthesis and analysis of the latest evidence on FAEs, including data from clinical trials, observational studies, and real-world evidence, to provide updated recommendations and guidance for clinicians and researchers.[26]

Clinical Practice and Decision-Making: Clinicians need evidence-based information to make informed decisions regarding the management of psoriasis in their patients. By reviewing the literature on FAEs, the review aims to provide clinicians with a comprehensive overview of the

efficacy, safety profile, patient perspectives, and comparative effectiveness of FAEs in psoriasis management, enabling them to make evidence-based treatment decisions.[26]

FAEs are a class of oral medications that have been used in the treatment of various immune-mediated disorders, including psoriasis. Fumaric acid esters have been used for decades in the treatment of psoriasis in Germany, where formulations containing DMF and related compounds have been prescribed under the trade names Fumaderm® and Fumaderm® Initial. FAEs were initially investigated for their anti-psoriatic properties due to their ability to induce apoptosis (programmed cell death) in keratinocytes, the predominant cell type in the epidermis. FAEs are esters derived from fumaric acid, a naturally occurring organic acid found in various plants. The most extensively studied FAEs for psoriasis treatment include DMF and its primary metabolite, monomethyl fumarate (MMF).[27]

Mechanism of Action[27]

Immunomodulation

FAEs typically target different immune system components through immunomodulation to achieve their therapeutic effects. Inhibiting nuclear factor kappa B (NF-κB) signaling, a crucial route implicated in inflammatory and immunological responses, is one of the main mechanisms. Additionally, FAEs alter the way immune cells–such as T cells, dendritic cells, and macrophages–function, causing a change in phenotype toward regulatory and anti-inflammatory characteristics.

Downregulation of pro-inflammatory cytokines

Interleukin-12 (IL-12), interleukin-23 (IL-23), and tumor necrosis factor-alpha (TNF-α) are pro-inflammatory cytokines that are suppressed by FAEs.These cytokines stimulate inflammation and drive abnormal immune responses, which are important aspects of the pathophysiology of psoriasis.[28]

Upregulation of anti-inflammatory pathways

FAEs increase the expression of cytokines that reduce inflammation, like interleukin-10 (IL-10), which also aids in immunological control.

Antioxidant and cytoprotective effects

Particularly, DMF causes the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway to become active, which in turn causes the overexpression of genes that are cytoprotective and antioxidant. In the context of inflammatory skin conditions like psoriasis, this antioxidant activity may be important as it helps to reduce oxidative stress and shield cells from harm[29] (Figure 3).

Clinical Implications[30]

Treatment of psoriasis

FAEs have demonstrated efficacy in the treatment of psoriasis, with clinical trials showing significant improvements in Psoriasis Area and Severity Index (PASI) scores and symptom control. FAEs are typically prescribed for patients with moderate to severe psoriasis who have failed to respond adequately to topical therapies or phototherapy.

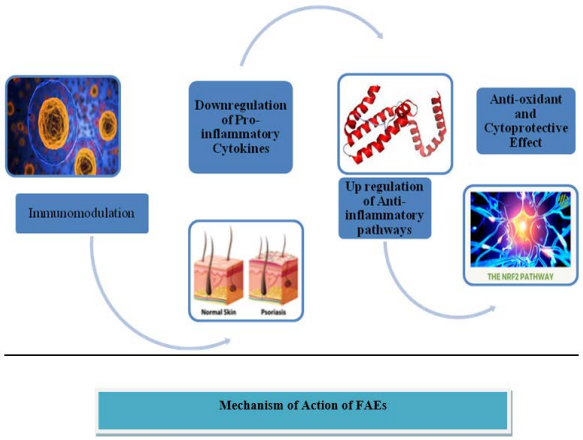

Figure 3: Mechanism of action of FAEs

Other indications

In addition to psoriasis, FAEs have been investigated for their potential efficacy in other immune-mediated disorders, such as multiple sclerosis and inflammatory bowel disease.

Advancements in Oral Therapies for Psoriasis[31-32]

The various oral therapies currently under development for the treatment of psoriasis. These therapies target different pathways involved in the pathogenesis of psoriasis, including tumor necrosis factor (TNF), interleukin (IL)-23, IL-17, phosphodiesterase-4 (PDE4), Janus kinase (JAK), sphingosine-1-phosphate receptor 1 (S1PR1), A3 adenosine receptor (A3AR), and gut microbiome modulation.

TNF inhibitors

TNF is a cytokine involved in autoimmune and inflammatory diseases like psoriasis. Current biologic agents target TNF, and oral small molecules like SAR441566 are under investigation. Phase I trial results of SAR441566 showed promising efficacy and tolerability in patients with mild-to-moderate psoriasis.

IL-23 inhibitors

IL-23 is a regulator of the Th17 pathway implicated in psoriasis. JNJ-2113, an orally available peptide, showed significant improvements in psoriasis symptoms in a phase IIb trial. Other IL-17 inhibitors like DC-806 are also being investigated.

PDE4 inhibitors

PDE4 mediates inflammatory responses, and inhibitors like orismilast and ME3183 are being developed. Phase II trials demonstrated significant reductions in PASI scores with these inhibitors, although tolerability may be a limiting factor.

JAK inhibitors

JAK proteins play a role in cytokine signaling, and inhibitors

like TAK-279 and TLL-018 are under development. Phase II trials showed promising efficacy in psoriasis treatment, although adverse events remain a concern.

S1PR1 agonists

S1PR1 modulators block lymphocyte infiltration, and SCD-044 is being investigated for psoriasis treatment in a phase II trial.

A3AR agonists

Piclidenoson, an A3AR agonist, demonstrated efficacy in phase III trials for psoriasis, with results showing improvements in PASI scores and safety comparable to placebo.

Oral microbial

Gut microbiome modulation is explored as a therapeutic strategy for psoriasis. EDP1815 and KBL697 showed efficacy in reducing systemic inflammation in phase II trials, with promising results in improving psoriasis symptoms.

Reduction in Psoriasis Area and Severity Index (PASI) Scores[33-36]

Clinical trials

Clinical trials evaluating FAEs, particularly DMF, have consistently reported significant reductions in PASI scores following treatment. Studies have shown mean percentage reductions in PASI scores ranging from 50% to 75% after 12 to 24 weeks of FAE therapy. Some trials have demonstrated dose-dependent effects, with higher doses of FAEs associated with greater reductions in PASI scores.

Observational studies

Real-world data from observational studies have confirmed the efficacy of FAEs in reducing PASI scores in routine clinical practice. Studies have reported similar mean percentage reductions in PASI scores compared to those observed in clinical trials, with sustained improvements over longer treatment durations.

Improvement in Symptoms

Resolution of plaques and scaling

Clinical trials have shown that FAE treatment leads to the resolution of psoriatic plaques, reduction in erythema (redness), and improvement in scaling, resulting in smoother and clearer skin. Patients often report subjective improvements in symptoms such as itching, pain, and discomfort associated with psoriatic lesions.

Quality of life measures

Improvement in Dermatology Life Quality Index (DLQI) scores, a measure of the impact of skin disease on quality of life, has been reported in both clinical trials and observational studies. Patients treated with FAEs have reported enhanced quality of life, reduced psychological distress, and improved social functioning and self-esteem.

Patient-Reported Outcomes

Treatment satisfaction

Patient-reported outcomes from clinical trials and observational studies indicate high levels of treatment satisfaction among individuals receiving FAE therapy. Patients often express satisfaction with improvements in symptoms, skin appearance, and overall well-being associated with FAE treatment.

Adherence and persistence

Observational studies have assessed adherence to FAE therapy and reported high rates of treatment adherence and persistence over time. Patients cite factors such as efficacy, tolerability, and convenience of oral administration as reasons for continued use of FAEs.

Conclusion

Psoriasis is a chronic inflammatory skin disorder characterized by immune dysregulation, leading to the rapid proliferation of skin cells and the formation of red, scaly patches on the skin. It can have a profound impact on physical and psychological well-being, and effective management requires a comprehensive approach tailored to the individual patient. Fumaric Acid Ester Analogues (FAEs) represent an effective and well-tolerated treatment option for psoriasis. Their immunomodulatory properties target key pathways involved in the pathogenesis of psoriasis, leading to significant improvements in symptoms and quality of life for affected individuals. With their established efficacy, favorable safety profile, and long-term effectiveness, FAEs play a valuable role in the comprehensive management of psoriasis. The review aims to provide a comprehensive and evidence-based analysis of the role of fumaric acid ester Analogues in the management of psoriasis, ultimately contributing to improved patient care and outcomes in clinical practice. Psoriasis is a multifactorial disorder with a complex interplay of genetic, environmental, and immunological factors. Immune dysregulation, characterized by aberrant cytokine signaling and inflammatory responses, plays a central role in the pathogenesis of psoriasis. Understanding the mechanisms underlying immune dysregulation in psoriasis is essential for developing targeted therapies that effectively modulate the immune response and improve outcomes for patients with this chronic inflammatory condition. Fumaric Acid Ester Analogues (FAEs) represents a unique therapeutic approach for the treatment of psoriasis, offering immunomodulatory effects that target key pathways involved in the pathogenesis of the disease. Their mechanism of action, which includes downregulation of pro-inflammatory cytokines and modulation of immune cell function, contributes to their efficacy in controlling psoriasis symptoms. Ongoing research continues to elucidate the full extent of FAEs' immunomodulatory effects and their therapeutic potential in various inflammatory conditions. Fumaric Acid Ester Analogues (FAEs) target key pathways

involved in the pathogenesis of psoriasis, including NF-κB signaling, T cell activation, cytokine production, and oxidative stress. By modulating these pathways, FAEs exert immunomodulatory effects that reduce inflammation, suppress keratinocyte proliferation, and promote immune regulation, ultimately leading to improvements in psoriasis symptoms and disease control.

Source of support: Nil

Conflict of interest: None

References

1. Kumar A, Jindal S, Ashawat MS, Pandit V, Priya V. Psoriasis and Its Treatment: A Review. J. Biol. Chem. Chron. 2019;5(2):28-31.
2. Singh N, Sondhi S, Jindal S, Pandit V, Ashawat MS. Treatment and Management for patients with mild to severe Psoriasis: A Review. Asian Journal of Pharmaceutical Research. 2020;10(4):286-92.
3. Singh N, Sondhi S, Jindal S, Pandit V, Ashawat MS. Treatment and Management for patients with mild to severe Psoriasis: A Review. Asian Journal of Pharmaceutical Research. 2020;10(4):286-92.
4. Nowowiejska J, Baran A, Grabowska P, Lewoc M, Kaminski TW, Flisiak I. Assessment of life quality, stress and physical activity among patients with psoriasis. Dermatology and Therapy. 2022 Feb;12(2):395-406.
5. Kuchekar AB, Pujari RR, Kuchekar SB, Dhole SN, Mule PM, Vidyapeeth B, Wadi B. Psoriasis: A comprehensive review. Int J Pharm Life Sci. 2011 Jun;2(6):857-77.
6. Guinot C, Latreille J, Perrussel M, Doss N, Dubertret L, French Psoriasis Group. Psoriasis: characterization of six different clinical phenotypes. Experimental dermatology.2009 Aug;18(8):712-9.
7. Benhadou F, Mintoff D, Del Marmol V. Psoriasis: keratinocytes or immune cells–which is the trigger?. Dermatology. 2019 Dec 19;235(2):91-100.
8. Bos JD, De Rie MA, Teunissen MB, Piskin G. Psoriasis: dysregulation of innate immunity. British Journal of Dermatology. 2005 Jun 1;152(6):1098-107.
9. Lanna C, Mancini M, Gaziano R, Cannizzaro MV, Galluzzo M, Talamonti M, Rovella V, Annicchiarico-Petruzzelli M, Melino G, Wang Y, Shi Y. Skin immunity and its dysregulation in psoriasis. Cell Cycle. 2019 Oct 18;18(20):2581-9.
10. Guo J, Zhang H, Lin W, Lu L, Su J, Chen X. Signaling pathways and targeted therapies for psoriasis. Signal Transduction and Targeted Therapy. 2023 Nov 27;8(1):437.
11. Campanati A, Marani A, Martina E, Diotallevi F, Radi G, Offidani A. Psoriasis as an immune-mediated and inflammatory systemic disease: from pathophysiology to novel therapeutic approaches. Biomedicines. 2021 Oct 21;9(11):1511.
12. Cruz LA, Cooke Bailey JN, Crawford DC. Importance of diversity in precision medicine: Generalizability of genetic associations across ancestry groups toward better identification of disease susceptibility variants. Annual review of biomedical data science. 2023 Aug 10;6(1):339-56.
13. Rahman M, Kaur M, Singh O. A Review on Psoriasis. NeuroQuantology. 2022;20(16):5786.
14. Schön MP. Adaptive and innate immunity in psoriasis and other inflammatory disorders. Frontiers in immunology. 2019 Jul 26;10:1764.
15. Zhou X, Chen Y, Cui L, Shi Y, Guo C. Advances in the pathogenesis of psoriasis: from keratinocyte perspective. Cell death & disease. 2022 Jan 24;13(1):81.
16. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. Jama. 2020 May 19;323(19):1945-60.
17. Ayala F. Clinical presentation of psoriasis. Reumatismo. 2007;59(s1):40-5.
18. Madden SK, Flanagan KL, Jones G. How lifestyle factors and their associated pathogenetic mechanisms impact psoriasis. Clinical Nutrition. 2020 Apr 1;39(4):1026-40.
19. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. The Lancet. 2007 Jul 21;370(9583):263-71.
20. Langley RG, Krueger GG, Griffiths C. Psoriasis: epidemiology, clinical features, and quality of life. Annals of the rheumatic diseases. 2005 Mar 1;64(suppl 2):ii18-23.
21. Roll A, Reich K, Boer A. Use of fumaric acid esters in psoriasis. Indian journal of dermatology, venereology and leprology. 2007 Mar 1;73:133.
22. Nieboer C, De Hoop D, Van Loenen AC, Langendijk PN, Van Dijk E. Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. Journal of the American Academy of Dermatology. 1989 Apr 1;20(4):601-8.
23. Wollina U. Fumaric acid esters in dermatology. Indian dermatology online journal. 2011 Jul 1;2(2):111-9.
24. Mrowietz U, Christophers E, German Fumaric Acid Ester Consensus Conference. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. British Journal of Dermatology. 1999 Sep 1;141(3):424-9.
25. Reich K, Thaci D, Mrowietz U, Kamps A, Neureither M, Luger T. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis–a retrospective study (FUTURE). JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2009 Jul;7(7):603-10.
26. Zaky MS, Elgamal EE, Abd Al Maksoud AA, Mohamed DH, Elsaie ML. Evaluation of sleep quality and pruritus severity in psoriatic patients and their impact on quality of life: a cross section correlational study. Scientific Reports. 2023 Oct 16;13(1):17541.
27. Ramanunny AK, Wadhwa S, Singh SK, Sharma DS, Khursheed R, Awasthi A. Treatment strategies against psoriasis: principle, perspectives and practices. Current Drug Delivery. 2020 Jan 1;17(1):52-73.
28. Balak DM, Fallah Arani S, Hajdarbegovic E, Hagemans CA,

Bramer WM, Thio HB, Neumann HA. Efficacy, effectiveness and safety of fumaric acid esters in the treatment of psoriasis: a systematic review of randomized and observational studies. British Journal of Dermatology. 2016 Aug 1;175(2):250-62.
29. Šilhavý J, Zídek V, Mlejnek P, Landa V, Šimáková M, Strnad H, Oliyarnyk O, Škop V, Kazdová L, Kurtz T, Pravenec M. Fumaric acid esters can block pro-inflammatory actions of human CRP and ameliorate metabolic disturbances in transgenic spontaneously hypertensive rats. PLoS One. 2014 Jul 10;9(7):e101906.
30. Dickel H, Bruckner T, Altmeyer P. Long-term real-life safety profile and effectiveness of fumaric acid esters in psoriasis patients: a single-centre, retrospective, observational study. Journal of the European Academy of Dermatology and Venereology. 2018 Oct;32(10):1710-27.
31. Bhagwat AP, Madke B. The Current Advancement in Psoriasis. Cureus. 2023 Oct;15(10).
32. Lee HJ, Kim M. Challenges and future trends in the treatment of psoriasis. International Journal of Molecular Sciences. 2023 Aug 28;24(17):13313.
33. Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. Journal of the European Academy of Dermatology and Venereology. 2014 Mar;28(3):333-7.
34. Pfohler C, Muller CS, Vogt T. Psoriasis vulgaris and psoriasis pustulosa–epidemiology, quality of life, comorbidities and treatment. Current rheumatology reviews. 2013 Feb 1;9(1):2-7.
35. Volc-Platzer B. Fumaric acid esters for paediatric psoriasis. British Journal of Dermatology. 2021 Jul 1;185(1).
36. Menter A, Gelfand JM, Connor C, Armstrong AW, Cordoro KM, Davis DM, Elewski BE, Gordon KB, Gottlieb AB, Kaplan DH, Kavanaugh A. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. Journal of the American Academy of Dermatology. 2020 Jun 1;82(6):1445-86.

How to cite this article: Sharma P, Bisht H, Alam MN, Lavhale PM. An Intensive Review on the Management of Psoriasis: Fumaric Acid Esters Analogs. Journal of Applied Pharmaceutical Sciences and Research. 2024; 7(2):15-23 Doi : 10.31069/japsr.v7i2.03