Review Article

Safety and Efficacy of Apremilast in Psoriasis Patients with Diabetes: A Comprehensive Review

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ABSTRACT

Psoriasis, a chronic inflammatory skin disease, has been increasingly associated with diabetes mellitus (DM), suggesting shared pathophysiological mechanisms between the two conditions. Apremilast, a novel phosphodiesterase 4 (PDE4) inhibitor, has emerged as a promising treatment option for psoriatic arthritis and psoriasis, and recent studies have explored its potential benefits in patients with diabetes. This review provides a thorough investigation of the current literature on apremilast's mechanism of action, pharmacokinetics, therapeutic potential, and safety in psoriasis management, particularly in patients with diabetes. Studies have shown that apremilast's PDE4 inhibition leads to increased cAMP levels, which may improve metabolic inflammation and insulin resistance. Observational studies have also indicated the potential benefits of apremilast in managing insulin resistance among psoriasis patients. In addition, drug interaction studies have shed light on the effects of co-administering apremilast with other substances, emphasizing the importance of cautious prescribing. In conclusion, apremilast holds promise as a powerful and secure treatment option for psoriasis patients, with potential benefits in managing insulin resistance in patients with diabetes. Further research and larger clinical trials are needed to validate and expand upon these findings, paving the way for more personalized and effective therapeutic approaches.

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1. Introduction

Psoriasis, a genetically influenced immune-mediated condition, presents itself in the form of skin or joint manifestations, or a combination of both. The successful management of this complex disease often requires a broad range of healthcare experts with various areas of expertise. Challenges associated with psoriasis include its widespread occurrence, chronic nature, potential for disfiguration, disability, and linked comorbidities. A comprehensive comprehension of the immune function's involvement and the interrelationship of the adaptive and innate immune systems has significantly contributed to the effective treatment of psoriasis, impacting patients beyond just the skin manifestations (Figure 1) [1]. Psoriasis is a chronic inflammatory skin disorder that often coexists with various comorbidities, including diabetes mellitus. The expanding understanding of the underlying mechanisms driving psoriasis (PsO) has brought attention to its associations with type 2 diabetes (T2D) and metabolic syndrome [2]. The Apremilast introduction has provided a new therapeutic

avenue for patients with psoriasis [3,4]. However, the safety implications in patients with concurrent diabetes require careful evaluation. Apremilast (**1**), marketed as Otezla®, is an oral small molecule inhibitor that targets type-4 cyclic nucleotide phosphodiesterase (PDE-4). Celgene Corporation is currently developing this drug for the treatment of several medical conditions, including psoriasis, psoriatic arthritis, Behçet's syndrome, ankylosing spondylitis, rheumatoid arthritis, and atopic dermatitis [5-8]. Apremilast is a flexible therapeutic choice for psoriasis and can be used as a standalone treatment or combined with biologic therapy other anti-psoriatic drugs, including acitret in (**3**), methotrexate (**2**), and cyclosporine (**4**) (Scheme 1) [9-11].

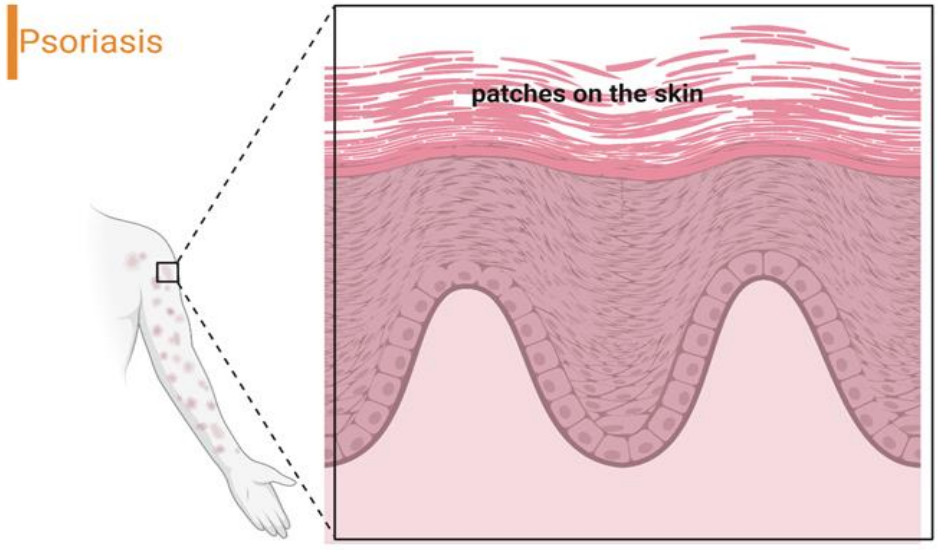
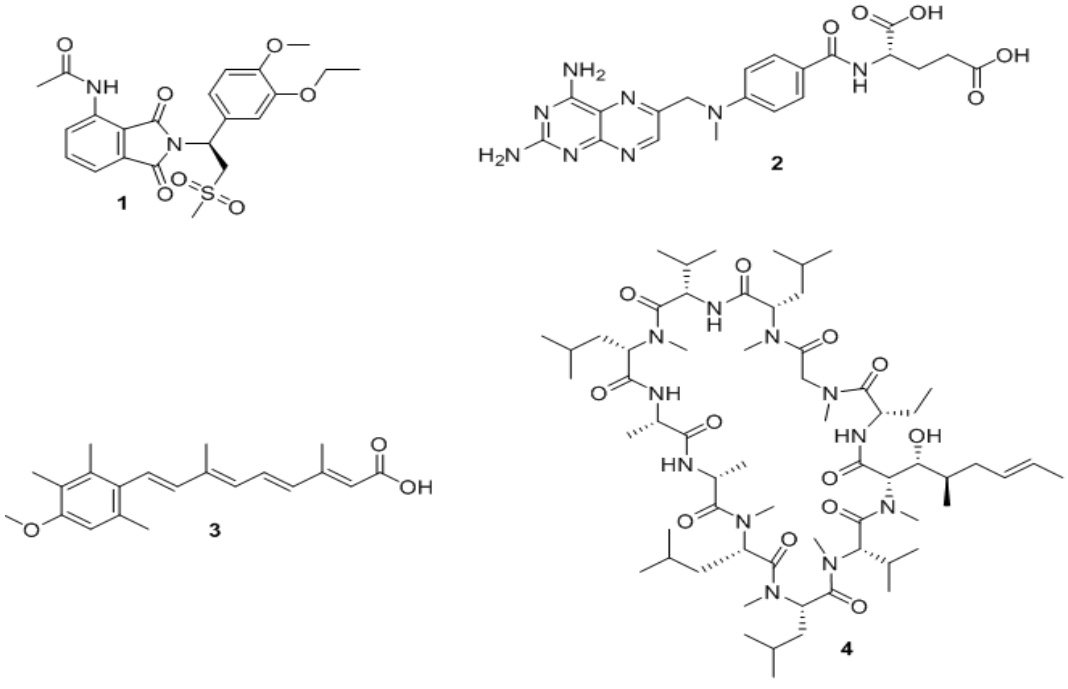


Figure 1. Clinical illustration of psoriasis: redefining the dermatological landscape created with BioRender.com



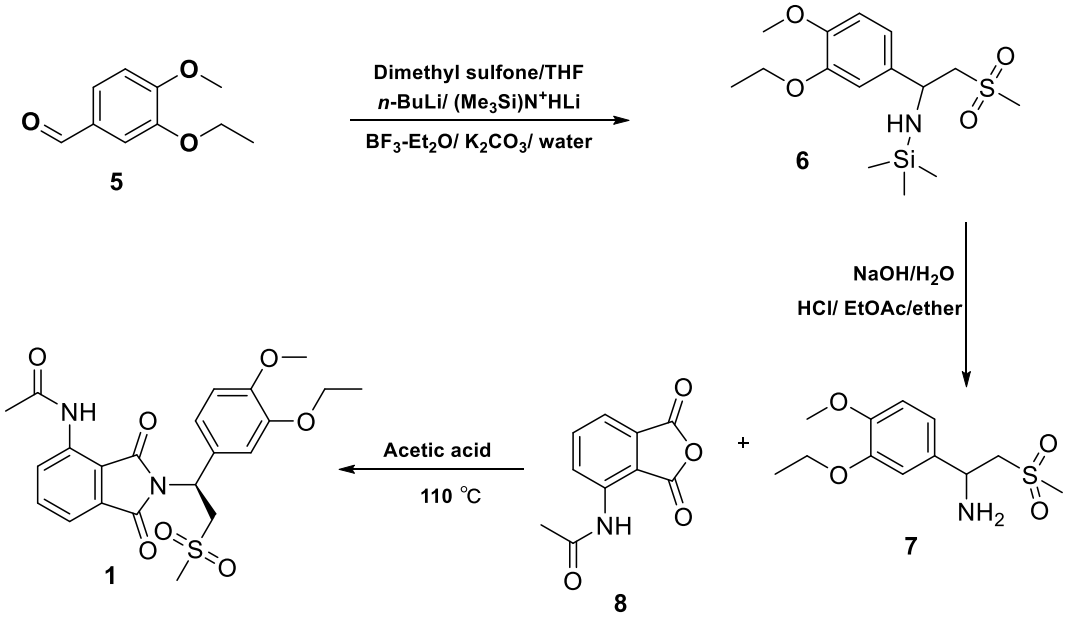
Scheme 1. Structures of family **1**-**4**

1.1. Synthesis of apremilast

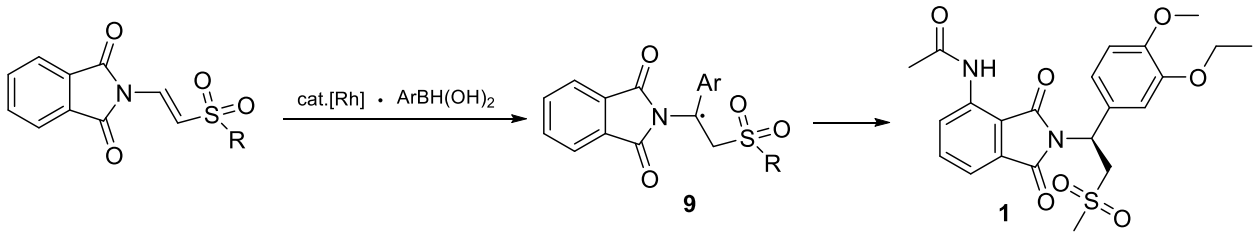
The United States' Celgene Corporation reported the first total synthesis of racemic apremilast. The synthesis commenced with compound (**5**) and dimethyl sulfone, yielding compound (**7**) in a 39% yield. Subsequently, this compound was condensed compound (**8**) in acetic acid at 110 °C, resulting in the production of target (**1**) with a 59% yield (Scheme 2) [12-14]. Using a chiral rhodium(I)–diene catalyst, researchers achieved a one-step synthesis of compound 9 under mild reaction conditions and successfully synthesized thus the target (Scheme 3) [15].

2. Clinical Pharmacology

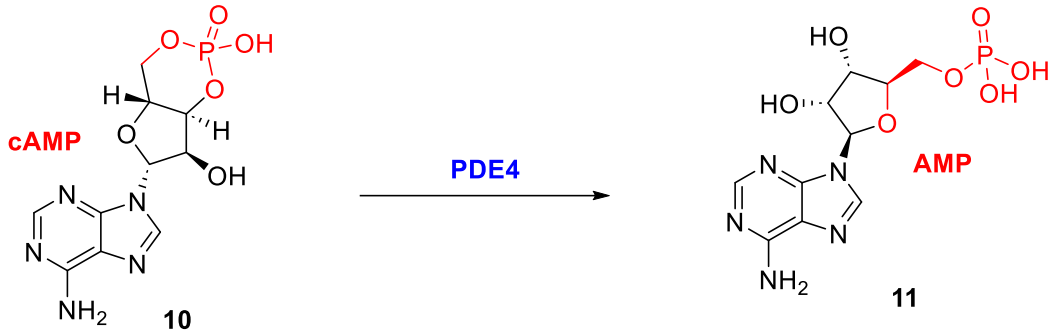
(PDE4) is an enzyme found inside cells, mainly in the immune system. Its primary function is to break down cyclic adenosine monophosphate (cAMP) **10** into AMP **11** (Scheme 4) [16]. This breakdown produces pro-inflammatory cytokines, which includes tumour necrosis factor (TNF)-alpha, interferon-gamma, interleukin (IL)-2, IL-12, IL-8, and IL-23. Moreover, PDE4 inhibition hinders the preparation of anti-inflammatory cytokines, including IL-10 [17]. PDE4 inhibitors exhibit a diverse array of anti-inflammatory will effects in different types of inflammatory cells by increasing cAMP levels [18]. PDE4 inhibition causes elevated intracellular cAMP levels, resulting in the stimulation of protein kinase A and other effectors that contribute to regulating pro-inflammatory cytokines. This activation, in turn, affects processes like chemotaxis,



Scheme 2. Synthesis of apremilast



Scheme 3. Apremilast synthesis using a chiral rhodium (I)–diene catalyst



Scheme 4. Breakdown of cAMP to AMP

neutrophil degranulation, and adhesion to endothelial cells, contributing to the inflammatory response [19-21]. Apremilast, a selective PDE4 inhibitor, has received approval to treat various diseases that cause inflammation. It falls under the classification of a BCS-IV (Biopharmaceutics classification system - Class IV) drug, indicating that it possesses low solubility and high permeability characteristics. In addition, Apremilast exists in seven polymorphic forms, contributing to its unique properties and potential applications in pharmaceutical formulations [22].

3. Mechanism of Action

Apremilast is a medication that operates by preventing the enzyme phosphodiesterase 4 (PDE4). Normally, PDE4 is responsible for breaking down cyclic adenosine monophosphate (cAMP) in the cells. However, when apremilast blocks PDE4, it leads to an increase in cAMP levels inside the cells. This, in turn, affects the generation of various inflammatory mediators, including TNF-α, IL-17, IL-23, CX-CL9, CX-CL10, IFN-γ, and others, which play significant roles in psoriatic conditions and Behcet's disease. By reducing inflammation, apremilast can help improve the symptoms of these diseases [23]. Apremilast further disrupts the generation of inducible (NO) synthase, leukotriene B4, and matrix metalloproteinase, leading to the reduction of complex inflammatory processes like epidermal skin thickening, dendritic cell infiltration, and joint destruction. By targeting these crucial aspects of inflammation, this innovative PDE4 inhibitor Shows potential as a prospective therapeutic choice for treating chronic inflammatory conditions affecting the skin and joints [24]. Apremilast significantly improves the pathological symptoms or manifestations of Systemic Sclerosis (SSc), including collagen deposition and skin dermal thickness. It suppresses macrophage and T cell activation and reduces inflammatory cytokine secretion, modulating pro-fibrotic processes. Apremilast's inhibition of PDE4 offers a promising new therapeutic option for SSc patients [25]. It has been reported that Apremilast, a powerful PDE4 inhibitor, tackles inflammation in psoriasis and arthritis. It boosts cAMP levels in both non-immune and immune cells, activating PKA and CRE-driven transcription. This increases anti-inflammatory gene expression like IL-10, while decreasing NF-kB activity and suppressing pro-inflammatory mediators like IL-23, TNF-α, and IFN-g. The outcome is a balanced immune response, reducing inflammation, immune cell infiltration, and keratinocyte/synoviocyte activation. Apremilast's skillful mechanism brings hope to those afflicted with these conditions (Figure 2) [26-28].

4. Pharmacokinetics

In this study involving 42 patients (21 teenage group and pediatric group); apremilast was administered at different dosages. The pharmacokinetics analyses showed that weight-based dosing in pediatric and teenage resulted in exposure comparable to that in adults. The safety profile was similar across age groups, and most participants expressed a favourable liking for the tablet's taste.

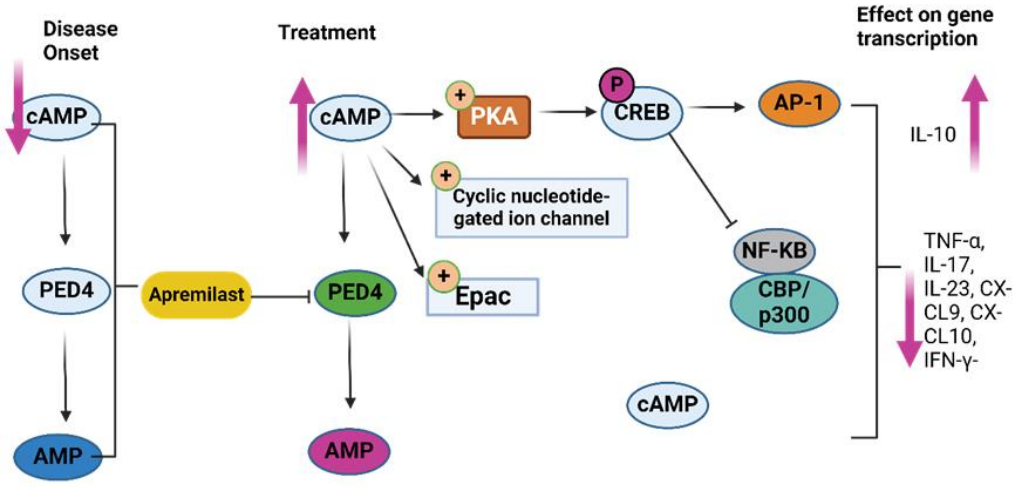


Figure 2. Mode of action of apremilast: Apremilast, a potent inhibitor of PDE4, holds the key to combating inflammation in psoriasis and arthritis. By elevating cAMP levels within immune and non-immune cells, it activates PKA and CRE-driven transcription. This leads to increased expression of anti-inflammatory genes like IL-10, while dampening NF-kB activity and reducing pro-inflammatory mediators such as IL-23, TNF-α, and IFN- γ. Created with BioRender.com

The study demonstrated a 68% the Psoriasis Area and Severity Index has improved in the teenage group and a 79% improvement in the pediatric group with the use of apremilast [29]. Over the course of 104 weeks, a study involving apremilast, a treatment for substantial to extreme plaque psoriasis, revealed promising and enduring results, as those who were administered apremilast experienced noteworthy and enduring enhancements in various aspects of the condition, including skin, scalp, and nails. Moreover, they reported reduced pruritus (itching) and experienced an enhanced quality of life. The treatment's safety profile remained consistent with the existing knowledge about apremilast, indicating that it is well-tolerated over an extended duration. These findings suggest that apremilast it can be a valuable long-term option for managing moderate to extreme plaque psoriasis, offering both clinical benefits and improved patient-reported outcomes [30].

5. ADME Profile of Apremilast in Patients with Psoriatic Arthritis

5.1. Absorption

Apremilast, oral administration, is absorbed with an approximate bioavailability of 73%, and it reaches its peak plasma concentrations (Cmax) at approximately 2.5 hours after administration. The absorption of apremilast is not affected by co-administration with food [31].

5.2. Distribution

Approximately 68% of apremilast binds to human plasma proteins, and it exhibits a mean apparent volume of distribution (Vd) of 87 litres [31].

5.3. Metabolism

After being taken orally, apremilast becomes the primary circulating component at 45% concentration, alongside its inactive metabolite M12, which accounts for 39% of the total. Human plasma, urine, and feces contain twenty-three identified apremilast metabolites. Both CYP oxidative metabolism, with non-CYP mediated hydrolysis, and subsequent glucuronidation contribute to apremilast metabolism. *In vitro*, CYP3A4 primarily mediates apremilast metabolism, with minor involvement from CYP2A6 and CYP1A2 [32].

5.4. Elimination

In healthy subjects, apremilast has a plasma clearance of approximately 10 L/hr and a half-life ranging from 6 to 9 hours. nearly 58% of

the drug is excreted in urine, while about 39% is eliminated through feces [32].

5.5. Recommended dosage

For optimal use, it is advised to take apremilast at a recommended dosage of 30 mg twice daily (b.i.d.) every 12 hours, with no restrictions on food intake. In cases of severe renal function impairment, the dosage should be adjusted accordingly, while patients with hepatic disorders do not require any dosage adjustments [33,34].

6. Pharmacodynamic Effects of Apremilast

During the PALACE phase III clinical trial, apremilast was shown to be an efficacious treatment for active psoriatic arthritis. The anti-inflammatory pharmacodynamic effects of apremilast on plasma biomarkers were evaluated in the PALACE 1 trial. Using plasma samples from the peripheral blood of 150 patients, 47 proteins linked to systemic inflammatory immune responses were identified. At week 24, apremilast substantially decreased proinflammatory mediators including IL-8, TNF-, IL-6, MCP-1, MIP-, and ferritin in comparison to placebo. Changes in TNF- levels were associated with a 20% improvement in modified ACR response criteria (ACR20 response) at both apremilast concentrations. At week 40, apremilast (30 mg twice daily) decreased IL-17, IL-6, IL-23, and ferritin levels compared to placebo, while increasing anti-inflammatory mediators such as IL-1 and IL-10 receptor antagonists. In patients with active psoriatic arthritis, apremilast effectively increased anti-inflammatory mediators and decreased proinflammatory mediator levels in circulation [35]. Apremilast was evaluated in the PALACE 2 trial active psoriatic arthritis treatment (PsA). For up to 52 weeks, the study revealed that apremilast resulted in noteworthy enhancements in PsA symptoms, psoriasis and physical function. The prevalent undesirable occurrences were controllable and no new safety concerns were noticed [36]. In a phase III sub-study, apremilast's effects on plasma biomarkers were investigated in psoriatic arthritis patients. Apremilast therapy resulted in significant reductions in pro-inflammatory cytokines such as ferritin, TNF-α, IL-8, IL-6, MIP-1α, and MCP-1 after 16 and 24 weeks. Moreover, IL-6, IL-17, and IL-2 concentrations decreased after 40 weeks, suggesting long-term inhibition of Th-17-driven inflammation. Notably, apremilast also increased the production of anti-inflammatory mediators IL-1RA and IL-10. These findings indicate that apremilast has a substantial impact on the IL-17 pathway, locally and systemically, potentially influencing various immune cells involved in the psoriatic inflammatory cascade [37,38].

7. Psoriasis and Diabetes: An Intricate Cardiometabolic Link

Since the first reported incidence of comorbidity among psoriasis patients by Strauss in 1897, there has been growing interest in understanding the shared pathogenic mechanisms between psoriasis and other comorbid diseases. This has led to the proposition that psoriasis may either pre-exist or coexist with these other diseases [39]. Patients with psoriasis often experience various interconnected disorders, including cardiometabolic and autoimmune diseases. Comprehending the molecular connections between psoriasis and its related comorbidities is essential for the efficient management of patient care. By employing a comprehensive and impartial network analysis, researchers identified a noteworthy genetic convergence between psoriasis and related conditions, such as obesity, atherosclerosis, ischemic stroke, type II diabetes, and dyslipidaemia. The investigation found significant gene commonality among the comorbidities associated with psoriasis. Patients with psoriasis often have elevated rates of dyslipidaemia and type II diabetes, two conditions that were linked to the disease using a molecular comorbidity score. By a wide margin, the most similar diseases to psoriasis were dyslipidaemia, type 2 diabetes, obesity, ischemic stroke, and atherosclerosis, as measured by the Jaccard coefficient indexes. Psoriasis and associated comorbidities were found to have around 45 common pathways. Many of these pathways were also reported

among numerous psoriatic comorbidities. Ultimately, the study established a plausible connection between psoriasis and its associated diseases, suggesting potential therapeutic targets for managing both psoriasis and its comorbid conditions [40]. Psoriasis is a genetically complex immune-mediated skin disorder, with identified disease susceptibility loci on chromosome 6p21 and several genetic determinants of smaller effect. CDKAL1, a gene previously linked to type II diabetes (TIID) and Crohn's disease (CD), has been strongly linked with psoriasis. To verify this connection, a study examined the CDKAL1 genetic variant (SNP rs6908425) in a separate psoriasis dataset. The link was validated in the combined sample. Importantly, the psoriasis's connection to CDKAL1 appears to be unaffected by the relationship with TIID. Moreover, gene expression investigations revealed that CDKAL1 transcripts are scarce in skin keratinocytes but highly expressed in immune cells, particularly CD19+ and CD4+ lymphocytes. Interestingly, CDKAL1 expression is significantly reduced in activated immune cells. These findings suggest variation at the CDKAL1 locus, indicating that different CDKAL1 gene variants may influence susceptibility to distinct conditions by exerting diverse effects on disease-specific cell types [41]. Cheng *et al.* conducted an analysis of LNPEP (Leucyl-cystinyl Aminopeptidase) gene polymorphisms, also known as insulin-responsive aminopeptidase, this enzyme plays a crucial role in the pathway of the renin-angiotensin system and has been recognized as an angiotensin IV receptor [42]. LNPEP, along with its genetic variations, has been associated with diabetes and hypertension [43, 44]. These associations are attributed to the impact of LNPEP and its genetic variants on serum sodium regulation, vasopressin clearance, and glucose uptake. These effects are mediated through interactions with the insulin receptor signaling and GLUT4, the insulin-responsive glucose transporter [45]. Significantly, the researchers identified a missense mutation, LNPEP A763T, in psoriasis patients, causing a dysfunction in peptide activity. Moreover, they observed reduced LNPEP expression in psoriatic skin compared to control and uninvolved patient skin. These findings indicate that LNPEP could be involved in the development of both metabolic conditions and psoriasis as well, including diabetes and hypertension [42,46]. A comprehensive meta-analysis of 27 observational studies demonstrated a clear link between psoriasis and a higher prevalence and incidence of diabetes. Severe psoriasis showed a stronger link to diabetes compared to mild cases. Studies using patients' self-reporting indicated a more significant association than those relying on billing data. Psoriasis carries a relative risk of 1.27 for developing diabetes [47]. In a cross-sectional study utilizing data from Maccabi Healthcare Services (MHS) in Israel, researchers aimed to elucidate the correlation between psoriasis, atherosclerosis, and diabetes mellitus. In this study, researchers examined 46,095 individuals with psoriasis and a control group of 1,579,037 subjects without psoriasis. The results revealed that psoriasis patients had a higher prevalence of diabetes and atherosclerosis in comparison to the control group, even after adjusting for age. Multivariate analyses suggested a link between the use of systemic medication or potent topical steroids for psoriasis and diabetes, as well as linkage between atherosclerosis and usage of phototherapy in psoriasis patients. However, the study had some limitations, including potential overestimation or underestimation of psoriasis cases due to the digital diagnosis method and possible selection bias. Furthermore, the dataset's coverage was limited to records from 1997 onwards, without capturing the date of disease onset. In conclusion, this study validates past research of connections between psoriasis and both diabetes and atherosclerosis, but further research is needed to confirm these associations [48]. Cross-sectional research was conducted to investigate the association between psoriasis and diabetes, utilising the Clalit Health Services (CHS) database. The study included a total of 16,851 participants diagnosed with psoriasis and a control group consisting of 74,987 persons without psoriasis. The results of the study revealed a significantly greater occurrence of diabetes among individuals with psoriasis (odds ratio [OR] 1.38,

p < 0.05), even after controlling for age and gender (OR 1.58, p < 0.001). The findings presented in this study align with prior research and emphasise the need of taking into account diabetes risk factors in persons diagnosed with psoriasis [49]. In a comprehensive population study, researchers conducted a follow-up investigation to evaluate how often new cases of diabetes mellitus (DM) occurred in patients with psoriasis compared to a group without psoriasis for comparison. The study involved a sizeable population of 65,449 patients, among whom 1,061 new cases of DM were identified. Of these cases, approximately 59% had a history of psoriasis, leading to a crude incidence rate ratio of 1.36 (95% CI 1.20-1.53). Upon adjusting for various variables that could potentially affect results, the researchers found that the risk of developing DM was significantly higher in patients with psoriasis, particularly in those who had psoriasis for a duration of two years or more and received more than two oral psoriasis treatments per year (adjusted OR 2.56, 95% CI 1.11-5.92). Surprisingly, the analysis also showed that even among patients with a normal BMI (Body Mass Index), the risk of DM remained elevated in individuals with psoriasis (adjusted OR 2.02, 95% CI 1.31-3.10).

These findings suggest a clear and positive association between psoriasis and diabetes, with the risk of developing DM increasing in correlation with duration and severity of psoriasis. Importantly, the increased risk is not solely driven by high BMI, indicating that psoriasis itself might be an independent risk factor for diabetes. This extensive observational study offers valuable insights into the temporal relationship between psoriasis and the incidence rates of DM, shedding light on the potential health implications of psoriasis [50].

8. Epidemiology

Psoriasis, an inflammatory and chronic skin condition, has the potential to impact people across all age groups. It exhibits two peak periods of occurrence, with the first peak observed around 16-20 years of age (early onset) and the second peak around 57-60 years (late-onset). Interestingly, the majority of patients, about 70%, experience the onset of psoriasis before the age of 40, which often coincides with their reproductive years. As life expectancy continues to rise, healthcare providers are likely to face a notable therapeutic challenge due to the increasing number of older patients with psoriasis, particularly those aged 65 and above. This demographic shift emphasizes the importance of effective and age-appropriate management strategies for psoriasis to ensure the well-being of patients across different age groups [51]. As more research accumulates, it becomes increasingly evident that there exists a robust link between diabetes mellitus (DM) and psoriasis. Over time, investigators have put forward the hypothesis that psoriasis could act as a risk factor for the onset of DM, while simultaneously; DM might worsen the severity of psoriasis. Numerous systematic reviews and meta-analyses have been conducted, all providing compelling and convincing evidence to support this association [52,53]. In the year 2013, Armstrong *et al.* conducted research that encompassed a systematic review and meta-analysis of 27 observational studies. The researchers' investigation revealed a notable 59% rise in the overall occurrence of diabetic mellitus (DM) among persons with psoriasis. Significantly, the incidence of this condition increased even more, reaching a remarkable 97%, among those diagnosed with severe psoriasis. In addition, the research findings revealed that those suffering with psoriasis had a 27% increased probability of having diabetes mellitus in comparison to those who did not have this dermatological disorder. The numerical value provided is 52. Wan *et al.* conducted an independent experiment to further examine the correlation between the severity of psoriasis and the occurrence of diabetes mellitus (DM). The research findings indicated a notable increase in the prevalence of diabetes mellitus (DM) among those with psoriasis who had a more comprehensive manifestation of the disease. This suggests a potential association between the severity of psoriasis and the likelihood of getting diabetes [54]. In a more recent study, Mamizadeh *et al.* conducted a meta-analysis and systematic review of 38 studies, involving a substantial

number of nearly 1 million patients with psoriasis. The results of this comprehensive investigation provided further support for the substantial link between diabetes mellitus (DM) and psoriasis. The study's findings emphasized that psoriasis extends beyond skin involvement, indicating that it has broader implications on systemic health, particularly in relation to the development and presence of diabetes [55]. Based on this cumulative evidence, it is becoming evident that DM and psoriasis share common pathophysiologies and are interconnected rather than merely being co-morbidities.

The understanding of this interplay between the two diseases is akin to viewing them as facets of the same prism, the objectives were to shed light on the connection between these two conditions and gain a comprehensive understanding of how they are interrelated. By exploring the shared pathophysiological mechanisms, through these investigations, the study endeavours to shed light on the broader implications of psoriasis on systemic health, with special attention to its association with diabetes mellitus, paving the way for improved management and treatment approaches for patients with both conditions [56].

9. Pathogenesis and Pathophysiology

Psoriasis is a persistent inflammatory dermatological condition, involves complex pathogenesis with genetic, environmental, and immunological factors. Notably, cytokines like IL-17 and IL-23p19, along with innate lymphoid cells (ILC3), play crucial roles in the pathogenesis of psoriasis. In addition, psoriasis is linked to cardiovascular disease, metabolic syndrome, and various inflammatory disorders. This exploration sheds light on the pathogenesis, immunological loop, keratinocyte signals, and morphological aspects of psoriasis, while also drawing comparisons with atopic dermatitis. Interestingly, the gut bacteria in individuals with psoriasis have similarities to those found in diabetic patients, potentially hinting at a link to its pathogenesis [57].

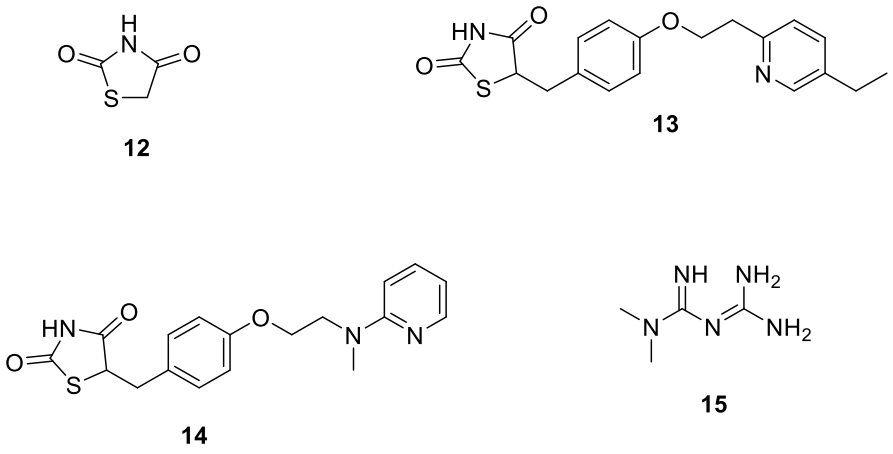
According to reports, the diverse range of diabetes mellitus (DM) can be ascribed to a same fundamental cause, namely the impaired beta cell. The aforementioned primary flaw emerges as a result of four main pathophysiologic mechanisms encompassing genetic and epigenetic modifications, inflammation, environmental influences, and insulin resistance. As a result, the occurrence of hyperglycaemia arises through a multitude of routes, commonly referred to as the "Egregious Eleven." The impairment of beta cells, in conjunction with the consequent surplus of endogenous fuel, initiates oxidative stress and epigenetic modifications across the organism, hence intensifying beta-cell failure. There exists a proposition that some illnesses associated with DM, such as psoriasis, frequently exhibit coexistence owing to overlapping pathophysiologies, namely involving common genes and epigenetic changes [56,58].

Emerging evidence suggests that psoriasis, a multifaceted skin disease, involves intricate interactions between immune cells and gene regulation. Several studies have shown increased activity of EREG and PTPN1 genes, while the SERPINB7 gene exhibits reduced expression in psoriatic skin. Notably, the severity of the illness is correlated with lower SERPINB7 expression. These findings explain the significance of these genes in psoriasis development and indicate potential targets for future treatments. Understanding these mechanisms could lead to more effective therapeutic approaches for managing psoriasis [59].

9.1. Therapeutic potential of antidiabetic drugs in psoriasis management

The underlying pathophysiological mechanisms of psoriasis and diabetes exhibit similarities and recent data suggest that certain antidiabetic medications might have a positive impact on severity of psoriasis in people with diabetes. Psoriasis Area and Severity Index scores have been reported to decrease with the use of hypoglycaemic medications such as thiazolidinediones (**12**), glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and biguanides.

In addition to lowering blood sugar levels, these drugs may also affect keratinocyte proliferation, immunological inflammatory



Scheme-5. Family of compounds 12-16

pathways, differentiation indicators, and the signalling of calcium channels and mitogen-activated protein kinases. Most importantly, these medicines have not been associated with serious side effects. However, bigger and longer-term randomised controlled studies are required to develop more solid evidence. In diabetic individuals with plaque psoriasis, current data shows that pioglitazone (**13**) may be beneficial, while rosiglitazone (**14**) and metformin (**15**) are not. To further understand the potential advantages of these antidiabetic medications in psoriasis therapy and to overcome biases and limitations in prior trials, more research including psoriasis patients with and without diabetes mellitus is needed (Scheme 5) [60].

9.2. Empowering psoriasis patients: The apremilast treatment option

PDE4 inhibition, caused by increased cAMP levels, helps regulate the systemic inflammatory state by activating alternative macrophage polarization and promoting regulatory T cells, which suppress inflammation. These alternative macrophages produce catecholamines, leading to increased fat breakdown, improved thermogenesis in brown adipose tissue, and reduced adiposity. In addition, PDE4 inhibition improves hepatic steatosis, aiding in insulin resistance improvement. PDE4 is also found in the hypothalamus, controlling food intake and central sympathetic discharge. Elevated cAMP levels stimulate insulin production in pancreatic islets, maintaining glucose homeostasis. Thus, PDE4 inhibition contributes to improving metabolic inflammation and insulin resistance [61].

Apremilast, a novel small molecule acting as a PDE4 inhibitor, is administered orally and has shown both efficacy and safety in treating Psoriasis (PsO) through various randomized controlled trials. To further investigate its real-world impact, researchers conducted a retrospective chart review of electronic medical records in a community dermatology practice. Among 99 patients prescribed apremilast, 81 patients took the medication, and among them, 63 experienced improved clinical disease severity. Notably, 37% of these patients achieved a body surface area of less than 1%. The administration of apremilast was usually well-tolerated, and there were no instances of major side effects reported. Nevertheless, a subset of patients chooses to quit the prescribed drug as a result of experiencing modest adverse effects, specifically nausea and vomiting. In summary, the research revealed that apremilast had a favourable safety profile and was well-tolerated as a therapeutic alternative, resulting in notable advancements in the clinical condition of the individuals comprising the study cohort [62].

A study involved 341 patients who were exposed to apremilast and 4981 patients who did not receive apremilast treatment. No new safety issues were identified by the researchers in relation to the utilisation of apremilast.

Furthermore, the enduring safety of apremilast in the treatment of psoriasis and psoriatic arthritis was determined to be in line with the results obtained from clinical studies. The occurrence rates of unfavourable occurrences were similar in the apremilast and non-apremilast cohorts, except for a decreased frequency reported in the cohort receiving just injectable medication. Nevertheless, it is important to acknowledge that the study encountered several limitations. These constraints encompassed a relatively limited number of patients who were exposed to apremilast, as well as the possibility of exposure misclassification. Notwithstanding these constraints, the findings of the study yielded significant insights on the safety characteristics of apremilast and its application in the treatment of psoriasis and psoriatic arthritis [63].

In a study, researchers observed a significant improvement in psoriatic disease among patients treated with apremilast. Notably, there was a substantial 79.1% reduction in the in Psoriasis Area and Severity Index (PASI) scores at weeks 24 and 52. Pain levels decreased by 77% (measured by visual analog scale), and DLQI saw a 79% reduction during the same period. Apremilast treatment in diabetic patients resulted in better psoriasis severity and cholesterol reduction. In addition, glucose levels significantly reduced after apremilast treatment. Notably, patients without diabetes and low LDL cholesterol levels experienced improved metabolic markers with apremilast. The study had limitations, such as patient stratification based on diabetic medications and reliance on blood glucose instead of HbA1c for assessing blood sugar control. Overall, apremilast's pleiotropic effects offer an intriguing opportunity for future clinical trials exploring its role as a metabolic regulator. Expanding its usage to a larger population with psoriasis and cardiometabolic conditions may validate the promising data. Apremilast's efficacy in diabetic psoriatic patients suggests potential as a personalized therapy. Additional pharmacogenomic research can identify individuals benefiting from apremilast or other small molecule protocols [64].

9.3. Apremilast for treating psoriasis in patients with diabetes: An observational study on insulin resistance.

According to a study, there is a correlation between psoriasis severity, as measured by the Psoriasis Area and Severity Index (PASI), and hemoglobin A1c (HbA1c) levels. This finding suggests a potential link between psoriasis and an increased risk of diabetes mellitus [47,65]. Furthermore, the impact of apremilast, a phosphodiesterase inhibitor, on insulin resistance in Japanese psoriasis patients was investigated.

The study, conducted retrospectively with 86 enrolled patients prescribed apremilast, demonstrated a reduction in fasting serum insulin levels and an improvement in insulin resistance for patients with high insulin levels. Conversely, for patients with low insulin levels, fasting serum insulin levels increased after apremilast treatment. These observations indicate that apremilast may hold promise in managing insulin resistance among psoriasis patients, thus providing valuable insights for further research and clinical consideration [66].

It has been demonstrated in a case report that psoriatic lesions improved rapidly in a patient with type 2 diabetes following insulin treatment and glucose level reduction. This suggests that glycemic control may play a vital role in managing psoriasis in individuals with diabetes [67].

9.4. Safety and efficacy of apremilast in psoriasis: Clinical trials

Jeffrey Crowley *et al.* evaluated the long-term safety of oral apremilast in psoriasis patients over a period of 0 to ≥156 weeks. Apremilast showed efficacy and safety in treating moderate-to-severe plaque psoriasis and psoriatic arthritis. Common adverse events during the initial 0 to ≤52 weeks included diarrhea, nausea, and headaches. However, during the extended 0 to ≥156-week period, no new adverse events affecting ≥5% of patients were reported. Long-term exposure to apremilast did not lead to an increase in serious adverse events, study drug discontinuations, or major cardiac events, malignancies, depression, or suicide attempts. The study provided

reassuring evidence for the acceptable safety profile and tolerability of apremilast as a long-term treatment option for psoriasis patients [68].

The objective of a Phase 3 clinical trial was to evaluate the efficacy of apremilast at a dosage of 30 mg administered twice daily in individuals diagnosed with mild-to-moderate psoriasis. The study employed a double-blind, placebo-controlled design and included adult participants who exhibited either insufficient control or sensitivity to topical treatment for psoriasis. The study successfully achieved its primary objective, which was defined as attaining a Physician Global Assessment score of clear or almost clear with a decrease of at least two points by week 16. The group administered with apremilast had a notably greater rate of response compared to the group given a placebo (21.6% vs. 4.1%; P < .0001). The study successfully achieved secondary objectives, which encompassed enhancements in many metrics, with all results demonstrating statistical significance (P < .0001). The occurrence of commonly reported side effects, such as diarrhoea, headache, nausea, nasopharyngitis, and upper respiratory tract infection, aligns with findings from prior research. The study did not include an active-comparator arm. In summary, apremilast demonstrated efficacy in the treatment of mild-to-moderate psoriasis, while exhibiting a safety profile consistent with previously published research findings [69].

Numerous empirical investigations have consistently demonstrated the heightened effectiveness of risankizumab in comparison to alternative therapeutic interventions for psoriasis, such as adalimumab, ustekinumab, and secukinumab. In a recent phase 4 research spanning 52 weeks, a comparison was made between the efficacy of risankizumab and apremilast in adult patients diagnosed with moderate plaque psoriasis who met the criteria for systemic treatment. During the 16th week of the study, the risankizumab efficacy was shown to be significantly higher compared to apremilast. Specifically, 55.9% of patients treated with risankizumab achieved a PASI 90 response, indicating a substantial improvement in their psoriasis symptoms. In addition, 75.4% of patients treated with risankizumab had a sPGA score of 0 or 1, indicating clear or very clear skin, respectively. In contrast, only 5.1% of patients treated with apremilast achieved a PASI 90 response, and only 18.4% achieved a sPGA score of 0 or 1. Patients who did not achieve a 75% improvement in Psoriasis Area and Severity Index (PASI) scores after 16 weeks of treatment with apremilast were subjected to re-randomization.

They were either assigned to receive risankizumab or to continue their treatment with apremilast. At the conclusion of the 52-week period, it was shown that 72.3% of those who transitioned to risankizumab successfully attained a PASI 90 response, but a mere 2.6% of those who remained on apremilast obtained the same degree of response. The most often reported adverse effects associated with risankizumab were COVID-19 and nasopharyngitis, whereas apremilast was found to be more frequently associated with diarrhoea, nausea, and headache. The study emphasises the enhanced effectiveness and safety of Risankizumab, particularly among individuals who did not initially respond to apremilast [70].

9.5. Drug interactions

Two clinical studies examined potential drug interactions between apremilast and two different substances: ketoconazole, a strong CYP3A4 inhibitor, and rifampicin, a potent CYP3A4 inducer. The main goals were to assess how ketoconazole affects the pharmacokinetics of apremilast and its metabolites, as well as to evaluate the impact of rifampicin on apremilast's pharmacokinetics. Ketoconazole was found to have a slight impact on reducing apremilast clearance, leading to a small increase in the AUC. However, this increase was likely not clinically significant. In contrast, rifampicin's induction of CYP3A4 had a much more noticeable effect on apremilast clearance compared to ketoconazole's CYP3A4 inhibition. Strong CYP3A4 inducers like rifampicin may potentially reduce apremilast's efficacy due to decreased drug exposure. Therefore, it is recommended to avoid co-administration of OTEZLA (apremilast) with strong cytochrome

P450 enzyme inducers like rifampin, phenobarbital, carbamazepine, and phenytoin. This precaution is crucial to ensure the optimal therapeutic effects of OTEZLA treatment [71].

9.6. Apremilast in pregnancy: Limited data and precautionary considerations

Data on the safety of IL-17 inhibitors, JAK inhibitors, IL-23p19 inhibitors, and apremilast during human pregnancy is limited or unavailable. Therefore, these treatments should be avoided in pregnancy as a precautionary measure.[72] Women with psoriasis may experience a greater impact on their quality of life and have a higher risk of depression. Pregnancy and lactation pose challenges as some systemic treatments are contraindicated. More research is needed to ensure safe and effective management during these periods [51].

10. Future Perspectives

1. **Novel Therapeutic Targets:** Identifying new drug targets to address both skin and metabolic abnormalities.
2. **Combination Therapies**: Exploring benefits of combining antidiabetic drugs with existing psoriasis treatments.
3. **Long-term Safety Monitoring**: Continue monitoring the safety of apremilast over extended periods to detect any rare or delayed adverse events that may emerge.
4. **Real-world Evidence:** Investigate apremilast's safety in routine clinical practice to validate findings from controlled trials.
5. **Comparative Studies:** Conduct head-to-head studies comparing apremilast with other psoriasis treatments to establish its safety profile relative to established therapies.
6. **Age-Specific Considerations**: Explore the safety and effectiveness of apremilast in pediatric and geriatric populations.
7. **Pharmacovigilance and Reporting**: Strengthen pharmacovigilance efforts and encourage adverse event reporting to promptly identify and address safety concerns.

8. **Comorbidities and Drug Interactions:** Consider the presence of comorbidities and potential drug interactions when evaluating apremilast's safety.

9. **Personalized Medicine:** Investigate personalized treatment approaches based on individual patient characteristics and disease severity.

10. **Patient Education and Adherence:** Promote patient education and support programs to improve treatment adherence and safety outcomes.

11. **Biomarker Research**: Identifying high-risk psoriasis patients for early diabetes intervention. Conduct research to identify biomarkers that can predict the risk of diabetes development in psoriasis patients, allowing for early intervention and better management of both conditions.

11. Conclusion

Psoriasis and diabetes mellitus share common pathophysiological mechanisms, and emerging evidence suggests that apremilast, as a PDE4 inhibitor, presents a valuable treatment option for managing both conditions. The current literature supports apremilast's efficacy and safety in treating psoriasis, with recent studies indicating potential benefits in managing insulin resistance in psoriasis patients with diabetes. Apremilast's unique mechanism of action, involving PDE4 inhibition and increased cAMP levels, offers a promising avenue for addressing both skin inflammation and metabolic disturbances. However, more research is needed to fully elucidate the specific interactions and benefits in patients with diabetes and psoriasis. Drug interaction studies have highlighted the importance of cautious prescribing and avoiding co-administration with strong CYP3A4 inducers to ensure optimal therapeutic effects. As we move forward, continued research and larger clinical trials will be instrumental in establishing apremilast's role as a personalized therapy for patients with psoriasis and diabetes. Overall, apremilast shows great potential in empowering psoriasis patients, especially those with diabetes, with improved disease management and better quality of life.

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References

[1]. W.H. Boehncke, M.P. Schön, Psoriasis, Lancet (London, England), **2015**, *386*, 983-994. [Crossref], [Publisher]

[2]. a) J.G. Holm, S.F. Thomsen, Type 2 diabetes and psoriasis: links and risks, *Psoriasis (Auckland, N.Z.)*, **2019**, *9*, 1-6. [Google Scholar], [Publisher] b) H. khajeh, A. Bahari, A. Rashki, TCF7L2 polymorphisms in type 2 diabetes, insight from HRM and ARMS techniques, *International Journal of Advanced Biological and Biomedical Research*, **2021**, *9*, 204-214. [Crossref], [Google Scholar], [Publisher] c) S. Azizi, R. Behzadi Andohjerdi, H. Mohajerani, Evaluation of two types of vitamin D receptor gene morphism in patients with type 2 diabetes and obesity, *International Journal of Advanced Biological and Biomedical Research*, **2020**, *8*, 86-91. [Crossref], [Google Scholar], [Publisher]

[3]. B.J. Shah, D. Mistry, N. Chaudhary, S. Shah, Real-world efficacy and safety of apremilast monotherapy in the management of moderate-to-severe psoriasis, *Indian Dermatology Online Journal*, **2020**, *11*, 51-57. [Crossref], [Google Scholar], [Publisher]

[4]. G.M. Keating, Apremilast: A review in psoriasis and psoriatic arthritis, *Drugs*, **2017**, *77*, 459-472. [Crossref], [Google Scholar], [Publisher]

[5]. R.M. Poole, A.D. Ballantyne, Apremilast: First global approval, *Drugs*, **2014**, *74*, 825-837. [Crossref], [Google Scholar], [Publisher]

[6]. E.D. Deeks, Apremilast: A review in oral ulcers of behçet's disease, *Drugs*, **2020**, *80*, 181-188. [Crossref], [Google Scholar], [Publisher]

[7]. S.L. Haber, S. Hamilton, M. Bank, S.Y. Leong, E. Pierce, Apremilast: A novel drug for treatment of psoriasis and psoriatic arthritis, *Annals of Pharmacotherapy*, **2016**, *50*, 282-290. [Crossref], [Google Scholar], [Publisher]

[8]. B. Shutty, C. West, M. Pellerin, S. Feldman, Apremilast as a treatment for psoriasis, **2012**, *Expert Opinion on Pharmacotherapy*, *13*, 1761-1770. [Crossref], [Google Scholar], [Publisher]

[9]. M. Rajagopalan, S. Dogra, A. Saraswat, S. Varma, P. Banodkar, The use of apremilast in psoriasis: An indian perspective on real-world scenarios, *Psoriasis (Auckland, N.Z.)*, **2021**, *11*, 109-122. [Google Scholar], [Publisher]

[10]. M.G. Ivanic, A. Thatiparthi, S. Walia, W. Liao, J.J. Wu, Review of apremilast combination therapies in the treatment of moderate to severe psoriasis, *Journal of Drugs in Dermatology: JDD*, **2021**, *20*, 837-843. [Crossref], [Google Scholar], [Publisher]

[11]. M. Gyldenløve, F. Alinaghi, C. Zachariae, L. Skov, A. Egeberg, Combination therapy with apremilast and biologics for psoriasis: A systematic review, *American Journal of Clinical Dermatology*, **2022**, *23*, 605-613. [Crossref], [Google Scholar], [Publisher]

[12]. T. Saindane Manohar, C. Ge, Processes for the preparation of aminosulfone compounds,

Celgene Corp, **2009**. [Google Scholar], [Publisher]

[13]. G. Stavber, J. Cluzeau, Processes for the preparation of beta-aminosulfone compounds, Google Patents, **2018**. [Google Scholar], [Publisher]

[14]. H. Narode, M. Gayke, G. Eppa, J.S. Yadav, A Review on Synthetic Advances toward the synthesis of apremilast, an anti-inflammatory drug, *Organic Process Research & Development*, **2021**, *25*, 1512-1523. [Crossref], [Google Scholar], [Publisher]

[15]. J.F. Syu, B. Gopula, J.H. Jian, W.S. Li, T.S. Kuo, P.Y. Wu, J.P. Henschke, M.C. Hsieh, M.K. Tsai, H.L. Wu, Asymmetric synthesis of *β*-Aryl *β*-imido sulfones using rhodium catalysts with chiral diene ligands: Synthesis of apremilast, *Organic Letters*, **2019**, *21*, 4614-4618. [Crossref], [Google Scholar], [Publisher]

[16]. V. Furlan, U. Bren, Insight into inhibitory mechanism of PDE4D by dietary polyphenols using molecular dynamics simulations and free energy calculations, *Biomolecules*, **2021,** 11, 479. [Crossref], [Google Scholar], [Publisher]

[17]. C. Brideau, C. Van Staden, A. Styhler, I.W. Rodger, C.C. Chan, The effects of phosphodiesterase type 4 inhibitors on tumour necrosis factor-α and leukotriene B4 in a novel human whole blood assay, *British Journal of Pharmacology*, **1999**, *126*, 979-988. [Crossref], [Google Scholar], [Publisher]

[18]. S.L. Jin, S.L. Ding, S.C. Lin, Phosphodiesterase 4 and its inhibitors in inflammatory diseases, *Chang Gung Medical Journal*, **2012**, *35*, 197-210. [Crossref], [Google Scholar], [Publisher]

[19]. R.E. Petty *et al.,* Textbook of pediatric rheumatology, **2016**, 161-175. [Google Scholar], [Publisher]

[20]. J.B. Taylor, D.J. Triggle, Comprehensive medicinal chemistry II, Elsevier, Oxford, **2007**, 969-985. [Google Scholar], [Publisher]

[21]. U. Food, OTEZLA®(Apremilast) prescribing information, **2017**. [Publisher]

[22]. Q. Zhang, T. Durig, B. Blass, R. Fassihi, Development of an amorphous based sustained release system for apremilast a selective phosphodiesterase 4 (PDE4) inhibitor, *International Journal of Pharmaceutics*, **2022**, *615*, 121516. [Crossref], [Google Scholar], [Publisher]

[23]. I.S. Padda, R. Bhatt, M. Parmar, Apremilast, *The National Center for Biotechnology Information*, **2023**. [Google Scholar], [Publisher]

[24]. G. Schett, V.S. Sloan, R.M. Stevens, P. Schafer, Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases, *Therapeutic Advances in Musculoskeletal Disease*, **2010**, *2*, 271-278. [Crossref], [Google Scholar], [Publisher]

[25]. Q.k. Lu, C. Fan, C.g. Xiang, B. Wu, H.m. Lu, C.l. Feng, X.q. Yang, H. Li, W. Tang, Inhibition of PDE4 by apremilast attenuates skin fibrosis through directly suppressing activation of M1 and T cells, *Acta Pharmacologica Sinica*, **2022**, *43*, 376-386. [Crossref], [Google Scholar], [Publisher]

[26]. P. Schafer, Apremilast mechanism of action and application to psoriasis and psoriatic arthritis, *Biochemical Pharmacology*, **2012**, *83*, 1583-1590. [Crossref], [Google Scholar], [Publisher]

[27]. H. Abdulrahim, S. Thistleton, A.O. Adebajo, T. Shaw, C. Edwards, A. Wells, Apremilast: a PDE4 inhibitor for the treatment of psoriatic arthritis, *Expert Opinion on Pharmacotherapy*, **2015**, *16*, 1099-1108. [Crossref], [Google Scholar], [Publisher]

[28]. G.M.J.D. Keating, Apremilast: A review in psoriasis and psoriatic arthritis, *Drugs*, **2017**, *77*, 459-472. [Crossref], [Google Scholar], [Publisher]

[29]. A.S. Paller, Y. Hong, E.M. Becker, R. de Lucas, M. Paris, W. Zhang, Z. Zhang, C. Barcellona, P. Maes, L. Fiorillo, Pharmacokinetics and safety of apremilast in pediatric patients with moderate to severe plaque psoriasis: Results from a phase 2 open-label study, *Journal of the American Academy of*

Dermatology, **2020**, *82*, 389-397. [Crossref], [Google Scholar], [Publisher]

[30]. K. Reich, M. Gooderham, A. Bewley, L. Green, J. Soung, R. Petric, J. Marcsisin, J. Cirulli, R. Chen, V. Piguet, Safety and efficacy of apremilast through 104 weeks in patients with moderate to severe psoriasis who continued on apremilast or switched from etanercept treatment: findings from the LIBERATE study, *Journal of the European Academy of Dermatology and Venereology*, **2018**, *32*, 397-402. [Crossref], [Google Scholar], [Publisher]

[31]. A.B. Gottlieb, B. Strober, J.G. Krueger, P. Rohane, J.B. Zeldis, C.C. Hu, C. Kipnis, An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast, *Current Medical Research and Opinion*, **2008**, *24*, 1529-1538. [Crossref], [Google Scholar], [Publisher]

[32]. M. Hoffmann, G. Kumar, P. Schafer, D. Cedzik, L. Capone, K.L. Fong, Z. Gu, D. Heller, H. Feng, S. Surapaneni, O. Laskin, A. Wu, Disposition, metabolism and mass balance of [*C*]apremilast following oral administration, *Xenobiotica*, **2011**, *41*, 1063-1075. [Crossref], [Google Scholar], [Publisher]

[33]. S. Busa, A. Kavanaugh, Drug safety evaluation of apremilast for treating psoriatic arthritis, *Expert Opinion on Drug Safety*, **2015**, *14*, 979-985. [Crossref], [Google Scholar], [Publisher]

[34]. L. Bianchi, E. Del Duca, M. Romanelli, R. Saraceno, S. Chimenti, A. Chiricozzi, Toxicology, pharmacodynamic assessment of apremilast for the treatment of moderate-to-severe plaque psoriasis, *Expert Opinion on Drug Metabolism & Toxicology*, **2016**, *12*, 1121-1128. [Crossref], [Google Scholar], [Publisher]

[35]. P.H. Schafer, P. Chen, L. Fang, A. Wang, R. Chopra, The pharmacodynamic impact of apremilast, an oral phosphodiesterase 4 inhibitor, on circulating levels of inflammatory biomarkers in patients with psoriatic arthritis: substudy results from a phase III, randomized, placebo-controlled trial (PALACE 1), *Journal of Immunology Research*, **2015**, *2015*, 906349. [Crossref], [Google Scholar], [Publisher]

[36]. M. Cutolo, G.E. Myerson, R.M. Fleischmann, F. Lioté, F. Díaz-González, F. Van den Bosch, H. Marzo-Ortega, E. Feist, K. Shah, C. Hu, R.M. Stevens, A. Poder, A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: Results of the PALACE 2 trial, *The Journal of Rheumatology*, **2016**, *43*, 1724-1734. [Crossref], [Google Scholar], [Publisher]

[37]. L. Bianchi, E. Del Duca, M. Romanelli, R. Saraceno, S. Chimenti, A. Chiricozzi, Pharmacodynamic assessment of apremilast for the treatment of moderate-to-severe plaque psoriasis, *Expert Opinion on Drug Metabolism & Toxicology*, **2016**, *12*, 1121-1128. [Crossref], [Google Scholar], [Publisher]

[38]. A. Chiricozzi, Pathogenic role of IL-17 in psoriasis and psoriatic arthritis, *Actas Dermo-Sifiliograficas*, **2014**, *105 Suppl 1*, 9-20. [Crossref], [Google Scholar], [Publisher]

[39]. A.K. Srivastava, T. Chand Yadav, H.K. Khera, P. Mishra, N. Raghuwanshi, V. Pruthi, R. Prasad, Insights into interplay of immunopathophysiological events and molecular mechanistic cascades in psoriasis and its associated comorbidities, *Journal of Autoimmunity*, **2021**, *118*, 102614. [Crossref], [Google Scholar], [Publisher]

[40]. S. Choudhary, N.S. Khan, R. Verma, P. Saxena, H. Singh, A.K. Jain, G. Thomas, D. Pradhan, N. Kumar, Exploring the molecular underpinning of psoriasis and its associated comorbidities through network approach: Cross talks of genes and pathways, *3 Biotech*, **2023**, *13*, 130. [Crossref], [Google Scholar], [Publisher]

[41]. a) M. Quaranta, A.D. Burden, C.E.M. Griffiths, J. Worthington, J.N. Barker, R.C. Trembath, F. Capon, Differential contribution of CDKAL1 variants to psoriasis, Crohn's disease and type II diabetes, *Genes & Immunity*, **2009**, *10*, 654-658. [Crossref], [Google Scholar], [Publisher] b) P.A. Kalvanagh, Y.A. Kalvanagh, Comparison of exons 2 and 3 of DIRAS3 gene in mastectomies and lumpectomies women,

Eurasian Journal of Science and Technology, **2023**, *3*, 147-157. [Crossref], [Publisher]

[42]. H. Cheng, Y. Li, X.B. Zuo, H.Y. Tang, X.F. Tang, J.P. Gao, Y.J. Sheng, X.Y. Yin, F.S. Zhou, C. Zhang, Identification of a missense variant in LNPEP that confers psoriasis risk, *Journal of Investigative Dermatology*, **2014**, *134*, 359-365. [Crossref], [Google Scholar], [Publisher]

[43]. a) S. Enhörning, M. Leosdottir, P. Wallström, B. Gullberg, G. Berglund, E. Wirfält, O.J.T.A.j.o.c.n. Melander, Relation between human vasopressin 1a gene variance, fat intake, and diabetes, *The American Journal of Clinical Nutrition*, **2009**, *89*, 400-406. [Crossref], [Google Scholar], [Publisher] b) M. Irajian, S.H. Ghaffari, Investigating the effect of diabetes on the incidence of carpal tunnel syndrome, *Eurasian Journal of Science and Technology*, **2024**, *4*, 66-75. [Crossref], [Publisher]

[44]. B.M. Patel, A. Mehta, Aldosterone and angiotensin: Role in diabetes and cardiovascular diseases, *European Journal of Pharmacology*, **2012**, *697*, 1-12. [Crossref], [Google Scholar], [Publisher]

[45]. T.-a. Nakada, J.A. Russell, H. Wellman, J.H. Boyd, E. Nakada, K.R. Thain, S.A. Thair, H. Hirasawa, S. Oda, K. Walley, Leucyl/cystinyl aminopeptidase gene variants in septic shock, *CHEST*, **2011**, *139*, 1042-1049. [Crossref], [Google Scholar], [Publisher]

[46]. S. Piaserico, G. Orlando, F. Messina, Psoriasis and cardiometabolic diseases: Shared genetic and molecular pathways, *International Journal of Molecular Sciences,* **2022**, *23*, 9063. [Crossref], [Google Scholar], [Publisher]

[47]. a) A.W. Armstrong, C.T. Harskamp, E.J. Armstrong, Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis, *JAMA Dermatology*, **2013**, *149*, 84-91. [Crossref], [Google Scholar], [Publisher] b) F. Haghi, S. Ebrahimi, M. Afzali, H.M. Bidhendi, Investigating the relationship between diabetes and the consequences of kidney transplantation, *Advanced Journal of Chemistry, Section B: Natural Products and Medical Chemistry*, **2023**, *5*, 108-114. [Crossref], [Publisher]

[48]. J. Shapiro, A.D. Cohen, M. David, E. Hodak, G. Chodik, A. Viner, E. Kremer, A. Heymann, The association between psoriasis, diabetes mellitus, and atherosclerosis in Israel: a case-control study, *Journal of the American Academy of Dermatology*, **2007**, *56*, 629-634. [Crossref], [Google Scholar], [Publisher]

[49]. a) A. Cohen, J. Dreiher, Y. Shapiro, L. Vidavsky, D. Vardy, B. Davidovici, J. Meyerovitch, Psoriasis and diabetes: A population-based cross-sectional study, *JEADV*, **2008**, *22*, 585-589. [Crossref], [Google Scholar], [Publisher] b) S. Charsouei, A.R. Lotfi, Symptoms and complications of nervous system in patients with mucormycosis: A systematic review, *Advanced Journal of Chemistry, Section B: Natural Products and Medical Chemistry*, **2022**, *4*, 261-270. [Crossref], [Publisher]

[50]. Y.B. Brauchli, S.S. Jick, C.R. Meier, Psoriasis and the risk of incident diabetes mellitus: A population-based study, *British Journal of Dermatology*, **2008**, *159*, 1331-1337. [Crossref], [Google Scholar], [Publisher]

[51]. A. Di Cesare, F. Ricceri, E. Rosi, M.T. Fastame, F. Prignano, Therapy of PsO in special subsets of patients, *Biomedicines*, **2022**, *10,* 2879. [Crossref], [Google Scholar], [Publisher]

[52]. J. Takeshita, S. Grewal, S.M. Langan, N.N. Mehta, A. Ogdie, A.S. Van Voorhees, J. Gelfand, Psoriasis and comorbid diseases: Epidemiology, *Journal of the American Academy of Dermatology*, **2017**, *76*, 377-390. [Crossref], [Google Scholar], [Publisher]

[53]. M. Mamizadeh, Z. Tardeh, M. Azami, The association between psoriasis and diabetes mellitus: A systematic review and meta-analysis, *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, **2019**, *13*, 1405-1412. [Crossref], [Google Scholar], [Publisher]

[54]. M.T. Wan, D.B. Shin, R.A. Hubbard, M.H. Noe, N.N. Mehta, J.M. Gelfand, Psoriasis and the risk of diabetes: A prospective population-based cohort study, *Journal of the American Academy of Dermatology*, **2018**, *78*, 315-322.e311. [Crossref], [Google Scholar], [Publisher]

[55]. E.A. Chandran, V. M., N. Mathew Valooran, A. Kumar R., A Recent update on pyridine derivatives as a potential lead for diabetes mellitus, *Journal of Chemical Reviews*, **2023**, *5*, 159-182. [Crossref], [Publisher]

[56]. R. Abramczyk, J.N. Queller, A.W. Rachfal, S.S. Schwartz, Diabetes and psoriasis: Different sides of the same prism, *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, **2020**, *13*, 3571-3577. [Google Scholar], [Publisher]

[57]. K. Yamanaka, O. Yamamoto, T. Honda, Pathophysiology of psoriasis: A review, *The Journal of Dermatology*, **2021**, *48*, 722-731. [Crossref], [Google Scholar], [Publisher]

[58]. a) S.S. Schwartz, S. Epstein, B.E. Corkey, S.F.A. Grant, J.R. Gavin Iii, R.B. Aguilar, M.E. Herman, A unified pathophysiological construct of diabetes and its complications, *Trends in Endocrinology and Metabolism: TEM*, **2017**, *28*, 645-655. [Crossref], [Google Scholar], [Publisher] b) K. Aminu, A. Uzairu, S. Abechi, G. Adamu, A. Umar, A search for novel antidiabetic agents using ligand-based drug design and molecular docking studies employing human intestinal maltase-glucoamylase as model enzyme, *Advanced Journal of Chemistry, Section A*, **2023**, *6*, 155-171. [Crossref], [Google Scholar], [Publisher]

[59]. H.H. Ayvaz, K.H. Öztürk, M.A. Seyirci, E. Atay, S. Korkmaz, İ. Erturan, M. Yıldırım, The role of EREG, PTPN1, and SERPINB7 genes in the pathogenesis of psoriasis: May SERPINB7 be protective and a marker of severity for psoriasis?, *Dermatology Practical & Conceptual*, **2023**, *13*, e2023085. [Crossref], [Google Scholar], [Publisher]

[60]. M.X. Zhang, B.Y. Zheng, H.X. Chen, C.W. Chien, Clinical effects of antidiabetic drugs on psoriasis: The perspective of evidence-based medicine, *World Journal of Diabetes*, **2021**, *12*, 1141-1145. [Crossref], [Google Scholar], [Publisher]

[61]. C. Wu, S. Rajagopalan, Phosphodiesterase-4 inhibition as a therapeutic strategy for metabolic disorders, *Obesity Reviews*, **2016**, *17*, 429-441. [Crossref], [Google Scholar], [Publisher]

[62]. J.N. Mayba, M.J. Gooderham, Real-world experience with apremilast in treating psoriasis, *Journal of Cutaneous Medicine and Surgery*, **2017**, *21*, 145-151. [Crossref], [Google Scholar], [Publisher]

[63]. R. Persson, M. Cordey, M. Paris, S. Jick, Safety of apremilast in patients with psoriasis and psoriatic arthritis: Findings from the UK clinical practice research datalink, *Drug Safety*, **2022**, *45*, 1403-1411. [Crossref], [Google Scholar], [Publisher]

[64]. S. Mazzilli, C. Lanna, C. Chiaramonte, G.M. Cesaroni, A. Zangrilli, V. Palumbo, T. Cosio, A. Dattola, R. Gaziano, M. Galluzzo, M.S. Chimenti, P. Gisondi, L. Bianchi, E. Campione, Real life experience of apremilast in psoriasis and arthritis psoriatic patients: Preliminary results on metabolic biomarkers, *The Journal of Dermatology*, **2020**, *47*, 578-582. [Crossref], [Google Scholar], [Publisher]

[65]. M. Adiguna, M. Wardhana, F. Nathania, Positive correlation between psoriasis vulgaris severity degree with HbA1C level, *Bali Dermatology and Venereology Journal*, **2019**, *1*. [Crossref], [Google Scholar], [Publisher]

[66]. K. Ikumi, K. Torii, Y. Sagawa, Y. Kanayama, A. Nakada, H. Nishihara, A. Morita, Phosphodiesterase 4 inhibitor apremilast improves insulin resistance in psoriasis patients, *The Journal of Dermatology*, **2022**, *49*, e125-e126. [Crossref], [Google Scholar], [Publisher]

[67]. M. Ogoshi, T. Horikawa, Rapid improvement of psoriasis in diabetes subsequent to glucose lowering, *International Journal of Dermatology*, **2014**, *53*, e106-e107. [Crossref], [Google Scholar], [Publisher]

[68]. J. Crowley, D. Thaçi, P. Joly, K. Peris, K.A. Papp, J. Goncalves, R.M. Day, R. Chen, K. Shah, C. Ferrándiz, J.C. Cather, Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2), *Journal of*

the American Academy of Dermatology, **2017**, *77*, 310-317.e311. [Crossref], [Google Scholar], [Publisher]

[69]. L. Stein Gold, K. Papp, D. Pariser, L. Green, N. Bhatia, H. Sofen, L. Albrecht, M. Gooderham, M. Chen, M. Paris, Y. Wang, K. Callis Duffin, Efficacy and safety of apremilast in patients with mild-to-moderate plaque psoriasis: Results of a phase 3, multicenter, randomized, double-blind, placebo-controlled trial, *Journal of the American Academy of Dermatology*, **2022**, *86*, 77-85. [Crossref], [Google Scholar], [Publisher]

[70]. L.F. Stein Gold, J. Bagel, S.K. Tyring, H.C.-h. Hong, L. Pavlovsky, R. Vender, A. Pinter, A. Reich, L. Drogaris, T. Wu, M. Patel, A.M. Soliman, H. Photowala, V. Stakias, S. Richter, K.A. Papp, Comparison of risankizumab and apremilast for the treatment of adult patients with moderate plaque psoriasis eligible for systemic therapy: results from a randomised, open-label, assessor-blinded phase IV (IMMpulse) study, *British Journal of Dermatology*, **2023,** *189***,** 540-552. [Crossref], [Google Scholar], [Publisher]

[71] Y. Liu, S. Zhou, Y. Wan, A. Wu, M. Palmisano, The impact of co-administration of ketoconazole and rifampicin on the pharmacokinetics of apremilast in healthy volunteers, *British Journal of Clinical Pharmacology*, **2014**, *78*, 1050-1057. [Crossref], [Google Scholar], [Publisher]

[72] R. Fischer-Betz, M. Østensen, Biologics and small molecules in the management of psoriatic arthritis: Reproduction related issues in female and male patients, *Expert Review of Clinical Pharmacology*, **2021**, *14*, 979-989. [Crossref], [Google Scholar], [Publisher]