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Literature Review

Effectivity and Safety Profile of Metformin as an Adjuvant Immunomodulator in Psoriasis: A Literature Review

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ABSTRACT
Background: Psoriasis is a chronic inflammatory skin disorder associated with an increased risk of comorbidities and reduced quality of life. Metformin, a first-line therapy for type 2 diabetes mellitus (T2DM), has been investigated for its potential as an adjuvant therapy for psoriasis. **Objective:** This literature review aims to explore the molecular mechanisms by which metformin exerts immunomodulatory effects and assess clinical studies that evaluate its efficacy and safety profile. **Methods:** A literature search was conducted in PubMed, MDPI, Epistemonikos, ScienceDirect, and Wiley Online Library, with the keywords: metformin AND psoriasis AND immunomodulator AND safety. **Results:** Qualitative synthesis revealed that metformin exhibits anti-inflammatory, anti-proliferative, and pro-apoptotic effects through induction of G0/G1 cycle arrest and inhibition of mechanistic target of rapamycin (mTOR), nuclear factor-kappa B (NF-κB), and Raf/MEK/extracellular signal-regulated kinase (Raf/MEK/ERK) pathways. These mechanisms correlate with improvements in psoriasis severity indices, including Psoriasis Area Severity Index (PASI), Erythema, Scaling, and Induration (ESI), and Physician Global Assessment (PGA) scores ($p < 0.05$. A rare case of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome has been reported. **Conclusion:** Metformin demonstrates potential as an adjuvant immunomodulatory treatment for psoriasis. However, a rare adverse effect highlights the need for careful patient selection and evaluation.

Keywords: immunomodulator, metformin, psoriasis, safety

1. Introduction

Psoriasis is a chronic inflammatory skin disease characterized by hyperproliferation and abnormal differentiation of keratinocytes, as well as infiltration of immune cells [1]. Although it most commonly affects the skin, psoriasis can manifest in other organs, making it a systemic disease [2]. Psoriasis is associated with an increased risk of several comorbid conditions such as metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), cardiovascular diseases, and even psychiatric disorders [3]. In recent years, there has been an increase in the incidence and prevalence of psoriasis [4]. The World Health Organization (WHO) reported that the global prevalence of psoriasis ranges from 0.09% to 11.4% [5].

Treatment options for psoriasis vary depending on the severity and comorbid conditions, including topical treatments, phototherapy, biological agents, and non-biological treatments [6]. For moderate to severe psoriasis, biological agents exhibit higher effectiveness compared to other treatment modalities [7]. However, there are patients who do not respond to treatment, leading to primary treatment failure [8]. Additionally, one group of biological agents, tumor necrosis factor alpha (TNF-α) inhibitors, has been reported to have many serious side effects such as tuberculosis, reactivation of hepatitis B and C, drug-induced lupus (DIL), and central nervous system demyelination disorders [9].

Several studies highlight the relationship between psoriasis and diabetes mellitus (DM) due to the parallel involvement of genetic predisposition, environmental influences, and inflammatory pathways [10-12].

Metformin as a first-line therapy for type 2 diabetes mellitus (T2DM) has been proven by many studies to have effects beyond merely controlling blood sugar levels [13-15], including its impact on psoriasis. Unfortunately, there is limited research within this scope. Therefore, this literature review aimed to comprehensively evaluate the underlying molecular mechanism, effectiveness and safety profile of metformin as an adjuvant immunomodulator in psoriasis.

2. Methods

2.1 Literature Search Strategy

This literature review was conducted by gathering literatures across five databases, namely PubMed, MDPI, Epistemonikos, ScienceDirect, and Wiley Online Library in March 2023 with the keywords metformin AND psoriasis AND immunomodulator AND safety. While we prioritized selecting the latest articles, we also considered including older articles with strong sources of information and evidence. Eligible studies were included if they met one of the following criteria: 1) studies published in English; 2) study populations consisting of psoriasis patients with and without comorbidities; 3) studies using metformin as an adjunctive therapy in addition to the main anti-psoriasis treatments; 4) study outcomes include psoriasis severity assessment using either Psoriasis Area Severity Index (PASI), Erythema, Scaling and Induration (ESI), or Physician Global Assessment (PGA) scores, levels of inflammatory biomarkers, or the number of severe psoriasis patients and mortality. This literature review also included in vitro studies in the purpose of uncovering the multifaceted molecular mechanism of metformin.

2.2 Data Collection

The data obtained from the included studies were processed and organized in two tables. Table 1 summarized data from the included clinical studies [16-20], while Table 2 presented data from the included in vitro studies [21-25].

3. Results and Discussion

3.1 Psoriasis and Diabetes Mellitus: Underlying Biological Links

For years, DM and psoriasis were considered distinct conditions; one primarily a metabolic disorder, the other a chronic immune-mediated skin disease. In recent years, there is a growing recognition that these conditions share a common pathway involving inflammatory, metabolic, environmental, and genetic factors that ultimately result in beta-cell damage and variable clinical manifestations. Psoriasis is now considered a complex immune-mediated disease that affects beyond the skin, as proinflammatory cytokines production is not confined solely to the skin. The dominant interleukin (IL)-23 and T-helper (Th)-17 lymphocytes, commonly referred to as IL-23/Th17 axis, drives uncontrolled keratinocyte proliferation, dysfunctional differentiation, and neovascularization, linking psoriasis to various chronic conditions, including cardiometabolic diseases such as DM [26].

Numerous studies have identified overlapping genetic loci that contribute to both conditions, underscoring their intrinsic relationship. A trans-disease meta-analysis on 8,016,731 well-imputed genetic markers from hospital-based studies involving 42,112 patients identified a causal relationship using multivariable mendelian randomization (MR) between psoriasis and T2DM ($p = 1.6 \times 10–4$, OR = 1.01) and highlighted the impact of body mass index (BMI). Four genome-wide significant loci (ACTR2, ERLIN1, TRMT112, and BECN1) were found to be shared between psoriasis and T2DM, independent of BMI. ACTR2 and TRMT112 were found to be upregulated in lesional psoriatic skin when compared to healthy skin. Additionally, ACTR2 showed increased expression in the skeletal muscle and subcutaneous adipose tissue of patients with T2DM but was downregulated in the pancreas. Similarly, BECN1 was upregulated in skeletal muscle while being downregulated in the pancreas. Both TRMT112 and ERLIN1 exhibited reduced expression in the pancreatic tissue of T2DM patients compared to healthy controls. Through MR analysis, this study found that there is a modest causal relationship between psoriasis and T2DM in which psoriasis slightly increases the risk of T2DM, and to a lesser extent, T2DM may increase the risk of psoriasis [27].

These findings are congruent with a case control study by Brazzelli *et al.* in which they found that in non-diabetic psoriasis patients the levels of fasting plasma glucose (FPG), fasting plasma insulin (FPI), glycated hemoglobin (HbA1c), and the homeostatic model assessment for insulin resistance (HOMA-IR) are higher compared to healthy controls. However, among these parameters, only the increase in FPI levels reached statistical significance ($p < 0.0001$). These findings support the hypothesis that psoriasis may be considered a pre-diabetic condition [28]. In relation to BMI, multiple studies have consistently shown that the levels of adipocytokines are altered in psoriasis, similar to obesity. Adipokines, secreted by adipose tissue, are essential for regulating lipid and glucose metabolism. Adiponectin, in particular, improves insulin sensitivity

and offers vasoprotective benefits through its antioxidant and anti-inflammatory effects, especially during early atherogenesis. Studies have demonstrated that adiponectin levels are notably reduced while the levels of leptin and resistin which have antagonistic effects to adiponectin increases in patients with psoriasis even in the absence of metabolic syndrome (MS) compared to healthy controls [29-31]. These findings indicate that psoriasis and diabetes share the same pathomechanism, namely insulin resistance.

Insulin resistance, which is found in both psoriasis and diabetes, is closely entwined with inflammation. Inflammatory mediators, such as cytokines and adipokines, play a key role in the development of insulin resistance and are known to be dysregulated in individuals with psoriasis [28]. This supports the association between insulin resistance and psoriasis, as studies have shown a significant correlation between insulin resistance and both the extent and severity of psoriasis, even in those without MS. Additionally, in conditions characterized by insulin resistance, such as T2DM, elevated insulin levels in its early stages can interact with insulin growth factor (IGF) receptors, promoting the proliferation of keratinocytes and fibroblasts [29-31].

3.2 Metformin Suppresses NF-κB Signaling via TNF-α and p65 Inhibition

Psoriasis is a chronic inflammatory disease that causes excessive keratinocytes proliferation which subsequently leads to skin lesion. Normally, keratinocytes regenerate every 28 to 30 days; however, in psoriasis patients, this process occurs more frequently which is every 3 to 5 days. It has been well-established by multitude of studies that interleukin IL-23/Th17 axis is the major driving force behind the immunopathogenesis of psoriasis. IL-23 is a member of the IL-12 family of cytokines and is a potent enhancer of the expansion of Th17 cells, reinforcing its role in inflammatory autoimmune responses [32, 33]. Upon tissue injury or pathogenic insults, dendritic cells (DCs) in the dermis release IL-23, which enhances the expansion and effector function of Th17 cells, sustaining the inflammatory response. This activation triggers the production of proinflammatory cytokines, including IL-17A, IL-17F, IL-22, and IL-26. These cytokines act on keratinocytes, leading to epidermal hyperplasia, acanthosis, and hyperparakeratosis. Subsequently, keratinocytes amplify the immune response by secreting IL-23 as well. This further enhances Th17 cells, maintaining a positive feedback loop characterized by persistent keratinocyte hyperproliferation [34, 35]. Hence, many psoriatic treatments are being developed to target the IL-23/Th17 axis (Fig. 1) [36, 37].

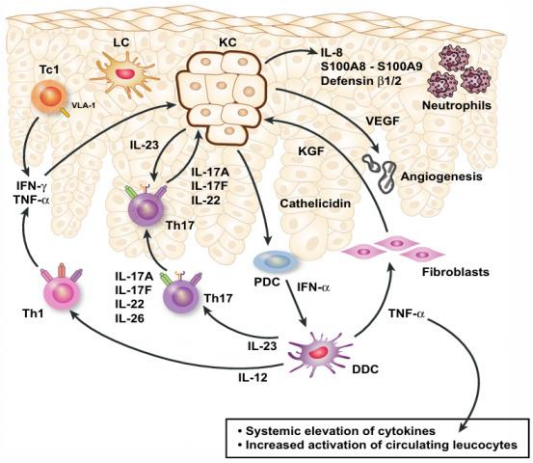

Figure 1. Immunopathogenesis of psoriasis [35]

However, in recent years, studies also found that another pro-inflammatory cytokine, IL-36, also contributes to the development of psoriasis by being a potent inducer of IL-23 and are found to be highly expressed in psoriatic epidermis [38]. IL-36 are produced by epithelial and immune cells and include three pro-inflammatory agonists (IL-36α, IL-36β, and IL-36γ) along with two inhibitory antagonists (IL-36RN/IL-36Ra and IL-38). Despite having opposing functions, all of these molecules interact with the same receptor, IL-36R. In healthy skin, IL-36α and IL-36β are typically present at normal levels, whereas IL-36γ is significantly elevated in psoriatic lesions. Within the skin, epidermal keratinocytes are the main producers of IL-36α, IL-36β and IL-36γ, although other cells such as DCs also release them. Studies have shown that these three cytokines are overexpressed in both the skin and bloodstream of individuals with psoriasis. Moreover, their levels have been found to correlate with the severity of the disease, suggesting that these cytokines play a significant role in its progression (Fig. 2) [39].

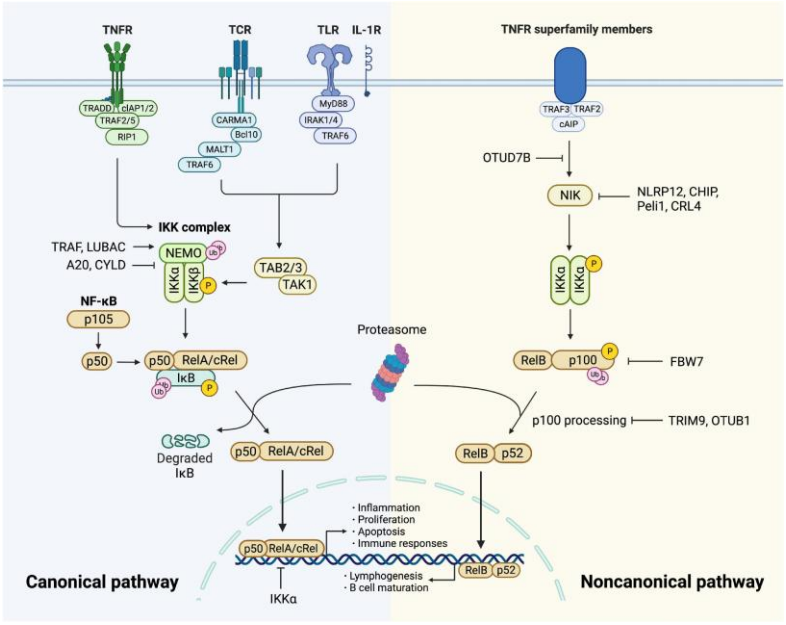

Figure 2. NF-kB signaling pathway [40]

IL-36 signaling leads to IL-23 upregulation through the nuclear factor-kappa B (NF-κB), which is a central transcription factor in inflammation, regulating the expression of various pro-inflammatory cytokines, including IL-23. Its activation plays a critical role in the immunopathogenesis of psoriasis. Upon IL-36 binding to its receptor, myeloid differentiation primary response 88 (MyD88) is recruited, triggering the activation of the inhibitor of kB (IkB) kinase (IKK) complex, which phosphorylates IκBα, marking it for proteasomal degradation. This releases the NF-κB heterodimer, mainly composed of p65 (RelA) and p50, allowing its translocation into the nucleus. Once NF-κB is in the nucleus, p65 is phosphorylated. Phosphorylation of p65 is important because it enhances the transcription of pro-inflammatory genes, including the nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor zeta (Nfkbiz). Nfkbiz is a gene that encodes inhibitor of kB zeta (IκBζ), an atypical member of the IκB protein family, which in spite of its name acts as a transcriptional coactivator rather than an inhibitor. IκBζ then interacts with IL-23 subunit genes, particularly Il23a, thereby promoting IL-23 production (Fig. 3) [41].

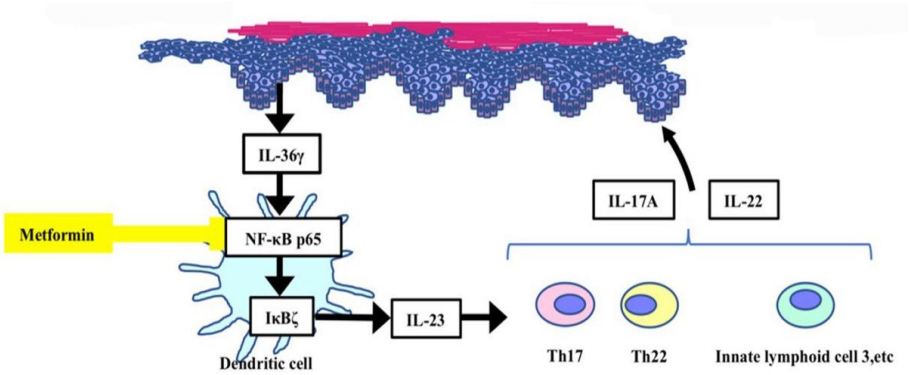

Figure 3. Metformin inhibition of NF-kB Pathway through the disruption of p65 translocation and phosphorylation [25].

In a study by Matsuda-Taniguchi *et al.* using bone marrow-derived dendritic cells (BMDCs), metformin is found to inhibit the p65 phosphorylation, leading eventually to the downregulation of IL-23 and therefore blocks the vicious cycle of IL-23/Th17 axis. To assess p65 phosphorylation, this study stimulated the BMDCs with IL-36γ for varying durations (10, 20, 30, 40, 50, and 60 minutes) in the presence or absence of metformin (5 mM) using Western blot analysis and the result showed a gradual decrease of p65 phosphorylation, signifying the fast-acting nature of metformin in blocking this pathway [25]. While the metformin dose used in this study exceeds physiologically achievable plasma levels, the included clinical

trials have demonstrated improvements in PASI, ESI, and PGA scores with much lower, clinically feasible doses [16, 18, 19], highlighting the need for caution when extrapolating in vitro findings to human treatment.

Similar effect was also observed in another in-vitro study by Ba *et al*. in which metformin does not only block p65 phosphorylation, but also subsequent to metformin administration into HaCaT cells, p65 remains in the cytoplasm in the presence of TNF-α. Previously, when TNF-α was added without metformin, p65 was translocated into the nucleus due to the ability of TNF-α to degrade IκBα. This inhibitory effect of metformin on TNF-α was proven by the significant reduction of not only TNF-α messenger RNA (mRNA) expression but also other pro-inflammatory cytokines, namely IL-6, IL-8, and IL-1β. Consistently, protein levels of TNF-α, IL-6, IL-8, and IL-1β were also markedly decreased, indicating a suppression of cytokine production at both the transcriptional and translational levels. Notably, higher doses of metformin maintained cytokine expression at basal levels, suggesting a dose-dependent effect in mitigating inflammation. Interestingly, this study also compared metformin with BI605906, a selective IKKβ inhibitor. To evaluate the inhibitory effects of metformin on NF-κB activity, they assessed the mRNA levels of key pro-inflammatory cytokines (TNF-α, IL-6, IL-8, and IL-1β) using quantitative polymerase chain reaction (qPCR). Upon TNF-α stimulation, the expression of these cytokines significantly increased, confirming the activation of the inflammatory cascade. However, treatment with either metformin or BI605906 markedly suppressed their expression, demonstrating a potent anti-inflammatory effect. Furthermore, both metformin and BI605906 treatment inhibited NF-κB transcriptional activity, as evidenced by reduced nuclear NF-κB levels. These findings suggest that metformin effectively blocks TNF-α-driven inflammation through a mechanism comparable to that of a selective IKKβ inhibitor [21].

By targeting the process that leads to IL-23 formation, metformin acts not only disrupts the positive feedback loop between keratinocyte and Th17 but also diminishes further recruitment of Th17 by DC induced by IL-23. We have mentioned earlier that while IL-23/Th17 axis is the major driving force of psoriasis, it is not the only pathway because DCs also recruit other immune cells, such as Th1 and Th22. Consequently, inhibition of this axis may not cure psoriasis altogether but rather potentially prevent its progression.

3.3 Anti-proliferative and Pro-apoptotic Effects of Metformin

Anti-proliferative effect of metformin is achieved through the inhibition of the mechanistic target of rapamycin (mTOR) pathway. mTOR is a central regulator of cellular growth, metabolism, angiogenesis, and immune responses. As a serine/threonine kinase, mTOR functions within two distinct protein complexes namely mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). In the context of psoriasis, mTORC1 plays a pivotal role in disease pathogenesis. Under normal conditions, mTORC1 activity is tightly regulated to maintain a balance between keratinocyte proliferation and differentiation. However, in psoriasis, inflammatory cytokines induce aberrant mTORC1 activation, disrupting this balance and resulting in excessive keratinocyte proliferation. This dysregulation is further exacerbated by the downregulation of tuberous sclerosis complex 2 (TSC2), a negative regulator of mTORC1. During inflammation, certain pro-inflammatory cytokines are able to promote TSC2 degradation and subsequent activation of Rheb, a GTPase that activates mTORC1, therefore inducing cellular proliferation (Fig. 4) [41].

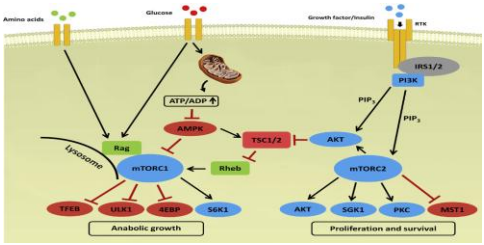

Figure 4. mTOR signaling pathway [42].

Within the cell, mTORC1 activity is also regulated by AMP-activated protein kinase (AMPK) which is a key energy sensor in cells. Under high ATP levels, AMPK is inhibited because cells have sufficient energy. In contrast, when ATP levels are low, AMPK is activated in an attempt to induce catabolism while inhibiting anabolism [43]. One of the ways metformin exerts its therapeutic effects is by activating AMPK, which not only reduces hepatic gluconeogenesis but suppresses excessive proliferation of keratinocytes. A study by Liu *et al*. using HaCaT cells demonstrated that in addition to proliferation arrest, metformin induces cellular morphological changes in which they appear shrunken and round with decreased cytoplasm. These happened in a dose-dependent manner, ranging from 25 mM, 50 mM, and 100 mM [22].

However, in a study by Wu *et al.* it is revealed that metformin effects on suppressing mTORC1 can be independent of AMPK activation and instead through a mitochondrial enzyme called Acyl-coenzyme A dehydrogenase 10 (ACAD10), which is a part of the mTOR signaling pathway. ACAD10 knockdown reversed metformin-induced apoptosis and restored cell proliferation, confirming that activation of ACAD10 mediates the cytostatic effects of metformin. When HaCaT cells are treated with an AMPK agonist, there was no upregulation of ACAD10 mRNA or protein in the range of 0-100 nM concentration, suggesting its independence of AMPK signal in HaCaT cells. Furthermore, this study also found that metformin induced G0/G1 cell cycle arrest, strengthening its role in suppressing keratinocyte proliferation (Fig. 5) [23].

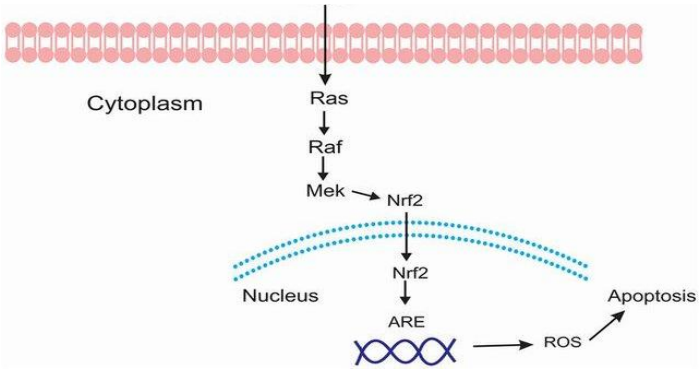

Figure 5. Raf/MEK/ERK signaling pathway [44].

In addition to its antiproliferative effect, metformin also possesses a pro-apoptotic effect through reactive oxygen species (ROS) generation by nuclear factor erythroid 2-related factor 2 (Nrf2) suppression due to inactivation of the Raf/MEK/extracellular signal-regulated kinase (Raf/MEK/ERK), one of the four major cascades of mitogen-activated protein kinase (MAPK) pathway. The Raf/MEK/ERK pathway is responsible for variable cellular processes, mainly driving proliferation in response to mitogens or growth factors. However, this pathway is also able to mediate other processes, such as apoptosis through the activation of Nrf2, a transcription factor involved in antioxidative mechanisms. ROS are highly reactive forms of oxygen that are a byproduct of aerobic metabolism. At normal levels, ROS can be beneficial, such as in the case of respiratory burst as a part of immune defense. However, excessive ROS production contributes to the development of various diseases by causing cellular damage [45]. Nrf2 protects cells against ROS by binding itself to antioxidant response element (ARE), a specific DNA sequence found in the promoter regions of cytoprotective genes, and thus initiating the transcription of those genes. Inhibition of Raf/MEK/ERK leads to Nrf2 suppression, resulting in increased ROS accumulation and apoptosis [46].

Wang *et al.* investigated this pathway by treating HaCaT cells with metformin at concentrations ranging from 10 to 60 mM for 24 hours, followed by assessments of cell viability, apoptosis, intracellular ROS levels, and protein expression. Metformin treatment resulted in a dose-dependent increase in intracellular ROS levels, which correlated with reduced cell viability and increased apoptosis. To confirm the role of ROS in this process, cells were pretreated with N-acetyl-cysteine (NAC), a ROS scavenger, prior to metformin exposure. NAC administration significantly reduced ROS levels, increased cell survival, and attenuated apoptosis, suggesting that oxidative stress is a key driver of metformin-induced keratinocyte apoptosis. Western blot analysis further demonstrated that metformin treatment led to dose-dependent suppression of both total and phosphorylated Raf-1 and ERK1/2, suggesting inactivation of the Raf/MEK/ERK signaling pathway [24].

Table 1. Characteristics of included clinical trials

Reference	Study Design	Population	Control and Intervention	Result
Tam *et al*., 2022[17]	RCT	n = 66 Patients aged 18 to 70 with vulgaris psoriasis and metabolic syndrome.	The intervention group (n = 35) was given methotrexate (7.5 mg per week for 12 weeks) and metformin 500 mg per day after a meal. The control group (n = 31) was given methotrexate alone at the same dosage as the intervention group.	A significant decrease in PASI scores was observed in the intervention and control groups (58.72% and 50.22%, respectively) ($p < 0.05$). After 3 months, in the intervention group, 34.3% of patients achieved a "very good" PASI score (a reduction of 90-100%) and "good" (a reduction of 75-<90%), while no patients in the control group reached these outcomes ($p < 0.05$). No serious side effects were found. No significant changes in liver function were observed. There were no patients who experienced hypoglycemia during the study.
El-Gharabawy *et al.*, 2016[17]	RCT	n = 150 Adult patients with moderate chronic plaque psoriasis (PASI ≥ 6 and/or DLQI ≥ 6) and metabolic syndrome or impaired glucose tolerance.	Patients (n = 150) are divided into 5 groups: 1. Normal control group 2. Psoriasis patients who do not consume anti-psoriasis medication 3. Psoriasis patients who consume anti-psoriasis medication 4. Psoriasis patients who consume anti-psoriasis medication and metformin (850 mg twice a day) 5. Psoriasis patients who consume anti-psoriasis medication and pioglitazone (15 mg daily).	CD4+ T cells, IL-2, CRP, CP, ALT, and AST serum levels decreased with both anti-psoriasis treatment and metformin compared to patients who were only treated with anti-psoriasis ($p < 0.05$). Psoriasis and pioglitazone group showed greater reduction in inflammatory markers (IL-2, CRP, ceruloplasmin) and improvement in immune cell profiles (CD4+/CD8+ ratio) compared to psoriasis and metformin group ($p < 0.05$). No serious side effects were found. No significant differences were observed in the biochemical analysis of fasting blood sugar, HbA1C, total cholesterol, HDL, LDL, and triglycerides.
Singh and Bhansali, 2017[18]	ROLCT *(systemic treatment cohort)*	n = 38 Patients over 18 years old with metabolic syndrome and moderate (3-10% body surface area)	The intervention group (n = 20) was given metformin 1000 mg once a day for 12 weeks. The comparison group (n = 18) was given a placebo. All patients (n = 38)	Significant developments or changes can be observed in the average percentage change in ESI scores ($p = 0.048$). There is a significant difference in the percentage of patients experiencing a

		to severe (>10% body surface area) plaque psoriasis, both those who have and have not undergone psoriasis treatment.	received standard treatment with methotrexate and folic acid.	75% reduction in ESI scores in the metformin group (75%) compared to the placebo group (38.9%) (p = 0.024). No significant side effects were found in the metformin group.
Singh and Bhansali, 2016[19]	ROLCT *(topical treatment cohort)*	n = 60 Patients over 18 years old with metabolic syndrome and mild to moderate plaque psoriasis (less than 10% body surface area) who have and have not undergone psoriasis treatment.	Patients (n = 60) participated in the study for 12 weeks and were divided into 3 groups: 1. Placebo group (n = 23) 2. Oral metformin 1000 mg once daily group (n = 21) 3. Oral pioglitazone 30 mg group (n = 16) All patients (n = 60) received standard topical treatment with coal cream. tar 5 %.	Significant developments can be observed in the PASI, ESI, and PGA scores in the metformin group (p = 0.001, 0.016, 0.012) compared to the placebo group. There is a significant difference in the percentage of patients experiencing a 75% reduction in PASI scores in the metformin group (85.7%) versus the placebo group (4.3%) (p = 0.001), as well as in ESI in the metformin group (61.9%) compared to the placebo group (8.7%) (p = 0.001). The mean changes in PASI and ESI scores from baseline were slightly higher in the pioglitazone group (PASI: 4.3, ESI: 4.3) compared to the metformin group (PASI: 3.9, ESI: 4.2), although the slight difference was not statistically significant (p > 0.05). No significant side effects were found in the metformin group.
Su *et al.*, 2019 [20]	Retrospective cohort	n = 8,582 Patients aged 20 and older with type 2 diabetes mellitus and psoriasis.	Patients were divided into metformin and non-metformin groups. A matching process (pairing patients with similar characteristics from each group) was carried out so that the sample size was reduced, resulting in 2,277 patients for each group.	No significant side effects were found in each group. The metformin group did not experience an increase in mortality, severe psoriasis, or hospitalization due to psoriasis complaints.

RCT: Randomized Controlled Trial; ROLCT: Randomized Open Label Controlled Trial; PASI: Psoriasis Area and Severity Index; ESI: Erythema, Scaling and Induration; PGA: Physician Global Assessment; ALT: Alanine aminotransferase; AST: Aspartat aminotransferase; IL-2:Interleukin-2; CRP: C-reactive protein; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein

Table 2. Characteristics of Included In Vitro Studies

Reference	Type of Study	Findings
Ba *et al.,* 2018[21]	Keratinocyte cell culture (HaCaT)	Metformin inhibits the production of IL-23 through the disruption of NF-κB signaling pathway by inhibiting both p65 translocation to the nucleus and its phosphorylation within the nucleus. Metformin also prevents IκBα degradation by degrading TNF-α
Liu *et al., 2016*[22]	Keratinocyte cell culture (HaCaT)	Metformin exhibits an anti-proliferative effect through the inhibition of mTORC1 by activating AMPK. Additionally, metformin also disrupts the cell viability by affecting its morphology.
Wu *et al., 2017*[23]	Keratinocyte cell culture (HaCaT)	Metformin exhibits an anti-proliferative effect through the induction of cell cycle arrest in the G0/G1 phase and a pro-apoptotic effect through the inactivation Raf/MEK/ERK signaling pathway and its subsequent Nrf2 downregulation.
Wang *et al., 2018*[24]	Keratinocyte cell culture (HaCaT)	Metformin exhibits a pro-apoptotic effect by inactivating the Raf/MEK/ERK signaling pathway and subsequently Nrf2 downregulation.
Matsuda Taniguchi *et al., 2021*[25]	*Bone marrow-derived dendritic cells Culture* (BMDCs)	Metformin inhibits the production of IL-23 by disrupting p65 phosphorylation in the NF-κB signaling pathway

NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; TNF-α: Tumor Necrosis Factor-α; mTORC1: mechanistic Target of Rapamycin Complex1; AMPK: Adenosine Monophosphate-Activated Protein Kinase; Nrf2: Nuclear erythroid 2-related factor 2; ROS: Reactive Oxygen Species; Raf/MEK/ERK: Raf/MEK/extracellular signal-regulated kinase

3.4 The Safety Profile of Metformin in Psoriasis

All included studies reported no significant side effects in the metformin groups. According to a study by Tam *et al*., although liver function tests revealed no significant alterations in aspartate transferase (AST) and alanine transaminase (ALT) levels in either metformin plus methotrexate (intervention) and methotrexate only (control) group, the gamma-glutamyl transferase (GGT) index significantly increased after 12 weeks in the methotrexate monotherapy group, a finding consistent with other studies highlighting the hepatotoxic potential of methotrexate [47, 48]. On a side note, this study addressed that the lack of AST and ALT alterations can be due to the methotrexate dosage and duration, which is 7.5 mg per week for three months meanwhile methotrexate-induced hepatotoxicity is associated with long term use. In contrast, although not statistically significant, GGT index decreased in the intervention group after 12 weeks, highlighting the potential protective effect of metformin against methotrexate-induced hepatotoxicity. Moreover, histopathological evaluation of liver tissues in metformin-treated subjects revealed substantial structural improvements despite residual necrotic lesions, suggesting a hepatoprotective effect, which Tam *et al.* attributed to the anti-inflammatory and anti-oxidative effects of metformin [16]. While it may seem contradictory considering that an in-vitro study revealed that metformin can suppress Raf/MEK/ERK signaling pathway, metformin also exerts anti-oxidant effect through other mechanisms, one of which is through the activation of AMPK which inhibits inducible nitric oxide synthase (iNOS). Nevertheless, further studies are warranted to determine whether its Raf/MEK/ERK-suppressing effects extend to hepatocytes because understanding whether metformin exerts cell type-specific oxidative effects, particularly in the liver, is crucial for clarifying its role in mitigating methotrexate-induced toxicity (Table 1) [49].

Furthermore, according to Su *et al.*, the traditional contraindications of metformin for patients with chronic kidney failure should not limit the use of metformin because the beneficial effects of metformin have been well documented, though it is still warranted to keep a close eye on lactic acidosis in those patients. They also concluded that metformin does not lead to increased mortality, severe psoriasis, or hospitalization due to psoriasis complaints in the metformin group [20]. A study by Wu *et al.* also reported that in psoriasis patients with DM, frequent insulin usage is more associated with an increased incidence of severe psoriasis while frequent metformin usage showed greater psoriasis risk reduction compared to the infrequent group [50]. One possible explanation, as briefly mentioned, is because insulin structure is similar to insulin growth factor-1 (IGF-1), which is a growth factor that plays an important role in keratinocyte proliferation and differentiation [51]. Due to the structural similarity, insulin can bind to IGF-1 receptors and vice versa. While this cross-binding exhibits reduced affinity, high levels of insulin may potentially worsen psoriasis [52]. On the other hand, in regards to pioglitazone, one study showed a greater reduction in inflammatory markers in the pioglitazone group [17], while the other reported slightly higher PASI, ESI, and PGA score reductions although not statistically significant [19]. However, concerns remain regarding pioglitazone's association with an increased risk of bladder cancer, particularly in patients with chronic use, higher doses, advanced age, or a history of hematuria (Table 2) [53, 54].

Additionally, the percentage of the population with comorbidities such as hypertension, gout, coronary heart disease, and stroke was found to be higher in the non-metformin group (84.7%) compared to the metformin group (42.2%) [20]. A study conducted by Singh and Bhansali on patients with metabolic syndrome and psoriasis of varying degrees of severity also reported that the use of metformin did not worsen the metabolic panel but rather improved it by reducing LDL and triglyceride levels while slightly increasing HDL, which may benefit psoriasis patients with metabolic syndrome [18, 19]. That said, while metformin appears to be beneficial in improving metabolic parameters in psoriasis patients with comorbidities, rare but severe adverse reactions have been reported. A case report by Voore *et al.* documented a 40-year-old male with psoriasis, hypertension, hyperlipidemia, and newly diagnosed T2DM who developed Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome after initiating metformin therapy [55]. DRESS is a severe hypersensitivity reaction that can lead to multi-organ involvement. Certain patient populations may be more susceptible to DRESS, including patients with a history of drug-induced hypersensitivity reactions, autoimmune conditions, latent viral reactivation, and genetic predisposition such as specific human leukocyte antigen (HLA) alleles [56]. Given these considerations, careful risk assessment is warranted before initiating metformin therapy in psoriasis patients, particularly those with multiple comorbidities. Close monitoring during the first few weeks of treatment is essential, and any early signs of hypersensitivity should prompt immediate evaluation and discontinuation of the drug if necessary. While metformin remains a valuable adjunctive therapy, clinicians must balance its benefits with the potential risks, particularly in patients with a predisposition to severe drug reactions.

4. Conclusion

Metformin has demonstrated potential as an adjuvant immunomodulator in psoriasis, with well-documented anti-inflammatory, anti-proliferative, and pro-apoptotic benefits. By targeting multiple pathways involved in psoriasis pathogenesis, metformin may contribute to disease modulation while also addressing metabolic comorbidities commonly seen in these patients, mainly T2DM. Additionally, clinical studies have shown improvements in PASI, ESI, and PGA scores, reinforcing its therapeutic relevance. However, while metformin is generally well-tolerated, rare but serious adverse reactions, such as DRESS syndrome, highlight the need for individualized risk assessment prior to initiation. Future research should focus on refining patient selection criteria, exploring more molecular mechanisms of metformin in psoriasis, and conducting large-scale clinical trials to further establish its efficacy and safety profile.

5. Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations but are available from the corresponding author upon reasonable request.

6. Ethical Statement

Sumatera Medical Journal (SUMEJ) is a peer-reviewed electronic international journal. This statement below clarifies ethical behavior of all parties involved in the act of publishing an article in Sumatera Medical Journal (SUMEJ), including the authors, the chief editor, the Editorial Board, the peer-reviewer and the publisher (TALENTA Publisher Universitas Sumatera Utara). This statement is based on COPE's Best Practice Guidelines for Journal Editors

7. Author Contributions

All authors contributed to the design and implementation of the research, data analysis, and finalizing the manuscript.

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10. Conflict of Interest

Authors declares no conflict of interest.

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