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Metformin as a Therapeutic Option in Psoriasis: A Review of Pathophysiological Insights and Clinical Perspectives

Kinga Kozłowska [KK]
Provincial Hospital of Podkarpackie John Paul II in Krosno, Korczyńska 57 street, 38-400 Krosno, Poland
https://orcid.org/0009-0008-6541-207X
Kinga7839@gmail.com
Anna Ewelina Francuziak [AEF]
University Hospital in Krakow, Kopernika 36 street, 31-501 Krakow, Poland
https://orcid.org/0009-0005-9810-7758
anna.fr17@wp.pl
Piotr Mikołaj Dembicki [PMD]
Ludwik Rydygier Memorial Specialized Hospital, Osiedle Złotej Jesieni 1 street, 31-820 Krakow, Poland
https://orcid.org/0009-0005-0709-9220
piotr.dembickizmc@gmail.com
Tomasz Karol Książek [TKK]
University Clinical Hospital of Bialystok, Marii Skłodowskiej-Curie 24A street, 15-276 Białystok, Poland
https://orcid.org/0009-0000-9852-1434
ksitomasz@gmail.com
Aleksandra Szeliga [AS]
Medical University of Białystok, Jana Kliniśkiego 1 street, 15-089 Białystok, Poland
https://orcid.org/0009-0006-1832-5569
Aleksandra.sze97@gmail.com
Maciej Borowski [MB]
University Clinical Hospital of Bialystok, Marii Skłodowskiej-Curie 24A street, 15-276 Białystok, Poland
https://orcid.org/0009-0006-4185-2199
mborowski800@gmail.com
Natalia Dzieszko [ND]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0008-8743-6590
1nataliadzieszko9@gmail.com

Michał Szczepański [MS]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0002-4828-6709
michalszczepanski99@gmail.com
Weronika Kalinowska [WK]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0005-4630-467X
wkalinowska999@gmail.com
Paulina Sara Kulasza [PSK]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0003-5829-6721
pkulasza@onet.pl

Abstract
Aim of the study: This study synthesizes current preclinical and clinical evidence regarding the role of metformin as a potential therapeutic option in psoriasis, examining its mechanisms of action, efficacy, safety profile, impact on the common comorbidity of metabolic syndrome, as well as evaluating future directions for studies.
Material and methods: A literature review was conducted using the databases PubMed, Scopus, and ScienceDirect up to April 2025 with keywords “metformin” AND “psoriasis”.
Results: Preclinical studies demonstrate that metformin inhibits keratinocyte proliferation, promotes apoptosis, and suppresses key inflammatory mediators such as IL-23, IL-17, and TNF-α, mainly via AMPK activation and mTOR signaling inhibition. Clinically, adjunctive metformin therapy shows promising results in improving psoriasis severity indices, particularly in patients with coexisting metabolic syndrome, although study heterogeneity and dosing variability limit definitive conclusions. Moreover, metformin may improve metabolic parameters in psoriasis patients, potentially enhancing overall treatment outcomes. Safety data indicate a favorable profile with minimal adverse effects. Emerging research also suggests the potential application of metformin as a topical treatment.
Conclusions: Metformin is a promising candidate to be implemented as part of the therapy targeting not only dermatological symptoms, but also comorbid metabolic disorders in psoriasis, which may contribute to more comprehensive and effective patient care. Despite encouraging findings, further randomized controlled trials are warranted to clarify optimal dosing, long-term efficacy, and mechanistic pathways.

Key words: Metformin, topical metformin, hypoglycemic agents, psoriasis, psoriasis treatment, AMPK, metabolic syndrome, efficacy, safety.

1. Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disorder with a prevalence ranging from 2% to 3% globally [1], with the greatest rates observed in high-income countries such as Australasia or Central Europe [2]. There are several types of psoriasis, but the most common is plaque psoriasis, with an incidence of 80-90%. Clinically, the disease is characterized by erythematous and scaly plaques, predominantly affecting extensor surfaces, the scalp, and the torso [3]. Histologically, it involves epidermal hyperplasia, aberrant keratinocyte differentiation, and infiltration of T lymphocytes, neutrophils, and dendritic cells [4].

Beyond cutaneous presentation, psoriasis is now widely recognized as a systemic inflammatory disease co-occurring with psoriatic arthritis, cardiovascular diseases, inflammatory bowel disease (IBD) and, strongly emphasized, with metabolic comorbidities such as obesity, dyslipidemia, insulin resistance, and type 2 diabetes mellitus (T2DM) [5–8]. Epidemiological studies have consistently demonstrated an increased prevalence of metabolic syndrome (MS) among patients with psoriasis, suggesting a bidirectional relationship mediated by shared immunometabolic mechanisms [9,10]. Conversely, metabolic syndrome has been proposed as a potential risk factor for psoriasis development, and targeting its individual components, including impaired glucose homeostasis, might enhance the efficacy of psoriasis therapies [11,12].

Persistent chronic inflammation in psoriasis is associated with disruption of the IL-23/Th17 axis, playing a key role in the pathogenesis of psoriasis [13]. Interleukin 23 (IL-23), secreted by dendritic cells and macrophages, promotes the differentiation of type 17 T helper cells (Th17) and the secretion of IL-17A, IL-17F, IL-22 [14]. A significant increase in pro-inflammatory factors such as IL-23, IL-17A, IL-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) is widely observed in psoriasis patients and is associated with the induction of inflammatory responses and keratinocyte differentiation [15].

In this context, pharmacological strategies targeting both immune and metabolic pathways are garnering increasing attention in psoriasis treatment. One such agent is metformin, a biguanide compound used as the main-line therapy for T2DM [16]. Its primary mechanism involves the activation of AMP-activated protein kinase (AMPK), a cellular energy sensor

that regulates glucose and lipid metabolism while exerting anti-inflammatory effects [17]. Through inhibition of mitochondrial complex I, metformin reduces oxidative phosphorylation and cellular ATP levels [18], leading to AMPK activation and downstream suppression of mammalian target of rapamycin (mTOR) signaling [19]. Furthermore, metformin inhibits nuclear factor-kappa B (NF-κB) activity, reduces the production of TNF-α [20], which may be particularly relevant in the context of psoriatic inflammation.

Emerging evidence supports the potential use of metformin in inflammatory and autoimmune dermatological conditions, including psoriasis [21–23]. Beyond dermatology, metformin's pleiotropic effects are being explored in a range of chronic diseases, including cardiovascular disorders [24], malignancies [25], and polycystic ovary syndrome [26].

Considering the immunometabolic effects of metformin and the growing interest in its use in various other diseases, not just diabetes, along with numerous reports on the beneficial effects of metformin in psoriasis, the aim of our literature review is to present current data on the mechanisms and role of metformin in the treatment of psoriasis and to discuss new research directions in this field.

2. Material and Methods

A literature review was conducted using databases PubMed, Scopus, and ScienceDirect up to April 2025 with keywords "metformin" AND "psoriasis". Only articles available in full-text in English were considered. To include publications, titles and abstracts were first reviewed, followed by the full text of the selected ones.

3. Results and Discussion

3.1. Mechanisms of metformin action in psoriasis: preclinical studies

Metformin demonstrates a range of beneficial mechanisms that may be relevant in the context of psoriasis treatment. Numerous preclinical scientific investigations have attempted to clarify and demonstrate the exact points of action of metformin as a potential antipsoriatic drug (Table 1). In vitro studies have confirmed metformin's strong ability to regulate key pathological features of psoriasis, such as hyperkeratosis and epidermal thickening, first, through the inhibition of the proliferation of human keratinocytes [27–31] , and second, through the promotion of keratinocyte apoptosis [27–29,32]. These effects may be mediated, among other things, by activation of the AMPK pathway or inactivation of the mTOR, Raf-1-ERK1/2-Nrf2 pathway [27–29,31].

Metformin also exerted strong anti-inflammatory properties, as evidenced by its inhibition of NLRP3 inflammasome activation and IL-1β secretion in keratinocytes [33] , as well as suppression of NF-κB activity, a key transcription factor in the inflammatory response [34] . In addition, metformin reduced IL-23 production in dendritic cells, which may be particularly relevant to the IL-23/Th17 axis central to psoriasis pathogenesis [35] . Furthermore, as an in vivo study in rat models showed, the treatment also modulated KGF/STAT3 protein levels, other important components of the IL-17 pathway [31]. Collectively, the data supported the anti-inflammatory and immunomodulatory potential of metformin.

An especially interesting aspect seems to be the effect of metformin on oxidative stress in psoriasis. Scientific reports have shown that it can reduce oxidative stress induced by psoriasis [30] and, on the other hand, promote keratinocyte apoptosis by increasing Reactive Oxygen Species (ROS) levels [32].

Taken together, these findings suggest that metformin acts through multiple mechanisms, including antiproliferative, pro-apoptotic, antioxidant, anti-inflammatory, and immunomodulatory effects, which may support its use as an adjunctive agent in the treatment of psoriasis.

Table 1. Characteristics of the mechanisms and effects of metformin in psoriasis based on preclinical studies.

Main effect	Reference	Type of study	Molecular target	Findings
Antiproliferative, Proapoptotic	Li et al. 2014	In vitro	Human keratinocytes (HaCaTs)	Metformin induced morphological changes and significantly reduced cell viability in keratinocytes. The treatment increased the expression of phosphorylated ERK1/2, suggesting that the antiproliferative effect of metformin may be mediated through activation of the MAPK signaling pathway.
Antiproliferative, Proapoptotic, Anti-inflammatory	Liu et al. 2016	In vitro	Human keratinocytes (HaCaTs)	Metformin significantly reduced proliferation, induced keratinocyte apoptosis, decreased cell viability, and lowered the expression of IL-6, TNF-α and VEGF proteins in a dose- and time-dependent manner, presumably by inhibiting the mTOR pathway, likely in correlation with AMPK activation.

Main effect	Reference	Type of study	Molecular target	Findings
Antiproliferative, Proapoptotic	Wu et al. 2017	In vitro	Human keratinocytes (HaCaTs)	Metformin reduced proliferation and induced keratinocyte apoptosis, which was concurrently associated with an increase in ACAD10 expression. Further analyses demonstrated that the upregulation of ACAD10 was mediated by the attenuation of mTORC1 activation signaling rather than by AMPK signaling.
Proapoptotic, Oxidative stress induction	Wang et al. 2018	In vitro	Human keratinocytes (HaCaTs)	Metformin suppressed keratinocyte proliferation and triggered apoptosis and ROS levels in a dose-dependent manner. Pro-apoptotic and oxidative stress-enhancing effects have been shown to be associated with the mitigation of the Raf-1-ERK1/2 pathway, leading to a diminished expression of Nrf2 protein levels.
Antiproliferative, Oxidative stress reduction	Zhang et al. 2022	In vitro	Human keratinocytes (HaCaTs)	The cells were pharmacologically treated with FFA to induce a hyperlipidemic state. Metformin reversed the FFA-induced ROS upregulation, autophagy suppression, and inhibition of FOXO3 activity.
Anti-inflammatory	Ba et al. 2018	In vitro	Human keratinocytes (HaCaTs)	Metformin considerably declined protein levels of IL-6, IL-8, IL-1β. It was shown that this action of metformin was due to inhibition of p65 nuclear translocation and IκBα degradation.
Anti-inflammatory	Tsuji et al. 2020	In vitro and in vivo	Human epidermal keratinocytes (NHEKs) and mice	Metformin disrupted NLRP3 inflammasome activity by lowering the caspase-1 protein expression, potentially via activation of AMPK and SIRT1, which led to decreased IL-1β secretion. Furthermore, in an imiquimod-induced psoriasis mouse model, metformin treatment resulted in a depletion of epidermal thickness and IL-17A-producing cells infiltration in the skin.
Anti-inflammatory	Matsuda-Taniguchi et al. 2021	In vitro	Murine bone marrow-derived DCs (BMDCs)	Metformin treatment lowered IL-23 protein levels. The effect was due to suppressed IL-36γ-induced enhancement of Nfkbiz mRNA and IκBζ protein expression.
Anti-inflammatory, Improving metabolic profile, Antiproliferative	Hassan et al. 2024	In vivo	Rats	The study involved rat groups were stratified by the presence of diabetes and psoriasis, as well as by the form of metformin administration (systemic or topical). Metformin treatment downregulated triglyceride levels and improved insulin sensitivity. It also decreased the levels of pro-inflammatory cytokines, including TNF-α, IL-17, and IL-

Main effect	Reference	Type of study	Molecular target	Findings
				1β. Metformin enhanced AMPK activation and reduced KGF and STAT3 protein expression.

ERK 1/2 - extracellular signal-regulated kinase 1/2; **MAPK** - mitogen-activated protein kinase; **IL-1β** – interleukin 1 beta; **IL-6** – interleukin 6; **IL-8** – interleukin 8; **IL-17A** – interleukin 17A; **IL-23** - interleukin 23; **IL-36γ** - interleukin 36 gamma; **TNF-α** - tumor necrosis factor-alpha; **VEGF** - vascular endothelial growth factor; **mTOR** - mammalian target of rapamycin; **AMPK** - adenosine monophosphate-activated protein kinase; **ACAD10** - Acyl-coenzyme A dehydrogenase family member 10; **mTORC1** - mammalian target of rapamycin complex1; **ROS** – reactive oxygen species; **Raf-1** - serine/threonine kinase; **Nrf2** - nuclear factor erythroid 2-related factor 2; **FFA** - free fatty acids; **FOXO3** - forkhead box O3; **IκBα** - IkappaBalpha; **NLRP3** - NOD-like receptor protein-3; **SIRT1** – sirtuin 1; **Nfkbiz** - NF-kappa-B inhibitor zeta; **IκBζ** – IkappaBzeta; **KGF** - keratinocyte growth factor; **STAT3** - signal transducer and activator of transcription 3.

3.2. Efficacy of metformin in psoriasis

Several clinical studies have been conducted, presenting the positive effects of metformin treatment on the course of psoriasis. Metformin has demonstrated improvement in key measures of psoriasis severity, including the Psoriasis Area and Severity Index (PASI), Erythema, Scaling, and Induration (ESI) scores, and the Physician's Global Assessment (PGA).

In a randomized open-label controlled trial, Singh and Bhansali observed statistically significant amelioration in PASI, ESI, PGA scores, as well as a higher proportion of patients attaining a 75% reduction in PASI and ESI scores against to placebo. The study participants were divided into three groups. Group 1 received placebo, group 2 received 1000 mg of metformin per day, and group 3 received 30 mg of pioglitazone per day for 12 weeks. All qualifiers had mild to moderate severity plaque psoriasis, metabolic syndrome, and were additionally treated with standard 5% coal tar ointment [36].

In line with the previous study, another randomized open-label controlled trial, also conducted by Singh and Bhansali, showed a statistically significant change in the average ESI score percentage and a higher percentage of patients attaining a 75% reduction in ESI score compared to placebo. Interestingly, the observed changes in PASI and PGA scores were not

statistically significant, which is inconsistent with the previously cited study. In this analysis, patients with moderate to severe plaque psoriasis and metabolic syndrome, treated with an additional 10-30 mg of methotrexate once weekly and 5 mg of folic acid twice weekly, received 1000 mg of metformin once daily (study group) or placebo (control group) for 12 weeks [37].

This theme was also emerged in Tam et al.'s research, where a significantly lower PASI score was noticed in the group treated with a combination of metformin 500 mg/day and methotrexate 7.5 mg/week for 12 weeks compared to the group receiving methotrexate alone, in patients with both psoriasis and metabolic syndrome [38].

These results are supported by Huang et al. in meta-analysis study, which confirmed a statistically significant PASI 75% reduction and ESI 75% reduction associated with metformin treatment in psoriasis patients with metabolic syndrome [39].

The latest double-blind randomized clinical trial in Iraqi patients with moderate to severe psoriasis, but without diabetes mellitus, revealed that the addition of 850 mg metformin once daily to the 40 mg adalimumab therapy significantly greater reduced the PASI score compared to the group receiving adalimumab alone [40].

Taken together, these results indicate that metformin may improve the clinical outcome of patients with psoriasis, especially as an additive therapy to standard psoriasis treatment. Despite the promising evidence, it must be emphasized that the studies were used varying doses of metformin and included patients with varying comorbidities, such as with or without metabolic syndrome or diabetes.

3.3. Impact of metformin treatment on metabolic syndrome in psoriasis

Numerous scientific reports have established a strong association between psoriasis and metabolic syndrome [41]. Accordingly, several assessments have attempted to answer the question of whether the use of metformin in patients with psoriasis, especially those with co-morbid metabolic syndrome, would improve metabolic parameters. Analyses have yielded inconsistent results.

Metformin treatment significantly reduced fasting plasma glucose (FPG), total cholesterol, triglyceride (TG) levels, waist circumference [36], weight, Body Mass Index (BMI), and low-density lipoprotein cholesterol (LDL-C) [37] compared to the placebo group. In contrast, Tam et al. showed a reduction in venous blood glucose and triglyceride levels in the

metformin group when comparing results before and after treatment, but no significant changes were observed in comparison to the placebo group. No changes in high-density lipoprotein cholesterol (HDL) and total cholesterol levels were not noted either [38].

Interestingly, the meta-analysis of the three studies mentioned above demonstrated a statistically significant reduction in FPG, total cholesterol, TG, and LDL-C levels opposed to the placebo group [39].

Conversely, El-Gharabawy et al. did not find any significant differences in total cholesterol, HDL, LDL, TG, glycated haemoglobin (HbA1c), and fasting blood glucose levels between the study groups [42].

These discrepancies may be attributed to the use of different doses of metformin, various additional treatments for psoriasis, small sample sizes, and excessive heterogeneity of the evaluated groups in the studies.

Currently, the available evidence is insufficient to draw firm conclusions, and more rigorous trials are required to establish the precise effect of metformin on metabolic syndrome parameters in patients with psoriasis.

3.4. Safety of metformin in psoriasis

The previously mentioned clinical trials did not show essential negative effects of metformin treatment in patients with psoriasis. No significant differences in adverse effects were noted between the analyzed groups, aside from weight gain in the non-metformin group [37] and the group with pioglitazone [36]. Similar findings were reported by Tam et al., who additionally evaluated the effect of metformin on liver parameters. No considerable changes in AST, ALT levels were noticed. Interestingly, a significant increase in GGT was noted in the control group treated with methotrexate alone, confirming its hepatotoxicity revealed in the literature. No differences in GGT were observed in the metformin treated group, which, according to the researchers, may hypothesize a protective role of metformin in methotrexate-induced liver irregularities. Furthermore, it was emphasized that no patient had a hypoglycaemic episode during this trial [38].

To the best of our knowledge, only one cohort study has assessed the long-term safety of metformin in psoriasis. The data demonstrated that metformin use did not increase overall mortality, the risk of severe psoriasis, hospitalization due to psoriasis, and rehospitalization

for any other reason in patients with psoriasis and type 2 diabetes, compared to a control group without metformin. These findings were dose-independent [43].

In contrast to previous outcomes, a single case report described the onset of psoriasis-like skin lesions following the initiation of oral metformin hydrochloride for polycystic ovary syndrome (PCOS), which regressed after metformin withdrawal and reappeared after a challenge test [44]. There is also one report of a first-time correlation between metformin and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome in a patient with, among other conditions, coexisting psoriasis and type 2 diabetes [45]. However, these are only single case reports published a long time ago. Since then, numerous observational and clinical studies have not shown such significant negative effects of metformin when treating patients with psoriasis.

Although some discrepancies exist, the topic remains insufficiently clarified, and some reports carry a high risk of bias, it can be assumed that the use of metformin in patients with psoriasis is potentially safe. Naturally, it should be noted that the use of metformin is not free from the well-documented standard side effects it causes, and its effects will also depend on the individual circumstances of each patient. Patients' reactions to newly introduced metformin during the first weeks of use should be carefully observed.

3.5. Metformin treatment and reduced risk of developing psoriasis

The effect of metformin as a potential protector against the development of first-time psoriasis in patients with diabetes is poorly examined in the literature.

Brauchli et al., in their case-control study, suggested that ongoing long-term treatment with metformin may slightly reduce the risk of psoriasis in men [46]. Another case-control study performed by Wu et al. pointed the possibility to reduce the risk of psoriasis in regular users versus rare users of metformin, in patients with previous diagnosis of diabetes mellitus. This analysis also showed that the risk of psoriasis may be higher in patients with diabetes, and itself use of insulin as an antidiabetic drug may also increase the risk of psoriasis depending on the dose [47]. Rather, both studies indicated a positive effect of thiazolidinediones on the risk of first-time psoriasis. Nevertheless, these results should be interpreted with caution. The researchers themselves noted a high risk of error, weak evidence, the possibility of not reflecting results in a large heterogeneous population and highlighted the need for further more rigorous research.

In a retrospective cohort study, Tseng only indirectly suggested a correlation between metformin use and reduced incidence of psoriasis by demonstrating a significantly lower risk of immune-mediated skin diseases, including psoriasis, among patients with type 2 diabetes treated with metformin [48].

A Mendelian randomization study uncovered a relevant relationship between a higher AMPK genetic risk score (inversely correlated with AMPK activation) and an increased risk of late-onset psoriasis (LOP) in the male group rather than in the female group, with no such association found for early-onset psoriasis (EOP). Following up on these findings, the researchers suggested that metformin may reduce the risk of psoriasis through AMPK pathway activation. Importantly, the aforementioned study shed new light on the relevance of the involvement of the AMPK pathway in the development of psoriasis. Moreover, it indicated potentially better results with metformin in the context of psoriasis in men compared to women, which may be due to gender differences in AMPK pathway activity [49].

3.6. Topical use of metformin in psoriasis

While systemic administration of metformin is widely used in medicine, its topical application for treatment is a relatively new direction, especially in dermatology. Although most scientific reports on topical metformin gel relate to periodontal disease, the use of metformin in the form of various ointments, creams, gels, and lotions has also found a particular place in skin diseases [50].

Given the suggested beneficial effects of metformin on the treatment of psoriasis, and the potential side effects of its oral use, Al-Saedi et al. conducted a study evaluating the effect of metformin gel on imiquimod-induced psoriatic lesions in mice. They compared erythema and scaling scores, as well as IL-17 and IL-23 levels in five mouse groups. The control group was applied with a vaseline base, group II imiquimod cream, group III received imiquimod cream and clobetasol ointment, group IV imiquimod cream and 10% metformin gel, and group V imiquimod cream and 15% metformin gel for six days. The results demonstrated a substantial decrease in IL-17 and IL-23 levels in the clobetasol and 10% or 15% metformin treatment groups compared to group II, respectively. Similar improvements were observed in relation to erythema and scaling scores. Nevertheless, when comparing the effects of 10% and 15% metformin gels on clinical outcomes, the 15% gel proved to be more effective, and to be

emphasized, only the 15% gel showed a significant reduction in erythema and scaling compared to clobetasol in mice with induced psoriasis [51].

The move towards metformin's potential as a topical drug for the treatment of psoriasis has resulted in some interesting research into the development of new formulations, forms and application techniques using innovative technologies. Pawar et al. explored the possibility of creating a nanosponges-loaded hydrogel of metformin hydrochloride, which could be a promising form of topical drug delivery. However, the potentially superior properties of such a formulation in psoriasis remain only speculative and require further research [52].

Especially interesting is the work of Jenabikordi et al., who uniquely focused on the combination of metformin and ginger (potentially beneficial in psoriasis through anti-inflammatory and presumably synergistic effects with metformin) together in liposomal carriers as an optimization of the properties and effects of metformin on the course of psoriasis. The study showed that the use of liposomes for the co-encapsulation of metformin and ginger was possible, and that liposomal formulations ensured a prolonged, gradual release, and greater skin permeability for the compounds compared to aqueous solutions of these substances. Liposomal forms also presented greater efficacy in improving in vivo clinical outcomes in imiquimod-induced psoriasis mice. Moreover, the combination of metformin and ginger in one formulation lowered PASI scores, IL-22 and TNF-α levels more effectively, showing the greatest improvement of psoriatic skin lesions in histopathological observations, which may indicate a mutual enhancement of the anti-psoriatic effects of these compounds. However, part of these results depended on the concentration level of ginger [53].

A recent contribution to this subject matter is the study committed by Gao et al., which also focused on combining two potentially anti-psoriatic substances (metformin and curcumin) into a modern topical form of drug application to co-treat the effects of psoriasis and diabetes. The researchers created a combination of site-specifically launched microneedles of short-range missiles (with curcumin nanoparticles) so that the substance could remain in the skin and there show a beneficial therapeutic effect for psoriasis, and long-range missiles (with metformin) so that the drug could not only act in the skin but also penetrate through the skin barrier into systemic circulation, thereby demonstrating not only a local antipsoriatic effect it could also show a systemic antidiabetic effect [54].

4. Conclusions

Metformin, a widely used hypoglycemic drug, exhibits important anti-inflammatory, immunomodulatory, and antiproliferative properties, which may have therapeutic potential in the treatment of psoriasis. Preclinical data indicate that this substance affects key pathophysiological mechanisms of the disease through its primary effects on AMPK/mTOR and IL-23/Th17 pathways. Nevertheless, its exact mode of action appears not to be fully understood. The findings of the available clinical studies, although limited in terms of sample size and follow-up time, present that the use of metformin, particularly as an adjunctive therapy in patients with psoriasis coexisting with metabolic syndrome, may improve skin symptoms, resulting in reduction of PASI, ESI, and PGA scores, and promote metabolic control. In addition, they suggest gender differences in efficacy, with a better results in the male population, as well as reduction in the risk developing psoriasis in patients using metformin. Importantly, metformin demonstrates reasonably good tolerability and relative safety of use.

Interestingly, new lines of research indicate the possibility of using metformin as topical therapy. In summary, metformin may represent a valuable therapeutic option for a selected group of patients with psoriasis. However, due to the limited number of high-quality clinical trials, further well-designed randomized, placebo-controlled trials involving large groups of patients with different disease phenotypes, especially those without comorbid diabetes, are needed to clearly define the efficacy, safety, and precise role of metformin in a psoriasis treatment strategy. It is also essential to identify the most effective dosage of the drug and assess its impact across different severity levels of the disease.

Disclosure

Author's contributions:

Conceptualization: KK, AEF, PSK;

Methodology: KK, AEF, PSK;

Software: PMD, TKK;

Check: AS, MB, ND, MS, WK;

Formal analysis: KK, AEF;

Investigation: KK, AEF, PSK, PMD;

Resources: KK, AS, MB;

Data curation: KK, AEF, PMD, TKK, AS, MB, ND, MS, WK, PSK;

Writing - rough preparation: KK, ND, MS, WK;

Writing - review and editing: KK, AEF, PSK, PMD, MS, WK;

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