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Evaluation of Antipsoriatic Effect of Ivermectin in Animal model of Psoriasis

Ahmed Salim Mahmood[*,1], Zeena Ayad Hussein[2] and Nabaa Mohammed Ibrahim[3]

[1]College of Pharmacy, Al-Ameen University College, Baghdad, Iraq.
[2]Department of Pharmacology, College of Medicine, Al-Nahrain University, Baghdad, Iraq.
[3]Department of Pharmacognosy, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
***Corresponding author**
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Abstract

Ivermectin (IVR) is widely used for the treatment of onchocerciasis and other nematode infections. Recent studies have reported that IVR has an anti-inflammatory effect and is used in the treatment of allergic asthma, dermatitis, and arthritis. Psoriasis is a chronic immune-mediated inflammatory skin disease in which IL-17 and VEGF play an important role as pro-inflammatory and angiogenic mediators. To evaluate the therapeutic effect of IVR in psoriasis, an imiquimod (IMQ)-induced psoriasis model in rats was used. Twenty-four male Wister-albino rats, aged 3-4 months and weighing 170-200 g were used in this study. They were assigned at random into four groups, each group including 6 animals. Rats in each group (except normal control group) were topically administered 62.5 mg of IMQ cream for 10 days, then they were treated for 12 days with one of the following drugs starting from day four after first application of IMQ cream: the first group treated with subcutaneous (SC) injection of normal saline once daily and consider as psoriasis model group; the second one is Methotrexate (MTX) treated group using conventional dose in autoimmune disease (1.0 mg/kg/week, intraperitoneal injection); and last group is IVR treated group (0.5 mg/kg/day, SC injection). Subcutaneous administration of IVR and intraperitoneal administration of MTX to the rats significantly minimized the Psoriasis Area Severity Index (PASI) regarding the thickness, scaling, and erythema (3.00 ± 2.19), (3.5 ±1.87) respectively compared to the psoriasis model group (6.83 ± 1.16) with p-value < 0.05. Furthermore, IVR attenuates the histopathological changes of skin lesions with no significant differences compared to MTX treated group. In addition to that, the level of IL-17 and VEGF in psoriatic skin lesions were significantly reduced by IVR and MTX compared to the psoriasis model group ($p < 0.05$), suggesting the ability of IVR in the alleviation of psoriasis by interfering with effects of these two cytokines (IL-17 and VEGF) on the pathogenesis of psoriasis.

Keywords: Imiguimod-Induced Psoriasis, Ivermectin, Methotrexate, Psoriasis Area Severity Index, And Psoriasis.

Introduction

Around 125 million individuals worldwide are affected by psoriasis, a prevalent chronic inflammatory disease with incidence rates of 0.3% to 0.6% in various racial groups[(1)]. The scientific basis of psoriasis has been revealed, and it is now known to be an autoimmune disease with serious health consequences that go beyond the skin[(2)]. The cutaneous psoriasis signs can be treated with a variety of topical and systemic medications. The selection of treatment modalities is based on the severity of the condition, any pertinent comorbidities, patient preference (including cost and convenience), effectiveness, and assessment of the specific patient response [(3)]. The risk of undertreating psoriasis, which could result in insufficient clinical improvement and patient unhappiness, must be considered against the importance of pharmaceutical safety in the treatment selection[(4)]. Many medical professionals still view methotrexate as the primary therapy option for generalized plaque psoriasis due to its effectiveness, affordability, ease of administration, and effectiveness in treating psoriatic arthritis. It is a folic acid derivative that primarily inhibits the dihydrofolate reductase enzyme, inhibiting the proliferation of immune cells and keratinocytes[(5)]. However, the use of MTX for treating psoriasis patients in routine care was linked to a greater incidence of anemia and hepatotoxic side effects[(6)]. Accordingly, the seeking of new drugs with a wide margin of safety continues to eradicate this disease with high efficacy and minimum side effects. Ivermectin was first used in humans in 1978 to treat onchocerciasis, which causes river blindness. Nowadays approved by the FDA for the treatment of a variety of nematoid infections such as Ascariasis, Filariasis, and Cutaneous larva migrants [(7)]. In 2010 , an interesting article was published

exploring the anti-inflammatory effects of ivermectin of which IVR is a member. The study demonstrated the ability of this drug to reduce the nuclear transcription factor Kappa-B and mitogen-activated protein kinase activation pathway [8]. Further studies evaluate the anti-inflammatory effect of IVR both in vivo and in vitro by down-regulating the production of tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1) and interleukin-6 (IL-6), and suppression the mucus hypersecretion in respiratory bronchi through a marked reduction in the recruitment of immune cells and cytokines' release with IgE/IgG1 in bronchoalveolar lavage [9;10]. In the development of psoriasis, the immunologic cascade mediated by the interleukin-17 (IL_17) pathway is very significant. In plaque psoriasis, the IL-17 effectors (IL-17A, IL-17C, IL-17E, and IL17F) induce epidermal hyperplasia and the pro-inflammatory feed-forward loop by acting on keratinocytes, endothelial cells, and immune cells [11]. The role of vascular endothelial growth factor (VEGF) in the pathogenesis of psoriasis has been studied by researchers. The VEGF-A transgenic mice exhibit human psoriasis-like skin lesions by the time they are six months old, indicating that persistent exposure to high levels of VEGF-A is necessary for the emergence of psoriasis-like lesions. Epidermal hyperplasia, parakeratosis, and a moderate rete ridge development in the ear skin are features of these lesions. The binding of VEGF-A to VEGFR-2 in blood vascular endothelial cells leads to the activation of a network of downstream signaling pathways that mediate angiogenesis [12; 13]. This research was constructed to evaluate the efficacy of this IVR in attenuating the severity of psoriasis and minimizing the clinical signs of psoriatic lesions.

Materials and Methods

Methods and protocols for induction of psoriasis in rats, histopathological study, and measurement of serum IL-17 and VEGF by ELISA are available as a collection in protocols.io 10.17504/protocols.io.8epv5xn16g1b/v1.

Materials and Drugs

Ivermectin vial injection (Calier company, Spain), Imiquimod cream (Aldara, MEDA, Sweden), Methotrexate vial injection (Mylan, USA), Ketamine vial injection (Demo Dose, USA) and vial injection (Biotur company, Romania) all these drugs are diluted by Sodium Chloride 0.9% infusion bottle (pioneer co for pharmaceutical industries, Iraq). Veet cream for hair remover is used to remove the hair of rats from dorsal skin. ELISA kits for rat IL-17 and VEGF were purchased from Sunlong Biotech Co.LTD, Zhejiang, China. The drugs used in this research were purchased from local pharmacies and drug stores and the ELISA kit was purchased from the Scientific Bureau for laboratory appliances.

Experimental animals

Wister albino-male rats (age 4-5 months), weighing 170-200 g were brought from the animals' house of the National Center for Drug Control and Research in Iraq and used in this experiment. Then, for more than a week before the experiment, they were kept at the animals' house in the Pharmacy department of Al-Rasheed University College in a particular pathogen-free environment at room temperature. All the animals have matched the same age and weight. The Research Ethics Committee of the University of Baghdad/College of Pharmacy college gave its approval to the protocol employed in this research (Approval Number: RECAUBCP2022023A February 2023).

Induction of psoriatic-like lesion model in rat

To create an IMQ-induced psoriasis model, rat (8–10 weeks old) had their dorsal hair removed at a surface area of about 4 × 5 cm by shaving using an electric hair shaver, while depilatory Veet cream was used to remove the remaining hairs one day before used IMQ cream. The rats were then treated daily with 62.5 mg of topical 5% IMQ cream for 10 days [14].

Experimental design

The following groups of rats were assigned at random into four groups (each group including 6 rats) depending on a dice method in randomization. Rats in each group (except normal control group) were topically administered 62.5 mg of IMQ cream for 10 days, then they were treated for 12 days with one of the following drugs starting from day four after the first application of IMQ cream: the first group treated with SC injection of normal saline (5 ml/kg) once daily and consider as psoriasis model group; the second group is MTX treated group using conventional dose in autoimmune disease (1.0 mg/kg/week, intraperitoneal injection); as previously published [15] and last group is IVR treated group (0.5 mg/kg/day, SC injection) as approved by a previous study [16]. Severity was scored using the Psoriasis Area Severity Index (PASI) depending on assessments of thickness, scaling, and erythema [17]. The measurement system included no symptoms (0), mild (1), moderate (2), severe (3), or very severe (4). Throughout the experiment, the body weight changes of rats were recorded on the 1st, 5th, 10th, and 15th days. Weighing took place at noon hr in the light period using an electronic balance (Movel, Shanghai). At the end of the experiment (day 15) all animals were sacrificed using a high dose of intramuscular injection of Ketamine (300mg/kg) and Xylazine (30 mg/kg) cocktail [18]. Skin samples from the back lesions of each mouse have been collected and divided into two pieces. One piece was used for

histopathological analysis, and the second piece of skin sample was stored in the refrigerator (-20 °C) to be used for biochemical analysis of cytokines levels in the skin tissue homogenate.

Histopathological examination

The skin tissues from the back were preserved in a 4% paraformaldehyde solution and embedded in blocks of paraffin. Hematoxylin and eosin (H/E) were used to stain the materials, which were divided into sections that were 5 µm thick [19]. To assess the histological alterations in skin lesions, an automated microscope (Lionheart FX) was utilized by a professional pathologist.

Enzyme-linked Immunosorbent Assay (ELISA)

A tissue extraction reagent (FNN0071, Bender MedSystems GmbH, Vienna, Austria) was used to lyse skin samples. After centrifuging the samples at 10,000 g for 20 min, the supernatant was collected. Quantitative sandwich-type enzyme-linked immunosorbent assay (ELISA) kits were used to measure the levels of IL-17 and VEGF in skin tissue lysates following the manufacturer's instructions (Cloud-Clone Corp, USA). Briefly, the microtiter well plates are pre-coated with particular antibodies that correlate to each antigen being tested in the kit. The lysate sample is introduced into the wells and allowed to incubate for one hour to facilitate the antigen-antibody interaction. Subsequently, the plate is rinsed with phosphate buffer to eliminate any unbound substances present in the sample. Next, an abundance of biotinylate antibodies, which specifically target the antigen being assessed, is introduced to interact with the antigen that has been immobilized on the wells. This interaction is allowed to occur for one hour, after which the well is thoroughly rinsed. After that, streptavidin-horseradish peroxidase (HRP) is introduced to attach to the biotinylate antibody and allowed to incubate. Subsequently, the wells are rinsed to eliminate any unbound streptavidin-HRP. Next, the substrate solution is introduced, resulting in the manifestation of color as a consequence of the reaction facilitated by the conjugated enzyme. The color's intensity is directly proportionate to the antigen's concentration. Subsequently, an acidic stopping solution is introduced into the well then, and the absorbance was determined at 450–550 nm using a microplate reader (Tecan, Männedorf, Switzerland).

Statistical analysis

Initially, all the data for all parameters were examined for normality of distribution. A descriptive analysis of body weight changes, laboratory analysis, and morphological changes of the lesion was calculated (mean, standard deviation (SD)). Comparative analysis was performed between animal groups using a one-way ANOVA post hoc test for normally distributed data and a non-parametric test (Mann-Whitney test) for non-normally distributed one. All analysis was performed depending on IBM SPSS statistical program version 20. A two-sided p-value < 0.05 was considered statistically significant. On the other hand, GraphPad Prism software was used in the presentation of graphs.

Results

Effects of IVR on the severity of skin inflammation

A grading system called the PASI is used to assess the severity of psoriasis. It evaluates the thickness, scaling, erythema (redness), and extent of psoriatic lesions on the dorsal body of the rat's skin areas. The index helps to assess therapy efficacy and track the development of the disease. Scores from the treatment groups are illustrated in Figure 1 (A-D). As presented in Figure. 1 (D), on the last day of evaluation (Day 15), the condition with the highest total PASI score was with psoriasis model group (6.83 ± 1.16), followed by rats treated with IVR (3.00 ± 2.19), MTX (3.5 ± 1.87) and finally, normal control group rat (0 ± 0) with significant differences between treatment group and psoriasis model group (p-value < 0.05). Furthermore, the exposed area demonstrated erythema, scaling, and thickened layers of skin during the first few days. However, treatment with MTX and IVR attenuated the skin lesions on the exposed area and also attenuated the level of skin thickness, scaling, and erythema with significant differences between the treatment groups and the positive control group (p-value < 0.05).

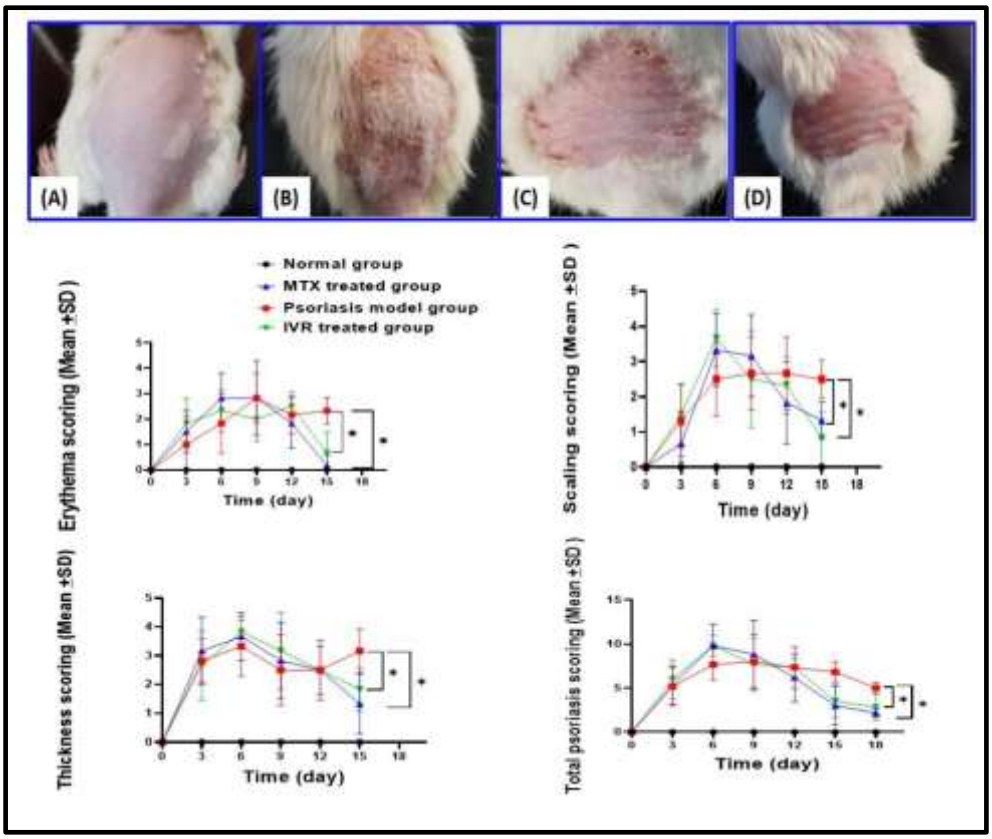

Figure 1. Effect of IVR on PASI in IMQ-induced in rat. Gross section of a skin lesion for the normal control group (A); psoriasis model group (B); MTX-treated group (C) and IVR-treated group (D). The figure also includes line graphs of PASI for erythema, scaling, thickness, and total psoriasis scoring. Data are expressed as means ± SD (n= 6 per group). * P < 0.05 versus the psoriasis model group.*Microscopical*

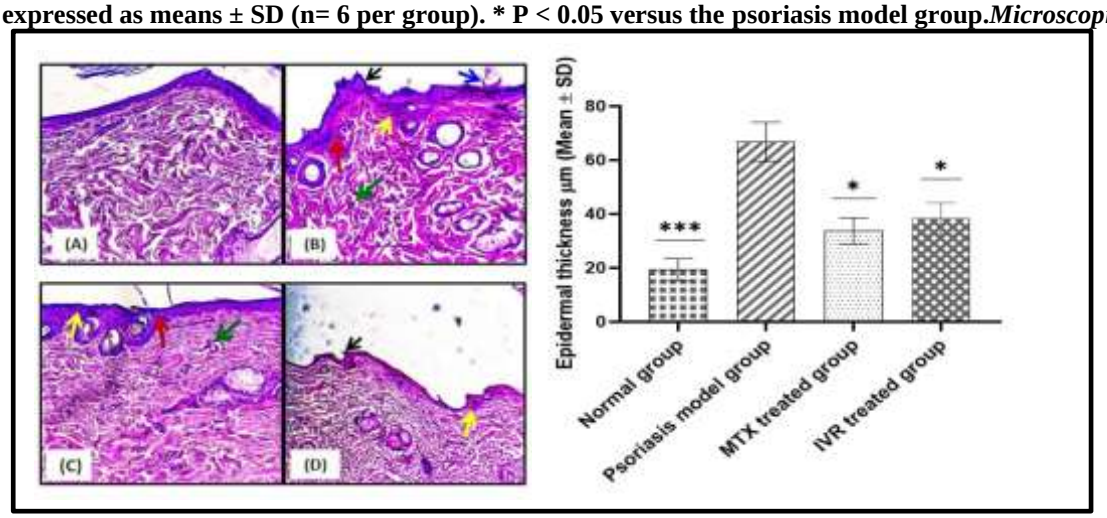

Figure 2. Skin section from rat back skin: normal control (A), psoriasis model group (B), MTX treated group (C), and IVR treated groups (D). The psoriasis model group illustrates hyperkeratosis (blue arrow), acanthosis (black arrow), epidermal hyperplasia (red arrow), Munro micro-abscess (yellow arrow) associated with thickening of the epidermis overlying the dermal papillae layer and dilated blood vessel (green arrow) (H&E) 40X. The bar chart represents the microscopical differences in the epidermal thickness between experimental groups. The normal control group shows the normal architecture of the dermis, epidermis, and stratum corneum. MTX and IVR treated groups show miner changes compared to the psoriasis model group.

Effect of Ivermectin on inflammatory cytokines and expression of proliferation markers

The main cytokines that play a role in skin inflammation and epidermal hyperplasia are IL-17 and VEGF [11; 12]. Accordingly, these parameters were measured in the skin lesions of all groups and we found that the levels of IL-17 and VEGF were significantly increased in the psoriasis model group induced by IMQ ($p < 0.05$). ELISA analysis also demonstrated a significant reduction in IL-17 and VEGF in psoriatic lesions taken from rats that were treated with IVR or MTX compared to the untreated psoriatic group ($p < 0.05$) (Figure. 3).

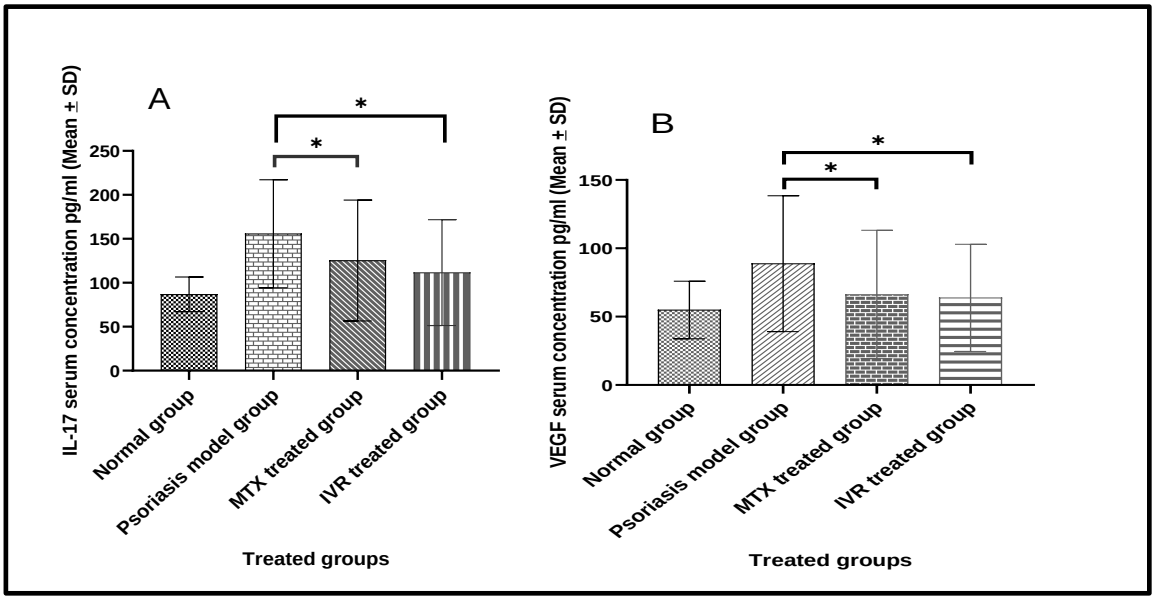

Figure 3. Effect of IVR treatment on the level of IL-17 (A) and VEGF (B) in skin specimens. The data represent a means ± SD (n= 6 per group). * P < 0.05 regarding normal control versus the model group.

Effect of Ivermectin on Body Weight Changes

After the first application of IMQ on the dorsal rat's skin, a slight reduction of body weight has been observed in all treated groups. However, with subsequent application of the IMQ cream and as soon treatment started, the body weight continued to increase in all treated groups except those treated with MTX (figure. 4). At the end of the experiment the non-parametric statistical analysis showed no significant changes in the body weight of the psoriasis model group and IVR treated group (182.33 ± 66.02, 214.50 ± 55.45 respectively) compared to the normal control group (264.67 ± 61.72) with p-value > 0.05. On the other hand, MTX treated group showed a significant reduction in body weight at the end of the experiment (171.67 ± 54.44) when compared with the normal control group with p value < 0.05.

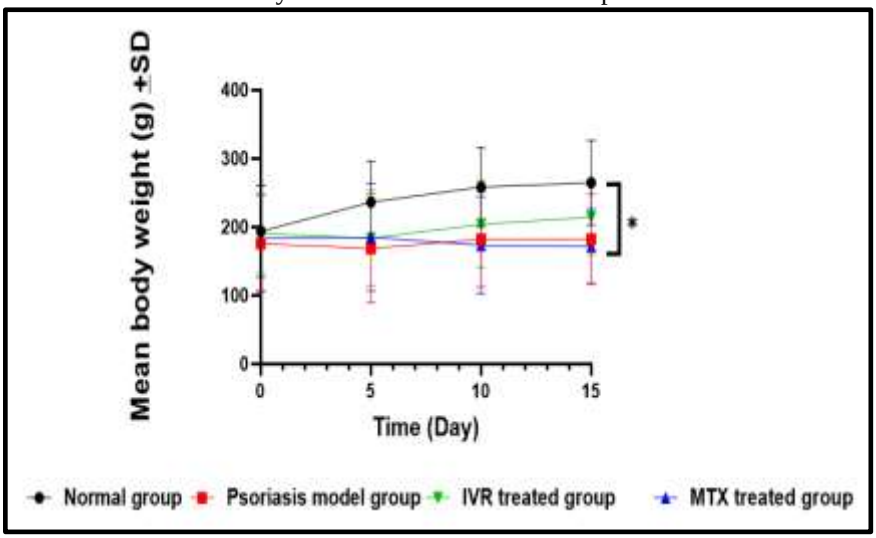

Figure 4. Body weight changes during the experimental period. The result represents a Mean ± SD and p < 0.05 considering a significant reduction in the body weight compared to the normal control group.

Discussion

Recently, the anti-inflammatory effect of IVR has been studied by many researchers to be used in the treatment of many diseases like allergic asthma, atopic dermatitis, and arthritis [10; 20; 21]. Schaller and his colleague have shown that topical application of 1% IVR has an anti-inflammatory effect when used in papulopustular rosacea. The underlying mechanism behind this topical anti-inflammatory effect of IVR may be attributed to the reduction in IL-8, LL-37, HBD3, TLR4, and TNF-α [22]. However, the efficacy of this drug in the treatment of psoriasis is still not explored. This study aimed to evaluate the anti-psoriatic effect of IVR in IMQ-induced psoriasis in rats. The typical clinical features involved in scoring the severity of psoriasis are erythema, scaling, infiltration, and extent of body surface area [23]. Subcutaneous injection of IVR significantly improves the prognosis of psoriasis in the induced model and lowers the erythema, scaling, and thickness of the skin lesion which sheds light on the effectiveness of this medicinal drug in the treatment of this disease. Generally, psoriasis is characterized by persistent inflammation that triggers unchecked keratinocyte growth and defective differentiation. The inflammatory infiltrates of dermal dendritic cells, macrophages, T lymphocytes, and neutrophils are visible on the histology of the psoriatic plaque and are overlaid by acanthosis (epidermal hyperplasia) [24]. Another noticeable characteristic is neovascularization which is also seen under a light microscope of psoriatic lesions [25]. The results of this study demonstrated the ability of the IVR to minimize the pathological changes induced by IMQ. Studies on human psoriatic lesions reveal that IL-17 and IL-23 play a part in the development of psoriasis. IL-23 released by dendritic cells in the dermis of psoriasis patients causes CD4+ T cells to produce IL-17 [26; 27; 28]. IL-17 directly affects keratinocytes, causing them to multiply and produce cytokines, chemokines, and antimicrobial peptides associated with psoriasis. The positive feedback loop is stimulated by factors secreted by the keratinocytes, which also encourage the growth of more inflammatory and IL-17-producing cells [29]. Although IMQ causes a marked elevation in IL-17 in skin specimens, IVR treatment reduces this cytokine significantly. Numerous studies have looked at the involvement of VEGF in psoriasis and found that elevated levels of this protein in the serum and tissues were connected with the severity of the condition [30; 31; 32]. Recent research suggests that VEGF modulates keratinocyte differentiation in addition to angiogenesis [33]. Additionally, there has been talk of a connection between psoriasis and associated comorbidities and vascular endothelial growth factors [34]. In the present study, IVR caused a significant reduction in VEGF suggesting the important role of IVR in attenuating the pathogenic pathway of psoriasis. The IL-23/IL-17 axis, which primarily depends on Th17-cell function, is thought to be the most important mechanism of psoriasis, as demonstrated by the exceptional success of molecularly targeted therapy [35]. In addition to that, researchers have shown that S100A7 (psoriasin) acts as a chemoattractant for lymphocytes, granulocytes, and macrophages, forming an inflammatory loop. Proinflammatory cytokines deeply involved in the pathogenesis of psoriasis, such as IL-36, IL-17, and TNF, can independently and synergistically induce S100A7 expression in epidermal keratinocytes [36]. Although the anti-inflammatory effect of IVR is not fully understood, the anti-psoriatic effect of this drug may be related to the targeting of TNF-alpha, IL-1, and IL-6 [8]. The limitation of this study is a small sample size, using a conventional dose of IVR and measurement of fewer cytokines involved in the pathogenesis of psoriasis. Therefore, clinical and experimental studies will pay close attention to explaining the underlying molecular mechanism of IVR in the treatment of psoriasis.

Conclusion

This experimental research study demonstrates that the IVR alleviates IMO-induced psoriasis in rats by minimizing the PSAI and changing the histopathological alterations exerted by IMQ. Furthermore, IVR reduces the IL-17 and VEGF in skin lesions significantly.

Acknowledgment

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Conflicts of Interest

The study's authors affirm that there were no financial or commercial ties that might be viewed as having a potential conflict of interest.

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Ethics Statements

The Research Ethics Committee of the University of Baghdad/College of Pharmacy gave its approval to the protocol employed in this research (Approval Number: RECAUBCP2022023A February 2023).

Author Contribution

Ahmed Salim Mahmood performed experiments, analyzed data, and wrote the paper. Zena experimented, prepared the images designed, and conducted the research. Nabaa M. Ibrahim drafted the manuscript and admitted technique material support.

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تقييم فعالية الأيفرمكتين كمضاد للصدفية في التجارب المصممة لأحداث الصدفية في الحيوانات

أحمد سالم محمود[١]، زينه أياد حسين[٢] ونبأ محمد ابراهيم[٣]

[١]قسم الصيدلة، كلية الرشيد الجامعة، بغداد، العراق.

[٢] قسم الفارماكولوجي، كليه الطب، جامعة النهرين، بغداد، العراق.

[٣]اقسم العقاقير والنباتات الطبية، كلية الصيدلة، جامعة بغداد، بغداد، العراق.

الخلاصة

يستخدم الأيفرمكتين على نطاق واسع لعلاج داء كلابية الذنب وغيرها من انواع عدوى الديدان الخيطية. وقد وثقت الدراسات الحديثة ان الأيفرمكتين له تأثير مضاد للالتهابات وقد استخدم مختبريا في علاج الربو التحسسي والتهاب الجلد والتهاب المفاصل. يعتبر مرض الصدفية من الأمراض المناعية التي تسبب التهاب مزمن في الجلد، حيث يلعب كل من الإنترلوكين -١٧ وعامل النمو البطاني الوعائي دورا مهما في عمليه تطور الالتهاب ونشوء الأوعية الدموية. ولتقييم فعالية الأيفرمكتين في علاج مرض الصدفية تم استخدام نموذج احداث الصدفية الناجم عن عقار الايمكومود في الجرذان. حيث تم استخدام اربعه وعشرون ذكرا من الجرذان نوع ويستر البينو بأعمار ٣-٤ أشهر وكانت بأوزان ١٧٠-٢٠٠ غرام وقد تم تقسيمها عشوائيا الى أربع مجاميع، كل مجموعه تضم ٦ جرذان. تم معالجه الجرذان في كل مجموعه (عدا مجموعة التحكم السالبة) ب ٦٢,٥ ملغم من كريم الايمكومود موضعيا على الجلد لمدة عشرة ايام , وقد تم علاجهم لمدة ١٢ يوم بأحد الأدوية التالية ابتدأ من اليوم الرابع بعد أول استخدام لكريم الايمكومود: المجموعة الاولى تم علاجهم بالحقن تحت الجلد بمحلول ملحي متعادل مره واحده يوميا واعتبارهم مجموعه النموذج للصدفية , المجموعة الثانية هي المجموعة المعالجة بالمثوتريكسيت باستخدام الجرعة التقليدية في امراض المناعة الذاتية (٠,١ ملغم/ كغم/اسبوع تحقن داخل الصفاق) ،والمجموعة الأخيرة هي المجموعة المعالجة بالأيفرمكتين بجرعه (٠,٥ ملغم/كغم/يوم، حقن تحت الجلد). أثبتت النتائج إن إعطاء الأيفرمكتين تحت الجلد أو المثوتريكسيت في كيس الصفاق للجرذان يقلل بشكل كبير احصائيا من مؤشر خطورة منطقة الصدفية فيما يتعلق بالسمك والتقشير والاحمرار (٣,٠٠ ± ٢,١٩)، (3.5 ±1.87) على التوالي مقارنة بمجموعة النموذج للصدفية (٦,٨٣ ± ١,١٦) وبتأثير احصائي بقيمة p <٠,٠٥. علاوة على ذلك، فإن الأيفرمكتين يخفف من التغيرات النسيجية المرضية للجلد مع عدم وجود فروق ذات دلالة إحصائية مقارنة بالمجموعة المعالجة والمثوتريكسيت. بالإضافة إلى ذلك، انخفض مستوى [1]الإنترلوكين -١٧ وعامل النمو البطاني الوعائي في عينه الجلد المصاب بالصدفية بشكل ملحوظ بواسطة الأيفرمكتين والمثوتريكسيت مقارنة بمجموعة النموذج للصدفية (P <٠,٠٥)، مما يشير إلى قدرة دواء الأيفرمكتين في تخفيف الصدفية عن طريق التعارض مع تأثير كل من الإنترلوكين -١٧ وعامل النمو البطاني الوعائي على عمليه تكوين مرض الصدفية.

الكلمات المفتاحية: صدفية محدثه بالايمكويمود، ايفرمكتين، مثوتريكسيت، مؤشر خطورة منطقة الصدفية، الصدفية.