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Effects of Topical Myricetin on Imiquimod Induced Psoriasis in Mice Model

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Abstract

Background Psoriasis is a protracting disorder of the skin that is immune mediated with a prolapsing characteristic making it difficult to fully treat.

Objective To investigate the effect of Myricetin in Imiquimod induced-psoriasis in mouse model and its possible therapeutic effect.

Methods Twnety-eight albino mice were randomly divided into 3 groups, 1st group involved healthy mice did not receive any medication, 2nd group (induction group) received only topical Imiquimod, and the 3rd group involved mice that received a topical Myricetin 10% ointment. All the mice received the test substances on the shaved back for 7 consecutive days and scoring for skin inflammation severity (scaling, erythema and thickness) was recorded on daily basis, and the animals were sacrificed on day 15. Skin samples were collected to evaluate the histopathological scores (Baker's and Psoriasis area and severity index (PASI), in addition to measurement of tissue inflammatory biomarkers Interleukin (IL)-10, IL-17, tumor necrosis factor- alpha (TNF-α) and vascular endothelial growth factor (VEGF) by enzyme-linked immunosorbent assay (ELISA).

Results Psoriasis induction was successful by Imiquimod, and psoriasis like lesions developed on the skin and decreased the IL-10 and increased levels of other studied biomarkers. Topical Myricetin showed a significant increase in IL-10 levels ($P < 0.001$) and a significant reduction in TNF-α ($P < 0.001$), VEGF ($P < 0.05$) and IL-17 levels ($P < 0.001$). There was also a significant reduction in Baker's score and PASI.

Conclusion Topical Myricetin possesses anti-psoriasis activity and could be used successfully for the alleviation of psoriatic symptoms and further studies of the skin inflammatory diseases.

Keywords Myricetin, Imiquimod, interleukin-10, interleukin-17, tumor necrosis factor-alpha, vascular endothelial growth factor

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List of abbreviations: H&E = Hematoxylin and Eosin (stain), IKK = Inhibitor-κB kinase, IL = Interleukin, IMQ = Imiquimod, MAPK = Mitogen-activated protein kinase, MMPs = Matrix metalloproteinases, PASI = Psoriasis Area and Severity Index, PDE = Phosphodiesterase, PI3K/Akt = Phosphoinositide 3-kinase/Protein kinase B, TIMPs = Tissue inhibitors of metalloproteinases, TNF-α = Tumor necrosis factor-alpha, NF-κB = Nuclear factor kappa-B, VEGF = Vascular endothelial growth factor

Introduction

Psoriasis is a chronic immune-mediated inflammatory disease that affects 2-4% of the world's population [1,2]. Psoriasis is described by sharply defined scaly, red, coin-sized skin lesions mostly on the elbows, knees, scalp, hands and feet, with other symptoms that consist of itching, irritation, stinging and pain. Rarely, all the skin surface of the body can be involved. The skin lesions in psoriasis

patient can have different symptoms according to the type of psoriasis; they are mostly described by having red scaly irritated skin patches, which sometimes can affect the whole body [(3)]. The histopathological features of psoriasis that can be seen by microscopic examination are: hyperkeratosis, parakeratosis, thickening of the spinous layer, capillary dilatation and hyperemia, and peripheral inflammatory cell infiltration [(4)].

There are many treatment options for psoriasis but none are curative; the available therapies for now are only symptomatic. Treatment options are based on the type of psoriasis and its severity and if a patient doesn't respond to topical therapy, systemic therapy is initiated. The choice of medication depends on the patient's general health, comorbidities, age, form and severity and most of the drugs, especially the new drugs, need close monitoring for the potential adverse effects [(5)]. All of which have many adverse effects, hence, there is a continuing need for researching new psoriasis medications, and hence, the investigation was begun on Myricetin for its possible anti-psoriatic effects.

Myricetin (3,3',4',5,5',7-hexahydroxyflavone) is one of the flavonoid classes of polyphenolic compounds (Figure 1) that have antioxidant properties and many effects on the benefit of human health. It's largely present in nature in berries, vegetables, and fruits, in the form of glycosides and it is structurally similar to quercetin [(6)]. It has many strong biological effects, such as anti-inflammatory, antioxidant, anti-hypertensive, analgesic, anti-allergic, and immunomodulatory function [(7)]. Therefore, it is implicated in many conditions like anticancer, anti-inflammatory and antidiabetic activities. And it also shows many actions related to the health of the central nervous system and many studies suggested that the compound may be valuable to protect against diseases such as Alzheimer's and Parkinson's disease [(8)].

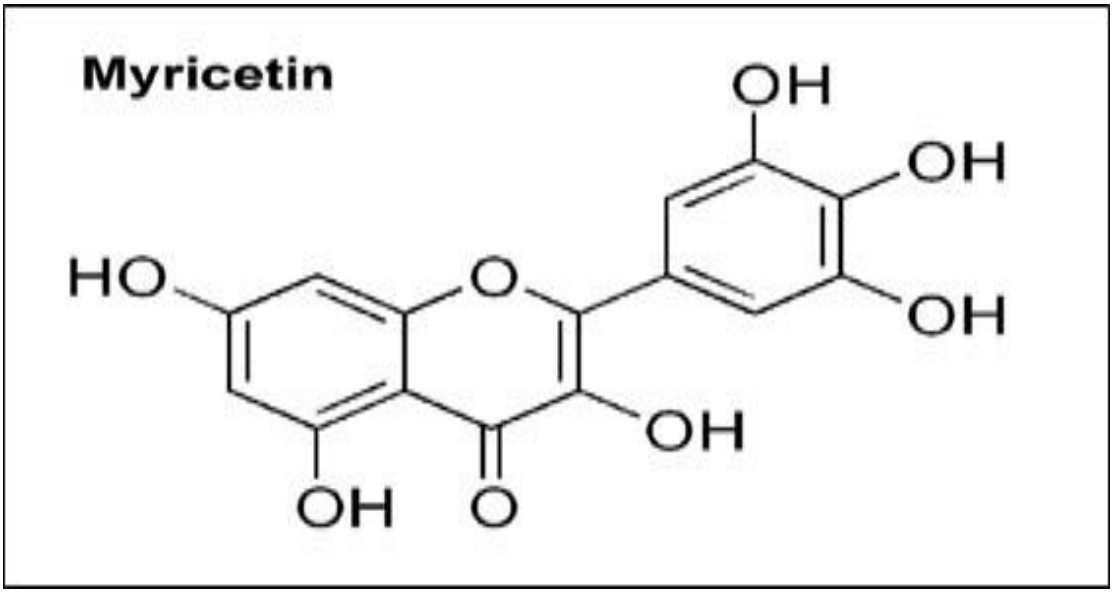

Figure 1. Chemical structure of Myricetin

This study aimed to investigate the effect of Myricetin in Imiquimod induced-psoriasis in mice model and its possible therapeutic effect by measuring the levels of interleukin (IL)-10, IL-17, tumor necrotic factor alpha (TNF-α) and vascular induthelial growth factor (VEGF) with

a histopathologic investigation in comparison and combination with Clobetasol.

Methods

Myricetin powder was purchased from Hangzhou Hyper Chemicals from China, batch no. P1416800. Imiquimod cream 5% by MEDA Pharmaceuticals was used for induction of psoriasis and it was purchased commercially in Iraq, and Clobetasol ointment was also obtained commercially from Iraq as (Dermovet 0.05%) by GSK Pharmaceuticals.

Pharmaceutical preparation

Preparation of Myricetin

The preparation of the used ointments occurred via the method of fusion according to the Xu et al. based on British Pharmacopoeia [9]. The concentration of the Myricetin (10%) is selected in this study based upon the earlier studies of the similar compounds [10], as well as the previous biological activities of this compound itself [11].

The formula is prepared by adding 2.5 g of Myricetin powder is used to prepare 10% (w/w) ointment; the 2.5 g of Myricetin powder were mixed with 22.5 g of petrolatum that was previously melted in a beaker on a water bath at 75°C in a separate container [12].

Experimental animals

The study is conducted in Biotechnology Center, Al-Nahrain University in Baghdad in December 2022 after gaining the approval of the Iraqi Board Review (IRB) of Al-Nahrain University, College of Medicine.

Twenty-eight albino mice in the age range between (2-3) months with an average weight of 30±2 g randomly divided into three groups (n=10) as follows:

- Group 1 (healthy) did not receive anything.
- Group 2 (induced) received only topical Imiquimod (IMQ).
- Group 3 received a topical Myricetin 10% ointment

Mice were kept in a room with controlled conditions of 25°C and 12 hr light/night cycle and were given free access to food and water. The mice back were all shaved and all (except for the normal control group) were applied Imiquimod 5% cream daily for 6 consecutive days [13].

Scoring inflammation severity of the skin

The inflammatory signs and the severity were recorded according to the Psoriasis Area and Severity Index (PASI) scoring system [14]. Scaling, erythema and thickness of the skin were scored on a scale from 0 to 4 (0 = none; 1 = slight; 2 = moderate; 3 = marked and 4 = very marked) and the total cumulative score indicates the severity of inflammation (on a scale from 0 to 12).

The histopathological skin changes were recorded according to the Bakers Scoring System for assessing epidermal thickness, hyperkeratosis, parakeratosis, Munro abscess, acanthosis, papillary congestion and lymphocytic infiltrate on a scale ranging from 0 to 10 [15].

Analytical procedure and measurement of tissue biomarkers level in the skin

To evaluate the levels of these cytokines in the mice skin, enzyme-linked immunosorbent assay (ELISA) kits were used as according to the manufacturer guidelines (Cloud-Clone Corp.) and the absorbance was read at 450 nm with a microplate spectrophotometer.

Sample collection

On day 14, the animals were euthanized by ketamine plus xylazine and sacrificed by cervical decapitation, and the skin tissues were cut into two pieces the first is kept in 10% formaldehyde for further investigations After that the skin tissues were treated to get the final tissue–paraffin embedded blocks and it was divided into sections of 5 µm in thickness, then stained with hematoxylin and eosin (H&E) and observed under a light microscope [16]. The second piece was kept at -18°C and used after tissue homogenization for further analysis that include the measurement of tissue biomarkers'

levels (IL-10, IL-17, TNF-a, and VEGF) using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer guidelines (Cloud-Clone Corp.) and the absorbance was read at 450 nm with a microplate spectrophotometer. In addition, histopathological scores (Baker score) and observational score (PASI score) were calculated.

Statistical analysis

Data entry and analysis were performed using Microsoft Excel 2019 and statistical package for the social sciences (SPSS) version 26. Test of Normality (Shapiro-Wilk) for continuous variables showed that most of the data was non-normally distributed, thus non parametric tests (Mann Whitney) was used for comparison between groups, while those data that was normally distributed, unpaired ttest was used for comparison between groups. Statistical analysis of different parameters in this study was expressed as Mean±SD and Median with range. P values considered as significant when ($P < 0.05$) or highly significant when ($P < 0.001$) [17].

Results

On days 4-5 of starting the experiment, signs of psoriasis induction on mice skin such as erythema, skin thickening and scaling began to show on the skin treated with Imiquimod (group 2) and continued in the severity until the last day of induction as shown in figure (2). Then after, the mice were treated with petrolatum (group 3), topical Clobetasol (group 4), Myricetin (group 5) and combination of Myricetin with Clobetasol (group 6) as shown in figure (2), which indicates successful induction of psoriasis like dermatitis in mice and there was a significant difference between the normal group and the induced group regarding the psoriasis-like symptoms.

Scoring for skin inflammation severity

The skin of experimental mice was all observed for change during all days of experiment and scoring of skin condition was made based on the PASI scoring system. In the healthy group where nothing was applied on the skin, and there were no signs of erythema and the skin is pink and healthy and no signs of thickening or scaling appear.

While on the skin treated with Imiquimod the skin began to show an increase in redness and inflammation from day 3 and increase in severity along the days of experiment. There is also an increase in skin wrinkling and thickness and scales begin to appear as yellow spots on the skin that advance to become large flaky scales at the last day of induction.

The vehicle group showed no major changes occurred in skin after application and there was only a slight reduction in skin scaling, while there were significant changes in skin appearance when Clobetasol and Myricetin were applied. In the Clobetasol treated group there was a marked reduction in the skin erythema and the scaling of skin surface, there was also a reduction in skin thickness noted as a decrease in the skin puckering and wrinkling in the induced areas when compared to the vehicle and induced groups. This improvement continued until the last day of experiment.

In the group treated with Myricetin there was also a reduction in skin erythema, thickness and scaling that started from 2-3 days of Myricetin application when compared to the vehicle and induced groups and continued until the last day of experiment. The combination group also showed a marked reduction in skin erythema, thickness and scaling started 2-3 days upon treatment application when compared to the vehicle and induced groups and continued until the last day of experiment.

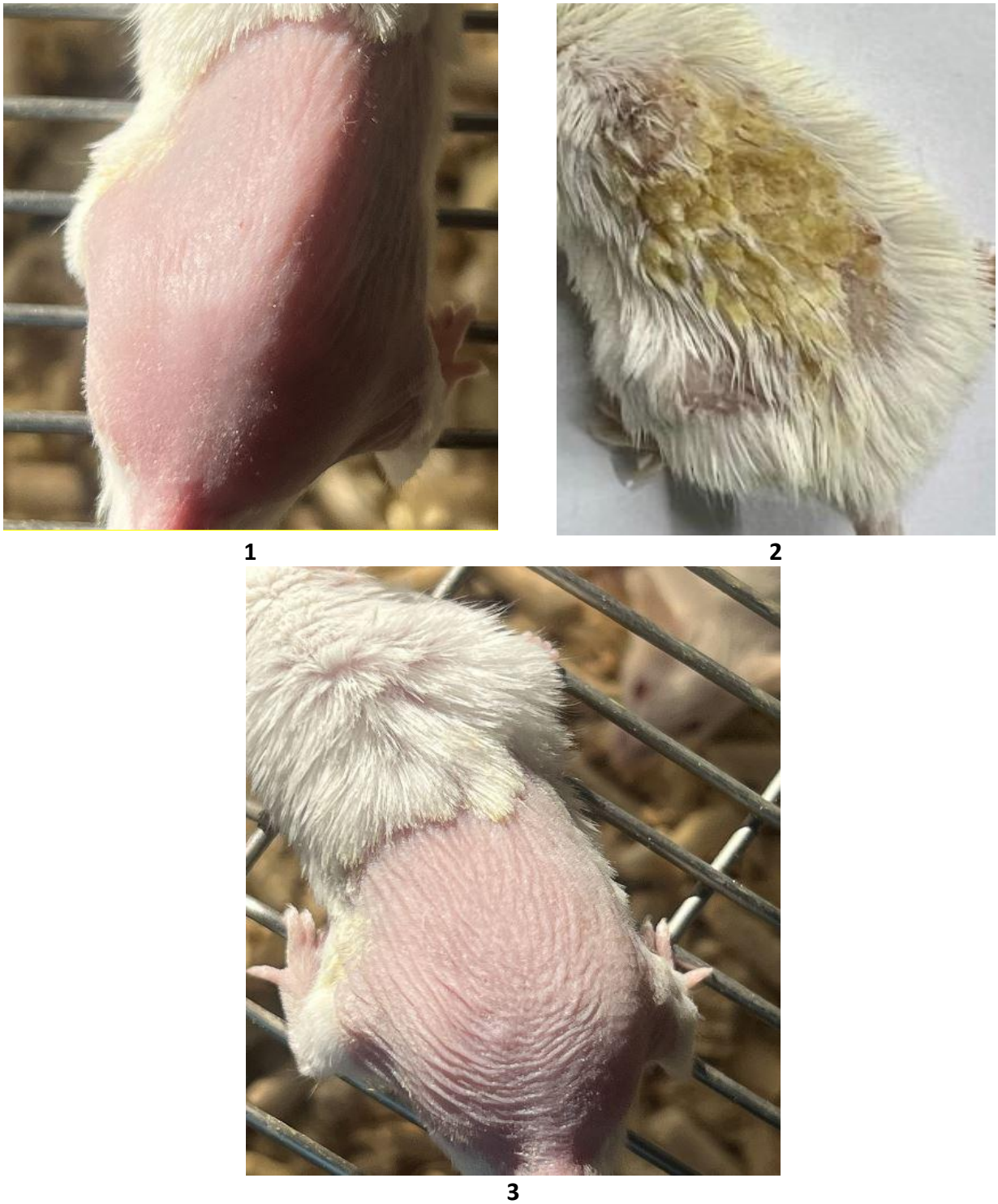

Figure 2. Scoring for skin inflammation severity, the pictures show different inflammation levels of the dorsal skin on which the test substances were applied on day 8 of the Experiment. 1. Represents the healthy group; 2. Represents the IMQ-induced group; 3. Represents the Myricetin treated group

Histopathological examination

Histopathologic skin section of healthy groups showed normal epidermal, dermal and subcutaneous tissue layer in 4X & 10X (H&E) stain (Figures 3a and b).

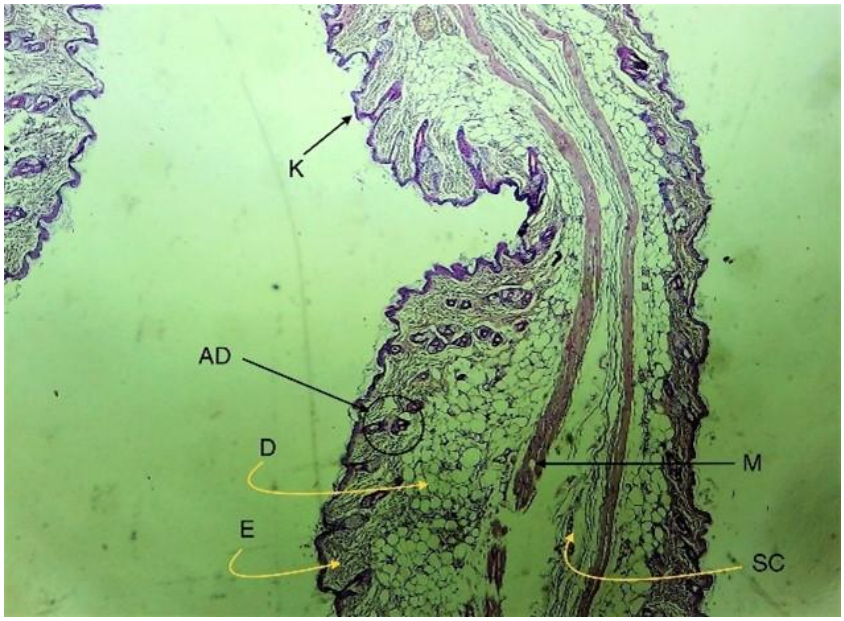

Figure 3a. Histopathological section of mice skin (healthy control group) showing normal skin architecture including: K = keratin, E = epidermis, D = dermis, AD = adnexa, SC = subcutaneous tissue, M = muscles. Bakers score = zero, H&E stain (4X)

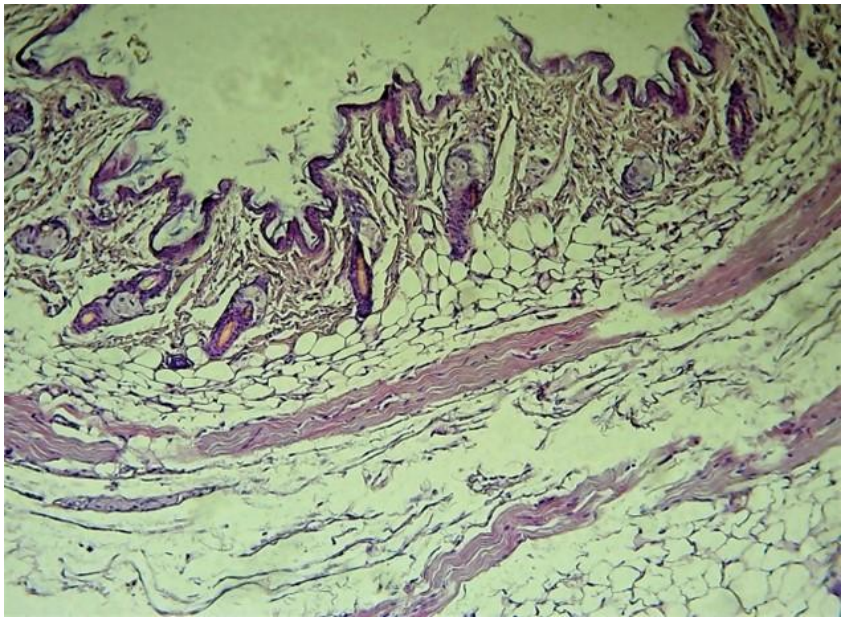

Figure 3b. Histopathological section of mice skin (healthy control group) showing normal skin architecture. Bakers score = zero. H&E stain (10X)

The histopathological skin section of induction group (Figures 4a, b and c) showed focal (wide) area of sloughing, severe dense, neutrophilic infiltration, epidermal multifocal dense neutrophilic infiltration (the Munro's abscesses) and parakeratosis, hyperkeratosis, with lack of granular layer, acanthosis, and increased rete ridges with papillary thinning. The dermis showed moderate to severe lymphocytic infiltration and vascular congestion in 4X & 10X H&E stain.

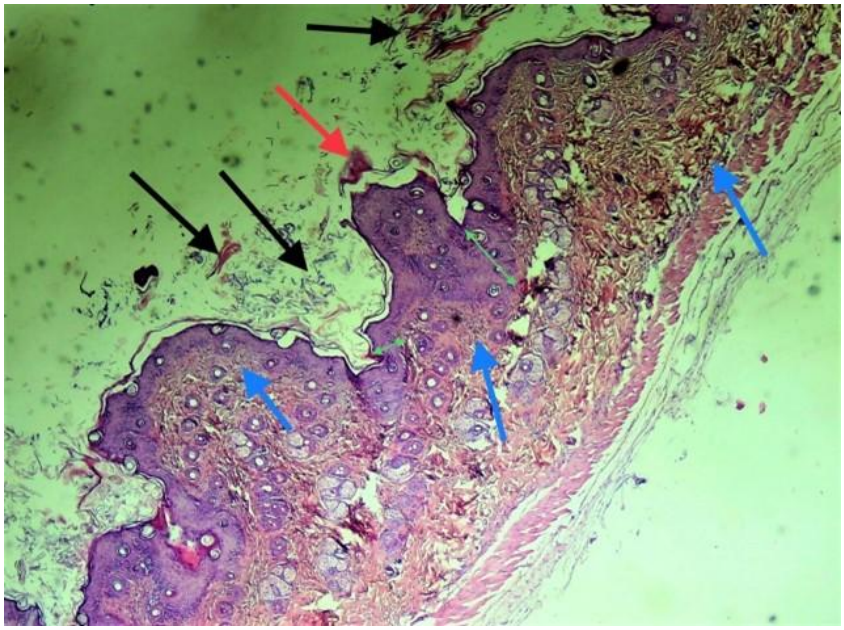

Figure 4a. Histopathological section of mice skin (induction group) showing hyperkeratosis, parakeratosis (black arrow), with multifocal dense neutrophilic infiltration (the Munro's abscess) in red arrow, with epidermal acanthosis and thinning papillae and rete ridges appearance (green arrow), and lack of granular layer. The dermis showing moderate to severe inflammatory lymphocytic infiltration (blue arrow). Bakers score = 9. H&E stain (4X)

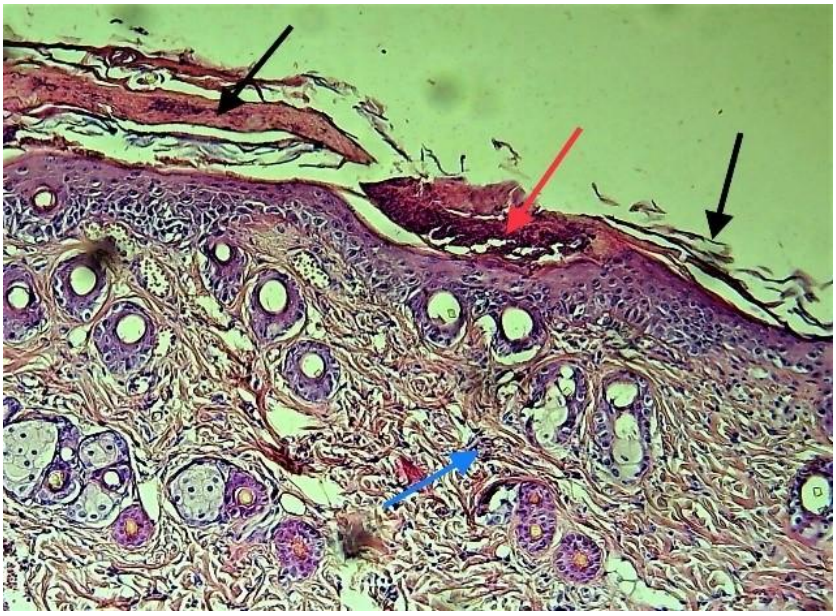

Figure 4b. Histopathological section of mice skin (induction group) showing hyperkeratosis, parakeratosis (black arrow), with multifocal dense neutrophilic infiltration (the Munro's abscess) in red arrow, with epidermal acanthosis and lack of granular layer. The dermis showing moderate to severe inflammatory lymphocytic infiltration (blue arrow). Bakers score = 9. H&E stain (10X)

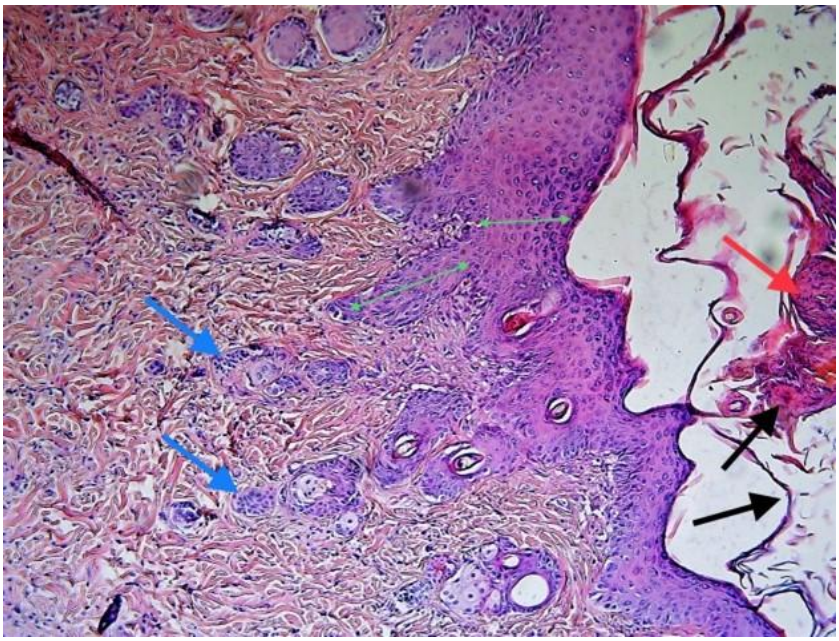

Figure 4c. Histopathological section of mice skin (induction group) showing hyperkeratosis, parakeratosis (black arrow), with multifocal dense neutrophilic infiltration (the Munro's abscess) in red arrow, with epidermal acanthosis and thinning papillae and rete ridges appearance (green arrow), and lack of granular layer. The dermis showing moderate to severe inflammatory lymphocytic infiltration (blue arrow). Bakers score = 9. H&E stain (10X)

In animals treated with Myricetin (Figure 5a and b), there was a significant reduction in the inflammatory response seen in the induced and vehicle groups and the histopathological section showed mild keratosis, absence of parakeratosis & Munro's abscess with very mild acanthosis & rete ridges. The dermis was showing mild lymphocytic infiltrate. In 4X, 10X H&E stain.

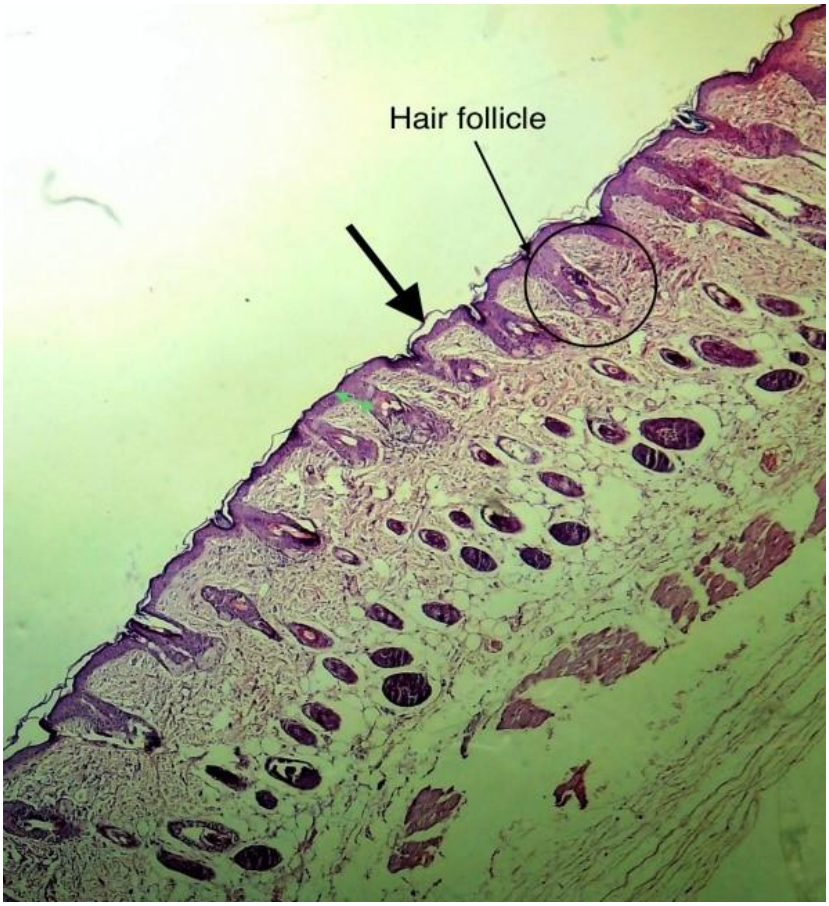

Figure 5a. Histopathological section of mice skin (Myricetin treatment group) showing mild hyperkeratosis (black arrow), absence of parakeratosis & Munro's abscess with very mild acanthosis and rete ridges (green arrow). Dermis showing mild lymphocytic infiltrate. Bakers score = 2. H&E stain (4X)

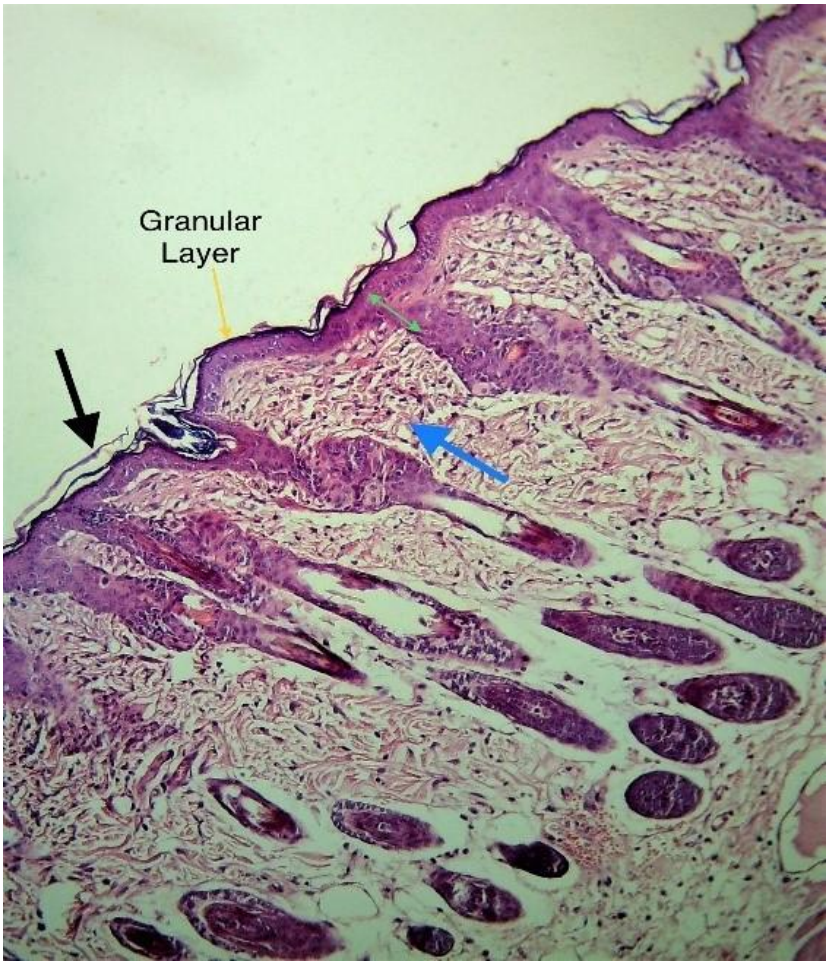

Figure 5b. Histopathological section of mice skin (Myricetin treatment group) showing mild hyperkeratosis (black arrow), absence of parakeratosis & Munro's abscess with very mild acanthosis (yellow arrow) and rete ridges (green arrow). Dermis showing mild lymphocytic infiltrate (blue arrow). Bakers score = 2. H&E stain (10X)

Inflammatory biomarker assay

Comparison between apparently healthy group and induced non-treated group in the level of tissue, histopathological scores and observational score

Tissue homogenate level of tissue biomarkers (IL-17, TNF-a, and VEGF), and histopathological scores (Baker score) and observational score (PASI score) were significantly highly increased, in addition, tissue homogenate level of IL-10 were significantly highly decreased among induced non treated group after induction in comparison with apparently healthy control group, (P <0.001) (Table 1).

Table 1. Comparison between apparently healthy control group and non-treated induced group regarding tissue biomarkers (IL-10, IL-17, TNF-a, and VEGF), histopathological scores (Baker score) and observational score (PASI score)

Variables	Apparently healthy Control N=9 Mean±SD Median (Range)	Induction group N=9 Mean±SD Median (Range)	P value
IL-10 (pg/ml)	79.82±12.83 72.81 (69.03-101.45)	295.18±40.43 279.66 (270.00-399.98)	<0.001**
IL-17 (pg/ml)	112.53±4.56 113.35 (105.51-119.09)	268.73±35.88 259.32 (234.42-335.01)	<0.001*
TNF-a (ng/l)	41.66±0.93 42.14 (40.141-42.53)	154.01±11.86 149.69 (142.21-180.48)	<0.001*
VEGF (pg/ml)	142.26±12.6 142.71 (127.24-159.42)	461.73±16.77 456.89 (444.91-498.81)	<0.001*
Baker score	0.50±0.00 0.5 (0.5-0.5)	9.00±0.00 8 (7.5-9)	<0.001**
PASI score	0.00±0.00 0 (0-0)	11.70±0.48 12 (11-12)	<0.001**

* P value by unpaired ttest, ** P value by Mann-Whitney U test, IL= Interleukin, TNF-a= Tumor necrosis factor alpha, VEGF=Vascular endothelial growth factor

Tissue homogenate level of tissue biomarkers (IL-17, TNF-a, and VEGF), and histopathological scores (Baker score) and observational score (PASI score) were significantly decreased, in addition, tissue homogenate level of IL-10 were significantly increased among Petrolatum group in comparison with induced non treated group, (P <0.05) (Table 2).

Table 2. Comparison between induced non-treated group and Petrolatum group regarding tissue biomarkers (IL-10, IL-17, TNF-a, and VEGF), histopathological scores (Baker score) and observational score (PASI score)

Variables	Induction group N=9 Mean±SD Median (Range)	Petrolatum group N=10 Mean±SD Median (Range)	P value**
IL-10 (pg/ml)	295.18±40.43 279.66 (270.00-399.98)	275.24±52.96 259.58 (214.58-354.05)	<0.001**
IL-17 (pg/ml)	268.73±35.88 259.32 (234.42-335.01)	274.08±18.97 277.35 (251.08-296.89)	0.006**
TNF-a (ng/l)	154.01±11.86 149.69 (142.21-180.48)	65.4±12.05 64.31 (46.77-82.15)	<0.001*
VEGF (pg/ml)	461.73±16.77 456.89 (444.91-498.81)	96.77±15.95 102.46 (72.32-117.36)	<0.001**
Baker score	9.00±0.00 8 (7.5-9)	7.60±0.84 6 (5-9)	<0.001**
PASI score	11.70±0.48 12 (11-12)	9.30±0.67 9 (8-10)	<0.001**

* P value by unpaired ttest, ** P value by Mann-Whitney U test, IL= Interleukin, TNF-a= Tumor necrosis factor alpha, VEGF=Vascular endothelial growth factor

Discussion

Myricetin is a common flavonoid, it is bioactive and isolated from the plant kingdom naturally [18] In this study, we investigated the topical effect of myricetin on mouse model of psoriasis. It established IMQ induced psoriasis and found myricetin had significant amelioration in the histopathological changes, inflammatory cells infiltration and keratinocyte hyper-proliferation. The results obtained from IMQ induced psoriasis showed a significant reduction of total PASI score of mice after treatment with Myricetin topical preparation as compared with induced group and vehicle group. This is achieved by the reduction in epidermal thickness, redness and scaling.

After IMQ application, the development of psoriasis characteristic signs was because IMQ is a ligand for the toll-like receptors TLR7 and TLR8, which when it is activated leads to an unwanted inflammatory response that resembles psoriatic lesions [19]. The inflammatory cells in the skin such as T cells, neutrophils, and dendritic cells; are also increased by IMQ [20]. Therefore, all IMQ-treated mice developed characteristic psoriatic signs such as erythema, skin thickening, scaling, and hyperkeratosis, which is due to the agonist action of IMQ on the TLR. Erythema caused by IMQ is because that it can act as a direct mast cell de-granulator through mechanisms linked to IgE production or may activate mast cells through IgE independent mechanisms [21].

The selection of Myricetin in this study was based on its anti-inflammatory and antioxidant and immunomodulatory effects that make it a promising agent for treating psoriasis. Topical preparation of Myricetin 10% was made based on the previous studies on similar compounds and the biological activities of myricetin itself [7].

The histochemical assay of Myricetin by ELISA showed that it markedly decreased the IL-17, TNF-a and VEGF levels as compared to induced group and vehicle group. This result is consistent with previous studies that reported the ability of Myricetin to decrease the pro-inflammatory cytokines [5,22,23], and this may

explain its anti-inflammatory properties and its ability to reduce the signs of IMQ induced psoriasis.

The ability of Myricetin to reduce the signs of IMQ induced psoriasis could be due to its antioxidant activities [24] and also due to its anti-inflammatory actions by decreasing the nuclear factor kappa B (NF-κB) activation by suppressing the inflammatory mediators [25]; studies had shown that NF-κB is one of the main molecules in psoriasis pathogenesis, where it is responsible of causing inflammation and epidermal hyperplasia that are main pathological features in psoriasis pathogenesis [26].

Myricetin is also known in its ability to inhibit IL-12 production by downregulation of the binding activity of macrophages to NF-κB [22], and the IL-12 is known to promote the T cells mediated cellular response in psoriasis that contributes in the inflammation process of psoriasis [27]. Myricetin also reported to decrease the activity and number of the matrix metalloproteinases (MMPs) [28] that can cause the extracellular matrix, and tissue inhibitors of metalloproteinases (TIMPs) components to be cleaved and slows down their activity; therefore, reducing the tissue remodeling and reduces the immune cells inflammation that occurs in psoriasis [29].

Myricetin also inhibits phosphodiesterase enzymes (PDE) that are involved in inflammatory responses against injuries or toxins [30], which might be mediated in the inflammatory responses in psoriasis [31]. It also suppresses protein kinase enzymes that many of them act as signaling molecules in the course of inflammation [32]. In the total typical 27 cytokines, the secretions of IL-1a, IL2, interferon gamma (IFNY), and TNF-a have been found to be inhibited by Myricetin treatment, it also suppressed TNF-α-mediated NF-κB activity by downregulation of inhibitor-κB kinase (IKK) [22]. All these effects of Myricetin can explain its effects on the psoriasis like skin lesions and the reduction of the epidermal acanthosis, parakeratosis and papillary thinning.

Even more, in the present study, the histochemical assay by ELISA showed that Myricetin markedly decreased the IL-17 level as compared to induced group and vehicle group. This result is consistent with previous studies that reported the ability of Myricetin to decrease the pro-inflammatory cytokines such as IL2, IL-6, IL-17A, IL-23 and TNF-a [22]. In this research, Myricetin showed significant reduction in the TNF-α level when compared to the levels of TNF-α in the induction group. This is supported by previous evidence that reported myricetin has ability to reduce the level of TNF-α and activity [6].

In the current study, Myricetin showed a significant reduction in the level of VEGF compared to the induced group, which is also consistent with previous studies that Myricetin has antiangiogenic activity by inhibiting of the level of VEGF and the expression of its receptors [33]. On the other hand, the level of the anti-inflammatory cytokine IL-10 was increased to a comparable level in the healthy group, which means the skin is healing and the inflammation is declining as the IL-10 is an anti-inflammatory cytokine [23].

In conclusions, Myricetin significantly reduced the number of psoriatic lesions and the signs of skin inflammation in all IMQ induced mice. Also, Myricetin caused more significant reduction in the inflammatory biomarkers (TNF-a, IL-17, VEGF) and a significant increase in the anti-inflammatory biomarker (IL-10). These findings suggest that topical Myricetin can be a promising agent that can be used safely and effectively in psoriasis patients.

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Author contribution

Almudaris: collection and analysis of data, interpretation of results, and manuscript writing. Dr. Gatea: study design, supervision all the processes of the research and final revision of the manuscript.

Conflict of interest

The authors have no conflict of interests.

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