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RESEARCH ARTICLE

Anti- psoriatic effect and phytochemical evaluation of Iraqi *Scabiosa palaestina* ethyl acetate extract

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Abstract

The purpose of this study was to confirm the antipsoriasis activity of *Scabiosa palaestina* (*S. palaestina*) ariel component extract and identify the active compound(s) responsible for this activity using a developed RP-HPLC technology. The active ethyl acetate extract of *S. palaestina* was extracted and fractionated by the hot continuous Soxhlet apparatus method. Psoriasis was induced in experimental animals after 4 days of imiquimod (IMQ) cream application on dorsal skin rats of 3 treated groups (6 rats for each) and the normal group (6 rats) left without treatment. Two of the psoriatic-induced groups were treated with ethyl acetate (EA) extract or methotrexate (MTX) for 12 days, starting from day 4 of the IMQ application. Assessment of psoriatic lesions was done during the experiment, depending on the psoriasis area severity index (PASI). At the end of the study (day 15), animals were sacrificed and 2 skin specimens were collected for histopathological examination and cytokine measurement. Compared with the positive control group, ethyl acetate extract shows significant improvement in PASI (p-value < 0.05) and histopathological changes exerted by IMQ. On the other hand, no significant reduction has been seen in the psoriatic and angiogenic mediator (IL-17 and VEGF) with a P-value > 0.05 compared with the positive control group, which may be attributed to other cytokines that could be affected by the ethyl acetate extract of *S. palaestina*. These results suggest that the antipsoriasis properties of ethyl acetate extract may possibly be due to the presence of flavonoid compounds (luteolin, apigenin, quercetin, vitexin and kaempferol).

Keywords

RP-HPLC; flavonoid compounds; antipsoriatic effect

Introduction

Psoriasis is a chronic, recurring and autoimmune inflammatory skin disease caused by the dynamic interaction of various genetic risk factors, environmental risk factors and excessive immunological abnormalities. Psoriasis affects around 2 % of the global population and significant progress has been made in understanding and treatment options for psoriasis. Recent advances in biological therapy have shown the critical involvement of tumor necrosis factor-α, interleukin (IL)-23p19 and the IL-17A axis as well as skin-resident immune cells and key signaling pathways, in the pathogenesis of psoriasis. In addition to T helper 17 cells, which produce IL-17, innate lymphoid cells, ILC3 induce psoriasis rashes in response to antimicrobial peptides produced by activated keratinocytes and inflammatory cytokines. In

the liver, ILC3 is known to express retinoic acid receptor-related orphan receptor gamma *t* (1-4).

Although most conventional medicines help alleviate psoriasis symptoms, there is no known cure for this illness. Further, many medicines have side effects, including atrophy, organ toxicity, immunosuppression, infection and carcinogenesis, limiting their long-term usage. To attain the goals of greater efficacy and fewer adverse effects, alternative treatments for psoriasis must be developed. Natural medicine has received a lot of attention in the search for new treatments. Natural products are rich in resources that contain potentially bioactive substances (5).

Patients prefer herbal medicine because it is readily available, inexpensive and effective. The structural diversity and different modes of action of herbal medications have resulted in synergistic activity that alleviates psoriasis. Herbal medications may also increase bioavailability due to the presence of permeability enhancers in the phytomedicine (6).

S. palaestina L. (*F. caprifoliaceae*) is a species in the genus *Scabiosa*, which is a large and taxonomically complicated genus with many species dispersed throughout Asia, the Mediterranean Basin and Southern Africa. *S. palaestina* L. is an annual shrub with rosettes of leaves and leafy stalks. It grows to 60 cm in height and has crowded, tiny heads of white to purple blooms (7-10).

According to numerous sources, *Scabiosa* species are used as medications in traditional medicine such as respiratory tract problems (asthma, bronchitis and influenza), diphtheria, high blood pressure, uterine diseases, menstrual problems, skin infections and liver abnormalities. Natural medicine found in *Scabiosa* flowers has recently been utilized traditionally in Mongolian medicine and tested for hepatoprotective efficacy (11, 12).

The abundance of secondary metabolites such as flavonoids, iridoids, phytosterols and pentacyclic triterpenoids in *Scabiosa* species may contribute to their usage in folkloric medicine (12-14). The quantity of secondary metabolites in *Scabiosa* species, such as flavonoids, iridoids, phytosterols and pentacyclic triterpenoids, may also contribute to their use in folkloric medicine.

The literature reveals the presence of many flavonoids in *Scabiosa* species, which provide a variety of health benefits in addition to their antioxidant and anti-inflammatory characteristics (15, 16). *Scabiosa* species have antibacterial, analgesic, antidiabetic, hepatoprotective, anti-inflammatory, antifungal, antioxidant, antiviral and antiparasitic activities, which are closely related to their high content of phenolic compounds; moreover, these activities support the beneficial properties of these medicinal plants (17, 18).

This study is established to identify and qualify certain flavonoids by HPLC in *S. palaestina* L. It also examines the antipsoriatic effects of the EA extract of this plant in rats with an IMQ-induced psoriasis model.

Materials and Methods

Plant material

S. palaestina L. aerial parts were collected in May 2022 from Kalobazian, north of Iraq, where it grows as a wild plant (Fig. 1). The plant was authenticated in the herbarium of the Department of Biology, College of Science, University of Baghdad, Iraq (No. 1197). The plant components were allowed to dry in the shade before being ground with an electric blender, weighed and extracted.

Preparation of *S. palaestina* L. extract

One hundred grams of powdered plant material of *S. palaestina* L. was defatted by a Soxhlet apparatus for one day in 1000 mL of n-hexane and then filtrated. The remaining plant components were extracted for 12 h with 1000 cc of ethyl acetate using a Soxhlet device. To obtain a dry residue, the crude extract was filtered and decreased in volume under vacuum, as illustrated in Fig. 2. The ethyl acetate extract was vacuum-dried and kept for subsequent study (19).

Qualitative analysis of, ethyl acetate extract, by high-performance liquid chromatography (HPLC)

At the Ministry of Science and Technology in AL-Jadriyah, qualitative assessments were performed for the identification of phytoconstituents present in ethyl acetate extract using RP-HPLC Shimadzu 10 AV-LC and the eluted peak was

Fig. 1. Collection of plant materials from North of Iraq.

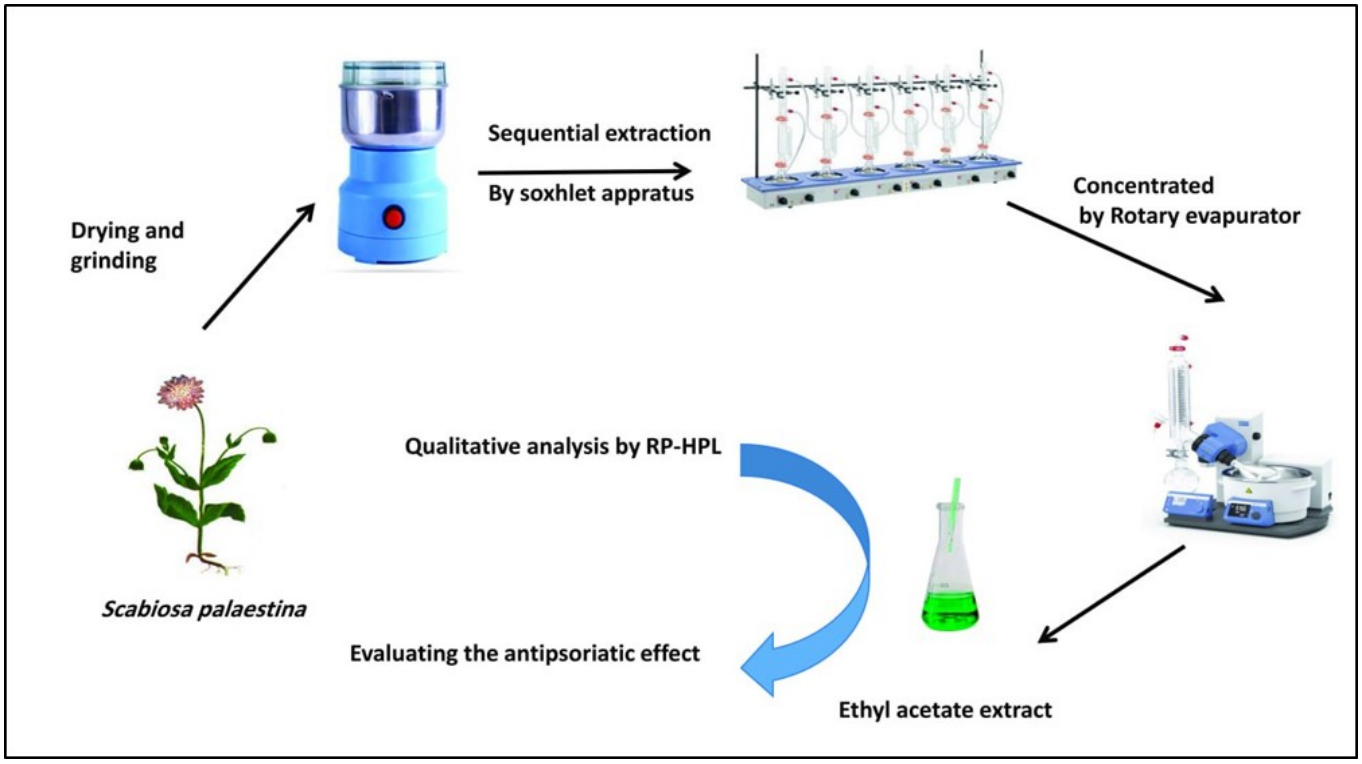

Fig. 2. Scheme of extraction, flavonoid determination and antipsoriasis activity of Iraqi *Scabiosa palaestina* were all evaluated.

monitored by a UV-Vis 10A-SPD spectrophotometer. The qualitative identifications were accomplished by comparing the retention durations of the examined samples to verifiable standards under defined chromatographic conditions.

RP-HPLC conditions for ethyl acetate extract

- Mobile phase: Linear gradient: 0.05 % trifluoroacetic acid in deionized water (solvent A) and 0.05 % trifluoroacetic acid in methanol (solvent B)
- Column: Nuclear C18 (50 mm x 2 mm, 3 µm particle size)
- Samples: EA extract of aerial parts
- Standards: Luteolin, apigenin, quercetin, vitexin and kaempferol
- Flow rate: 1.1 mL/min
- Injection volume: 50 µL
- UV detector at 285 nm (20)

Evaluation of antipsoriatic effect of EA extract of *S. palaestina*

The following medications used in the experimental study were brought from a local pharmacy and veterinary drug store, including imiquimod cream (Aldara, MEDA, Sweden); methotrexate injection (Mylan, USA); ketamine injection (Demo Dose, USA) and Xylazine injection (Biotur Business, Romania). Sodium chloride at 0.9 % (Pioneer Co. for Pharmaceutical Industries, Iraq) was used for dilution of the above medication when needed. Rat hair was removed from the dorsal skin using Veet cream, which was purchased from a nearby drugstore. We bought an ELISA kit for measuring rat IL-17 and VEGF from Sunlong Biotech Co. LTD. in Zhejiang, China.

Experimental animals

In this experiment, male rats (Wistar albino) were purchased from the National Center for Drug Control and Research's animal house in Baghdad. They were then kept in an environment that was specifically pathogen-free and at room temperature for more than a week before the experiment in the animal house located in the pharmacy department of Al-Rasheed University College. The age and weight of every animal are identical (4 to 5 months; 180-210 g). The research protocol used in this study received ethical approval from the Ethical Committee at the College of Pharmacy/University of Baghdad (RECAUBCP2020236).

Induction of psoriatic-like lesion model in rat

The induction of psoriasis was performed according to the previous study (21) with some modifications. Rats (8-10 weeks old) had their dorsal hair cut at a surface area of about 4-5 cm using an electric hair shaver and the remaining hairs were removed with depilatory Veet cream one day before imiquimod (IMQ) cream was applied. This procedure was done to establish an IMQ-induced psoriasis model. After that, the rats received daily treatments of 62.5 mg of topical 5 % IMQ cream for 10 days.

Experimental design

Twenty-four rats were assigned at random into 4 groups (each group included 6 rats). Rats in each group (except normal control) 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 4 after first application of IMQ cream: the first group treated with subcutaneous (SC) injection of normal saline once daily and considered as a positive control group; the second group treated with MTX (1.0 mg/kg/week, intraperitoneal injection) and the last group treated with EA (200 mg/kg/day, oral gavage).

Assessment of severity of inflammatory psoriatic lesion

The thickness, scaling and erythema of the psoriatic lesion were evaluated as part of a clinical examination that used the psoriasis area severity index (PASI). No symptoms (0), mild (1), moderate (2), severe (3), or extremely severe (4) were included in the scoring system. All animals were slaughtered on day 15, the last day of the experiment and 2 skin samples were taken right away from each animal's body: one for histopathological analysis the other to assess cytokine levels.

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 5 µm thick sections. To assess the histological alterations in skin lesions, an automated microscope (Lionheart FX) was utilized.

Enzyme-linked immunosorbent assay (ELISA)

A tissue extraction reagent (FNN0071, Bender Med Systems GmbH, Vienna, Austria) was used to lyse skin samples. After centrifuging the samples at 10000 g for 20 min, the supernatant was collected. ELISA kits were used to assess the amounts of IL-17 and VEGF in the skin lysates in accordance with the manufacturer's recommendations. Absorbance was determined at 450-550 nm using a microplate reader (Tecan, Männedorf, Switzerland).

Statistical analysis

All of the parameter data were initially checked for normality of distribution. Calculations were made for a descriptive study of changes in body weight, laboratory findings and morphological lesion alterations (mean, standard deviation [SD]). A one-way ANOVA post hoc test was used for data that had a normal distribution for comparative analysis between animal groups and a nonparametric test (the Mann-Whitney test) was used for data that were not normally distributed. Version 20 of the IBM SPSS statistical program was used for all analyses. Statistical significance was defined as a two-sided p-value of 0.05. On the other side, graphs were displayed using the Graph Pad Prism program.

Results

The aerial parts were extracted using the Soxhlet process, which is heat-dependent and allows solvent to penetrate through the walls of the aerial part pieces. Differences in polarities were used as a critical separation step in order to analyze interconnected chemicals in extracts preceded by different polarity n-hexane and ethyl acetate fractionation solvents, with the weight yield of each fraction being 10.8 and 5.6 g respectively.

Qualitative determination of phenolic compounds by RP-HPLC

HPLC was chosen as a qualitative approach for determining the active components in ethyl acetate extract because it is a simple, quick, efficient and comprehensive method for plant extract separation (22).

The results of the performed HPLC analysis of *S. palaestina* ethyl acetate extract (Table 1) confirmed the presence of 3 flavones, including luteolin, apigenin and vitexin, in addition to the presence of 2 flavanols (quercetin and kaempferol); these flavonoids were detected and showed the same retention time as those of the contributed standards in the HPLC chromatogram of EA extract (Fig. 3 and 4).

Table 1. Retention times (in minutes) of standards and the corresponding detected compounds in ethyl acetate extract of aerial parts of Iraqi *Scabiosa palaestina* L.

Extract	Standard used	RT of standards peaks (min)	RT of matched peaks (min)
Ethyl acetate extract	Luteolin	2.083	2.06
	Apigenin	2.983	2.95
	Vitexin	4.182	4.13
	Quercetin	4.847	4.8
	Kaempferol	6.268	6.21

Effect of EA extract of *S. palaestina* on body weight

In all groups that received treatment, a modest decrease in body weight was seen after the initial application of IMQ to the dorsal rat's skin. As soon as the therapy began and after each application of the IMQ cream, however, all treated groups except those receiving MTX saw an increase in body weight retention (Fig. 5). When compared with the normal control group (264.67 ± 61.72), the nonparametric statistical analysis after the trial revealed no significant differences in the body weight of the positive control group and the EA extract treatment group (182.33 ± 66.02, 194.5 ± 46.45 respectively). The body weight of the MT-treated group, however, was significantly lower at the end of the experiment (171.67 ± 54.44).

Effect of EA extract of *S. palaestina* on psoriatic inflammatory lesion

The PASI grading system is employed to determine the severity of psoriasis. It assesses the extent, erythema (redness), thickness and scaling of psoriatic lesions on the dorsal body of the rat's skin. The index is useful for monitoring the progression of the disease and evaluating the effectiveness of treatment. Fig. 7A–D present the PASI scores as flow charts for the therapy groups, with gross sections from each one. On day 15, the condition with the highest overall PASI score was in the positive control group (5.83 ± 1.16) (Fig. 7B), followed by the rats treated with EA extract (4.12 ± 1.01) (Fig. 7C), MTX (3.5 ± 1.87) (Fig. 7D) and the normal control group rat (0 ± 0) (Fig. 7A), with significant differences between treatment groups and the positive control group (p-value < 0.05). Further, the exposed area demonstrated erythema, scaling and thickened layers of skin during the first few days. However, treatment with MTX and EA extract 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).

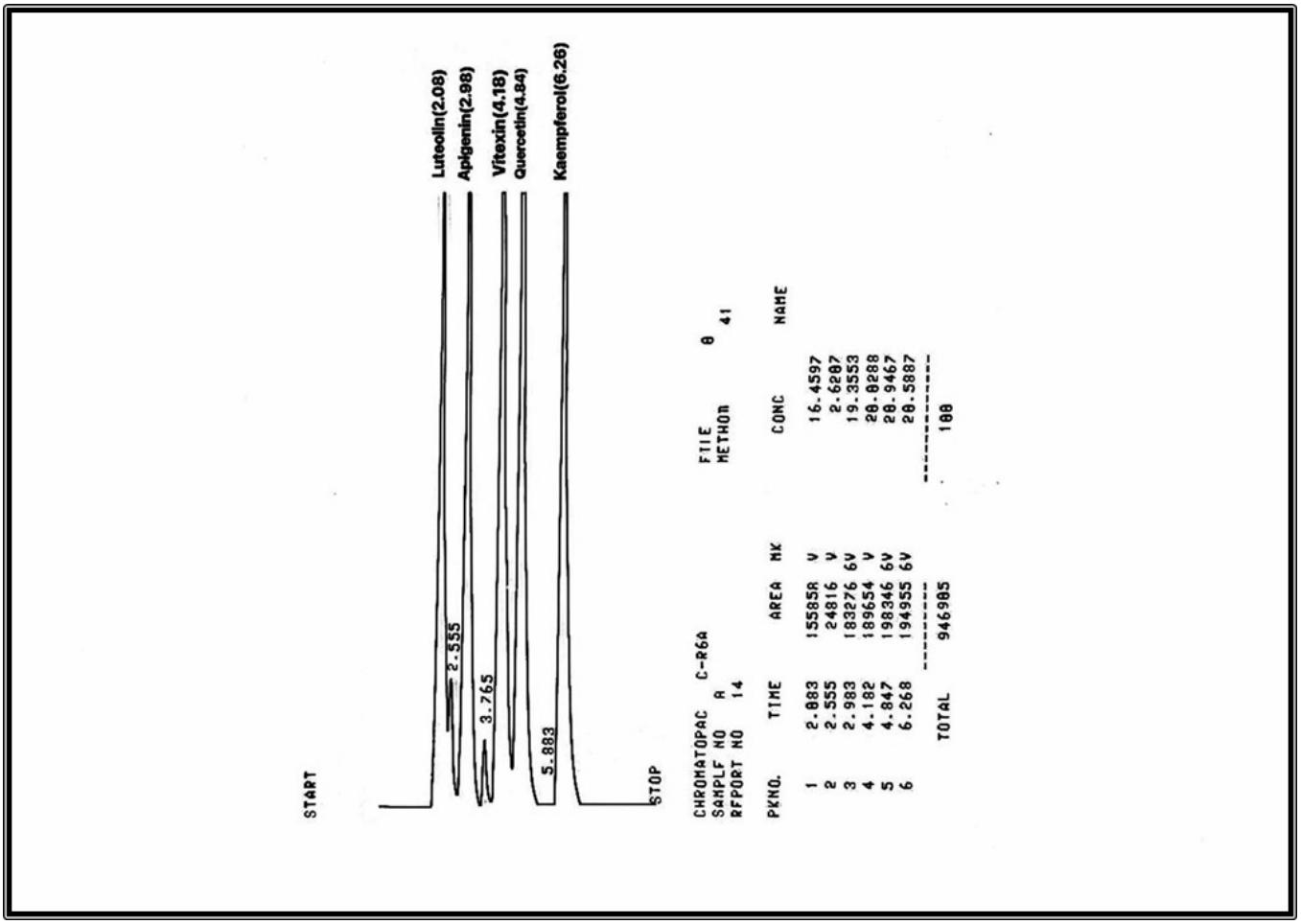

Fig. 3. HPLC chromatogram of luteolin, apigenin, vitexin, quercetin and kaempferol standards.

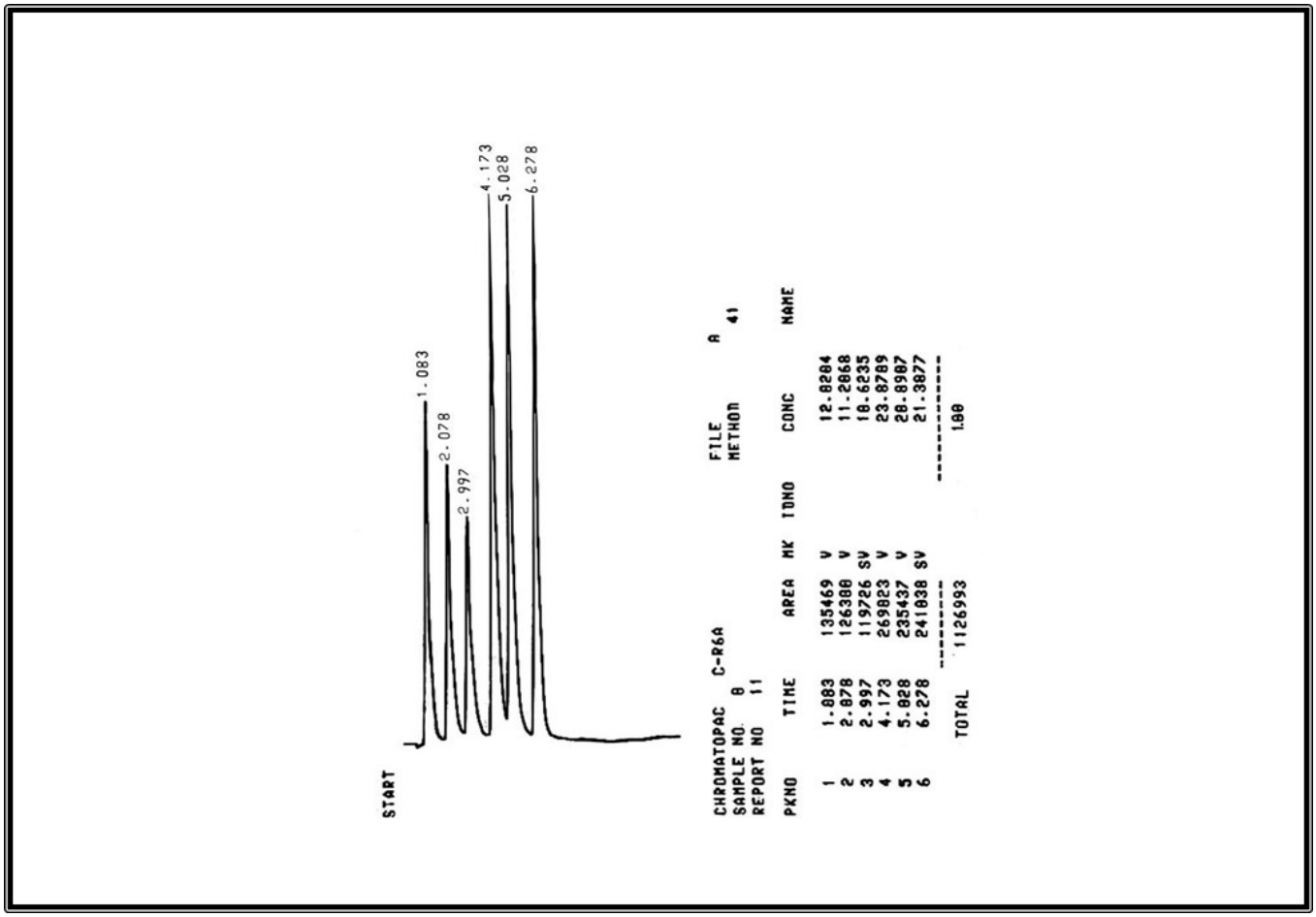

Fig. 4. HPLC chromatogram of EA extract of *Scabiosa palaestina* L.

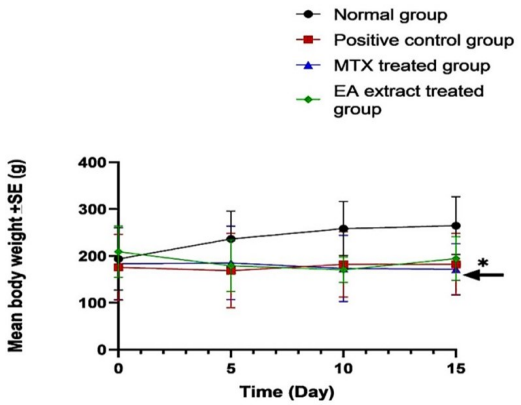

Fig. 5. Body weight changes during experimental period. The result represents as mean ± SD and p < 0.05 consider significant reduction in the body weight compared with normal control group.

Effect of EA extract of *S. palaestina* on inflammatory markers

Interlukine-17 and VEGF are the 2 primary cytokines that contribute to skin inflammation and epidermal hyperplasia. Accordingly, these variables were assessed in the skin lesions of all groups and we discovered that the positive control group caused by IMQ had significantly higher levels of IL-17 and VEGF ($p < 0.05$) (Fig. 6). Even though these treated groups have significantly improved in terms of clinical observations (erythema, scale and thickness), *S. palaestina* extract and MTX do not suppress these cytokines in the psoriatic skin lesion ($p > 0.05$) (Fig. 7).

Histopathological study

Analysis of H & E-stained sections from the IMQ-treated dorsal skin of positive control rats showed significantly increased hyperparakeratosis accompanied by psoriasiform acanthosis with epidermal hyperplasia associated with the thickening of the epidermis at the top of the dermal papillae in comparison with the normal control group, which shows normal layers of the dermis, epidermis and stratum corneum. At the dermis layer, dilated blood vessels and Munro microabscesses have also been developed upon induction by IMQ in the stratum corneum. Rats treated with MTX or EA extract treated groups had a skin lesion with a somewhat thickened epidermis, reduced acanthosis Munro micro abscesses and dilated blood vessels, which mitigated the psoriatic symptoms (Fig. 8).

Discussion

Current treatment of psoriasis is associated with many drawbacks, such as immune suppression (biological therapy and corticosteroid), unresponsiveness (topical corticosteroid and vitamin D analogue) and cost of therapy (biological therapy) (23).

Thus, the research for new medicines that can treat this disorder should be continued. Plants offer a lot of sources of active medicinal constituents, which have been used since ancient times for the management of many diseases (24).

According to a literature review, the *Scabiosa* species contain a variety of flavonoids, including quercetin, kaempferol, apigenin, astragalin, luteolin and others. These natural compounds are polyphenolic and have potential anti-inflammatory and antioxidant effects (25).

For this reason, this research included evaluating the antipsoriatic effect of an EA extract of *S. palaestina* on IMQ-induced psoriasis in rats. Erythema, scaling, infiltration and the amount of body surface area are the main clinical criteria used to assess the severity of psoriasis (26). The prognosis of psoriasis in the IMQ-induced model is greatly improved by EA extract when gave orally to the rats, thus reducing the erythema, scaling and thickness of the skin lesions, which sheds light on the efficacy of *S. palaestina* extract in treating this disorder. Persistent inflammation that leads to unregulated keratinocyte proliferation and

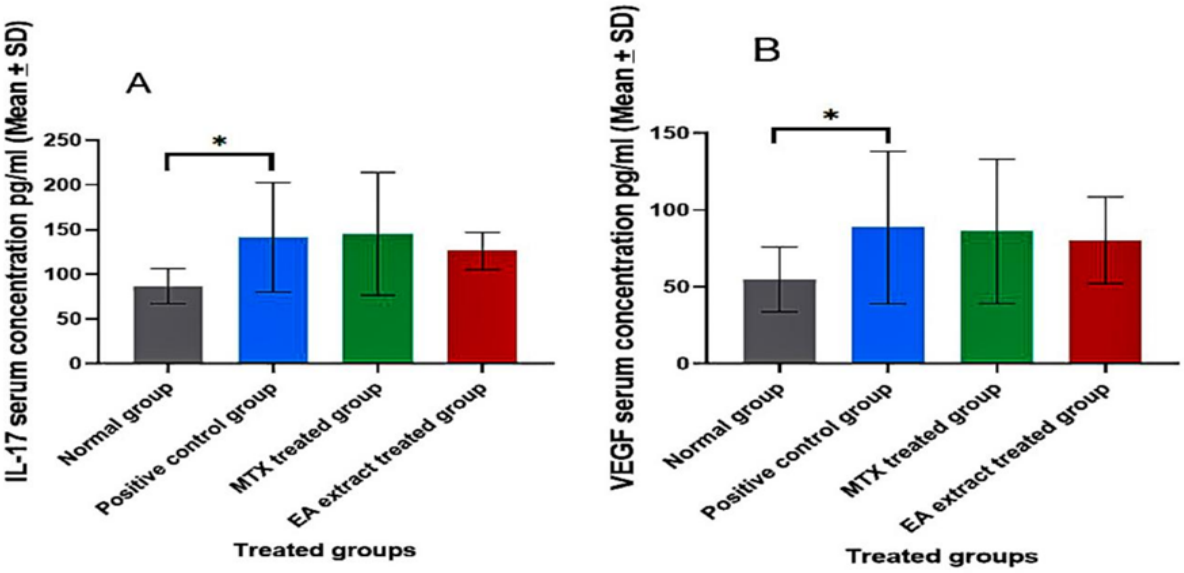

Fig. 6. Effect of EA extract of *Scabiosa palastina* treatment on the level of IL-17 (A) and VEGF (B) in skin specimen. The data represent as means ± SD (n= 6 per group). * P < 0.05 regarding normal control versus the positive control group.

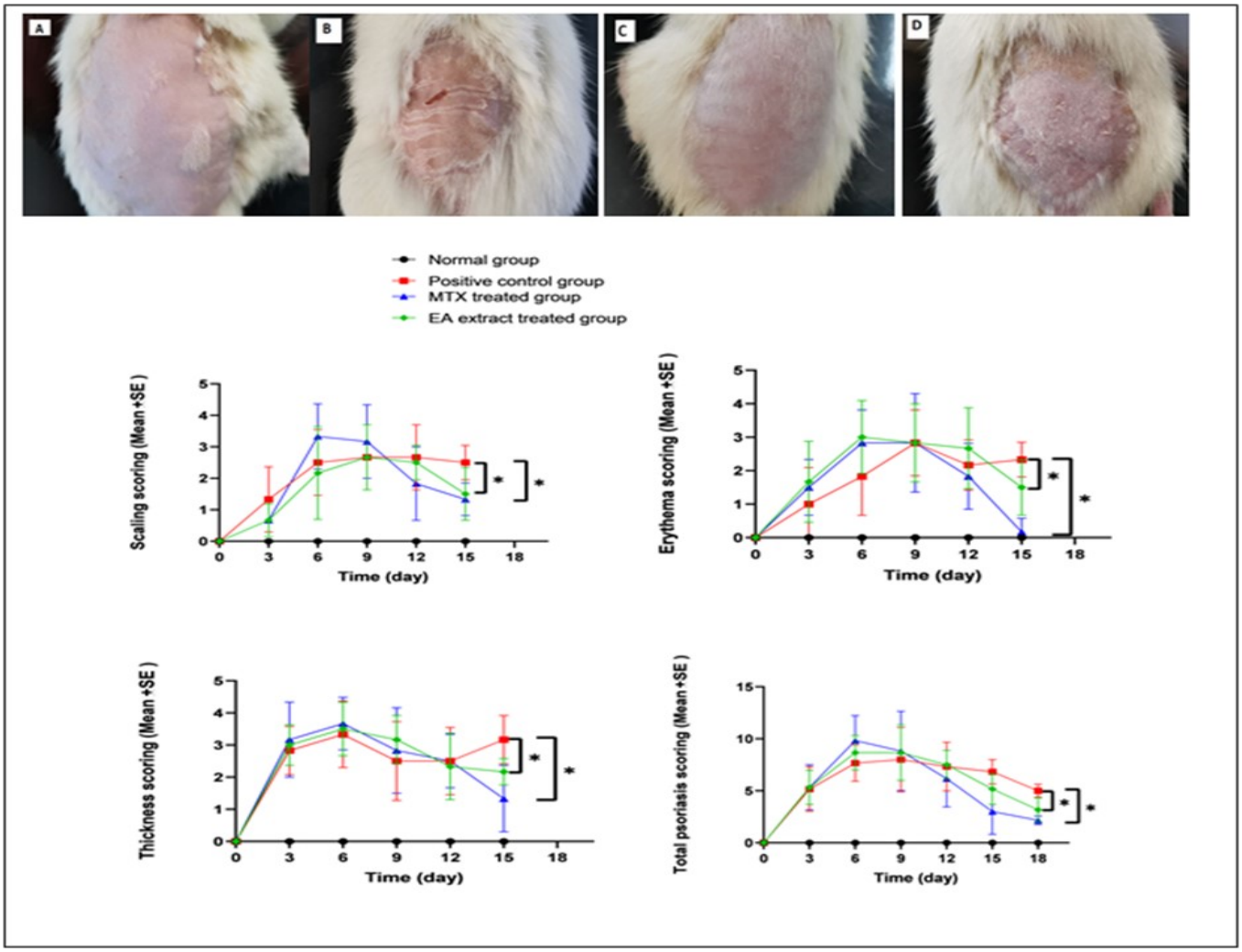

Fig. 7. Effect of IVR on PASI in IMQ-induced in rat. Gross section of skin lesion for normal control group (A); positive control group (B); MTX treated group (C and IVR treated group (D). The figure also includes line graphs of PASI for erythema, scaling, thickness and total psoriasis scoring. Data are expressed as means ± SD (n = 6 per group). * $P < 0.05$ versus the positive control group.

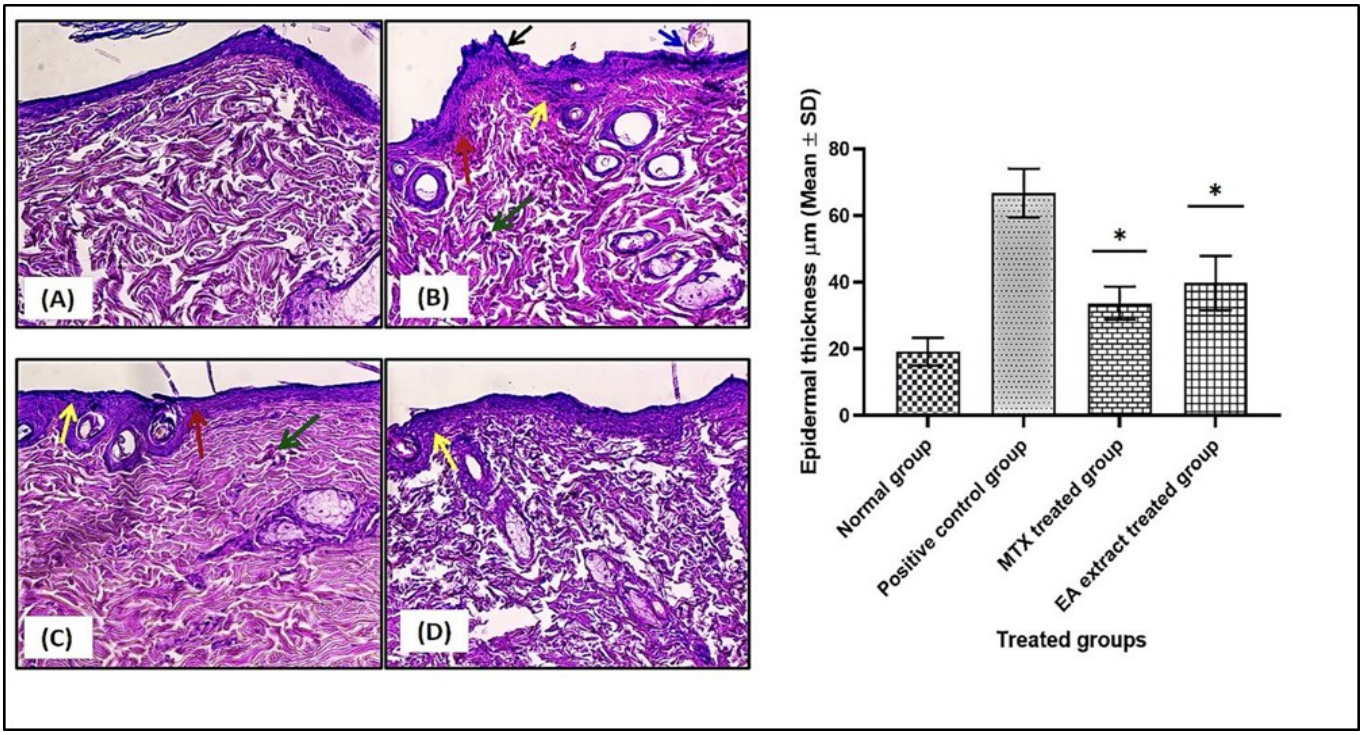

Fig. 8. Skin section from rat back skin: normal control (A), positive control (B), MTX treated group (C) and EA extract of *Scabiosa palastina* treated groups (D). Positive control illustrates hyperkeratosis (blue arrow), acanthosis (black arrow), epidermal hyperplasia (red arrow), Munro microabcess (yellow arrow) associated with thickening of the epidermis overlying the dermal papillae layer and dilated blood vessel (green arrow) (H & E) 10X. Bar chart represents the microscopical differences in the epidermal thickness between experimental groups. Normal control group show normal architecture of dermis, epidermis and stratum corneum. MTX and EA treated group shows miner changes compared with positive control group.

improper differentiation is the main characteristic of psoriasis. On the psoriatic plaque's histology, inflammatory infiltrates of dermal dendritic cells, macrophages, T lymphocytes and neutrophils are discernible and covered by acanthosis (epidermal hyperplasia). Another noticeable characteristic is neovascularization, which is also seen under a light microscope of psoriatic lesions (27).

The findings of this investigation showed that the EA extract can reduce the pathogenic alterations brought on by IMQ. Research on human psoriatic lesions has shown that IL -17 and IL-23 contribute to the onset of psoriasis. Patients with psoriasis' dermis secrete IL-23, which triggers the production of IL-17 by CD4+ T cells (28-30). Keratinocytes are directly impacted by IL-17, which increases their production of the cytokines, chemokines and antimicrobial peptides linked to psoriasis. The keratinocytes' released substances drive the positive feedback loop by promoting the expansion of inflammatory and IL-17-producing cells (31). Despite the fact that IMQ dramatically increases the level of IL-17 in skin samples, oral treatment with the EA extract of *S. palaestina* was unable to appreciably lower this cytokine. Numerous manuscripts on the role of VEGF in psoriasis have revealed a correlation between the severity of the condition and elevated levels of this protein in the serum and tissues. Recent studies reveal that VEGF regulates angiogenesis and keratinocyte development. The relationship among psoriasis, related comorbidities and vascular endothelial growth factor has also been discussed (32).

It was discovered that kaempferol therapy reduced the psoriasis-like mouse skin lesions brought on by topical IMQ injections. In the psoriatic mouse skin, kaempferol decreased the expression of key pro inflammatory cytokines and CD3+ T cell infiltration. In addition, kaempferol prevented Th17 development in mice with psoriasis brought on by IMQ. It also reduced the NF-B signaling pathway, which promotes inflammation in psoriatic skin. The therapeutic results were positively correlated with a considerable rise in CD4+ FoxP3+ Treg frequency in the spleen and lymph nodes; further, kaempferol treatment also improved FoxP3+ staining in the skin lesion (33).

In addition, kaempferol decreased the number of T17 cells in the lymph nodes of psoriatic mice and the gene expression of numerous proinflammatory cytokines, such as interleukin-23, IL-17A, TNF-, IL-6 and IL-1 as well as down regulated the proinflammatory JAK-STAT signaling pathway. Thus, by enhancing SOCS1 expression and activating IFN-R1 expression, Kaempferol altered the JAK-STAT signaling pathway that IFN-triggered (34).

The limitations of this study are the small sample size, using a conventional dose of EA extract, and the measurement of fewer cytokines involved in the pathogenesis of psoriasis. Accordingly, further research is required to identify the types of cytokines and inflammatory markers involved in the pathogenesis of psoriasis, which may be minimized by the EA extract of this plant. Additional clinical research on these substances is needed to determine the efficacy and safety of their use as dietary supplements with health benefits for psoriatic patients.

Conclusion

Herbs have long been known to provide numerous health benefits with few side effects. Natural substances derived from herbal treatments offer synergistic effects in the treatment of psoriasis and related comorbidities due to their structural variation and several active mechanisms. RP-HPLC analysis of *S. palastina* ethyl acetate extract, confirmed the presence of 3 flavones, including luteolin, apigenin and vitexin, in addition to the presence of 2 flavanols, i.e., quercetin and kaempferol. This study found that the EA extract of *S. palastina* aerial parts has significant antipsoriatic action and decreases the relative epidermal thickness of animal skin as well as other histological characteristics. The study suggests that *S. palastina* aerial parts and flavonoids could be employed as natural therapeutic medications to avoid psoriatic problems and validate the plant's folk claim in traditional medicine for the treatment of skin infection.

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Authors' contributions

NMI designed the current study. TZAJ gathered the samples from Kirkuk province and ASM assessed the antipsoriatic action. All authors carried out experiments and handled research data. The data were analyzed by the College of Pharmacy at the University of Baghdad and the Department of Pharmacy at Al-Rasheed University in Baghdad, Iraq.

Compliance with ethical standards

Conflict of interest: There is no conflict of interest regarding the publication of this manuscript.

Ethical issues: The research protocol used in this study received ethical approval from the Ethical Committee at the College of Pharmacy/University of Baghdad (RECAUBCP2020236).

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