Zagazig University Medical Journal
www.zumj.journals.ekb.eg
Volume 28, Issue 6, November 2022(164-170) Supplement Issue
Manuscript ID ZUMJ-1912-1648 (R2)
DOI **10.21608/zumj.2020.20702.1648**

ORIGINAL ARTICLE:

Turmeric Extract-Based Treatment for Psoriasis.

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Submit Date 2019-12-22
Revise Date 2020-01-07
Accept Date 2020-01-13

ABSTRACT:

Background: Psoriasis is a chronic inflammatory skin disease affects 3 % of world population on average. Psoriasis can have disfiguring and disabling impacts on patients with increased global burden of the disease. According to WHO, there is continuous need for establishing new modalities for treatment of psoriasis with emphasis on treatment safety concerns of the patients.The aim of this study is to assess the efficacy and safety of turmeric extract based ointment in the treatment of mild to moderate psoriasis

Methods: 10 patients with psoriasis vulgaris confirmed histopathologically were recruited at Dermatology Department outpatient clinic Zagazig University Hospitals. The disease severity was assessed clinically using PASI score and the histopathologic severity was assessed before and after 4 weeks of twice daily application of the turmeric extract based ointment.

Results: Significant reduction in disease severity in all patients used treatment with PASI before treatment was 19.44 ± 10.7, and after was 10.5 ± 6.3 *(P = 0.0007)*. There was 47% ± 12% improvement in disease severity, with 50% of patients already reached PASI 50 benchmark by 4th week of treatment.

Conclusions: In this pilot study, the effectiveness and tolerability of turmeric extract-based ointment in the treatment of moderate psoriasis vulgaris was evaluated and proved on both clinical and histopathological levels.

Keywords: Psoriasis; management; Turmeric

INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder. Patients with psoriasis suffer a state of systemic inflammation as evident with the disease association with comorbidities as hypertension, major adverse cardiac events, hyperlipidemia, psoriatic arthritis and obesity.

Psoriasis affects about 3% of world population with higher prevalence among US and Canadian population compared to African and Asians **[1,2]**. Although it can develop at any age psoriasis commonly develops either around 20 years old (early onset psoriasis) or at 50 years old (late onset type). Clinically, psoriasis may present as chronic plaque variant (most common), erythrodermic, guttate psoriasis or pustular variants of psoriasis **[3]**.Chronic plaque psoriasis is characterized by sharply demarcated, erythematous, thickened, and scaly plaques with symmetrical distribution. The elbows, knees, lumbosacral region, and scalp are the sites of predilection. Plaques are usually oval, circular or polycyclic (by union of multiple smaller lesions into larger one). Sometimes Woronoff's ring (a pale blanching halo) is seen surrounding lesions **[3]**.Being a chronic skin disease, psoriasis significantly affects patients' quality of life. Despite the fact that various therapeutics are out there to choose from, surveys indicate that current treatment options don't provide satisfactory long term answers to patients with psoriasis **[3,4]**. WHO has emphasized, in its global report on psoriasis, the need for more treatment options to be available for patients with psoriasis. WHO has called upon member states to provide more support for research purposes addressing new treatment options for psoriasis **[5]**. The choice of therapy should take in consideration many variables including disease type, severity -assessed by body surface area or psoriasis area and severity index (PASI)-, age, sex of the patient and the presence of other comorbidities. Systemic therapy for psoriasis is indicated for patients with extensive disease (affecting > 10% of body surface area), patients with refractory disease not responding to topical or phototherapy and patients with localized disease but interfering with daily life activity as in severe

scalp psoriasis, palmoplantar psoriasis and genital psoriasis **[6–8].**For mild to moderate psoriasis, which represents 80% of patients with psoriasis, the main stay of treatment is topical therapy as monotherapy or combined with phototherapy. In moderate to sever psoriasis, topical therapy can also be combined with systemic therapy for localized resistant lesions **[9]**. Topical therapies can be used short term or long term intermittently or continuously based on the patients' need. American guidelines recommend using potent therapeutics on short term basis for remission induction, to be used intermittently thereafter. Effective least potent therapeutic is to be used if continuous application is considered **[9]**. Topical therapeutics include corticosteroids, vitamin D analouges, tazarotene, calcineurin inhibitors, tar, anthralin and salicylic acid. There are different formulations that has been used based on the site and severity of the disease; ointments, creams, gels, lotions, sprays, foams as well as shampoos **[3]**. Topical corticosteroids are cornerstone therapeutic for psoriasis management **[3,9]**. Plant extracts has been used for ages in dermatologic therapy e.g. psoralens and anthralin. The prevalence of alternative medicine methods, including herbal extracts, among patients with psoriasis is 42% - 69%. The term "alternative medicine" is used to describe all health care remedies that are not included in conventional therapeutics. It covers the traditional chines medicine, climatotherapy, herbal therapies, dietary supplements and modification, mind/body interventions among others. Herbal therapies are the most frequently used **[10]**. Patients with psoriasis resort to herbal extracts among other complementary medicines as a monotherapy or commonly combined to traditional medicine. Patients prefer natural products because the expected safer profile along with the frustrations from the ineffectiveness and toxicities oftraditional therapeutics **[10]**. Various herbal extracts have been used for psoriasis treatment. They have been used either topically or orally as dietary supplement. Topical botanical remedies for psoriasis include aloe vera, avocado oil, bergamot oil, capsaicin, curcumin, Hypericum perforatum L (St. John's Wort), honey extracts, indigo naturalis, kukui nut oil, mahona aquifolium, and camptotheca acuminata nut **[11,12]**. The effectiveness of these various botanicals has been evaluated in studies. Some of them didn't show significant improvement in the disease while others proved efficacy **[11,12]**. Turmeric (Curcuma longa) is a rhizomatous plant native in Southeast Asia and India. Diferuloylmethane (curcumin) is the active component in the turmeric extract. Curcumin is hydrophopic so its bioavailability following oral ingestion is poor. Curcumin shows anti-inflammatory, antioxidant, anti-microbial and anti-cancerous activities **[13]**. Curcumin safety has been illustrated in animal studies as well as clinical trials. US Food and Drug Administration (FDA) has approved usage of curcumin in food as "Generally Recognized as Safe" (GRAS) **[14].** Turmeric extract has been used in alternative medicine for years for the treatment of dermatological conditions, obesity and digestive system inflammation. Recently, curcumin effectiveness has been evaluated in different conditions including metabolic syndrome, cardiac issues, cancer and depression **[10,13]**. For dermatological diseases curcumin has been evaluated as a treatment for acne, androgentic alopecia, eczema, atopic dermatitis, photoaging, oral lichen planus, pruritus, psoriasis, vitiligo and diabetic microangiopathy **[13,15]**. The proposed mechanisms of action of curcumin in psoriasis include anti-inflammatory, anti-microbial anti proliferative and antioxidant properties among others **[13,15]**. Animal studies showed the ability of curcumin to ameliorate inflammatory conditions as arthritis, edema and septic shock. Curcumin can also protect against some human conditions with inflammatory nature as cardiovascular disease, acute pancreatitis, enterocolitis, enteritis, ileitis, prostatitis, alcoholic and non-alcoholic hepatitis, diabetic neuropathy and asthma. Orally administered curcumin has reduced the serum level of TNF α among other pro-inflammatory cytokines in patients with diabetes and colorectal cancer **[16]**. In this paper, we evaluated the effectiveness of topical treatment of psoriasis with turmeric extract-based ointment.

METHODS

Patients were recruited and followed up at the outpatient clinic of Dermatology department, Faculty of Medicine, Zagazig University. Ten patients diagnosed clinically with mild to moderate psoriasis vulgaris were recruited. All patients didn't receive any systemic or topical therapies for psoriasis for 4 weeks before starting the drug administration. Any patients with known hypersensitivity towards the active constituents were excluded. Patients gave written informed consent to participate in the study. This study was approved by the institutional review board (IRB) of the Faculty of Medicine of Zagazig University and was performed in accordance with the 1964 Helsinki declaration and its later amendments.

Ointment Preparation: Turmeric ethanolic extract (*Turmeic HERB PHARM* ®) was levigated using glycerol mixed with petrolatum to form an ointment. Ointment preparation was stored at room temperature until use.Patients applied turmeric extract-based ointment twice daily for 4 weeks,

during the study no other topical or systemic anti-psoriatic treatments were allowed. The disease severity was assessed using Psoriasis Area and Severity Index (PASI) before the start of therapy and on weekly basis till the end of the 4th week.

Histopathological Evaluation: Five ml punch skin biopsies were taken at the baseline and 4 weeks after treatment. The biopsies were immersed in 10% formaldehyde then embedded in paraffin wax and processed for H&E staining. Using Leica DM 2000 LED microsystems, psoriasis diagnosis was confirmed histologically. The response to therapy was assessed histologically by an expert dermatopathologist using scoring system reported by **[17]** with modification.

STATISTICAL ANALYSIS:

For data analysis the statistical package "Stata" (statistics and data; StataCorp LLC, 4905 Lakeway Drive, College Station, TX, USA) version 15 was used. Data was summarized using mean (X), and standard deviation (SD) using paired samples t-test to compare the data before and after treatment. Statistical significance was set at $P \leq 0.05$ with 95 % confidence interval.

RESULTS:

A total of 10 patients, 8 males and 2 females, were included in the present study. These patients were 47.5 ± 19.6 years old on average (mean ± standard deviation), and plaque psoriasis had been diagnosed 12.6 ± 8.4 years earlier.***Clinical response:*** The average disease severity assessed by PASI before treatment was 19.44 ± 10.7, and after 4 weeks of treatment was 10.5 ± 6.3. All patients (100%) showed significant *(P = 0.0007)* reduction in their psoriasis severity **Figure 1**. The average improvement assessed by reduction in PASI score was (47% ± 12%). 50% of patients already reached PASI 50 benchmark by 4th week of treatment.

Histopathologic response: Curcumin treatment resulted in significant improvement in histopathological scoring with the score before (8.5 ± 1.6) and after (3.7 ± 1.1) *(P = 0.0001)*.

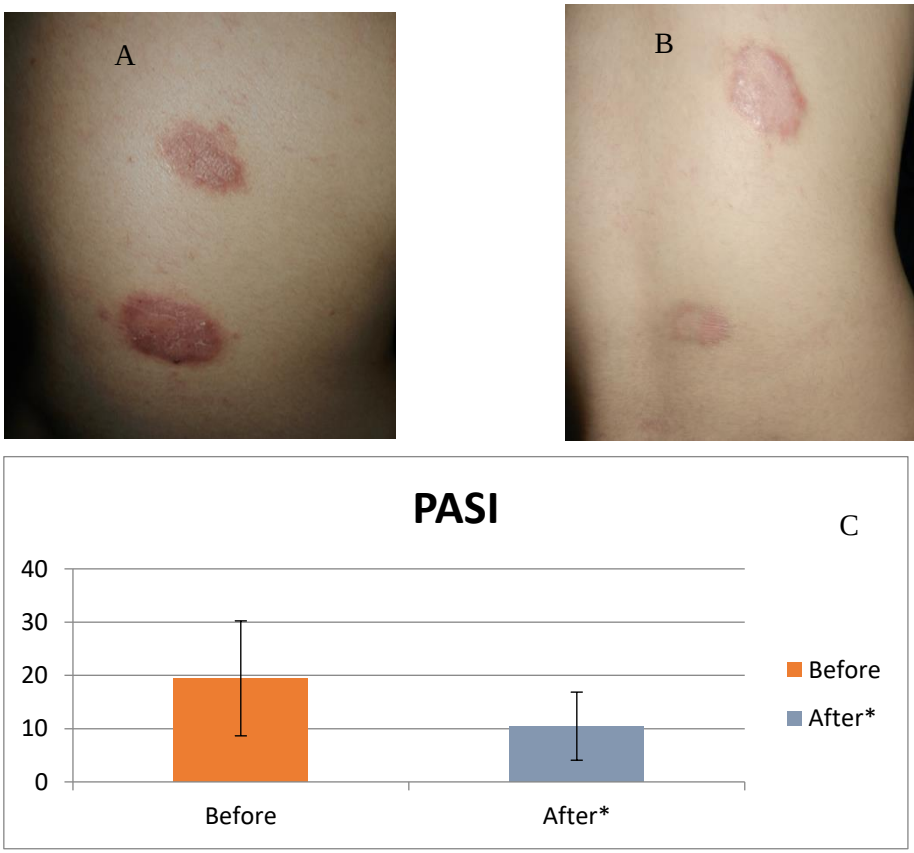

Figure 1: (Turmeric effectiveness in psoriasis treatment. A) (Patient before start of treatment. B) (Patient after 4 weeks of treatment. C) PASI significantly reduced after treatment for 4 weeks from (19.44 ± 10.7) to (10.5 ± 6.3) *(*P = 0.0007)*.

DISCUSSION:

Psoriasis is a chronic inflammatory skin disease. Despite the presence of many therapeutic interventions for psoriasis management, there is no single treatment that offer cure. This fact makes it essential to use treatment modalities for induction of remission followed by other less hazardous treatment options as long-term maintenance therapies. The treatment plan of psoriasis is usually drawn in cycles of alternating therapeutics to induce and maintain remission of the disease. WHO has called upon member states to support efforts for offering patients with psoriasis with more treatment options and to address the shortage

of available treatment modalities patient with psoriasis suffers from **[5]**. There is increasing trend among patients with psoriasis to prefer natural products for treatment since these products are expected to have safer profile compared with the toxicities of traditional therapeutics **[10]**. Curcuma longa (Turmeric) is a rhizomatous plant; with the active constituents is diferuloylmethane (curcumin). The Oral bioavailability of curcumin is controversial. The serum level of curcumin following oral ingestion is low. Whether this results from low absorption because of its hydrophobicity or due to its presence in a bound form or its rapid distribution into cells and tissues is not clear **[13,16]**. Oral curcumin supplements usually is combined with black pepper to increase its bioavailability **[18]**. Curcumin based formulations have been used for treatment of many health problems since ancient times, recently it has been investigated in clinical trials to establish its efficacy. Curcumin has been tried for treatment of many dermatological conditions as acne, photoaging, eczema, atopic dermatitis, psoriasis, vitiligo, pruritus, oral lichen planus, androgentic alopecia and diabetic microangiopathy **[13]**.

Three studies utilized animal models of psoriasis proved the effectiveness of curcumin-based formulations in alleviating psoriasiform phenotype and showed tolerability and safety of the drug **[19–21]**. Kang et al proved that 40 mg/kg oral curcumin was as effective as 40 mmol/kg oral cyclosporine in reversal of psoriasiform phenotype in *keratin 14-VEGF* transgenic mice. The effect of curcumin was associated with reduction of IFN-γ, TNF-α, IL2, IL12, IL22 and IL23 levels along with reduction of activated T cells number. Curcumin group did not show fibrotic kidney changes detected in cyclosporine treated group **[20].** On the other hand, San et al used curcumin in alcohol gel for imiquimode induced psoriasis mouse model. Curcumin gel reduced significantly the imiquimode mediated psoriasiform phenotype while clobetasole prevented the development of psoriasisfom inflammation. Curcumin effect was associated with reducing the level of IL17A, IL17F, IL22, IL1β, TNF- α and IL-6 compared to non-treatment control group **[21]**.Jain and coworkers tested curcumin/tacrolimus co-loaded liposphere gel formula for amelioration of imiquimode induced psoriasis mouse model which proved to be more effective than Betamethasone Valerate 0.1% **[19]**.Few studies addressed curcumin effectiveness for psoriasis in humans. Kurd and coworkers have tested orally administrated curcumin capsules 4.5 gm/d for 12 weeks for psoriasis treatment. Twelve patients were enrolled in the study eight of them continued the study. The response rate was low 16.7 %, however those who responded showed excellent response more than 80% reduction in their PASI. The low response rate was attributed to low oral bioavailability of curcumin so higher doses, coadministration with absorption enhancers, or usage of liposomal formulations were recommended for future studies **[22]**. Carrion-Gutierrez and coworkers combined the orally administered 600 mg curcumin extract containing tablets with UVA and only localized areas were exclusively treated with visible light. Overall, 95% of patients reached PASI 75 benchmark at the end of 18 treatment sessions (8 weeks). 81 % of the visible light exclusively treated areas showed improvement and 30% of the control (not receiving any light treatment) areas showed improvement. This indicated that combination of curcumin and visible light is an effective modality for treatment of psoriasis avoiding the safety concerns of UVA phototherapy. Even the areas did not receive any phototherapy showed improvement which confirmed the effectiveness of orally administered curcumin alone **[23]**. Heng and coworkers studied the effectiveness of topically applied curcumin in alcohol gel in treatment of moderate to severe psoriasis in ten patients. 50% of the curcumin treated group showed 90% improvement of psoriasis after 2-6 weeks of treatment; the other half showed 50-85% improvement after 3-8 weeks of curcumin treatment **[24]**. In another study Sarafian et al used curcumin microemulsion gel twice daily for mild psoriasis patients (n=34) with improvement of PASI before treatment 3.6 to 1.4 after 9 weeks of treatment **[25]**. Since orally administered curcumin showed low number of responders in two studies, we decided to use topically applied formula to avoid poor curcumin bioavailability. Only two reported studies used topical curcumin for treatment of psoriasis. Both studies used gel formula while in our formula an ointment base was chosen since the ointment formula is preferred than gel for dry lesions as in psoriasis. In Heng et al work **[24]** no quantitative assessment of the clinical status of the patients before or after therapy was recorded so their results of 90% improvement was not supported by any clinical data. In Sarafian work the enrolled patients were all of mild psoriasis with 3.6 PASI at the start of treatment, which continued for 9 weeks, and the final PASI score was 1.4 with 62% improvement of the initial PASI **[25]**. Our patients showed more improvement than Sarafian reported, since our patients started at much higher PASI scores (19.44 ± 10.7) and all our patients (100%) showed improvement of their psoriasis with (47% ± 12%) improvement in the baseline PASI. 50% of our patients passed PASI 50 benchmark at 4 weeks treatment. This can be attributed to the ointment

formula in our study. The clinically detected improvement of psoriasis with 4 weeks of treatment was confirmed with the reduction of the psoriasis pathology score from (8.5 ± 1.6) to (3.7 ± 1.1) *(P = 0.0001)*. Heng and coworkers reported that curcumin treatment was associated with reduction in parakeratosis, Ki67 expression, phosphorylase kinase activity and epidermal T cell infiltration [24]. While Sarafian et al only assessed the clinical response **[25]**. Regarding side effects, staining of clothes was evident, however wasn't problematic to all patients and didn't cause any withdrawal. 60% of patients complained of itching of variable degrees and some of them said that itching disappeared after few applications; none of patients reported itching withdraw from the study. Sarafian has reported dryness and irritation affecting 9 % of their patients as side effects **[25]**. Topical treatment modalities for psoriasis are prescribed for patients with mild to moderate psoriasis (typically with PASI < 10) and as adjuvant with phototherapy or systemic therapies for more severe disease. The topical therapeutic modalities include corticosteroids (CCS), Vitamin D analogues, tazarotene, anthraline, salicylic acid, tacrolimus and coal tar. The fastest to induce response is CCS with average start of response is 1-2 weeks while others usually start their response at 6-8 weeks. Reported adverse events with various topical therapeutics include tachyphylaxis, rebound and atrophy associated with topical steroids and irritation reported with calcipotriol, tazarotene, anthralin, salicylic acid and coal tar. That's why combination therapy is usually used. Steroid is used for rapid induction of remission combined with others, most commonly vitamin D analogues; e.g. alternating weekdays and weekend application to reduce the drug associated adverse effects and to avoid the long term adverse effects of steroid. Vitamin D analogues have slower onset of action than steroid but with longer period of remission **[3,4]**. Calcipotriol, a vitamin D analogue showed average of 50 % improvement at 4 week **[26]** and 6 week **[27]** point of application that reached 75% improvement at 12-week point **[26]**. In our study 100 % of patients showed average improvement of 47% ± 12% of baseline PASI with half of the patients already reached PASI 50 benchmark. Comparing calcipotriol treatment to curcumin in alcohol gel, Heng and coworkers reported that the calcipotriol group showed 70 -80 % of improvement in 30% of patients in 4 - 6 months and 50 – 65 % improvement in 70 % of patients after 6- 18 month. This was lower efficacy to their reported 1% curcumin gel efficacy with 90% improvement in 50 % of patients over one month period **[24]**. Based on our work and the reported results of Heng's, Zhu's and Körver's curcumin shows at least, if not better effectiveness, than calcipotriol in treating psoriasis. Regarding reported adverse events Calcipotriol showed skin irritation in 16 % of the enrolled patients that was severe enough to cause 4.2 % of patients to withdraw from the study **[26]**. Despite 60% of our patients reported pruritus however it wasn't severe to cause withdrawal from the study and some of the patients reported improvement of itching with time (temporary). Tazarotene is FDA approved for the treatment of stable plaque psoriasis for up to 20 % body surface area. Weinstein and coworkers reported that 35% of patients used tazarotene showed at least 50% improvement at 4-week assessment point and this percentage increased to 50% of patients at 12-week assessment point **[28,29]**. Compared to tazarotene curcumin showed at least 50% improvement in 50% of patients earlier than tazarotene; as early as 4 weeks. Regarding adverse event, 31% of patients used Tazarotene developed pruritus and skin irritation, which lead to withdrawal in 16 % of study subjects **[29]**. In our study curcumin related pruritus didn't cause any patient withdrawal and was temporary in some patients. Based on the above-mentioned data and our work curcumin ointment is showing similar efficacy to tazarotene and calcipotriol both are established treatment options for psoriasis.

Curcumin effectiveness in psoriasis can be attributed to its anti-inflammatory proapoptotic, antiangiogenic, antiproliferative, antimicrobial and antioxidant capabilities. Curcumin inhibits the production of proinflammatory cytokines e.g. IL1β, IL6, IL8, IL12, IL18, MCP1, TNF-α. All are elevated in psoriasis **[16,30]**. Curcumin inhibits the expression of growth factors involved in differentiation of monocytes, macrophages and other inflammatory cells enriched in psoriatic lesions e.g. GM CSF **[30]**. Curcumin inhibits T cells proliferation and activation through Kv1.3 channels blocking abilities. Curcumin depresses signaling through Kv1.3 channels and inhibits T cells' expression of TNF α, INF γ, IL2, IL8, IL17 and IL22 which ended in amelioration of psoriatic phenotype in mice **[20]**. Curcumin regulates variable transcription factors. Curcumin inhibits NFκB signaling with subsequent reduction in cytokines and adhesion molecules expression e.g., IL6, IL8, ICAM1, VCAM, VEGF and TRAF **[30].** Curcumin, similar to glucocorticoids, downregulates AP-1 transcription factor with subsequent reduction in GM-CSF, VEGF, and anti-apoptotic proteins (Bcl 2, Bcl XL). Curcumin suppresses STAT 3 signaling as well. STAT 3 is not only involved in Th17 differentiation but also VEGF expression **[30]**. Furthermore, curcumin inhibits angiogenesis via suppression of VEGF and TNF-α expression. Curcumin reduces keratinocyte

proliferation via decreasing proinflammatory cytokines and anti-apoptotic proteins **[16,30]**. Curcumin inhibits phosphorylase kinase activity, which is enhanced in psoriasis plaques and is reduced upon disease control with calcipotriol. Phosphorylase kinase regulates the signaling via epidermal growth factor receptor (EGFR), which promotes keratinocyte proliferation **[24,31]**. Curcumin suppresses the expression of EGFR as well **[30]**. Curcumin has antimicrobial properties; it has antibacterial and anticandidal activities [32]. Curcumin shows bactericidal activities against *Staphylococcus aureus* and *Enterococcus faecalis*, *Escherichia coli* and *Pseudomonas aeruginosa* through destruction of bacterial cell membranes [33]. Furthermore, curcumin inhibits *Staphylococcal* bacterial proliferation and increase its sensitivity towards β lactam antibiotics **[32]**. It is known that infection plays a role in initiating and exacerbating psoriasis. *Staphylococcus aureus* and *Streptococcus pyogenes* precipitate psoriasis especially in children in the form of guttate lesions. Skin microbiome differs in patients with psoriasis when compared to healthy controls **[34,35]**.

Furthermore, curcumin has potential photosensitizing nature implied by its the phototoxicity against *Salmonella typhimurium and Escherichia coli* **[16]**. Curcumin has substantial antioxidant activity. Curcumin inhibits lipid peroxidation via scavenging the free radicals by its β diketon group and phenolic rings **[36]**. Curcumin enhances the transcriptional factors control cellular responses to oxidative stresses and the expression of superoxide dismutase and glutathione peroxidase **[30]**. There is increased expression of inducible nitric oxide synthase (iNOS) in psoriasis lesions by both dendritic cells and neutrophils **[37,38]**. Nitric oxide is enriched in psoriasis plaques and is a central molecule in keratinocyte proliferation and differentiation **[39]**. Curcumin downregulates iNOS expression with subsequent reduction in nitric oxide formation **[30]**.

CONCLUSIONS

In this pilot study, the effectiveness and tolerability of turmeric extract-based ointment in the treatment of moderate psoriasis vulgaris was evaluated and proved on both clinical and histopathological levels.

CONFLICT OF INTEREST: None

FINANCIAL DISCLOSURE: None

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To Cite:

Ibrahim, S., Amer, A., Elkashishy, K., Sami, D., Nofal, H., Abdellatif, A. Turmeric Extract-Based Treatment for Psoriasis.*Zagazig University Medical Journal*, 2022; (164-170): -.doi: 10.21608/zumj.2020.20702.1648