

## ORIGINAL ARTICLE

# MELATONIN AS AN ADJUNCTIVE THERAPY WITH ETANERCEPT FOR IRAQI PSORIATIC PATIENTS

Ghadah Ali Al-Oudah<sup>1</sup>, Ihab I. Alkhalifa<sup>2</sup>, Shaimaa M. Mohammed<sup>3</sup>, Ali Ameer Al-Ameedee<sup>4</sup>

Departments of <sup>1</sup>Clinical pharmacology, <sup>3</sup>Clinical Biochemistry, College of Pharmacy, Al-Mustaqbal University, Babylon, <sup>2</sup>Department of Pharmacy department, Al-Rasheed University College ,Baghdad, Iraq, <sup>4</sup>Babil Health Directorate, Iraqi Ministry of Health, Iraq

## ABSTRACT

**Background:** Treatment with melatonin as anti-oxidant's supplements may has a role in psoriasis with diminished anti-oxidant system function. This medical trial targets the efficiency of melatonin as an adjunctive management with etanercept in mitigating the severity of chronic plaque psoriasis.

**Material & Methods:** A double-blind prospective randomized clinical trial study conducted over a three-month period from 1<sup>st</sup> January 2022 to 30<sup>th</sup> March 2022 at Department of Dermatology at Merjan Teaching Hospital in Babylon City / Iraq to assess the efficiency of melatonin as adjuvant therapy with etanercept in the management of psoriasis. Sixty adult patients (18 female, 42 males; age range 17-60 years) with psoriasis were selected through convenience sampling & distributed randomly into (2) groups. The group (A, n=30) received etanercept and placebo, whilst Group (B, n=30) received etanercept plus melatonin, orally, once daily. Psoriasis Area and Severity Index scores as a severity measuring index and blood levels of malondialdehyde and superoxide dismutase were assessed at baseline and at the completion of the intervention.

**Results:** A significantly improvement in the PASI score and oxidative indicators (MDA and SOD) were observed following both biological therapy and adjunctive melatonin treatment; For group A representing a 69.14% improvement. While for group D, PASI score, MDA and SOD representing an 81.87% improvement.

**Conclusion:** The daily administration adjuvant therapy 5 mg melatonin supplementation with etanercept to patients with psoriasis for 3months had reduce the severity of disease in a short period time.

**KEY WORDS:** Anti-Oxidant; Etanercept; Melatonin; Oxidative Stress; Psoriasis.

**Cite as:** Al-Oudah GA , Alkhalifa II, Mohammed SM, Al-Ameedee AA. Melatonin as an adjunctive therapy with etanercept for iraqi psoriatic patients. Gomal J Med Sci 2025 Jul-Sep;23(3):313-7. <https://doi.org/1046903/gjms/23.3.1921>

## INTRODUCTION

The immune system is playing a role in the chronic inflammatory skin disorder known as psoriasis. Around the world, 2-3% of people suffer from psoriasis with equal incidence both in males and females.<sup>1,2</sup> Psoriasis is a multiorgan idiopathic clinical condition. The interaction of immune cells and keratinocytes is a key pathophysiology

of psoriasis.<sup>3</sup> Strong hypotheses have linked it to defect in lymphokine release and oxidative stress, that is stress related to oxygen. Recent research suggests that diminished anti-oxidant system function or increase formation of Reactive Oxygen Species (ROS) could be main reasons in pathogenesis of this illness. ROS are formed by the partial reducing of oxygen molecule that rise from consumption of oxygen and cellular metabolism.<sup>4,5</sup> ROS-mediated oxidative stress has been shown to be contributed in a wide-ranging of the biological reactions, including peroxidation of lipid, alteration of DNA, and the release of cytokines which related to the inflammation. These processes may have played a role in etiology of inflammatory diseases related to skin, like psoriasis.<sup>6</sup>

There may be some evidence for oxidative stress playing a role in the pathophysiology of psoriasis in psoriatic patients, given the higher plasma

## Corresponding Author:

Dr. Ihab I. Alkhalifa  
Assistant Professor  
Department of Pharmacy  
Al-Rasheed University College  
Baghdad, Iraq  
E-mail: [dr\\_ihab75@yahoo.com](mailto:dr_ihab75@yahoo.com)

**Date Submitted:** 02-01-2025

**Date Revised:** 25-07-2025

**Date Accepted:** 08-08-2025

MDA levels and lower erythrocyte SOD levels.<sup>7</sup> Furthermore, the idea that oxidative stress playing a role in the pathophysiology of psoriasis may be supported by the clinical improvement or laboratory changes that follow anti-oxidant therapy in these patients.<sup>8</sup> This suggests that targeting oxidative stress could be a potential therapeutic strategy for managing psoriasis symptoms and improving overall skin health.

A hormone of melatonin is released primarily by the Pineal Gland in response to darkness, circulates throughout the body, influencing various systems. It circulates throughout the body, influencing various systems. Melatonin's primary function is regulating sleep-wake cycles and circadian rhythms. Beyond this, it acts as an anti-oxidant, protecting cells from damage.<sup>9</sup> Melatonin appears its special effects mainly through contacts with specific receptors, MT1 and MT2, found in many organs. Its roles extend to immune function, reproduction, mood regulation, and even cancer prevention.<sup>10</sup> Melatonin activity as anti-oxidant and potent free radical scavenger, made it a potential adjuvant therapeutic target for many chronic diseases, as it can lessen the harmful effects of a wide range of environmental and chemical exposures that cause oxidative stress.<sup>11-14</sup>

Melatonin can simply pass-through cell membranes and enter -all cells of the body, then influence on the function of the variety tissues because of its high lipophilicity. The metabolism of melatonin proceeds quickly, and after being administered exogenously, its half-life in humans varies from 10 to 60 minutes. The liver is primarily responsible for deactivating it, and it come out through the urine.<sup>15</sup> Melatonin's anti-oxidant properties are mediated by multiple pathways, additionally to direct elimination free radicals like (ROS) and (RNS) from activated skin cells or mitochondrial oxidative respiration.<sup>16</sup> In addition to regulating antioxidant enzymes to indirectly lower the concentration of free radicals, melatonin also enhanced the activities of (GPx), catalase, and SOD. It also elevated the glutathione (GSH) expression in fibroblasts, healthy controls skin, and diabetes mellitus patients.<sup>17</sup>

The melatonin-enhanced anti-oxidant enzymes might lessen ROS, stop the oxidative damaging to DNA, and prevent ultraviolet B (UV B) light-induced antioxidant depletion in human skin.<sup>18</sup> This medical trial target the efficiency of melatonin assessment as an adjunctive management with etanercept in mitigating the severity of chronic plaque psoriasis among Iraqi patients within a three-month timeframe.

## MATERIALS & METHODS

A double-blind prospective randomized clinical trial study was conducted over three months period from

1<sup>st</sup> January 2022 to 30<sup>th</sup> march 2022 on 60 patients with chronic plaque psoriasis at the Department of Dermatology at Merjan Teaching Hospital in Babylon City / Iraq. Patients were selected through convenience sampling method. Participants were allocated into 2 groups through computer generated random digit tables method. Group (A, n=30) is receiving etanercept [ 50mg, s/c, once weekly] and placebo, (corn starch in capsulation). while Group (B, n=30) is receiving etanercept [50mg, s/c, once weekly] plus melatonin [5 mg, orally, once daily at the night].

All patients were clinically assessed by the same dermatologist to establish severity of disease using (PASI) scores as a severity measuring index. Furthermore, the patients' sera were used to measure the plasma levels of (MDA) and superoxide dismutase (SOD), which were evaluated at zero and at the end of the intervention, by Enzyme-linked immunosorbent assay method by using the corresponding kit. The data was analyses using (SPSS) for conducted software (V,27) and GraphPad Prism 8. Descriptive statistics for study items expressed as frequency and percentages. Continuous variables also expression as mean  $\pm$  SE. Independent T- test was applied.

## RESULTS

Prior to the study's enrollment (zero time), every psoriatic patient in both groups had high PASI scores, a sign of severe or intense psoriasis symptoms as presented in table (1). Management with 50mg Etanercept only for (group A) caused significantly decrease in PASI score and around 69.14% (imp%) after 3months of therapy comparing to pre-treating value, and by combined adjunct therapy melatonin with etanercept for (group B) resulting in extra improving register about 81.87% improvement for PASI score, this reduction was highly significant.

Table (2) shows that there was no significant change in mean blood levels of MDA and SOD in all patient's groups at base line (zero time). Treatment with Etanercept, (group A) resulted in a high significant decrease in mean serum MDA, mean  $\pm$ SE was 4.27), after 3months treatment, as compared to baseline value 6.25 pg/ml), ( $p < 0.0001$ ). Meanwhile, treatment of psoriatic patients with the group B, using (Etanercept + melatonin) showed high significant reduction ( $p < 0.0001$ ) after treatment (4.34) when compared with Pre-treatment values (6.70).

The Mean  $\pm$ SEM of SOD in group-A, as existing in table (2) presented a high significant increase ( $p < 0.0002$ ) next 3 months management used Etanercept (397.9) when compared with base line level before treatments (190.5). Group B (Etanercept + melatonin) showed also a high significant increased after treatment (564.1pg/ml) when compared with patients Pre-treatment values (203.4pg/ml).

**Table 1: Number of participants in both groups based on PASI score.**

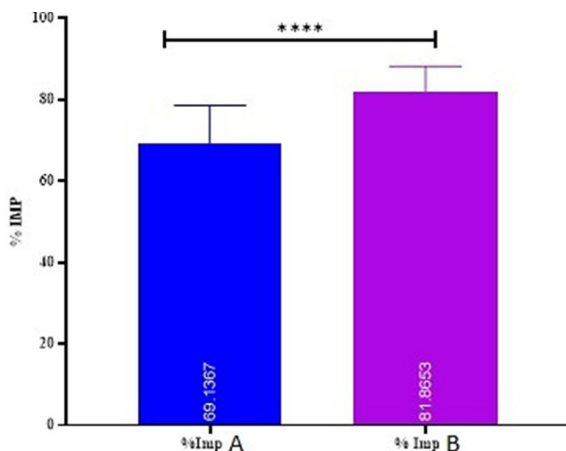
Group	N	PASI score Pre- Treatment	PASI score Post-Treatment	PASI improvement %	P- value
A	30	21.66 .95	6.42 0.26	69.14	.000*0
B	30	21.50± 1.2	3.56±0.12	81.87	.000*0

Each value represented mean ± SEM; group-A: patients were treated with Etanercept + placebo, group-B: patients were treated with Etanercept + melatonin

**Table (2): Effects of Treatment with Etanercept alone or with Melatonin on serum MDA & SOD level**

Group	N	MDA mean ±SE Pre- Treatment	MDA mean ±SE Post- Treatment	P- value	SOD mean ± SE Pre- Treatment	SOD mean ± SE Post- Treatment	P- value
A	30	6.25	4.27	<0.0001	190.5	397.9	0.0002
B	30	6.70	4.34	<0.0001	203.4	564.1	<0.0001

Each value was represented Mean ± SEM; group-A: patients were treated with Etanercept + placebo, group-B: patients were treated with Etanercept + melatonin daily single dose.



**Fig (1) Mean % Imp Group-A treatment with Etanercept, Mean % Imp Group-B treatment with Etanercept and melatonin**

## DISCUSSION

Psoriasis is a systemic condition characterized by cutaneous manifestations. Individuals with (moderate – severe) psoriasis experience a significantly diminished QOL. PASI is a commonly using a metric to assess disease severity. Oxidative stress, which result from an imbalance between Pro-oxidant and anti-oxidant, is implicated in the pathophysiology of chronic inflammatory diseases such as psoriasis.<sup>19</sup> Our findings indicate that melatonin supplementation in conjunction with biological therapy enhances treatment response and accelerates recovery time. According to previous studies oxidative stress is involving in the development of chronic diseases. Melatonin has been proposed to protect against oxidative stress by scavenging free radicals and activating anti-oxidant enzymes.<sup>20</sup> Melatonin pos-

sesses stronger anti-inflammatory and anti-oxidant properties, which may be direct linkage chronic skin inflammation and sleep irregularities characteristic of atopic dermatitis.<sup>14</sup>

The anti-inflammatory, anti-oxidant, and immune-modulatory properties of the melatonin have been a focus of numerous study activities lately. Melatonin employs defensive special effects against UV solar skin injury through its adaptable as scavenger of direct radical and stimulator actions of anti-oxidative enzyme, in addition of its metabolites.<sup>2</sup> Melatonin's anti-oxidant capacity also involves indirect effects. It up regulates several anti-oxidant enzymes like (SOD), (GPx), and glutathione reductase. Conversely, it down regulates pro-oxidant enzymes, particularly 5- and 12-lipoxygenases and nitric oxide (NO) synthases.

Furthermore, melatonin exerts significant anti-inflammatory actions by inhibited NO production and decreasing the activation of NF-κB, a key inflammatory signaling molecule. This anti-inflammatory effect occurs at numerous molecular steps, including reducing the nitric oxide synthase-2 (NOS-2) expression and prostaglandin (PG)-endoperoxide synthase-2 (COX-2), thereby inhibited NO and PG production.<sup>17</sup> Additionally, melatonin controls anti-oxidant enzymes to indirectly lower the concentration of free radicals by up regulating anti-oxidant defense systems such as (GPx), (CAT), and (SOD). It also increases the expression of (GSH) in fibroblasts, the skin of healthy controls, and patients with diabetes mellitus.<sup>20</sup> The improved anti-oxidant enzymes by melatonin may lessen ROS, and stop the oxidative damage to DNA, and stop ultraviolet (UV-B) light-induced anti-oxidase exhausted in human skin.<sup>19</sup>

Since the melatonin is basically nontoxic, easily ac-

cessible OTC in a variety of preparations, and several of its metabolites fall under the category of products from nature, their topical use and trans epidermal supply is a promising area for further investigation in future dermato-therapy and protective medication of skin. The melatonin and its metabolites can affect many features of human skin physiology.<sup>4</sup> This study elucidated the possible beneficial effects on using ROS scavengers for enhanced psoriasis treatment. Additionally, it gives an insight for the current state of nutrient and non-drug therapies for transdermal psoriasis treatment, highlighting their advantages and limitations. Based on these findings, we propose potential avenues for future research in developing novel nutrient or non-drug therapies targeting ROS in skin diseases.

## CONCLUSION

In order to improve therapeutic outcomes against psoriasis, this study will highlight the underlying molecular mechanism of ROS-based scavengers. It will also provide an overview of recent developments regarding the benefits and drawbacks of applying nutrient or non-drug therapy for transdermal administration and provide an update on possible future directions for this type of therapy in relation to ROS-related skin diseases.

**Ethical approval:** Taken from Department of Dermatology at Merjan Teaching Hospital in Babylon city / Iraq

## REFERENCES

- Raharja A, Mahil SK, Barker JN. Psoriasis: a brief overview. *Clin Med (Lond)*. 2021;21(3):170–3. <https://doi.org/10.7861/clinmed.2021-0257>
- Al-Oudah GA, Al-Hattab MK, Sahib AS, Mohammed SM. The effect of metformin and biological therapy on insulin resistance in Iraqi psoriatic patients. *Int J Drug Deliv Technol*. 2023;13(1):224–7. <https://doi.org/10.25258/ijddt.13.1.35>
- Al-Oudah GA, Mohammed MM, Al-Abbassi MG, Zaboon ZH, Al-Ameedee AA. The combined use of metformin and adalimumab in Iraqi psoriatic patients. *J Res Technol Dev Disabil*. 2023;6(2 Suppl):292–6.
- Napolitano G, Fasciolo G, Venditti P. Mitochondrial management of reactive oxygen species. *Antioxidants (Basel)*. 2021;10(11):1824. <https://doi.org/10.3390/antiox10111824>
- Huang MZ, Li JY. Physiological regulation of reactive oxygen species in organisms based on their physicochemical properties. *Acta Physiol (Oxf)*. 2020;228(1):e13351. <https://doi.org/10.1111/apha.13351>
- Ramessur R, Corbett M, Marshall D, Acencio ML, Barbosa IA, Dand N, et al. Biomarkers of disease progression in people with psoriasis: a scoping review. *Br J Dermatol*. 2022;187(4):481–93. <https://doi.org/10.1111/bjd.21627>
- Kizilyel O, Akdeniz N, Metin MS. Investigation of oxidant and antioxidant levels in patients with psoriasis. *Turk J Med Sci*. 2019;49(4):1085–8. <https://doi.org/10.3906/sag-1807-257>
- Zhang Y, Li Z, Ma Y, Mu Z. Association of total oxidant status, total antioxidant status, and malondialdehyde and catalase levels with psoriasis: a systematic review and meta-analysis. *Clin Rheumatol*. 2019;38(10):2659–71. <https://doi.org/10.1007/s10067-019-04676-1>
- Reiter RJ, Tan DX, Sharma R. Historical perspective and evaluation of the mechanisms by which melatonin mediates seasonal reproduction in mammals. *Melatonin Res*. 2018;1(1):59–77. <https://doi.org/10.32794/mr11250004>
- Ahmad SB, Ali A, Bilal M, Rashid SM, Wani AB, Bhat RR, et al. Melatonin and health: insights of melatonin action, biological functions, and associated disorders. *Cell Mol Neurobiol*. 2023;43(6):2437–58. <https://doi.org/10.1007/s10571-023-01324-w>
- Farid A, El-Dewak M, Safwat G, Diab A. Anti-apoptotic and antioxidant effects of melatonin protect spleen of whole-body  $\gamma$ -irradiated male Sprague-Dawley rats. *Int J Radiat Res*. 2021;19(4):861–72. <https://doi.org/10.52547/ijrr.19.4.12>
- Carlioni S, Facchinetti F, Pelizzi N, Buonocore G, Balduini W. Melatonin acts in synergy with hypothermia to reduce oxygen-glucose deprivation-induced cell death in rat hippocampus organotypic slice cultures. *Neonatology*. 2018;114(4):364–71. <https://doi.org/10.1159/000491859>
- Motta-Teixeira LC, Machado-Nils AV, Battagello DS, Diniz GB, et al. The absence of maternal pineal melatonin rhythm during pregnancy and lactation impairs offspring physical growth, neurodevelopment, and behavior. *Horm Behav*. 2018;105:146–56. <https://doi.org/10.1016/j.yhbeh.2018.08.006>
- Jaworek AK, Szepietowski JC, Hałubiec P, Wojas-Pelc A, Jaworek J. Melatonin as an anti-oxidant and immunomodulator in atopic dermatitis – a new look on an old story: a review. *Antioxidants (Basel)*. 2021;10(8):1179. <https://doi.org/10.3390/antiox10081179>
- Tan DX, Chen LD, Poeggeler B, Manchester LC, Reiter RJ. Melatonin: a potent, endogenous hydroxyl radical scavenger. *Endocr J*. 1993;1:57–60.
- Boutin JA, Kennaway DJ, Jockers R. Melatonin: facts, extrapolations and clinical trials. *Biomolecules*. 2023;13(6):943. <https://doi.org/10.3390/biom13060943>
- Suwannakot K, Sritawan N, Prajit R, Aranarochana A. Melatonin protects against the side effects of 5-fluorouracil on hippocampal neurogenesis and ameliorates antioxidant activity in an adult rat hippocampus and prefrontal cortex. *Antioxidants (Basel)*. 2021;10(4):615. <https://doi.org/10.3390/antiox10040615>
- Al-Oudah GA, Sahib AS, Al-Hattab MK, Al-Ameedee AA. Effect of CoQ10 administration to psoriatic Iraqi patients on biological therapy upon severity

- index (PASI) and quality of life index (DLQI) before and after therapy. *J Popul Ther Clin Pharmacol*. 2022;29(2):e52–60. <https://doi.org/10.47750/jptcp.2022.931>
19. Zarezadeh M, Barzegari M, Aghapour B, Adeli S. Melatonin effectiveness in amelioration of oxidative stress and strengthening of antioxidant defense system: findings from a systematic review and dose-response meta-analysis of controlled clinical trials. *Clin Nutr ESPEN*. 2022;48:109–20. <https://doi.org/10.1016/j.clnesp.2022.01.038>
20. Tan DX, Manchester LC, Esteban-Zubero E, Zhou Z, Reiter RJ. Melatonin as a potent and inducible endogenous antioxidant: synthesis and metabolism. *Molecules*. 2015;20(10):18886–906. <https://doi.org/10.3390/molecules201018886>
21. González-Flores D, López-Pingarrón L, Castaño MY. Melatonin as a coadjuvant in the treatment of patients with fibromyalgia. *Biomedicines*. 2023;11(7):1964. <https://doi.org/10.3390/biomedicines11071964>
22. Xu J, Chen H, Qian H, Wang F, Xu Y. Advances in the modulation of ROS and transdermal administration for anti-psoriatic nanotherapies. *J Nanobiotechnol*. 2022;20(1):448. <https://doi.org/10.1186/s12951-022-01651-y>

#### CONFLICT OF INTEREST

Authors declare no conflict of interest.  
GRANT SUPPORT AND FINANCIAL DISCLOSURE  
None declared.

#### AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	GAA, IIA
Acquisition, Analysis or Interpretation of Data:	GAA, IIA, SMM, AAA
Manuscript Writing & Approval:	GAA, IIA, SMM, AAA

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



Copyright © 2025. Ghadah Ali Al-Oudah, et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License, which permits unrestricted use, distribution & reproduction in any medium provided that original work is cited properly.