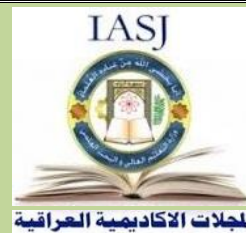




## Tikrit Journal of Pharmaceutical Sciences

Journal Homepage: <http://tjo-ps.com>



### Ginger Extract Reduces Oxidative Stress and Improves the Clinical Outcomes in Patients with Alopecia Areata

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DOI: <http://dx.doi.org/10.25130/tjops.15.1.03>

#### **ARTICLE INFO.**

##### **Article history:**

-Received: 20 / 12 / 2019

-Accepted: 31 / 3 / 2020

-Available online: 19 / 8 / 2020

##### **Keywords:**

*Alopecia areata, oxidative stress, hair loss, prednisolone.*

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#### **Abstract**

**A**lopecia areata is a common disorder of known autoimmune etiology and mostly treated with oral steroids to stimulate new hair growth with high chances of side effects. The present study was designed to assess the clinical significance of ginger in improving oxidative stress and reducing the dose of prednisolone in patients with alopecia. Forty patients (19 female and 21 male), with different lesions of stable localized on the scalp were enrolled in this pilot prospective open-label clinical study. Exclusion criteria include the use of any medication that may influence the course of the disease. The patients were allocated into two groups and treated with 500 mg of ginger powder once daily for 60 days with either 10 mg or 100 mg/day prednisolone tablets. Blood samples were obtained at zero time, day-30 and day-60 and utilized for the evaluation of the erythrocytes contents of reduced glutathione, and malondialdehyde. The change in body weight, incidence of acne and the hair loss were also monitored. The glutathione and malondialdehyde were compared with those of 20 healthy subjects served as control group. The results revealed that two-month treatment with ginger improved the rate of hair growth probably by attenuating free radicals-induced damage on immune system and addressed the possibility of reducing prednisolone dose from 100 mg to 10 mg administered each other day. In conclusion, the use of ginger may have a role in protecting radical-induced damage and decreasing side effects of high prednisolone dose in patients with alopecia areata.

مستخلص الزنجبيل يقلل من الإجهاد التأكسدي ويحسن النتائج السريرية في المرضى الذين يعانون من داء الثعلبية

اشواق نجم الدين عباس

### الخلاصة

يعتبر داء الثعلبية من أمراض المناعة الذاتية الشائعة ويتم علاجه غالبا باستخدام جرعة عالية من البريدنيزولون الذي يترافق مع زيادة في مخاطر الأعراض الجانبية. تم تصميم هذه الدراسة لتقييم فعالية الزنجبيل في تحسين معايير فرط الأوكسدة وتقليل جرعة البريدنيزولون المستخدم لعلاج المرض. تم اختيار 40 مريضا (19 اناث و 21 ذكور) من المصابين بداء الثعلبية المستقر للمشاركة في هذه الدراسة السريرية. تم تقسيم المرضى الى مجموعتين وتم علاجهم بجرعة مقدارها 500 ملغم/يوم من مادة الزنجبيل لمدة 60 يوم إضافة الى 10 ملغم/يوم أو 100/يوم ملغم من مادة البريدنيزولون عن طريق الفم. تم أخذ عينات من الدم قبل البدء بالعلاج وبعد 30 و 60 يوم على التوالي، واستخدمت لقياس مستوى الكلوتاتيون و المالونديالدهيد، بالإضافة الى قياس مستوى التغير في نمو الشعر في الرأس والزيادة في وزن الجسم إضافة الى ظهور حب الشباب. أظهرت النتائج أنه بعد 60 يوم من استخدام الزنجبيل انخفض مستوى المالونديالدهيد وارتفع مستوى الكلوتاتيون في الكريات الحمراء إضافة الى احتمال خفض جرعة البريدنيزولون من 100 ملغم الى 10 ملغم. كما أدى العلاج الى تحسن ملموس في نمو الشعر والحد من ظهور حب الشباب. يمكن الاستنتاج بأن استخدام الزنجبيل قد يكون له دور في الحماية من تأثير فرط الأوكسدة الناتجة عن المرض وكذلك الحد من الأعراض الجانبية الناتجة عن استخدام جرعة عالية من البريدنيزولون اثناء علاج داء الثعلبية

## Introduction

Alopecia areata (AA) is a common, unpredictable, non-scarring form of hair loss<sup>(1-4)</sup>. This disorder affects all age groups with a higher prevalence in children and adolescents<sup>(4)</sup>. Although the causes are not well characterized, its etiology is mostly associated with an alteration in the immunological responses of the biological system<sup>(5,6)</sup>. Although many pharmacological approaches are utilized for the management of AA, the current treatments are not directly targeting the etiology of the disorder but rather the resulting inflammatory consequences and the growth inhibitory factors produced by this response<sup>(5,6)</sup>. Moreover, the use of many effective agents in this regard may be associated with serious adverse effects that limit continuous and chronic use of these agents<sup>(7)</sup>. In this regard, the use of high systemic doses of corticosteroids (e.g., prednisolone) alone or in combination with topical agents<sup>(8-10)</sup> is associated with serious adverse effects including metabolic dysregulation, hypertension and weight gain<sup>(11,12)</sup>. Meanwhile, the use of natural supplements with powerful antioxidant properties for treatment of many chronic disorders including AA was considered as a common practice; this may be attributed to the significant

amelioration of the oxidative stress state accompanied with AA pathogenesis and improvement of the antioxidant capacity of the affected patient; this can influence the disease severity and improves treatment outcomes<sup>(13)</sup>. Although many natural agents including quercetin, *Houttuynia cordata*, *Perilla frutescens* and green tea are tried in experimental models of AA and clinical setting with inadequate evidence, some of the results seem to be promising<sup>(14-16)</sup>. The ginger extract (*Zingiber officinale* (L.) Rosc) is a well known product and widely used for its pleiotropic properties that includes antioxidant, anti-inflammatory, hypoglycemic, anticancer and antibacterial activities<sup>(17-20)</sup>. The present study was designed to evaluate the role of ginger extract in the amelioration of oxidative stress in patients with alopecia areata and the possibility of reducing the dose of prednisolone during treatment.

## Patients and Methods

### Participants

Enrollment of AA patients, intervention and the analysis of outcomes were performed during January-November 2017 in a private dermatology clinic, Al-Rusafa, Baghdad. For consistency, the AA diagnosis was performed by a consultant dermatologist according to the

National Alopecia Areata Foundation guidelines<sup>(18)</sup>. In the present study, a total of 62 AA patients were screened for eligibility and only 40 patients met the inclusion criteria (19 females, 21 males). Twenty healthy subjects (8 females, 12 males) age- and sex-matched with the AA patients were enrolled in the present study and served as a control group. As inclusion criteria, the average age of the patients ranged from 17 to 45 years; in addition, all the included AA patients have no other chronic illnesses or a history of chronic drug use. The severity of AA was assessed by combination of hair loss and hair density. According to the Severity of Alopecia Tool (SALT) scores, the cases are ranked into 5 categories that represent subgrouping of percent scalp hair loss, as S1, S2, S3, S4 and S5. All the AA patients had not treated previously with any systemic therapy such as corticosteroids, minoxidil, or anthralin within the last two months. They also were not exposed to a topical therapy that affects cellular immunity or photo chemotherapy.

### **Study Design**

The eligible AA patients were invited to participate in this prospective open-label clinical study. Firstly, all participants were addressed about the study protocol by providing a full description of the objectives, benefits and the expected adverse events of the administered treatment during the study. This open-label pilot clinical study was approved by the local ethical committee of the College of Medicine, University of Sulaimani (CS-1/9-2018). All participants were asked to sign informed consent before enrollment in the study. At the first visit, baseline data were obtained from the participants, and the AA patients were allocated into two groups using simple randomization method based of 1:1 ratio; the 1<sup>st</sup> group (20 patients) was treated with 100 mg/day prednisolone tablets while the other 20 patients received 10 mg/day prednisolone tablets (2<sup>nd</sup> group);

both groups concomitantly administered a single capsule/day containing 500 mg of a standard ginger powder (Green Plants of Life Pharmaceuticals Co., Iran) one hour after the breakfast for 60 days. The ginger capsules were provided to the patients in monthly bases to insure compliance with the treatment protocol. The AA patients were advised to follow a modified diet and physical activity plan, and avoid consumption of any dietary supplements and other treatments that may interfere with the study outcome. To ensure compliance of the participants about ginger capsules consumption, phone calls were made at the end of each 30 days. For comparison of the biochemical data, 20 healthy subjects age matched with patients were selected as a control group (3<sup>rd</sup> group).

### **Outcomes measurement**

#### **Clinical outcome**

The response rate to the treatment was followed by measurement of the size of alopecic area, in addition to the side effects of the systemic steroid through monitoring the increase in body weight and appearance of signs of acne. The effects of ginger extract when used with either 10 mg or 100 mg prednisolone were evaluated on hair growth using the pull test. The pull test enables the evaluation of diffuse scalp hair loss. Gentle traction was exerted on a bunch of hairs (about 60) in three areas of the scalp (frontal, temporal, and occipital) and the number of extracted hairs was counted<sup>(21)</sup>. The dermatologist takes a few strands between the thumb and forefinger and pulls them gently.

#### **Blood sampling and analysis of markers**

Venous blood samples (10 ml) were obtained from the AA patients at zero time, day-30 and after 60 days following an overnight fasting, kept in heparinized tube on ice at 4°C. The blood was centrifuged for 30 minutes at 400 x g and 20°C to obtain the erythrocytes fraction

utilizing a standard procedure<sup>(22)</sup>. Only single blood sample was obtained from subject in the control group and utilized for comparison. Using standard methods, the isolated erythrocytes were utilized for the assessment of reduced glutathione (GSH)<sup>(23)</sup> and malondialdehyde (MDA)<sup>(24)</sup>. The hemoglobin content of the erythrocytes was measured using Beckman AU5800 automatic blood analyzer (Beckman Coulter, Brea, CA, USA).

### **Statistical analysis**

Data was analyzed using GraphPad prism software 5.1 (GraphPad Software Inc., La Jolla, CA, USA). The results were expressed as numbers and percentages or means $\pm$ SD. Nonparametric continuous variables were compared with the Mann-Whitney U test. The parametric variables were compared using paired *t*-test for to compare the same mean in two occasions and unpaired *t*-test to compare means of different groups. *P* values < 0.05 were considered as statistically significant.

### **Results**

Table 1 showed the characteristic features of the AA patients enrolled in the study. Table 2 showed that the MDA content of the erythrocytes in AA patients was significantly elevated in both treatment groups (before treatment) compared with that reported in healthy control group. The combination of ginger extract (500mg/day) with either 10 mg or 100 mg of prednisolone decreases significantly the erythrocyte MDA concentration after 30 days compared with the baseline value and this significant reduction of the MDA content was continued after 60 days of treatment and found to be comparable in both

groups. In Table 3, the already reduced glutathione (GSH) content of the erythrocytes in AA patients before treatment was significantly decreased in both treatment groups compared with that reported in healthy control group. The combination of ginger extract (500mg/day) with either 10 mg or 100 mg of prednisolone increases significantly the erythrocytes GSH concentrations after 30 days compared with the baseline value; this significant elevation of the erythrocytes GSH content was continued after 60 days of treatment and found to be similar in both groups. Table 4 demonstrates the influence of using different doses of prednisolone with ginger extract on the body weight of the AA patients. This treatment approach produces significant increase in the body weight after 30 and 60 days of treatment and their values are comparable in both groups throughout the entire period of treatment. In table 5, the severity of acne formation (the side effect of using corticosteroids) was found to be lower in the group treated with the lower dose of prednisolone (10 mg/day) compared with the higher dose. Regarding the influence of using ginger on the clinical features of hair loss, Figure 1 showed that there is no significant difference ( $P=0.19$ ) between the two treatment groups regarding the percent reduction in hair pull test after 30 days of treatment. However, at day-60 the percent reduction in hair pull test of the group treated with 10 mg prednisolone + 500 mg ginger was significantly higher than that of the group treated with 100 mg prednisolone + 500 mg ginger ( $P<0.001$ ).

**Table (1):- The demographic and base-line characteristics of patients with alopecia areata**

Parameter	Mean.	SD
Age mean±SD (Year)	25.7	8.0
Disease duration mean±SD (Year)	6.2	1.2
<i>Gender</i>	No.	%
Male	21	52.5
Female	19	47.5
<i>SALT* score</i>		
S1	14	35.0
S2	12	30.0
S3	6	15.0
S4	6	15.0
S5	2	5.0
Total	40	100.0

\*SALT: Severity of Alopecia Tool

**Table (2):- Effect of the using 500 mg ginger extract with prednisolone tablets (10 or 100 mg/day) on the erythrocytes MDA contents in patients with alopecia areata.**

Treatment group	Erythrocyte MDA (nmol/g Hb)		
	Pre-treatment	Day-30	Day-60
Healthy subjects (n=20)	0.04±0.008	-	-
10 mg prednisolone+Ginger extract (n=20)	0.91±0.05* <sup>a</sup>	0.32±0.02 <sup>b</sup>	0.12±0.01 <sup>c</sup>
100 mg prednisolon+Ginger extarct (n=20)	0.92±0.04* <sup>a</sup>	0.32±0.01 <sup>b</sup>	0.13±0.02 <sup>c</sup>

Values are presented as mean±SD; n: number of subjects;\* significantly different compared with the healthy subjects(*t*-test for two indendent

samples); values with non-identical superscripts (a,b,c) within the same treatment group are significantly different (paired *t*-test; *P*<0.05).

**Table (3):- Effect of the using 500 mg ginger extract with prednisolone tablets (10 or 100 mg/day) on the erythrocytes GSH contents in patients with alopecia areata**

Treatment group	Erythrocyte GSH (µmol/g Hb)		
	Pre-treatment	Day-30	Day-60
Control (n=20)	23.2±3.7	-	-
10 mg prednisolone+Ginger extract (n=20)	8.3±0.51* <sup>a</sup>	13.0±0.42 <sup>b</sup>	19.3±0.74 <sup>c</sup>
100 mg prednisolon+Ginger extarct (n=20)	8.1±0.73* <sup>a</sup>	12.8±0.47 <sup>b</sup>	18.9±0.76 <sup>c</sup>

Values are presented as mean±SD; n: number of subjects;\* significantly different compared with the healthy subjects(unpaired *t*-test); values with non-

identical superscripts (a,b,c) within the same treatment group are significantly different (paired *t*-test; *P*<0.05).

**Table (4):- Effect of the using 500 mg ginger extract with prednisolone tablets (10 or 100 mg/day) on the changes in body weight of patients with alopecia areata**

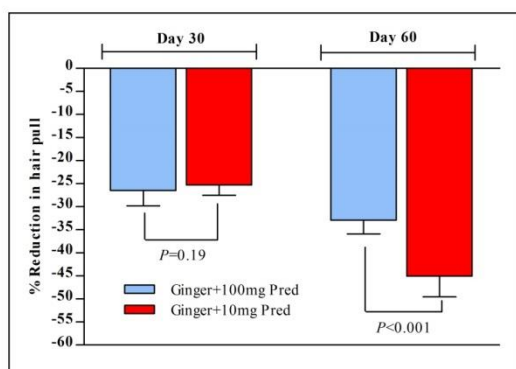
Treatment group	Body weight (Kg)		
	Pre-treatment	Day-30	Day-60
10 mg prednisolone+Ginger extract (n=20)	69.6±8.6 <sup>a</sup>	71.3±8.5* <sup>b</sup>	72.4±8.5* <sup>c</sup>
100 mg prednisolon+Ginger extarct (n=20)	67.2±5.3 <sup>a</sup>	70.3±5.2* <sup>b</sup>	77.1±4.7* <sup>c</sup>

Values are presented as mean±SD; n: number of subjects;\* significantly different compared with pre-treatment values(unpaired t-test); values with non-

identical superscripts (a,b,c) within the same treatment group are significantly different (paired t-test; P<0.05).

**Table (5):- Effect of the using 500 mg ginger extract with prednisolone tablets (10 or 100 mg/day) on the severity of acne formation in patients with alopecia areata**

Treatment group	Presence of Acne		
	Pre-treatment	Day-30	Day-60
10 mg prednisolone+Ginger extract (n=20)	negative	+	+
100 mg prednisolon+Ginger extarct (n=20)	negative	++	+++



**Figure (1):** Reduction in hair pull test score from baseline for the use of 500 mg ginger extract with 100mg or 10mg prednisolone. n=20 patients in each group.

## Discussion

Corticosteroids are part of the treatment in many disorders in which the inflammation is thought to be caused by excessive or inappropriate activation of the immune system like in Alopecia

areata<sup>(21,25-28)</sup>. When administered in high doses, corticosteroids can reduce the severity of inflammation by blocking the action of prostaglandins responsible for triggering the inflammatory response<sup>(29)</sup>. They also temporarily depress the immune system by reducing the activity of certain types of white blood cells. In the present study, the AA patients showed elevated oxidative stress state compared with healthy controls, and the use of ginger with different doses of prednisolone improves this condition in both groups. The extent of hair loss and the age of the patient are the bases utilized to select an appropriate treatment for patients with alopecia areata<sup>(3)</sup>. For those with more than 50% scalp hair loss one may consider the use of systemic corticosteroids but the concern about long-term use and the side effects of systemic corticosteroids must be taken into consideration<sup>(30)</sup>. The present study revealed the presence of endogenous oxidative stress in both groups of

patients, as manifested by the increased MDA levels and decreased GSH contents in the erythrocytes. This oxidative stress may result from the activated phagocytes that generated excessively many free radicals and predispose to lipid peroxidation<sup>(31)</sup>. Data of the present study also indicated that, despite the difference in oral prednisolone dose (10 vs. 100 mg) between the two groups, coadministration of a supplement with powerful antioxidant properties with prednisolone therapy resulted in comparable and significant decrease in MDA levels and correction of the GSH content in blood, as well as similar improvement in the rate of hair growth with less side effect (acne and weight gain) regardless of the dose of prednisolone. Previous study in our lab showed that, without antioxidant therapy, the effect of 100 mg prednisolone was more prevalent than the lower doses of prednisolone in improving hair growth in alopecic patients<sup>(13)</sup>. Therefore, the addition of supplement like ginger extract with powerful antioxidant properties, mostly attributed to its polyphenols and flavonoids content, to the corticosteroids attenuated the negative effects of oxidative stress on the immune system and decreased the need for higher doses of the systemic steroid; thereby decreased the unwanted side effects associated with the prolonged use of high doses. The present data represent the outcome of a pilot trial; hence many limitation may not enable a significant clinical conclusion including small sample size, duration of treatment and the use of ginger extract as add-on option with other treatment protocols. However, the presented data may be useful to initiate larger multi-center and placebo-controlled study.

### **Conclusion**

The addition of supplement like ginger extract with powerful antioxidant properties to the corticosteroids attenuates the alopecia areata-associated oxidative stress and may decrease the need for higher doses of the systemic

steroid during treatment of alopecia areata; thereby, decreased the unwanted side effects associated with the prolonged use of the high doses.

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