



# Low Level Laser versus Platelet-rich Plasma in Treatment of Alopecia Areata: A Randomized Controlled Intra-patient Comparative Study

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## Abstract

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**BACKGROUND:** Non-scarring alopecia areata (AA) is a disease that is mediated through autoimmunity. Recently, autologous platelet-rich plasma (PRP) and photobiomodulation (PBM), commonly known as low-level laser (or) light therapy (LLLT) have been suggested to provide a valuable role in stimulating the growth of hair follicles (HF)

**AIM:** Compare between the significance and well-being of PRP and LLLT in the management of AA.

**PATIENTS AND METHODOLOGY:** Thirty patients, each having three patches of AA participated in the study. Patches were assigned randomly to have one of the two treatments: PRP or LLLT. The third patch served as a control and received placebo treatment. PRP was done once weekly, whereas LLLT was done three sessions per week for a maximum of 6 weeks. The patients were followed up (FU) at 1 month and 3 months. The thickness and density of hair were evaluated by the folliscope.

**RESULTS:** A noteworthy higher improvement was detected in the thickness and the density of hair in the PRP treated patches as evaluated by the folliscope and patients satisfaction. The obtained outcomes were sustained during the 12 weeks FU period in most of the patients.

**CONCLUSION:** PRP and LLLT could be considered as efficacious alternatives for the treatments of AA with the least morbidity in addition to a little cost profit ratio.

## Introduction

Alopecia areata (AA) is a disorder of hair loss which has a life time incidence of about 2% [1], [2]. AA is the most common non-scarring hair loss disease after male/female pattern baldness and telogen effluvium [3], [4]. It is characterized clinically by well-demarcated single or multiple grouped macules or patches of sudden hair loss. It may progress to alopecia totalis or alopecia universalis [5]. Either males or females are affected but in equal proportions [6]. Young patients under 40 years of age are more prone to the disease [7]. The disease has an unpredictable course [8]. It is a condition of hair follicle (HF) cycle when exogen develops before anagen. This may lead to kenogen state. In this phase there is no detectable hair shaft left inside the follicle [9], [10]. AA patients usually suffer from psychological impact, especially anxiety, depression, aggression, and negative image perception [11], [12]. It was considered to be an inherited complex and an organ-specific T cell mediated disease with autoimmunity, resulting from loss of the immune

privilege of HF [13]. Different success rates were associated with several treatment options. Although the topical, intralesional and systemic corticosteroids, anthralin, minoxidil, cyclosporine, immunotherapy, phototherapy, antihistaminics, biologic treatment, and superficial cryotherapy for short duration [6], [7], [8], [14] have been applied, but the high cost, the long treatment period, the inconvenience of application, and its invasiveness have delayed the treatment effects as well as patient contentment. Hence, the treatment of AA is still very challenging and it has been a must to find out new effective therapies.

In the past few years, autologous platelet-rich plasma (PRP) had been established to be valuable for hair fall, as it enhances the hair survival and growth. Once the platelets alpha  $\alpha$ -granules are activated, numerous growth factors (GFs) are released. These GFs are believed to stimulate stem cells sited in HF at the bulge areas leading to growth of fresh follicles and enhancing angiogenesis [13], [15]. Despite of its promising results in AA, a paucity of randomized controlled clinical trials had been published to assess

the efficiency of PRP in management of AA [9], [13], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35].

Photobiomodulation (PBM), or low-level laser (or) light therapy (LLLT) is using red light (600–700 nm) or near infrared (700 nm–1000+nm) which is obtained from 5 to 500 mW light-emitting diode (LED) source [36], [37].

LLLT has been considered lately by investigators particularly in male and female pattern hair losses and to less extent in AA [38]. Epidermal stem cells found in follicular bulge are stimulated by LLLT thus determining follicular shift from anagen phase to the telogen one. Moreover, it increases the duration of anagen and prevents premature catagen development. Furthermore, it induces vasodilatation and increases the blood flow [39], [40].

The aim of this study is to compare between the PRP and LLLT in the treatment of AA. Objective evaluation of the thickness and density of hair was done by the folliscope.

## Patients and Methodology

This comparative randomized intra-patient controlled research was accomplished at Cairo University in the dermatology outpatient clinic of National Institute of Laser Enhanced Sciences. It was carried on over a period of 12 months. The consent of Dermatology Research Ethical Committee was gotten. Participants signed informed written consents. This scientific research was done in agreement with the Heliniski's Declaration (1975).

Thirty adult male and female patients (age >18 years) with AA were registered in this study. AA identification was established by the presence of well demarcated patches that are devoid of hair but with normally-appearing areas of skin. Exclamation marks such as hairs (with narrow proximal segment and a broader distal one) are found. Pull test is positive at the lesional margins. The inclusion criteria were: patients who suffered from chronic, recurrent disease of minimally 2 years period, which was resistant to other lines of treatment. Patients were selected with at least three patches of AA. Doctors demanded patients to stop any intralesional, topical, or systemic treatments for AA 90 days before their enclosure. Before treatment, the demographic data were collected from all patients following the recommendations of NAAF that is National AA Foundation [41], [42] for determining disease severity. In addition, several gathered parameters included: age of start of the disease, pattern of hair loss, period of the disease,

period of last relapse and other associated disorders. Exclusion criteria included: pregnancy, lactation, presence of any general disease (as thyroid diseases and blood clotting disorders), other local scalp or hair disorder and the consumption of medicines that impede growth of hair as chemotherapeutics.

### **Treatment protocol**

The three alopecia patches were randomly subjected to treatment protocol. The envelope concealment method was used. One patch was treated with PRP injection once a week. The second patch was subjected to treatment with LLLT 3 times weekly. The third patch served as a control where saline was applied topically 3 times/week. The duration of treatment of the three patches of every patient was 6 weeks. Follow-up (FU) was done at 4 weeks and 12 weeks after the end of sessions.

### **PRP group**

#### *Preparation of autologous PRP*

From the patient's median cubital vein ten mls, blood was withdrawn and put in a blood cell therapy tube then was revolved for ten minutes in a machine of centrifugation (centrifuge model 80-2A) at 3500 g rpm. Plasma was obtained easily being separated from other cellular sediment by a physical barrier in kit (thixotropic gel). Plasma volume in each kit is about 5 ml and concentration is 1.6×. Then, injection by insulin syringe of freshly prepared PRP (Sterfile European Conformity marked Regenlab®kit, Regen Lab SA, Le Mont-sur-Lausanne, Switzerland). Sessions were done once weekly for 6 weeks.

### **LLLT group**

Alopecia patches received LLLT for 25 min using the iGROW® laser hair rejuvenation system (Apira science, Boca Raton, Fla., US). It was a rigid helmet utilizing a combination of red laser diodes and LEDs. 21 Lasers Diodes were with an output <5 mW CW (655 nm ± 5 nm) and 30 LEDs (655 nm ± 20 nm). Before treatment, the patient's hair should be cleaned but with no sprays/gels. While one patch was exposed to LED the rest of hair and the other patches were covered with paper shields during the sessions that were done 3 times weekly for 6 weeks.

### **The control group**

Normal saline in a dark bottle was applied topically to the control patches. It was applied 3 times/week for 6 weeks.

## Assessment

The special effects of PRP and LLLT treatment on growth of hairs, density or hair number/cm<sup>2</sup> and breadth (diameter) were measured by photography, standardized phototrichograms, and patient's satisfaction scale.

## Objective evaluation

Standardized digital macrographs with high-resolution were obtained after using a 24.2 megapixels digital single-lens reflex camera with 18–55 mm lens (Nikon D5300 camera by Nikon Corporation, Tokyo, Japan). Macrographs were taken before treatment (T<sub>1</sub>), at the end of sessions (T<sub>2</sub>), at 1 month FU (T<sub>3</sub>) and 12 weeks after the last session (T<sub>4</sub>). Clinical appraisal was performed along with the degree of improvement at (T<sub>4</sub>) as follows: Treatment failure was considered if no response or worsening of the condition happened, if there was up to 50% improvement of the condition (mild response). If improvement was up to 75% (moderate response) and if improvement of the condition was more than 75% (significant outcome). The last three responses were recorded as efficacious therapy.

Phototrichograms of the patients were taken by a folliscope at 4 time points: at start (T<sub>1</sub>); at end of therapy (T<sub>2</sub>); at 1 month after therapy (T<sub>3</sub>) and at 3 months after therapy (T<sub>4</sub>). This folliscope evaluation was carried out using a digital folliscope. It uses a high-tech software with alopecia charts and it is supported by a micro viewer s/w (Model D Lite, STR Company, Felton, CA, USA) to measure density of hairs and their thickness. Density was assessed by calculating the sum of hairs in 1 cm<sup>2</sup>. The breadths/diameters were measured by finding the mean values of the breadths of 5 hairs in that area.

## Subjective evaluation

Patient's satisfaction was documented 12 weeks after the last session. It was categorized on a linear analogue scale from 1 to 10 where 1 represents no result and 10 represents the best result. Furthermore, doctors instructed patients to state skin side effects next sessions as well as at 1 month and 3-months FU.

## FU

All included patients were monitored for 1 month and 3 months next to the termination of sessions.

## Statistical analysis

Means plus or minus standard deviations, medians for metrics and proportions for categorical variables were used to perform descriptive statistics. Box plots were used to display means while tables

for categorical variables. Metric variables satiating the normality assumption were analyzed by paired t-test. Furthermore, Wilcoxon signed rank test was used to analyze both metric variables not satiating the normality assumption and ordinal variables that is patient satisfaction. To test significance of rapport between time and hair pull Friedman's test was done instead of one-way analysis of variance. This was because of the presence of violation of normality assumption, of outliers and the relatively small sample size. IBM SPSS ver. 22 (IBM Corp., Armonk, NY, USA) was used for all analyses.

## Results

The research included thirty patients with AA (26 males, 4 females). Their ages fluctuated between 18 and 35 years (mean 28.80 ± 6.8 years). Twenty-five patients (21 males 84%, 4 females 16%) continued the study until the last session. The five patients discontinued the treatment after the 2<sup>nd</sup> week of treatment because of inconvenience. Twenty cases (17 males, 3 females) continued the study until 3 months FU. The disease duration ranged from 2 years to 25 years (a mean of 5.24 ± 5.87 years). Patients' characteristics and demographic data are listed in the Table 1.

**Table 1: Summary of the demographic and clinical data of the patients**

Variable	Number	Mean ± SD and percentage			
Number of patients	30				
Age	18–35 years	28.80 ± 6.886			
Sex					
Males	26	76%			
Females	4	24%			
Family history					
Negative	20	66.7%			
Positive	10	23.3%			
Associated problems					
Teeth problems	17	56.7%			
Eye problems	8	26.7%			
Nail involvement	3	10%			
AA duration	2–25 years	5.24 ± 5.865			
Site	Posterior	Frontal	Right temporal	Left temporal	
Control	52%	16%	32%	–	
PRP	52%	24%	8%	16%	
LLLT	56%	28%	–	16%	

AA: Alopecia areata, PRP: Platelet-rich plasma, LLLT: Low level light therapy.

## Clinical results

The PRP treated patches showed better improvement than the LLLT treated patches and the placebo. Eleven (44%) PRP patches showed a significant change whereas ten (40%) patches showed no response. On the other hand, a significant improvement of hair densities and thicknesses were perceived at areas treated with LLLT in eight patches (32%) while eleven (44%) patches showed no response. Finally,

**Table 2: Summary of clinical results at 3 months FU (T4) among different treatment groups**

Clinical response	Placebo (%)	LLLT (%)	PRP (%)
Significant response	12	32	44
Moderate response	28	12	4
Mild response	8	8	0
No response	52	44	40
Relapse	0	4	12

PRP: Platelet-rich plasma, LLLT: Low level light therapy, FU: Follow-up.

three patches (12%) showed significant improvement in hair densities and thicknesses in placebo treated areas (Table 2 and Figure 1).

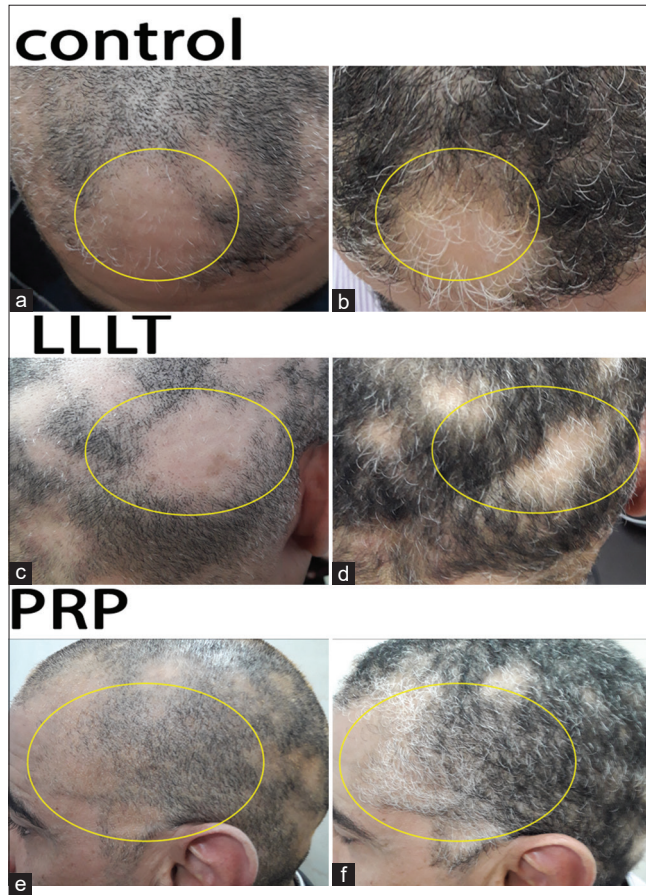


Figure 1: (a) macrograph of a male alopecia areata patient obtained by camera, (b) Before treatment by saline at the control site in the top at baseline (T1), (c) After treatment by saline at the control site in the top at 3 months follow-up (FU) (T4), (d) Before treatment by low level light therapy (LLLT) at the LLLT site in the back at baseline (T1), (e) After treatment by LLLT at the LLLT site in the back at 3 months FU (T4), (f) Before treatment by platelet-rich plasma (PRP) at the PRP site in the left side at baseline (T1), (g) After treatment by PRP at the PRP site in left side at 3 months FU (T4)

### Phototrichogram results

Two parameters were assessed: the density and the thickness of the hair at starting point (T<sub>1</sub>), at the termination of the treatment (T<sub>2</sub>), after 1 month FU (T<sub>3</sub>) and at 3 months FU (T<sub>4</sub>).

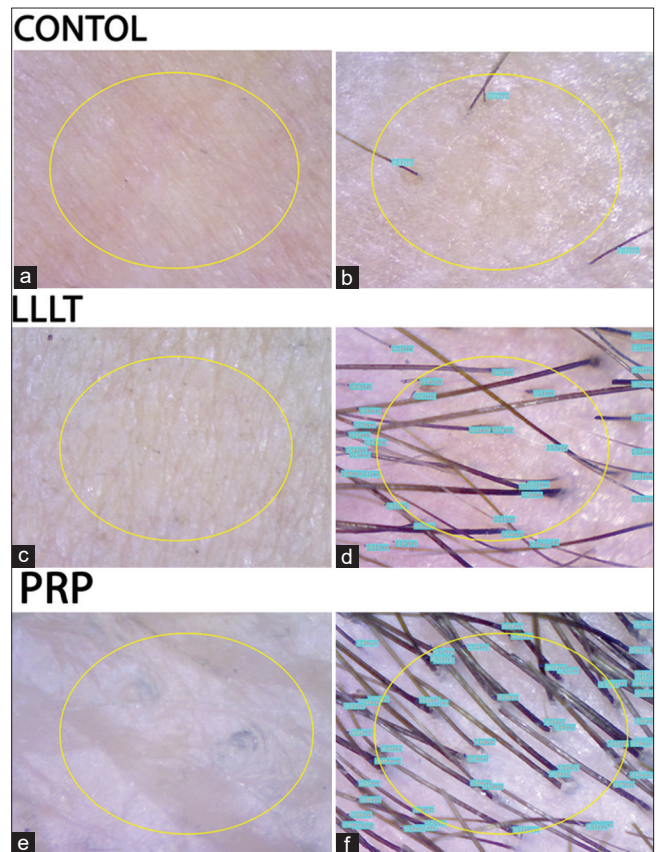


Figure 2: (a) Phototrichogram of patchy alopecia areata obtained by folliscope, (b) Before treatment by saline at the control site at baseline (T1), (c) After treatment by saline at the control site at 3 months follow-up (FU) (T4), (d) Before treatment by low level light therapy (LLLT) at the LLLT site at baseline (T1), (e) After treatment by LLLT at the LLLT site at 3 months FU (T4), (f) Before treatment by platelet-rich plasma (PRP) at the PRP site at baseline (T1), (g) After treatment by PRP at the PRP site at 3 months FU (T4)

At 12 weeks FU (T<sub>4</sub>); significant increases in the hair densities ( $p = 0.007$ ) were obtained in the PRP treated patches which also showed a significant improvement ( $p = 0.002$ ) in hair thickness. On the other hand, LLLT treated patches displayed a noteworthy improvement in hair densities only ( $p = 0.02$ ). None of the patches which were placebo treated showed significant increase in the hair densities or thicknesses ( $p < 0.05$ ) (Figures 2-5).

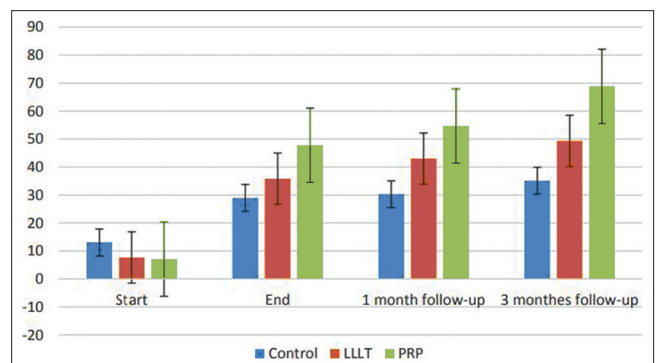


Figure 3: Comparison of mean hair density assessed by folliscope at treatment start (T1), end of treatment (T2), 1 month follow-up (FU) (T3), 3 months FU (T4) among different treatment groups

### Patient satisfaction

Concerning the two modalities of treatment, PRP and LLLT, an insignificant difference was reported between them ( $p = 0.14$ ). The maximum degree of contentment was reported at PRP treated areas with a mean of  $(5.92 \pm 4)$  on a scale of 1–10. While a mean of  $(5.4 \pm 3.9)$  and  $(4.68 \pm 3.89)$  was reported in LLLT treated areas and control areas, respectively (Figure 6).

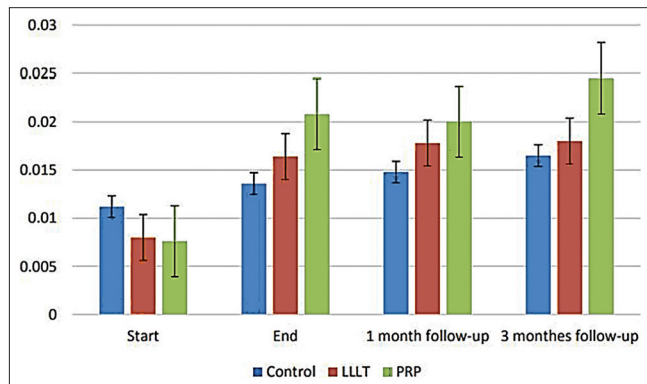


Figure 4: Comparison of mean hair thickness at treatment start (T1), end of treatment (T2), 1 month follow-up (FU) (T3), 3 months FU (T4) among different treatment groups

### Side effects

No adverse effects were informed with the two therapeutic modalities. In PRP treated areas, the patients experienced only temporary pain. Patients also reported warm sensation in LLLT treated areas, while only five (20%) patients reported scalp tenderness after LLLT; however, this resolved within 2 h without complications.

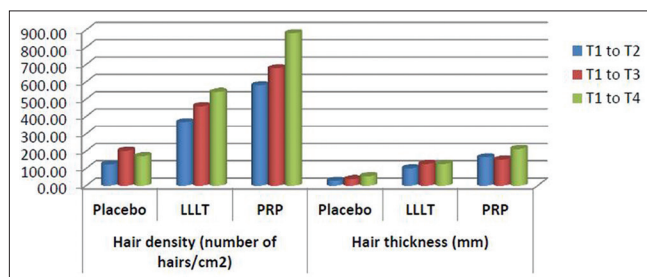


Figure 5: Comparison of mean hair density and thickness at treatment start (T1), end of treatment (T2), 1 month follow-up (FU) (T3), 3 months FU (T4) among different treatment groups

### Discussion

This study revealed that both PRP and LLLT are effective in recurrent and resistant AA. However, PRP was more effective than LLLT in treating such cases.

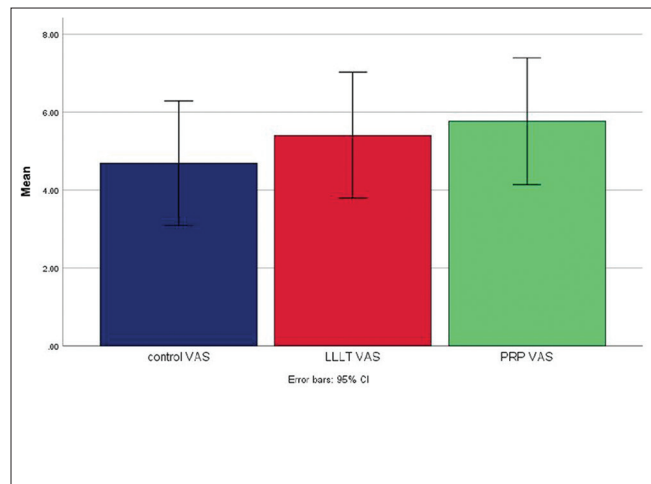


Figure 6: Comparison of Visual Analogue Score among treatment groups at 3 months follow-up (T4)

This randomized comparative intra-patient study is the earliest to compare PRP efficacy versus that of LLLT as therapeutic modalities of chronic as well as relapsing form of AA. As far as we know, only a few researches utilized folliscope for assessment of hair density and thickness [43]. Moreover, it is the earliest research to document benefit of low level laser in AA. The patients in this study served as their own controls, which helped to avoid the assignment bias. An objective assessment was provided by global macrographs and folliscope photographs.

Considering our results, at 3- month FU, the PRP treated patches, LLLT and placebo were better when compared to baseline. However, PRP treated patches showed better results when compared to LLLT treated areas concerning both hair thicknesses and hair densities at 3-months of FU. In addition, both treatment modalities have no major side effects with a high general patient contentment in favor of PRP.

In literature there are few clinical trials discussing treatment of AA with PRP [9], [16], [17], [18], [19], [20], [21], [22], [23], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35] and most of them agree with our results. On the other hand, D’Ovidio and Roberto in 2014 showed restricted usefulness of PRP in long standing cases (more than 2 years) and proposed that PRP effect may be held in reserve for mild cases [44].

The mechanism by which the PRP influenced the HF was suggested by Li *et al.* in 2012 [45]. They reported that the proliferation of dermal papillae cells were increased by the PRP. The later, stimulates many signal-regulated kinase pathways extracellularly. Furthermore, the activation of AKT signaling and B-cell lymphoma-2 protein regulation leads to an anti-apoptotic effect. Moreover, the FGF7 i.e fibroblast GF 7 regulation and beta-catenin leads to prolongation in the anagen phase. It also induced differentiation of the follicular stem cell. Another proposed

explanation was the angiogenesis which may be associated with the anagen [45]. PRP has a proved anti-inflammatory effect. It has a role in suppression of cytokine release hence limiting the local tissue inflammation. On previous basis AA benefits from PRP anti-inflammatory effects [7], [13] as it reduced the extensive inflammatory infiltrates which are considered responsible for production of inflammatory cytokines. Another explication of the obtained worthy results of PRP in this research was grounded on the increase of HF numbers after treatment by PRP when compared to those of baselines [5], [33].

LLLT elicited significant and important rise of hair densities when compared to baseline. Furthermore, there are limited trials that evaluated the effects of LLLT in AA [46], [47], [48], [49]. Similar to our study, Han and his coworkers in 2018 found that red light 655-nm as well as LED could serve as an additional and a beneficial choice for AA *in vitro* cultures models of human HF [49]. They found that PBM augmented the expressions of signaling molecules of the Wnt/B-catenin pathways, stimulating growth, and development of HF [49].

LLLT has a remarkable effect (650–900 nm) on the cellular level as a PBM which in turn reduced the hair loss [40]. LLLT elongated the time length of anagen phases besides stimulated the catagen and the telogen HF to move in anagen phases. Stimulation of mitochondrial electrons transport, proteins synthesis and generation of ATP triggered cell proliferation, tissue oxygenation, reactive oxygen species modulation and variations in the level of inflammatory mediators, cytokines, GFs can constitute the bimolecular mechanisms behind LLLT influences [40].

PBM induces hair growth in AA through an anti-inflammatory mechanism. Electron transport chain activation changes the macrophages from pro-inflammatory M1 to the anti-inflammatory M2 phenotype, hence decreasing the inflammation that then attacks the HF causing hair fall [37]. Our results were contradicted by another animal model study which was performed by King *et al.* in 2014 using the C3H/HeJ mouse model, didn't report a positive response to LLLT [50]. The weak points of the study done by King *et al.* were the short durations of both the treatment sessions and the study, low parameters, small number of mice and lack of combination with other therapy.

Despite its increasing efficacy and use in hair loss, knowledge on LLLT in AA remains limited. The debates among the published studies, the diversity in devices and irradiation parameters used (as power density, and treatment length and frequencies can influence clinical outcomes at several degrees making it hard to evaluate treatment standrization.

### Limitations of the study

The sample size being small as well as the short FU duration were considered to be the limitations of the study. Furthermore, the inability to use SALT score for clinical assessment of cases was due to the randomized distribution of AA patches.

### Conclusion

The current study suggests that PRP is a beneficial, effective and also a riskless tool for the management of AA. It was superior to the LLLT which has been verified to be also effective and safe. However, further controlled randomized studies with long-term FU are required to assess the frequency of relapse and to assess the usefulness of PRP and LLLT treatment in recurring AA.

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