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Trichogenic effect of low level laser therapy combined with platelet-rich plasma for the management of androgenetic alopecia

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***Abstract*---**Background: (AGA) is a very common hair disorder in men, Topical minoxidil and more recently low-level light therapy and Platelet-rich plasma therapy have been used in the management of (AGA). Objectives: To assess the Trichogenic effect of LLLT combined with PRP in the management of AGA. Patients and methods: Forty seven patients with AGAwere subjected to PRP therapy plus LLLT, affected area of all patients were treated for three months and then follow up for another three months. Efficacy was evaluated using global photography, folliscopic pictures analysis, answers for standardized hair growth questions and score of patient Gratification. Results: There was statistically significant improvement in diameter, vellus hair, terminal hair and density after treatment for three months although these improvements were decreased at three month after stoppage of treatment but still better than the baseline. Conclusion combination of LLLT with PRP could be a good treatment modality of AGA.

***Keywords*---**androgenetic alopecia, low-level laser therapy, platelet-rich plasma.

Introduction

Androgenetic alopecia (AGA) is a very widespread dermatological disorder in which hair of the scalp is gradually converted from terminal to vellus in reproducible pattern affecting both sex, this pathophysiology is known as miniaturization [1-3]. This is androgen-depended in males, while in women it's better to use female pattern hair loss (FPHL) term than androgenetic alopecia because there's no certain relationship between androgens and this pathology [4-6]. Management of AGA using Finasterideorally and Minoxidil topically has been approved by the Food and Drug Administration (FDA) and both of them generally give good results [7]. But sometimes patients who are experiencing ungratified response or complained of side effects ask about additional or alternative treatment. The efficacy of red light and laser therapy at wave length 660 nm has been approved for management of hair loss (HL) [8], and therefore light- emitting diodes (LEDs) as a phototherapy, has been widely used to enhance hair growth (HG) in AGA [9-10]. The combination between LLLT and LEDs improve the density of the hair through photobiomodulation and activation of the metabolism of hair follicles cells [11]. PRP is a relatively new option which provided good results in AGA. PRP which is an autologous preparation to obtain plasma containing highly concentrated platelets can provide a high quantity of more than 20 growth factors (GF). All of them have an important role in the bio- molecular metabolism of the hair re-growth (HR-G) [12]. Many published studies approved that PRP either a monotherapy or in combination with other treatment is effective in management AGA [13]. The current study aimed to evaluate the Trichogenic effect of photobiomodulation combined with PRP in management of AGA.

Patients and Methods

This clinical study was performed in Dermatology out-patient clinic, NILES, Cairo University. We obtained the approval of the Dermatology Research Ethical Committee, NILES, Cairo University about this clinical study moreover all patients included in this study were informed about the benefit and side effects of this therapy and each of them signed a written consent. Forty-seven adult male patients (age>22 years) with grade II-IV AGA, as classified by the Norwood–Hamilton classification scale (14), were included in this study. Patients who had another cause of hair loss like anemia, thyroid disorders and poor nutrition also those with diseases of immunosuppression, platelet disorders, sepsis, cancer, uncompensated diabetes or patients who utilized topical or oral drugs for management of AGA in the previous year were excluded. Patients were asked about their special habits or life style to know if they are exposed

to any factor can exacerbate AGA such as ultraviolet exposure or smoking. Diagnosis of AGA depended on a detailed medical history, clinical, and trichoscopy examination (Folliscope, Compare view, ver.1.5.09, CA -USA). Was used to assess the hair parameters, the hair density was assessed by counting the number of hairs within about 15mm² area which was the same area

investigated either pre, post treatment and followed up according to a map for each patient, while hair diameter was measured by calculating the mean value of the diameter of 5 hairs in this area. Also terminal to vellus ratio was measured.

Treatment Protocol

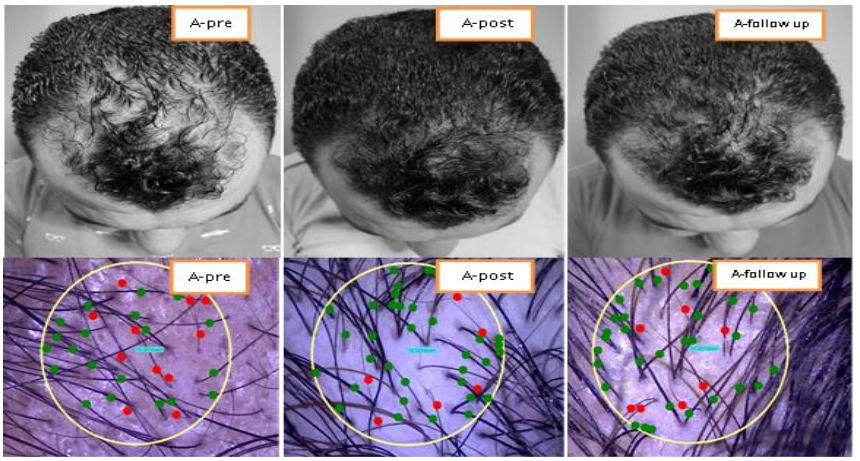
All included patients were treated by 4 sessions of PRP injections with 3 weeks apart combined with sessions of LLLT for 25 minutes using the iGROW1 helmet device (21 Lasers Diodes and 30 LEDs, 655nm red laser with output <5mW CW and LED wave length range from 650 to 670 nm) 3 times per week not consecutive days for 3 months. Follow up for another 3 months after cessation of treatment was performed for all involved patients.

Assessment of Hair Growth Parameters

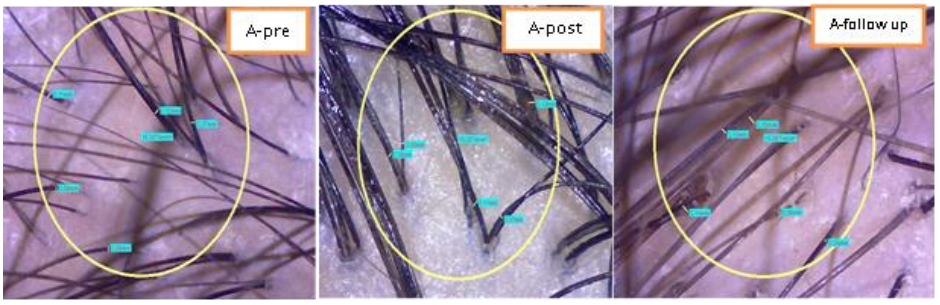
All patients were evaluated upon their initial visit, at 3 and 6 months from starting the treatment. Through Global clinical photography, Patients gratification and objectively by folliscopic assessing the hair measures (hair density, terminal/vellus ratio and hair diameter) in this study PRP was prepared with the same technique as Verma, et al [15]. Patient gratification was determined as a very gratified, gratified, neutral and ungratified. Any side effects or complains from the therapy was reported.

Results

Forty seven patients were included and completed this clinical study. Age of the studied patients varied from 22 to 37 years with mean 33.15years. Disease duration ranged from 1 to 16 year with median 14 years. About 53%, 38% and 9% had alopecia type III, II and IV respectively. Their demographic data are presented in table 1.



Pre	100.9/cm²Terminal= 20Intermediate= 11Total= 31%T= 64.5%%I= 35.5%
Post	123.7/cm²Terminal= 32Intermediate= 6Total= 38%T= 84.2%%I= 15.8%
Follow up	117.2/cm²Terminal= 28Intermediate= 8Total= 36%T= 77.8%%I= 22.2%



Pre	1	0.082	0.063	0.084	0.0850.056	0.06StatsAV	0.07SD0.01
Post	1	0.092	0.063	0.114	0.0850.096	0.13StatsAV	0.09SD0.02
Follow up	1	0.082	0.073	0.114	0.0650.066	0.12StatsAV	0.08SD0.03

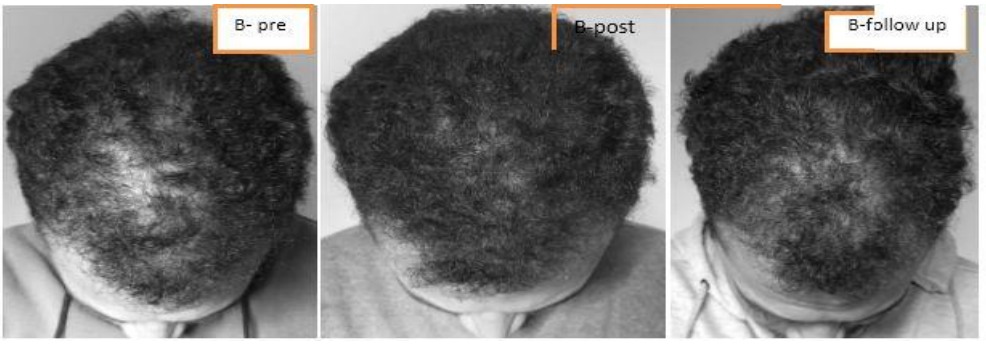
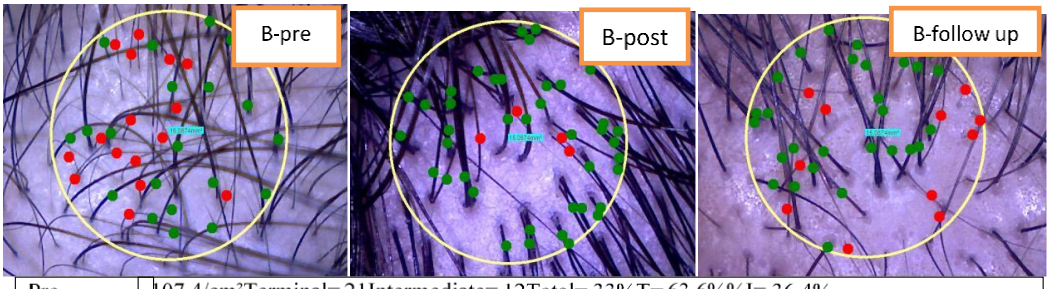
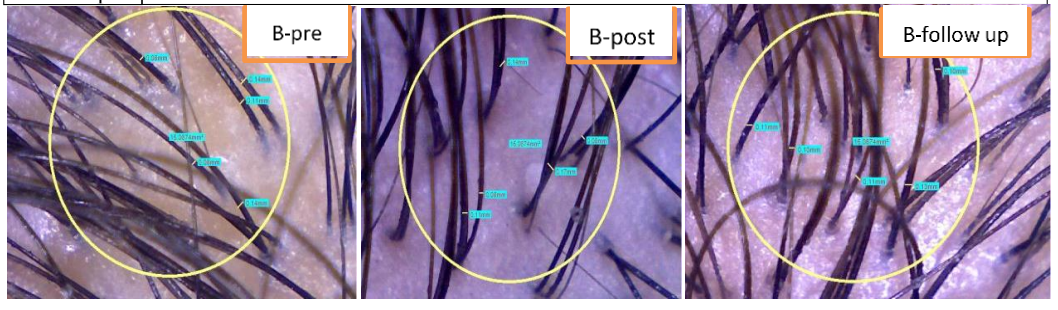


Fig (3) Patients A and B, pre (baseline), post (3months after treatment) and follow up 3 months after stoppage of treatment



Pre	107.4/cm²Terminal= 21Intermediate= 12Total= 33%T= 63.6%%I= 36.4%

Post	130.2/cm²Terminal= 29Intermediate= 11Total= 40%T= 72.5%%I= 27.5%
Follow up	123.7/cm²Terminal= 28Intermediate= 10Total= 38%T= 73.7%%I= 26.3%



Pre	1	0.072	0.073	0.064	0.115	0.076	0.07StatsAV	0.08SD	0.02
Post	1	0.102	0.163	0.104	0.085	0.096	0.08StatsAV	0.10SD	0.03
Follow up	1	0.122	0.113	0.064	0.115	0.086	0.08StatsAV	0.09SD	0.02

Figure (4) Folliscopic analysis of the same patients (A and B) hair density including terminal hair as green dots, vellus hair as red dots (magnification: ×50) and hair diameter as turquoise rectangular (magnification × 200)

Table 1: Distribution of the studied patients according to baseline data

Parameter	N=47 (%)
Age (year): Mean SD Range	 33.15 ± 3.6 22 – 37
Duration (year): Median Range	 14 1 – 16
Types: II III IV	 18 (38.3) 25 (53.2) 4 (8.5)

Table 2: Disease-specific parameters before and after treatment

	Before treatment	After treatment for 3 months	Three months after stoppage of treatment	p
Diameter Mean ± SD Range	 0.068 ± 0.007 0.06 – 0.08	 0.11 ± 0.009 0.09 – 0.12	 0.09 ± 0.01 0.08 – 0.11	 <0.001**
Paired t	P1 <0.001**	P2 <0.001**	P3 <0.001**	
Vellus hair: Mean ± SD Range	 29.53 ± 9.74 12.5 – 48.4	 17.06 ± 6.1 76.9 – 93.9	 22.09±4.46 12.8 – 26.8	 <0.001**
Paired t	P1 <0.001**	P2 <0.001**	P3 <0.001**	
Terminal hair: Mean ± SD Range	 70.47±9.72 51.6 – 87.5	 82.94±6.1 0.769 – 0.939	 77.91±4.46 73.2 – 87.2	 <0.001**
Paired t	P1 <0.001**	P2 <0.001**	P3 <0.001**	
Density(/cm2): Mean ± SD Range	 109.36±14.69 91.1 – 143.2	 128.34±16.78 110.7 – 166	 120.93±15.66 107.4 – 159.5	 <0.001**
Paired t	P1 <0.001**	P2 <0.001**	P3 <0.001**	

P for repeated measure ANOVA test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant p1 difference between values before treatment and after treatment for 3 months

p2 difference between values after treatment for 3 months and three months after stoppage of treatment P3 difference between values before treatment and three months after stoppage of treatment There was a significant increase in diameter of the hair after treatment for 3 months as compared to baseline level however the level showed significant decrease 3 months after stoppage of treatment. There was a significant increase in terminal hair and density after treatment for 3 months as compared to baseline level; however the level showed significantdecrease three months after stoppage of treatment yet to levels significantly higher than baseline level. There was a significant decrease in vellus hair after treatment for 3 months as compared to baseline level, however the level showed significant increase three months after stoppage oftreatment yet to levels significantly lowers than baseline level as shown in table 2 and Figure 1, 2, 3,4. On studying the factors that could affect the response such as platelet count and duration of disease, we reported the following: There was a statistically significant positive correlation between platelet count and all of diameter, terminal hair and density after treatment for 3 months and three months after stoppage of treatment as shown in table 3. There was a statistically significant negative correlation between disease duration and diameter after treatment for 3 months and 3 months after stoppage of treatment. While, there was a statistically non-significant correlation between disease duration and either density, vellus or terminal hair after treatment for 3 months and 3 months after stoppage of treatment as shown in table 4. As regard patient gratification as shown in table 5, 34% and 36% of patients were very gratified and gratified with look of hair respectively. Regarding gratification with look of front of hair, 12.58% were verygratified and 55% were gratified. Only 19% think that treatment is non-effective while 40.4% and 40.4% think that treatment is fairly and very effective. About 40% and 47% described hair growth as markedly and moderately and increased. While 51.1% agreed with that bald spots getting smaller.(As shown in table 5).

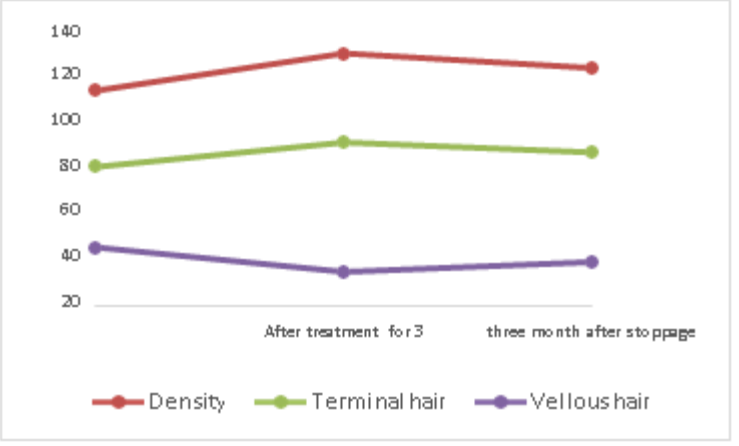


Figure 1: multiple line graph showing change in the studied parameters before and after treatment

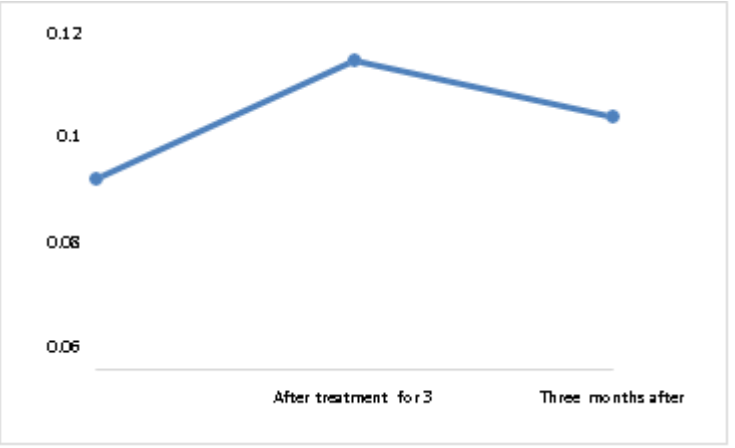


Figure 2: multiple line graph showing change in the diameter of hair before and after treatmentTable 3: Correlation between platelet count and the studied parameters

Parameter	Platelet count			
	After 3 months		Three months after stoppage	
	r	p	r	p
diameter	0.541	<0.001**	0.669	0.011*
Vellus hair	-0.467	0.001**	-0.559	0.001**
Terminal hair	0.467	0.001**	0.559	0.001**
Density	0.421	0.003*	0.365	0.012*

r Pearson correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table 4: Correlation between disease duration and the studied parameters

Parameter	Disease duration			
	After 3 months		Three months after stoppage	
	r	p	r	p
diameter	-0.468	<0.001**	-0.7	0.011*
Vellus hair	0.049	0.743	0.029	0.846
Terminal hair	-0.049	0.743	-0.029	0.846
Density	-0.02	0.896	0.021	0.889

r Pearson correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table 5: Distribution of the studied patients according to patient gratification

Variables	Items	N=47	%
Gratified with the look of hairgenerally	Ungratified NeutralGratified Very gratified	6 8 17 16	12.8 17 36.2 34

Gratified with the look of the top of hair	Ungratified Neutral gratified Very gratified	6 7 25 9	12.8 14.9 53.2 19.1
Gratified with the look of the front of hair	Ungratified Neutral Gratified Very gratified	5 10 26 6	10.6 21.3 55.3 12.8
What is your opinion about the effectiveness of this combination in management of your hair loss?	Not effective Fairly effective Very effective	9 19 19	19.2 40.4 40.4
What about the growth of your hair?	No change lightly increased Moderately increased Markedly increased	0 6 22 19	0 12.8 46.8 40.4
After treatment my bald spot improved and get smaller	Strongly disagree Disagree Neutral Agree Strongly agree	0 6 6 24 11	0 12.8 12.8 51.1 23.4

Discussion

AGA is the utmost etiology of men's hair loss as about fifty percent of males all over the world suffer from it [16]. It affects persons who have genetic susceptibility where gene expression is regulated by binding of androgen like testosterone and dihydrotestosterone as its derivative to the receptor of nuclear androgenic [17]. The main component of the pathogenesis of this disorder is the abnormality of androgen singling that result in disrupted activation of epithelial progenitor cell this lead to gradual and continuous conversion of susceptible hair follicles from terminal to vellus stage this process is called miniaturization [18-19]. Up to date transplantation of hair surgically, finasteride orally and Minoxidil topically are the most widely used modalities in management of AGA [16]. But not all patients obtain the desired results from these modalities as hair transplantation is expensive more ever the implanted hair is supplied from specific donor sites of the patients and sometimes there is scar at this sites, medical treatment need unlimited use and restricted by patient attachment [20]. Because of this, dermatologists look for another therapy which can give better result, LLLT is considered a new therapeutic modality and previous clinical studies recommended it for management of AGA in both sex either as a monotherapy or in combination with finasteride and Minoxidil [21]. PRP, a recent bioengineering technique which is the outcome of intensified work in the field of cell-based and tissue engineering therapy, which is determined as an autologous product of plasma with condensed platelets, it is rich with many various growth factors and cytokines, that can increase the body's intrinsic capability of repair

and regeneration [22-23]. To the date of writing this manuscript, only one published study [24] assessed combined PRP and LLLT for management of AGA and demonstrated good results. That is why in this study we aim for further evaluation of the efficacy of LLLT combined with PRP in the treatment of AGA. Forty seven patients were included and were treated by 4 sessions of PRP injections with 3 weeks apart combined with sessions of LLLT for 25 minutes using the iGROW1 helmet device 3 times per week not consecutive days for 3 months and were followed for extra 3 months after last treatment session. We demonstrated significant increase in the density of terminal hair also significant decrease of vellus hair density after treatment for 3 months as compared to baseline level; however the level showed significant decrease three months after stoppage of treatment yet to levels significantly higher than baseline level. Due to the variations in published study designs, using either LLLT or PRP, we have contributed a difficulty in comparing our results with other studies except for that of Gentile et al. [24] who treated 23 patients with AGA (13 male +10 female) with LLLT using helmet Hair Gentron® (DTS MG Co., Ltd., Seoul, Korea, #B108-147), two times per week for 24 weeks Combined with ANA-PRP 3 sessions 30 days apart, plus MN-T just before each PRP infiltration which was repeated every 15 days for 3 times. In spite of the difference of study protocol between this current study and Gentile et al study, both studies are in agreement that: the combination of LLLT with PRP is a good and safe modality in the management of AGA. This was clearly noticed by the statistically significant hair improvement (hair density, diameter) following treatment. This improvement may be contributed to the synergetic combined effect of LLLT and PRP. LLLT promote hair growth although the mechanism is still unclear, it is postulated that this action due to mitosis acceleration and also may be due to activation of follicular keratinocytes and stem cell, furthermore LLLT may change cellular metabolism as it photo dissociate the inhibitory nitric oxide from cytochrome c oxidase Unit four in mitochondrial respiratory chain lead to stimulation of production of ATP and activation of the cells [25-27]. Additionally subside of inflammation could be another mechanism of action of stimulation of hair growth by LLLT in AGA, as there is clinical studies recommended that LLLT lower the level of proinflammatory cytokines and inflammatory mediators like prostaglandin E-2, on the other side it elevate the anti-inflammatory cytokines as transforming growth factor beta1 and interleukin 10 [28-34]. Stem cells which arise from the bulge area of the hair follicle express receptors that bind with the growth factors found in PRP this binding enhance hair regrowth by stimulating the proliferation of the hair follicle and emerge it into the anagen phase [34-35]. Moreover, these growth factors evoke a serial of chemical reactions that stimulate angiogenesis and enhance the adnexal structures like keratinocytes which is present in the outer root sheath and dermal papillae fibroblasts to secrete vascular endothelial growth factor (VEGF), the latter is linked with angiogenesis and anagen phase stimulation as it stimulate the growth of dermal structures either normal or pathological [36]. Activated autologous PRP (AA- PRP) up regulate β-catenin and fibroblast growth factor 7, signaling of AKT and also extracellular cellular associated kinase, this up regulation lead to dermal papillae proliferation [36]. That is why we used the activated autologous PRP in this current study. This was in agreement with Gentile et al (37) who compared between autologous non-activated PRP (ANA- PRP) and AA-PRP in management of AGA and concluded that both modalities resulted in good effect and significant improvement as regard hair

parameters. This current study highlighted an important role of platelet count which affects the degree of improvement, which was clearly obvious by the positive correlation between platelet count and hair regrowth parameters, in this concern this current study is in agreement with Verma and his coworkers who treated 15 patients with AGA with PRP and concluded that PRP with higher platelets count give better clinical improvement than PRP with low platelet count [15]. Also, we demonstrated that whatever the duration of AGA, this combined modality of treatment has non-significant positive improvement on hair density and vellus/terminal hair ratio. Both are needed for further studies. As regard patient gratification which is the first priority at health system, we reported 70% of the patients were gratified to very gratified and this can determined the advantages of the combined treatment modality with no side effects.

Conclusion

Low level laser therapy combined with PRP could be a safe and good modality for themanagement of AGA as determined by the clinical and folliscopic analysis

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