THE EFFICACY OF 2% *Andrographis paniculata* EXTRACT CREAM IN REDUCING PERIORBITAL WRINKLES AND HYPERPIGMENTATION

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ABSTRACT
This study evaluated the efficacy of 2% *Andrographis paniculata* extract eye cream in reducing periorbital wrinkles and periorbital hyperpigmentation. Using a doubled blinded split face randomized controlled trial, the researcher analyzed improvements in skin elasticity, melanin index, and wrinkle score. Over a 12-week period, 19 participants aged 25 to 50 years applied the cream twice daily. Results showed a statistically significant improvement in wrinkle and hyperpigmentation scores compared to the placebo group, with no side effects reported. These findings suggest that *Andrographis paniculata* extract can be an effective natural treatment for periorbital wrinkles and hyperpigmentation concerns.
Keywords: *Andrographis paniculata*, Periorbital Wrinkles, Periorbital Hyperpigmentation, Eye Cream, Herbal Extract

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INTRODUCTION

Having a youthful appearance is associated with high self-esteem and improved social interactions. It has been demonstrated that an attractive appearance positively impacts on social functioning (Gupta & Gilchrest, 2005). Therefore, people try to achieve the attractive and youthful appearance. Common signs of aging face are wrinkles, thinning of skin and preceding of hair line (Panda & Chowdhary, 2021). As periorbital area is where it gets the most visual attention, it's one of the most important points for evaluation of aging (Lambros, 2007). This area, often the first place where skin aging is noticed, consists of the crow's feet and infraorbital region, which are not easily treated. It is also the part of the face that most people worry about the most (Kaczvinsky et al., 2009). There are two types of aging: intrinsic aging and extrinsic aging, which are influenced by environmental factors such as UV rays, pollution and poor lifestyle habits such as smoking and drinking (Baumann, 2007). While wrinkles are inevitable and cannot be completely eliminated, there are numerous ways to improve the appearance of fine lines and wrinkles. These include the use of topical antioxidants, procedures such as lasers, chemical peels, photorejuvenation, fat and volume restoration, skin augmentation, and systemic agents containing antioxidants and hormones (Zouboulis et al., 2019).

Andrographis paniculata is a medicinal herb, which has been used in Asian countries for centuries because of its beneficial properties like antioxidant, anti-inflammatory and even hepatoprotective effects. (You et al., 2015) In previous studies, it has been shown that it can reduce the oxidative stress and melanin production. (Mussard et al., 2019) (Adam et al., 2022) This study aims to evaluate the efficacy of 2% *Andrographis paniculata* extract eye cream for reducing periorbital wrinkles and periorbital hyperpigmentation. By addressing these concerns, the researcher aims to provide safe and effective alternative for daily use.

LITERATURE REVIEWS

Wrinkles

Wrinkles are folds of the skin, commonly found on the face and hand areas, as we age as the result of deterioration of connective tissue in the skin, which cause elastin and collagen fibers degradation leading to fine lines and wrinkles (Audonneau et al., 1999) (Al-Atif, 2022). These are greatly influenced by oxidative stress, UV rays, intrinsic aging, hormonal changes and intercurrent diseases.(Rinnerthaler et al., 2015). Wrinkles are formed by matrix metalloproteinases (MMP-1, MMP-9 and MMP-12), induced by UV rays. Wrinkle formation is also associated with many factors including volume loss of the skin and its adipose tissues. Additionally, it has been noted that muscle contractions and their alteration through surgery or injections significantly influence the extent to which wrinkles appear (Pessa et al., 2014). It has been stated that these methods are used to treat the skin aging: cosmetic skin care, topical applications, systemic agents, preventing risk factors and invasive methods (Ganceviciene et al., 2012).

Periorbital Hyperpigmentation

Periorbital hyperpigmentation is one of the common cosmetic issues. The periorbital hyperpigmentation can be seen as bilateral, evenly distributed dark patches around the eyes. It can be found in both upper and lower eyelids (Agrawal, 2018). It's still difficult to acknowledge what exactly causes the periorbital hyperpigmentation (Ranu et al., 2011). The cause of periorbital hyperpigmentation can be so many factors such as post inflammatory hyperpigmentation (PIH), melanin accumulation, contact dermatitis, anaemia, genetics, stress, oedema of the periorbital region, vascular structures being superficial. Moreover, loosening of the skin, deficiency in some nutrients, and even underlying diseases can cause periorbital hyperpigmentation (Mendiratta et al., 2019).

Andrographis paniculata

Andrographis paniculata, also known as the king of bitters, belong to the family Acanthaceae. It has been reported that for centuries, people in Asian countries have utilized it to treat gastrointestinal disorders, infections such as upper respiratory tract infections, herpes, and other infectious diseases (Mishra et al., 2007). It also has been stated that *Andrographis paniculata* have anti-pyretic, anti-inflammatory and anti-malarial properties. The plant also has the protective activity to the liver disorders (Jain et al., 2000). *Andrographis paniculata* is a well-known medicinal plant and has so many chemical constituents like flavonoids, andrographolide, diterpenoids, and polyphenols (Hanh et al., 2020). It has been proved to have many benefits: anti-inflammatory, anti-bacterial, anti-cancer, hypoglycemic in previous studies (Jain et al., 2000). Andrographolide is shown to have anti-inflammatory effect by suppressing inflammatory mediator pathways and reducing oxidative stress (Guo et al., 2012). Reactive oxygen species from environmental aging risk factors such as UV rays, smoking and pollutions, as well as the intrinsic aging, is the major factor to skin inflammation (Pillai et al., 2005). It has been stated that Full name of APE (APE) promotes proliferation of human epidermal stem cell. Increased expression of integrin β1 and production of Full name of VEGF (VEGF) in APE treated stem cells promote Type 1 collagen production in normal human fibroblasts (NHFs). It has been stated that there was a significance improvement in skin wrinkles and APE has anti-aging properties. (You et al., 2015) *Andrographis paniculata* leaf extract has been shown to be a safe and effective skin lightening agent by inhibiting melanin production through the suppression of TYR, MITF, and related proteins. It is considered a safe and reliable anti-melanogenic agent for treating hyperpigmentation. (Adam et al., 2022) Regarding side effects, The systemic side effects of *Andrographis paniculata* are associated with gastrointestinal, skin, and subcutaneous disorders. But the serious side effect such as anaphylactic reaction is rare. It's contraindicated in pregnant women, lactating women and in those with history of allergy to the plant with Acanthae family (Worakunphanich et al., 2021). In some studies, *Andrographis paniculate* is considered to be safe (Intharuksa et al., 2022). Moreover, semi-solid forms of *Andrographis paniculate* has no reported side effects (Oh et al., 2014).

Wrinkles, Periorbital Hyperpigmentation and *Andrographis paniculata*

It has been stated that APE promotes proliferation of human epidermal stem cell (EpSCs). Increased expression of integrin β1 and production of VEGF in APE treated stem cells promote Type 1 collagen production in normal human fibroblasts (NHFs). It has been stated that there was a significance improvement in skin wrinkles and APE has anti-aging properties (You et al., 2015). *Andrographis paniculata* leaf extract at a concentration of 25 μg/ml has been shown to be a safe and effective skin lightening agent by inhibiting melanin production through the suppression of TYR, MITF, and related proteins. It is considered a safe and reliable anti-melanogenic agent for treating hyperpigmentation (Adam et al., 2022).

RESEARCH METHODOLOGY

Study design

The researcher used a double-blinded, randomized, controlled and split face clinical study of AP extract on the periorbital winkles and periorbital hyperpigmentation for 12 weeks with those who want their peri orbital wrinkles and periorbital hyperpigmentation to be treated. In this study, the researcher enrolled healthy male and female volunteers aged between 25years to 50 years, according to inclusion and exclusion criteria. Follow up visits were done at Mae Fah Luang University Hospital, Bangkok, Thailand. The protocol of this study has been approved by Human Research Ethics Committee Mae Fah Luang University (Approval No. COA 85/2024).

Subjects

The volunteers were carefully instructed with steps-by-steps use of AP creams and placebo creams in details. After face washing, apply extract cream and standard base cream on the periorbital areas of the face in the morning and in the evening according to the instructions. A side effect record form was given to record if there was any. If any side effects occurred, the participants are informed to stop using the cream, notify the researcher as soon as possible.

Data collection and analysis

The researcher used the VISIA® skin complexion analysis system, Cutometer® MPA 580 and Mexameter®MX18 to evaluate skin elasticity, melanin index and wrinkle scores respectively. Each volunteer was fully explained of the aim and benefits of research, the steps of the procedure, and potential side effects of the treatment by the researcher. Before participating, each of the volunteers was asked to sign the informed written consent form by the researcher. Before the participant was given the AP creams and placebo creams, a patch test was done before application to these creams around eyes. The researcher used VISIA® Complexion Analysis System to take photographs of each participant at baseline, 4th, 8th, and 12th weeks.

RESEARCH RESULTS

Score for Skin Elasticity in Treatment Cream and Placebo Group

Table 1. Skin elasticity at crow's feet and under eye areas comparing the sides of *Andrographis paniculata* extract and placebo group (n=19)

	***Andrographis paniculata* extract**	**Placebo**	**Paired differences±SE**	**p-value(a)**
	Mean±SD	**Mean±SD**		
Crow's feet				
Baseline	78.21±10.04	80.12±11.67	-1.91±3.53	0.592
4th week	83.94±10.90	79.93±16.34	84.01±4.51	0.380
8th week	87.76±10.55	81.01±12.86	6.75±3.82	0.086
12th week	92.77±9.44	80.31±17.39	12.46±4.54	0.010
P-value(b)	**<0.001***	**0.996**		
Under eye				
Baseline	67.20±10.27	72.81±10.04	-5.61±3.29	0.097
4th week	78.25±12.01	73.45±13.02	4.80±4.06	0.045
8th week	87.04±10.96	73.01±13.09	14.03±3.92	0.001
12th week	96.11±14.34	74.79±13.67	21.32±4.55	<0.001
P-value(b)	**<0.001***	**0.966**		

Note Data were analyzed with Paired t-test and Repeated measure ANOVA
p-value (a): compares the treatment effect of *Andrographis paniculata* cream vs. placebo.
p-value (b): significant change within a group across time points.

The results show that the mean Cutometer scores for crow's feet on the *Andrographis paniculata* eye cream side were 78.21±10.04 at baseline, 83.94±10.90at the 4th week, 87.76±10.55 at the 8th week, and 92.77±9.44 at the 12th week. The increase in these scores across all time points was statistically significant, with p-values of <0.001*. On the placebo side, the mean scores were 80.12±11.67 at baseline, 79.93±16.34 at the 4th week, 81.01±12.861at the 8th week, and 80.31±17.39 at the 12th week, with p value of 0.996 ($p > 0.05$). When comparing the scores between the two sides, the *Andrographis paniculata* side demonstrated higher Cutometer scores at the 12th weeks, with p-values of 0.010 (<0.05).

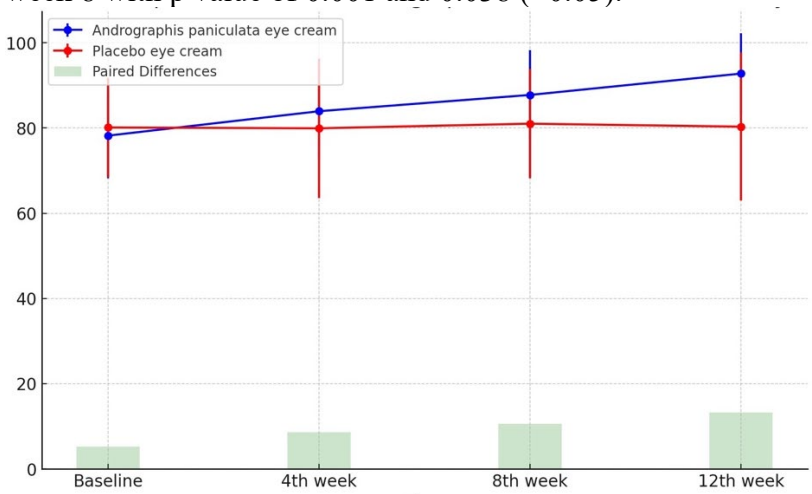
Regarding the under-eye area, the mean Cutometer scores for the *Andrographis paniculata* were 67.20±10.27 at baseline, 78.25±12.01at the 4th week, 87.04±10.96 at the 8th week, and

96.11±14.34 at the 12th week. These scores increased is statistically significantly over time, with p-values of less than 0.001. The placebo eye cream side had mean scores of 72.81±10.04at baseline, 73.45±13.02 at the 4th week, 73.01±13.09 at the 8th week, and 74.79±13.67 at the 12th week. However, the differences in mean scores between the time points for the placebo side were minor and not statistically significant, with p value of 0.966 (>0.05). When comparing the two sides, significant differences in cutometer scores were found at the 4th, 8th, and 12th weeks, with p-values of 0.045, 0.001, and less than 0.001, respectively.

Table 2 Mean Changes of skin elasticity by cutometer of *Andrographis paniculata* extract eye cream over 12 weeks (n=19)

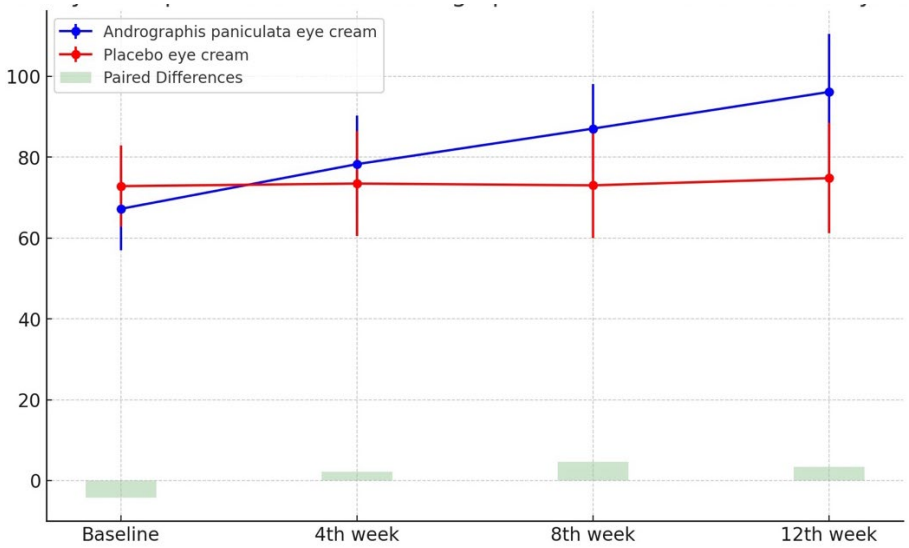
Variables	**Mean Changes from Baseline**		**p-value**	
Skin Elasticity by Cutometer	**Under Eye (Mean ± SD)**	**Crow Feet (Mean ± SD)**	**Under Eye**	**Crow Feet**
Baseline – week4	11.05±10.79	5.73±10.89		0.034
Baseline– week 8	19.98±11.97	9.55±13.01		0.005
Baseline – week12	28.91±16.99	14.57±10.20		<0.001
Week4 – week 8	8.93±8.19	3.82±8.23	<0.001	0.058
Week 4 – week12	17.86±12.61	8.83±9.86		0.001
Week8 – week12	8.93±9.94	5.01±9.77	0.001	0.038

The score of skin elasticity by cutometer on 12th week is significantly higher than baseline, week 4, week 8 with p value of 0.001 (<0.05) at under eye regions. Moreover, differences between baseline and each week is also statistically significant with p value of <0.001. In terms of crow's feet, differences between baseline to each week are higher p-value of 0.035, 0.005 and <0.001. However, data from week 12 is significantly higher than only from week 4 and week 8 with p value of 0.001 and 0.038 (<0.05).



X axis = time point, Y axis = skin elasticity score

Figure 1 Comparison of *Andrographis paniculata* eye cream and placebo over time (Crow's Feet)



X axis = time point, Y axis = skin elasticity score

Figure 2 Comparison of *Andrographis paniculata* eye cream and placebo over time (Under Eye)

Score for Melanin Index in *Andrographis paniculata* Eye Cream and Placebo Eye Cream

Table 3 Melanin index for the crow's feet and under eye comparing between *Andrographis paniculata* extract and placebo group (n=19)

	***Andrographis paniculata* eye cream side**	**Placebo eye cream side**	**Paired**	**p-value(b)**
	Mean±SD	**Mean±SD**		
Crow's feet				
Baseline	245.86±65.94	236.42±62.63	1.63±6.94	0.780
4th week	245.86±65.94	236.42±62.63	1.63±6.94	0.780
8th week	235.20±63.00	247.37±67.66	10.37±20.19	0.614
12th week	222.34±61.00	231.74±52.11	19.47±13.61	0.170
P-value(b)	**0.004**	**0.140**		
Under eye				
Baseline	214.04±52.58	201.47±52.38	0.440±5.13	0.864
4th week	202.89±53.50	210.58±48.47	7.70±4.30	0.727
8th week	196.40±52.10	218.26±50.23	12.10±4.15	0.923
12th week	190.20±53.00	210.21±48.62	16.80±4.20	0.005
P-value(b)	**0.229**	**0.210**		

Note Data were analyzed with Paired t-test and Repeated measure ANOVA
p-value (a): compares the treatment effect of *Andrographis paniculata* cream vs. placebo.
p-value (b): significant change within a group across time points.

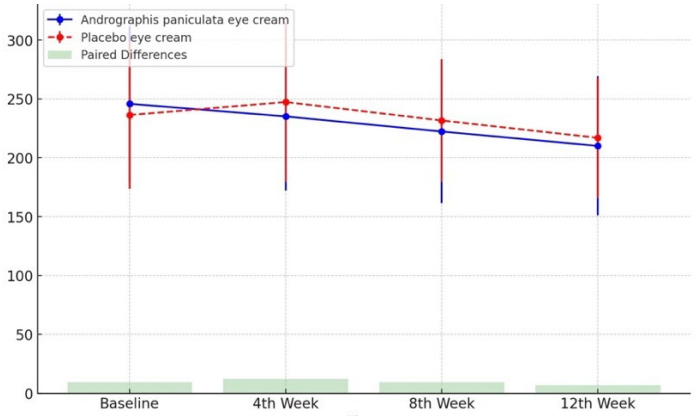
The mean scores for Crow's feet on the *Andrographis paniculata* eye cream side were 245.86±65.94 at baseline, 235.20±63.00 at the 4th week, 222.34±61.00 at the 8th week, and 210.12±59.00 at the 12th week. The results show a statistically significant reduction of melanin index in Crow's feet with time, with p-values of 0.004 (<0.05). In comparison, the placebo eye cream side had mean scores of 236.42±62.63 at baseline, 247.37±67.66 at the 4th week, 231.74±52.11 at the 8th week, and 216.95±50.85 at the 12th week, showing no significant improvement (P-value = 0.140). However, the paired differences between the two sides, the *Andrographis paniculata* cream showed not significantly statistically.

Regarding the under-eye area, the mean scores for the *Andrographis paniculata* side were 214.04±52.58 at baseline, 202.89±53.50 at the 4th week, 196.40±52.10 at the 8th week, and 190.20±53.00 at the 12th week. These results showed a decrease in melanin index, but with p-values of 0.229 (>0.05). Therefore, it can be determnined that the melanin index scores were decreased but it is not statistically significant. On the placebo eye cream side, it exhibited mean scores of 201.47±52.38 at baseline, 210.58±48.47 at the 4th week, 218.26±50.23 at the 8th week, and 210.21±48.62 at the 12th week, with no statistically significant improvement with p-value of 0.210 (>0.05). However, when comparing the two sides, the *Andrographis paniculata* extract eye cream showed significantly greater improvements in the under-eye area at 12th week, with p-value of 0.005(<0.05).

Table 4 Mean Changes of melanin index by Mexameter of *Andrographis paniculata* extract eye cream over 12 weeks (n=19)

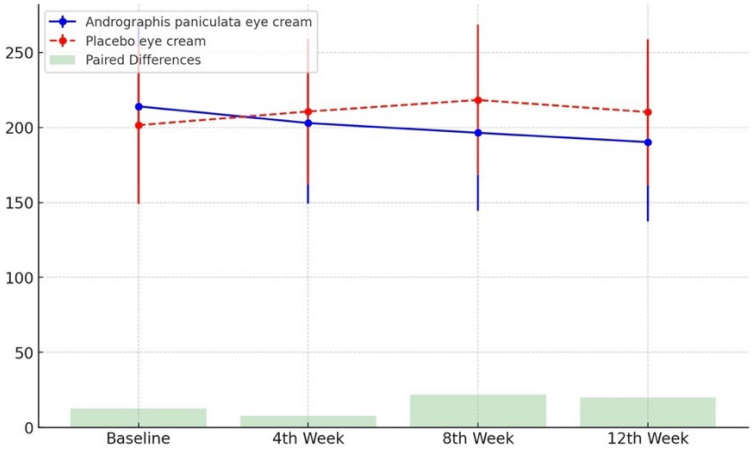
Variables	**Mean Changes from Baseline**		**p-value**	
Melanin Index by Mexameter	**Under Eye (Mean ± SD)**	**Crow Feet (Mean ± SD)**	**Under Eye**	**Crow Feet**
Baseline – week4	-8.32±73.08	-27.63±82.79	0.626	0.163
Baseline– week 8	7.16±104.72	-52.37±54.84	0.769	0.001
Baseline – week12	-43.05±73.30	-28.21±69.80	0.020	0.095
Week4 – week 8	15.47±75.79	-24.74±71.64	0.385	0.150
Week 4 – week12	-34.74±59.31	-0.58±72.63	0.020	0.973
Week8 – week12	-50.21±81.72	24.16±76.92	0.015	0.188

According to the above table, mean changes of melanin index by mexameter from week 8 is significantly lower than week baseline with p-value of 0.001 at crow feet region. At undereye area, mean changes from week 12 is significantly lower than baseline and week 4 with p value of 0.020 (<0.05).



X axis = time point, Y axis = melanin index score

Figure 3 Comparison of *Andrographis paniculata* Eye Cream and Placebo Over Time (Crow's Feet)



X axis = time point, Y axis = melanin index score

Figure 4 Comparison of *Andrographis paniculata* Eye Cream and Placebo Over Time (Under eye)

Table 5 Wrinkle score comparing between *Andrographis paniculata* extract and placebo eye cream on baseline, follow- up 4th, 8th, and 12th week (n=19)

	***Andrographis paniculata* extract**	**Placebo**	**Paired differences±SE**	**p-value(a)**
	Mean±SD	**Mean±SD**		
Baseline	49.63±2.24	56.16±3.01	-5.68±6.90	0.432
4th week	51.63±2.48	54.95±4.42	-2.76±4.50	0.019
8th week	54.68±3.42	54.05±7.65	3.88±4.32	0.935
12th week	57.89±4.89	51.74±8.86	9.67±3.72	0.010
P-value(b)	**0.002**	**0.196**		

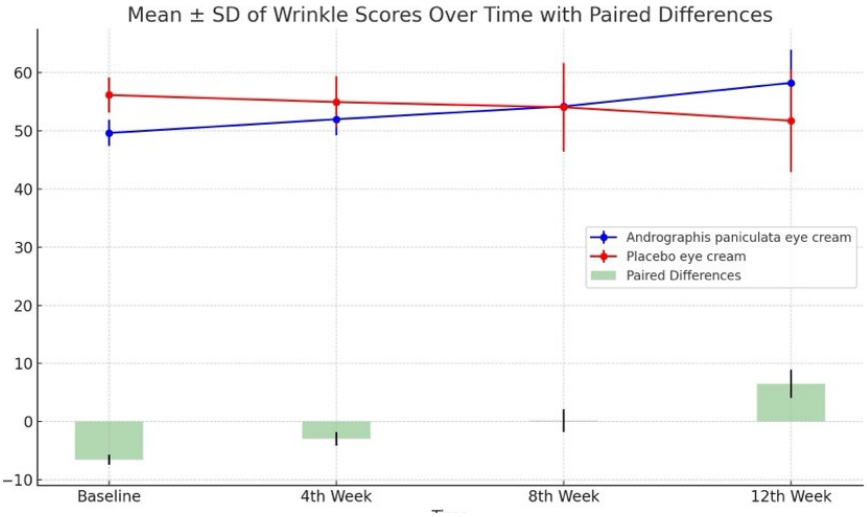
Note Data were analyzed with Wilcoxon Signed Ranks test
p-value (a): compares the treatment effect of *Andrographis paniculata* cream vs. placebo.
p-value (b): significant change within a group across time points.

According to the analysis of Visia scores, the results showed significant improvements for the *Andrographis paniculata* eye cream compared to the placebo eye cream side, at 4th week and 12th week. At baseline, the AP extract cream side had the score of 49.63±2.24, 51.63±2.48, 54.68±3.42, 57.89±4.89 with p value of 0.002 (<0.05), which is statistically significant. At the placebo eye cream side, the results did not show any improvement with p value of 0.196(>0.05).

Table 6 Mean Changes of wrinkle score by VISIA scan of *Andrographis paniculata* extract eye cream over 12 weeks

Variables	**Mean Changes from Baseline**	**p-value**
Wrinkle Scores by Visia Scan		
Baseline – week4	2.37±2.06	<0.001*
Baseline– week 8	4.58±3.32	<0.001*
Baseline – week12	8.63±4.88	<0.001*
Week4 – week 8	2.21±2.68	0.002
Week 4 – week12	6.26±4.12	<0.001*
Week 8 – week12	4.05±3.44	<0.001*

According to the analysis from the above table, mean changes were statistically significant over baseline to 4th, 8th, 12th week respectively with p value of less than 0.001. Moreover, baseline to week 4, week 8 and week 12 also showed statistically significant with p value of <0.001.



X axis = time point, Y axis = Wrinkle score

Figure 5 Comparison of *Andrographis paniculata* eye cream and placebo over time

Patients' Satisfaction Score

Table 7 Statistical analysis of patients' satisfaction score compare between *Andrographis paniculata* eye cream side and placebo eye cream side (n=19)

	***Andrographis Paniculata* Extract, n(%)**	**Placebo group n(%)**	**p-value**
No satisfaction (0)	0 (0.0)	8 (42.1%)	
Little satisfaction (1)	0 (0.0)	6 (31.6%)	
Average satisfaction (2)	3 (15.8%)	5 (26.3%)	<0.001
More satisfaction (3)	10 (52.6%)	0 (0.0)	
Most satisfaction (4)	6 (31.6%)	0 (0.0)	

Note Data were analyzed with McNemar test

A statistical analysis comparing patient satisfaction between the *Andrographis paniculata* extract eye cream and the placebo eye cream revealed 31.6% reported "Most satisfaction" with the *Andrographis paniculata* eye cream, whereas 26.3% of patients experienced "Average satisfaction," respectively, with placebo eye cream, resulting in a statistically significant difference with a p-value of less than 0.001. Satisfaction scores were collected using a 5-point Likert scale, where 0 represents "no satisfaction" and 4 represents "most satisfaction."

Dermatologists' Evaluation Score

Table 8 Frequencies of dermatologists' evaluation score

***Andrographis paniculata* extract**				**Placebo**		
	4th week	**8th week**	**12th week**	**4th week**	**8th week**	**12th week**
Worse (-1)	-	-	-	11	6	5
No change (0)	-	-	-	5	5	8
Fair improvement (1)	11	5	3	3	8	6
Moderate improvement (2)	8	10	10	-	-	-
Good improvement (3)	-	4	6	-	-	-
Excellent improvement (4)	-	-	-	-	-	-

Table 9 Statistical analysis of evaluation by 3 dermatologists on follow-up 4th, 8th, and 12th week

	***Andrographis paniculata* extract**	**Placebo**	**P-value(a)**
	Median (IQR)	**Median (IQR)**	
4th week	0.7(0.7-1.3)	-0.7 (-0.7-0.7)	0.7(0.7-1.3)
8th week	1.3(1.3-2)	0.7(0-0.7)	1.3(1.3-2)
12th week	1.3(1.3-2)	0.7(0-0.7)	1.3(1.3-2)
P-value(b)	**17.55(2), p<0.0001**	**7(2), p=0.03**	

Note Data were analyzed with Wilcoxon Signed ranks test (a), and Friedman test (b)

The above presents the statistical analysis of evaluations by three dermatologists at the 4th, 8th, and 12th weeks for both the *Andrographis paniculata* extract eye cream and the standard eye cream. For the *Andrographis paniculata* eye cream, the median evaluations were 0.7 (IQR: 0.7-1.3) at the 4th week, 1.3 (IQR: 1.3-2) at the 8th week, and 1.3 (IQR: 1.3-2) at the 12th week. In contrast, the standard eye cream side had median evaluations of -0.7 (IQR: -0.7-0.7) at the 4th week, 0.7 (IQR: 0-0.7) at the 8th week, and 0.7 (IQR: 0-0.7) at the 12th week. The statistical significance of the differences between the two treatments was evaluated using the Mann-Whitney U test and the Friedman test, with p-values of less than 0.0001 and 0.03, respectively, indicating a significant difference in the evaluations over time.

Side Effects

Table 10 Frequencies of side effects and complication

	***Andrographis paniculata* extract Placebo**					
	4th week	**8th week**	**12th week**	**4th week**	**8th week**	**12th week**
Itching (scale 0 to 10)	0	0	0	0	0	0
Duration of erythema	-	-	-	-	-	-
Allergic contact dermatitis	-	-	-	-	-	-
Post-inflammatory hyperpigmentation	-	-	-	-	-	-
Post-inflammatory hypopigmentation	-	-	-	-	-	-

The assessment of adverse effects for both the *Andrographis paniculata* eye cream and placebo eye cream treatment revealed no occurrences of itching at any of the measured time points (4th week, 8th week, and 12th week) for either treatment. Additionally, there were no reports of duration of erythema, allergic contact dermatitis, post-inflammatory hyperpigmentation, or post-inflammatory hypopigmentation for either the *Andrographis paniculata* eye cream side or the placebo side throughout the study period.

DISCUSSION & CONCLUSION

In this study, the researcher studied the efficacy of 2% *Andrographis paniculata* eye cream in reducing periorbital wrinkles and periorbital hyperpigmentation. The participants were 52.63% females and 47.37% males, with an average age of 26.95±2.12 years. The participants were students (73.68%), while the rest were government officers (26.32%). Only one participant reported an underlying medical condition, and none had undergone any treatments in the four weeks preceding the study. Most subjects had combination skin (57.89%), while the remaining participants had oily skin (42.11%).

The data were collected by VISIA scan, Cutometer, and Mexameter to assess skin elasticity, and melanin levels, and wrinkle scores comparing the side treated with *Andrographis paniculata* eye cream to the side treated with a placebo eye cream. The results showed a statistically significant reduction in periorbital wrinkles and periorbital hyperpigmentation on the *Andrographis paniculata*-treated side compared to the standard cream side. Additionally, the *Andrographis paniculata* extract eye cream showed greater efficacy and provided more satisfactory results than the standard cream

The study results can be summarized as follows:

Firstly, the topical application of *Andrographis paniculata* eye cream did not result in any allergic reactions during the patch test, and no allergic cases were reported throughout the study. Based on this, it can be concluded that *Andrographis paniculata* eye cream is safe for use around the eye area.

The mean Cutometer score at the crow's feet area on the *Andrographis paniculata* eye cream side showed a statistically significant increase at 12^{th} week with p value of 0.010(<0.05) at crow's feet area. Similarly, the mean Cutometer score at the undereye area on the *Andrographis paniculata* -treated side showed a statistically significant increase at 4^{th} week (0.045), 8^{th} week (0.001) and 12^{th} week (<0.001), compared to the placebo treated side. Moreover, there was statistically significant change improvement across all time points at crow's feet and under eyes regions on AP cream treated side with p value (<0.001) However, there was no statistically significant change in Cutometer scores at the crow's feet and undereye areas for the placebo eye cream. These findings indicate that *Andrographis paniculata* eye cream enhances skin elasticity around the eye area more effectively than the standard eye cream.

The *Andrographis paniculata* eye cream was also found to reduce the melanin index, as measured by Mexameter, at the crow's feet area from baseline to the 4^{th} week, 8^{th} week, and 12^{th} week with p value of 0.004(<0.05). In contrast, the Mexameter scores at the crow's feet on the placebo side did not show a statistically significant difference across visits at crow's feet area, with p value of 0.140. The Mexameter score on AP cream treated side at the under-eye area showed a statistically significant reduction at the 12^{th} week, with a significance level of 0.005 ($p<0.05$), compared to the placebo treated side. These results suggest that the *Andrographis paniculata* eye cream led to a greater decrease in melanin index around the under-eye area by the 12^{th} week compared to the standard eye cream at under eye area.

Based on the wrinkle scores by Visia scan, the side treated with *Andrographis paniculata* eye cream showed a statistically significant improvement between baseline and the 4^{th}week, 8^{th} week and 12^{th} week with p value of 0.002 ($p<0.05$). In contrast, the VISIA scores for the side treated with the placebo eye cream did not show a statistically significant difference with p value of 0.196(>0.05). This indicates that *Andrographis paniculata* eye cream is more effective at reducing skin wrinkles and hyperpigmentation compared to the placebo eye cream. Regarding patients' satisfaction, *Andrographis paniculata* eye cream treated side had statistically greater result than placebo eye cream treated side at follow up 12^{th} week.During the 12^{th}-week follow-up visit, three dermatologists assessed the volunteers and rated 3 of them as having shown good improvement, 10 as having moderate improvement, and 6 as having good improvement on the side treated with *Andrographis paniculata* extract cream. In

comparison, the majority (6 volunteers) were rated as having fair improvement on the side treated with the placebo eye cream.

The above data demonstrated a significant increase in skin elasticity on the side treated with *Andrographis paniculata* eye cream. This effect may be due to its ability to counteract the action of matrix metalloproteinases (MMP-1, MMP-3), which are known to be triggered by UV radiation, leading to the breakdown of collagen and elastin, and leading to wrinkles and skin laxity. (Büth et al., 2004) Andrographolide sodium bisulphate (ASB), a water-soluble form of andrographolide, has been proved to inhibit the activation of MMP enzymes. (Zhan et al., 2016) *Andrographis paniculata* extract can also stimulate collagen production and this results in a noticeable improvement in skin wrinkles. (You et al., 2015). Therefore, *Andrographis paniculata* eye cream enhances skin elasticity and can be an effective treatment for wrinkles around the eyes.

Andrographis paniculata leaf extract has been shown to significantly reduce the melanin index, making it a potent and safe natural ingredient for skin lightening. It effectively inhibits melanin production by suppressing TYR, MITF, and related proteins. Additionally, the extract is considered a reliable and safe option for managing hyperpigmentation, offering a natural solution for skin lightening (Adam et al., 2022). This anti-melanogenic property of AP cream can be the cause in reduction of melanin index and good for periorbital hyperpigmentation. Based on this study and its results, *Andrographis paniculata* extract eye cream is a safe and effective topical treatment for wrinkles and hyperpigmentation around the eyes. All participants tolerated the treatment well, with no reported side effects such as skin irritation, erythema, or hyperpigmentation throughout the study period. From the data, it can be concluded that *Andrographis paniculata* extract cream enhances skin elasticity and reduces the melanin index, likely due to the antioxidant and skin lightening properties of the compounds present in the cream.

Suggestion for Future Research and Clinical Applications

Future studies can investigate the long-term effects of *Andrographis paniculata* extract eye cream beyond 12 weeks.

Extending the duration of the study would be beneficial. Comparing *Andrographis paniculata* with other anti-aging ingredients could clarify its relative effectiveness.

The potential of combining this eye cream with other treatments like fillers or laser therapy should be explored.

Conclusion

Based on the clinical study, it can be concluded that *Andrographis paniculata* extract cream significantly enhances skin elasticity and reduces hyperpigmentation in participants without causing harmful side effects. In summary, 2% *Andrographis paniculata* extract cream appears to be a safe and effective topical treatment for periorbital wrinkles and periorbital hyperpigmentation.

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