

Madhu Kumari Lepa in Management of Periorbital Hyperpigmentation - Randomized Controlled Clinical Study

Dr. Purva Verma

BAMS (M. D), Assistant Professor & Consultant RK University Rajkot

Abstract: Background & Objectives: Periorbital hyperpigmentation is a common condition occurring in the dermis, epidermis, or both, is a darkening of the skin caused by an increase in production of or distribution of melanin it involves the lower eyelid sometimes extending to the upper eyelid. It is caused by various endogenous, exogenous, and lifestyle factors i. e. sun exposure, advanced age, heredity, thin skin, fatigue, hormonal therapy, lack of sleep, use of cosmetics and spectacles, anemia, overuse of alcohol. It is a cosmetic concern for a large number of individuals who relate it with significant impairment on quality of life. Despite its prevalence, there are not much or very few studies published on Periorbital hyperpigmentation, there are several treatment options available but there is a lack of evidence - based study virtuous description of the condition is unavailable. A variety of products are available commercially which are expensive and may have a side effect, folklore practices are cost - effective and need to be proven clinically. This study was taken up to evaluate the efficacy of Madhu Kumari lepa in the management of Periorbital Hyperpigmentation. **Method:** Methods: In the present study, 41 samples were screened and out of which 40 were selected and enrolled, randomly assigned into two groups, with 20 subjects in each group. The diagnosis was done based on Lakshana The trial drug Madhu Kumari lepa was administered to the subjects of Group A and the control drug Conventional topical cream was given to Subjects of Group B. Intervention was given for 10 days and the study period was of 30 days. The assessment was done on the 0th day, 10th day, 20th day, and 30th day using the Standard under eye score scale available in the market (fair and lovely fairness scale) The data obtained were statistically analyzed by using Paired and Unpaired t - test and the results were represented in the forms of tables and graphs. **Results:** Within Group A and B, there was a statistically highly significant difference in Periorbital Hyperpigmentation. Between the Groups statistically both Madhu Kumari lepa and Conventional topical cream had the same effect but clinically Madhu Kumari lepa had a slightly better effect than Conventional topical cream. No adverse drug reactions were observed during the study. **Interpretation and conclusion:** Madhu Kumari lepa and Conventional topical cream both were effective in reducing Periorbital hyperpigmentation. Madhu Kumari Lepa being both hydrophilic and lipophilic helps in drug penetration through the skin by modifying keratinized protein of stratum corneum and by disturbing hydrogen bond connection of Stratum corneum, it enhances skin tone by lowering eumelanin and reach to cellular level by regulating acid - alkaline ph which can be well correlated to pittahara and varnya karma and brings about the desired action of reducing Periorbital hyperpigmentation. Conventional topical cream acted as an antioxidant and has phytochemicals which had an impact on any stage in process of melanogenesis. Ingredients of Madhu Kumari lepa are easily available and cost - effective. Thus both interventions can be used as a remedy for Periorbital hyperpigmentation

Keywords: Ayurveda, Varnya, Lepa, Madhu, Kumari

1. Introduction

The eyes are the focal point of facial expression which convey human emotion and have a significant impact on how one is perceived in terms of health and beauty¹ Periorbital hyperpigmentation is a condition occurring in the dermis, epidermis, or both is a darkening of the skin caused by an increase in production or distribution of melanin¹.

Presents as bilateral, homogeneous, hyperchromic macules involve lower eyelid sometimes extending to an upper eyelid² It has various overlapping endogenous and exogenous lifestyle factors i. e sun exposure, advanced age, heredity, thin skin, use of spectacles, lack of sleep, cosmetic use, pre - menstrual phase, more screen time and reading hours, anemia, dehydration, overuse of alcohol¹

Prevalence of periorbital hyperpigmentation in Indian population is 30.76%.^{3,4}

Any condition related to skin affects the person emotionally and mentally causes social taboo leads to isolation of the individual from society. Periorbital hyperpigmentation is a cosmetic concern for many individuals, who are concerned

about it and relating it with significant impairment on quality of life.¹

Nevertheless, even mild to moderate improvement in appearance can enhance patients' quality of life; hence topical therapies can be used to treat patients seeking to improve the cosmetic appearance of the eye.⁵

A variety of products are available commercially, which are expensive, may contain preservatives that may cause side effects. Folklore practices are cost - effective and need to be proven clinically.

Acharya's have mentioned Madhu (Honey) as Varnya, Vrisya, and Sukshma soukumaryakaram, ropana⁶

Honey contains flavonoid that act as antioxidants, monosaccharides, disaccharide, essential amino acid, and all water - soluble vitamins including vitamin A and E⁷

Kumari was referred to as twagamayam and taruni by the acharya,⁸

In recent years, under the name "Aloe Vera gel, a stabilized viscous juice from mucilage - containing parenchyma in the

Volume 13 Issue 4, April 2024

Fully Refereed | Open Access | Double Blind Peer Reviewed Journal

www.ijsr.net

inner part of succulent leave has been an ingredient in cosmetic preparations, humectants⁹

Here an attempt was made to evaluate and analyse the efficacy of *Madhu Kumari lepa* (coined term) in the management of periorbital hyperpigmentation in 40 samples considering the inclusion and exclusion criteria

2. Objectives

- To evaluate the effect of madhu kumarai lepa in periorbital hyper pigmentation
- To re - evaluate the effect of conventional topical cream (unishade plus) in periorbital hyper pigmentation
- To compare the efficacy of madhu kumari lepa with conventional topical cream

Hypothesis

Null Hypothesis (H₀) –

The efficacy of *madhu kumari lepa* is same as that of conventional topical cream in management of periorbital hyperpigmentation

Alternate Hypothesis –

- H₁ - The efficacy of *madhu kumari lepa* is greater than the efficacy of conventional topical cream in management of periorbital hyperpigmentation.
- H₂ - The efficacy of *madhu kumari lepa* is less than the efficacy of conventional topical cream in management of periorbital hyperpigmentation

3. Methodology

Materials

Source of data

- Literary Source:** Data was collected from *Samhitas*, contemporary modern texts, reputed journals, research articles, web sources from different Universities, which further reviewed and documented for study
- Sample:** 40 subjects with Periorbital hyperpigmentation who attended OPD section of Sri Sri College of Ayurvedic Science and Research Hospital, Bengaluru fulfilling the inclusion criteria and who were willing to give consent for the study were selected
- Research Design:** Simple randomized controlled clinical trial.
- The 20 subjects each were allocated to group A and group B by using coin tossing, simple randomization method to avoid selection bias and maintain baseline balance between the groups.
- Diagnostic Criteria:** Diagnosis was done based *Lakshana* (symptom) – darkness around the eyes and assessed with the help of standard scale available in market - fair and lovely under eye scale

Inclusion Criteria

- Subjects diagnosed with periorbital hyper pigmentation

- Subjects of age group between 21 to 50 years irrespective of their gender, religion and socioeconomic status
- Subjects who were willing to participate in the study

Exclusion Criteria

- Subjects who were taking photosensitizing drugs like NSAIDS, anti –histamines, oral contraceptives, sulphonamides etc
- Chloasma / Melasma, post –inflammatory hyperpigmentation was excluded
- Smoking, alcoholism
- Anemia
- Subjects suffering from any other systemic illness were excluded

Withdrawal Criteria

- Subjects with acute illness requiring emergency management.
- Subjects who were not willing to continue the study.

Intervention

Group A

- Madhu Kumari lepa* (Trial Group): Good quality Aloe vera was collected from herbal garden, FSSAI certified honey was purchased from authentic source (Dmart, BENGALURU, Batch No. K38, Manufacturing Date – February 25, 2021, Expiry Date – August 25, 2022)
- Preparation: Leaf is washed cut is made allow the yellow exudate to flow out transparent white pulp is taken and crushed before application
- Method: The subjects were asked to clean the periorbital area with cotton. Honey is to be applied it should be kept for 15 minutes, gently wipe it with cotton, followed by application of Aloe vera pulp for 15 minutes then gently wipe it with cotton.
- Route External Application for 10 days

Group B

Conventional topical cream (Unishade Plus cream - Control Group)
Source - Commercially available cream for periorbital hyper pigmentation was procured directly from GMP certified pharmacy (Prakruti remedies Pvt. Ltd Shirwad, Kanwar Karnataka, Batch no R20337, Manufacturing date – 10 /2020, Expiry date – 10/2022)

Method

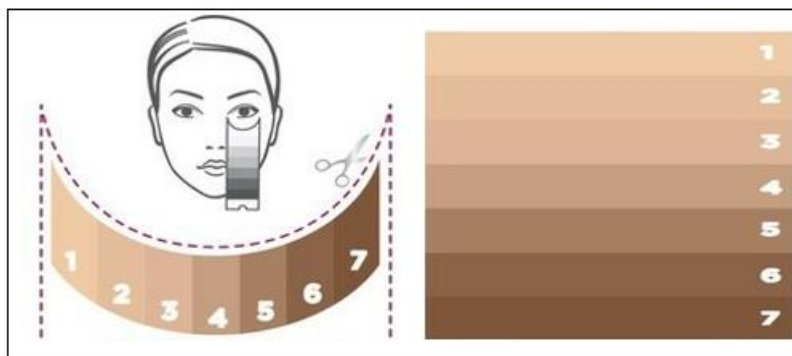
The subject was asked to clean the periorbital region with cotton, then apply the conventional topical cream in periorbital region and wipe it after 30 minutes with cotton.

Route - External application for 10 days

Assessment Criteria

Objective Criteria

Standard scale available in the market (fair and lovely under eye scale)



Assessment / Follow Up

Assessment / Follow up	Day
Pre – Study Assessment	0 day
1 st Assessment	10 th day
1 st Follow up	20 th day
2 nd Follow up	30 th day

4. Statistical Analysis

To carry out statistical analysis, the data from both the groups were recorded on the days of assessment and follow up, analysis was carried out using SPSS software version 20.

The following statistical analysis were done: -

Repeated measures of ANOVA was employed to analyse the Under eye scale score within the group A and group B as follows:

- Under eye scale score on 0th day and 10th day
- Under eye scale score on 0th day and 20th day
- Under eye scale score on 0th day and 30th day
- Unpaired t test was employed to analyse the under eye scale score between group A and group B.
- After the statistical analysis, interpretation of the results was done based on the mean value and P value, P value ≤0.05 was considered as significant

5. Result

Between Groups Independent t test Analysis	Results	Discussion
On 10 th day	No significant differences found between the efficacies of <i>Madhu Kumari lepa</i> and Conventional topical cream	Both have Par (equal) results in reducing Periorbital Hyperpigmentation
On 20 th day		
On 30 th day		

Overall Efficacy

Group	% Improvement		
	0 th day – 10 th day	0 th day – 20 th day	0 th day - 30 st day
Group A	23.80%	16.19%	11.42%
Group B	18.26%	12.50%	3.84%

Repeated measures of ANOVA - Within the Group A and B on 0thday, 10th day, 20th day, 30th day

Under eye scale score	0 th DAY	10 th DAY	20 th DAY	30 th DAY	Repeated period ANOVA	Inference
Group A	5.25±1.372	4.00±1.214	4.40±1.429	4.65±1.387	P=0.000	Highly significant
Group B	5.20±1.005	4.25±1.118	4.55±1.146	5.00±1.124	P=0.000	Highly significant

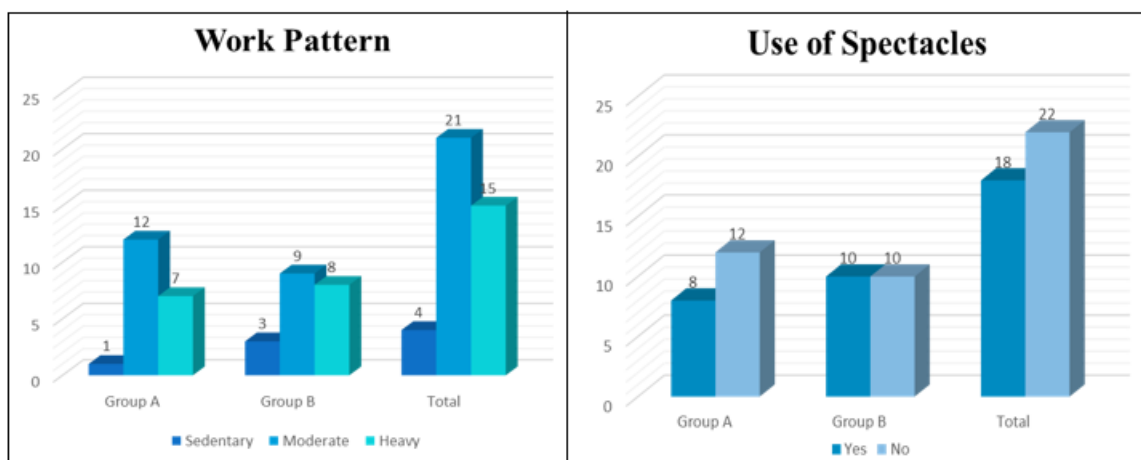
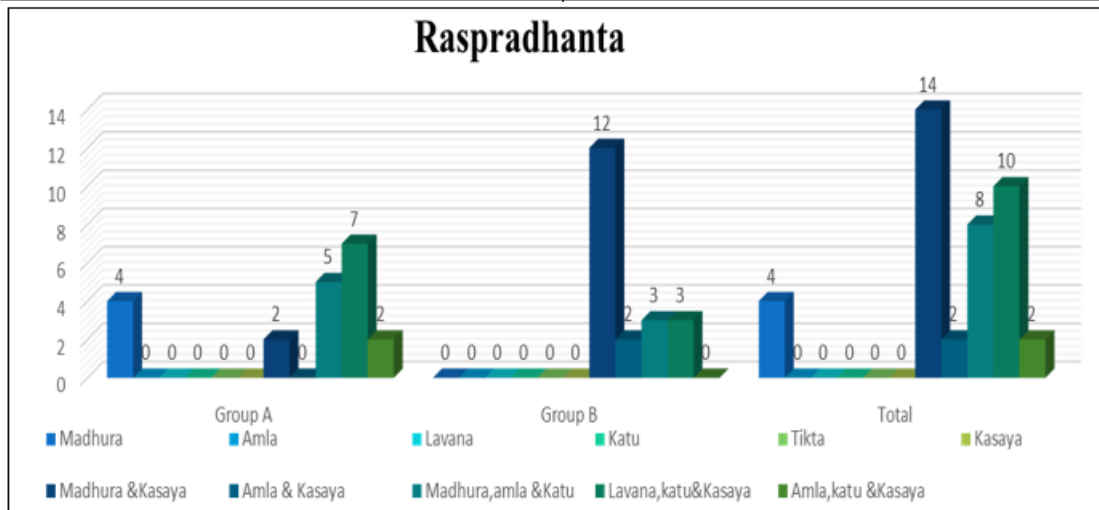
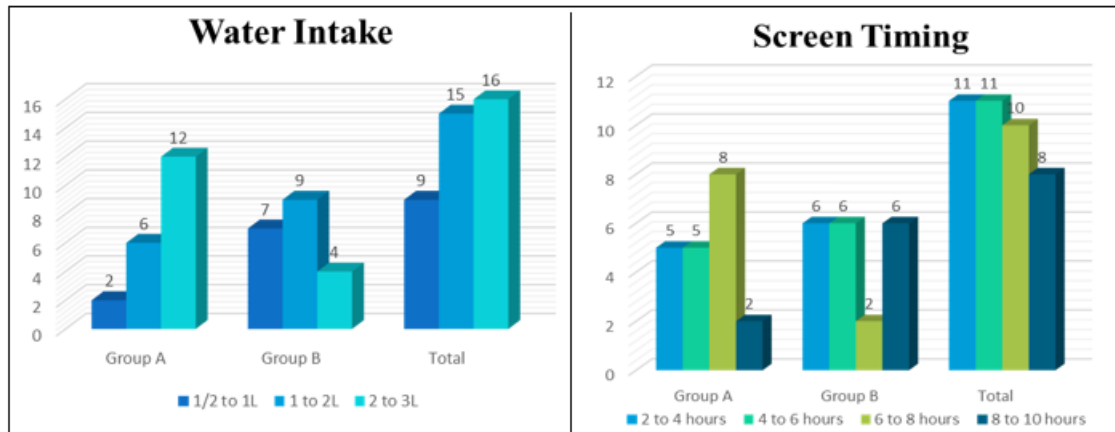
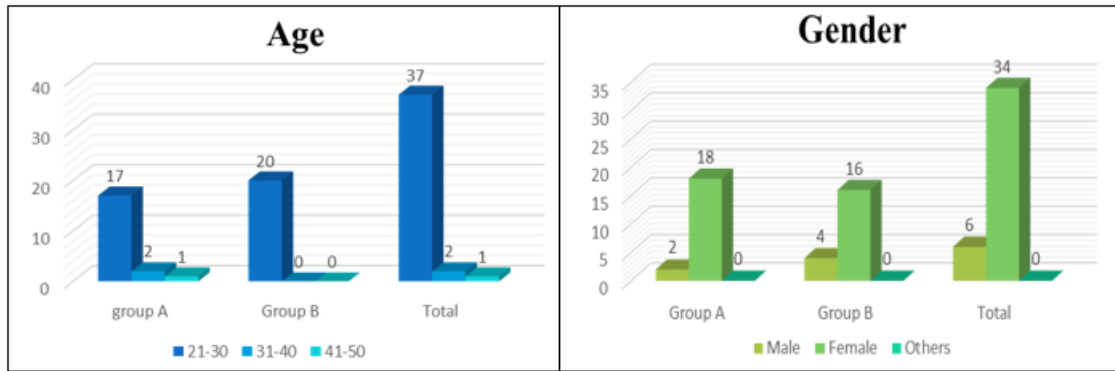
ANALYSIS - Repeated measures of ANOVA

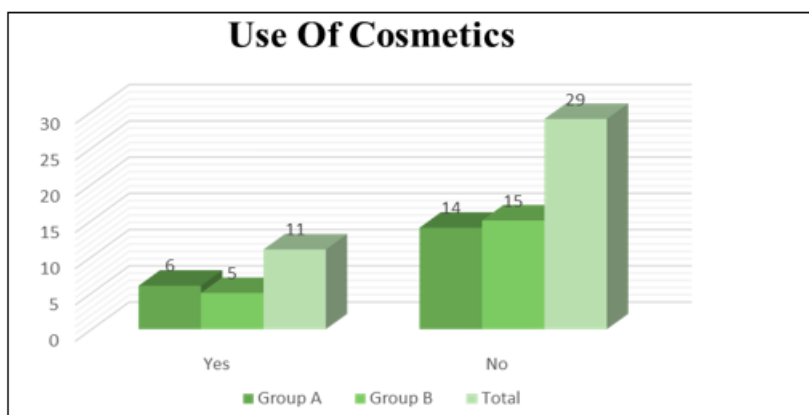
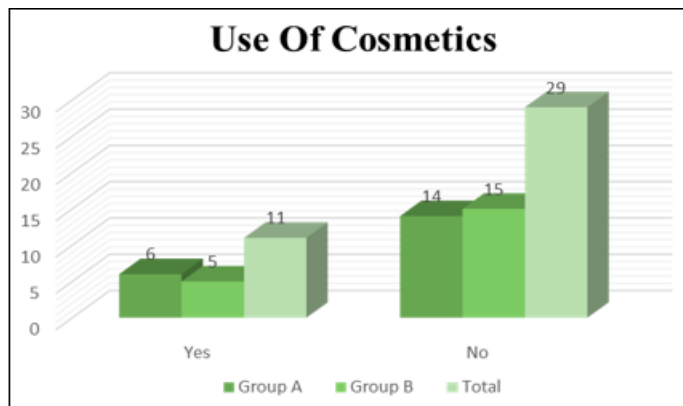
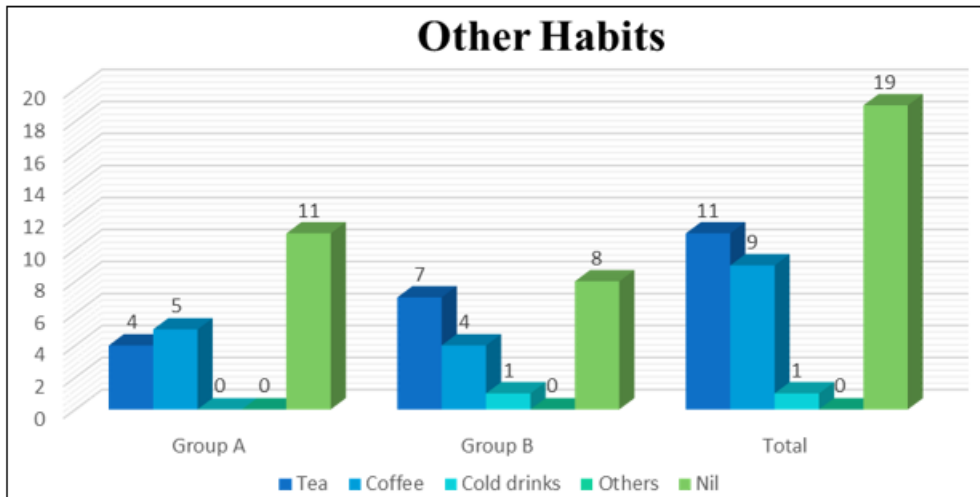
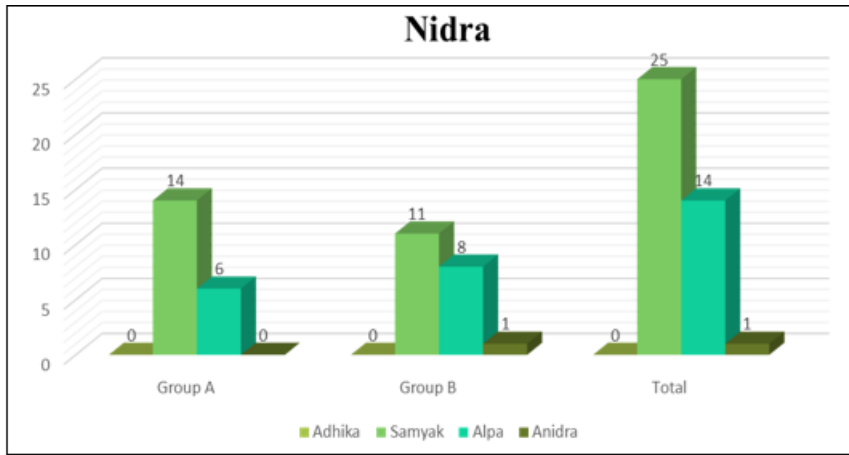
Within the Group A & Group B on 0th day, 10th day, 20th day (Under eye scale score)

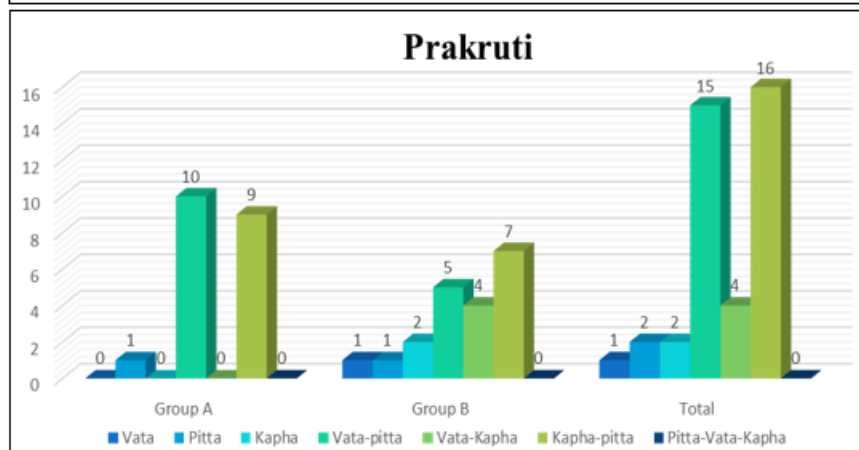
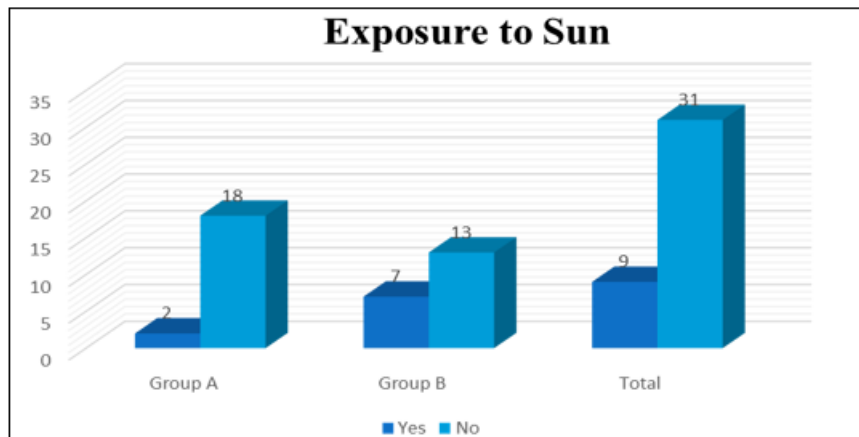
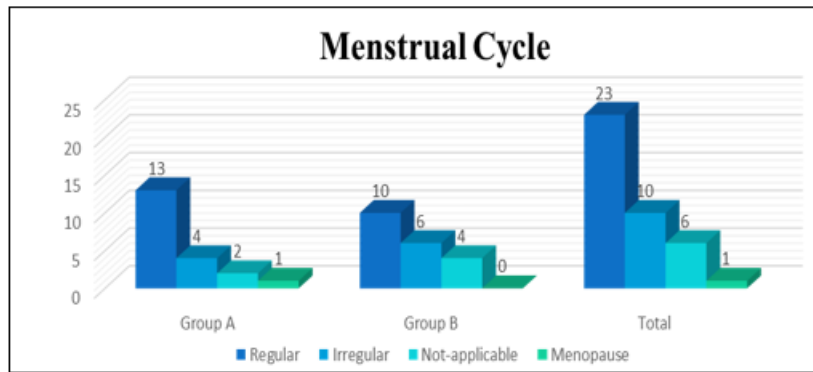
Results: Reduction in periorbital hyperpigmentation

Discussion: Both *Madhu kumari lepa* and Conventional topical cream are effective in reducing Periorbital hyperpigmentation

6. Observations







Discussion on observation

- **Age:** 21 to 50 years was selected as it comes under Pitta’s dominant Kala, it appears to be more common in adults, but it can affect people as early as childhood, the increased frequency in 21 - 30 years indicates the cosmetic inclination of this age group.
- **Gender:** Females are more concerned about their cosmetic appearance and some days of the month (e. g., 1 - 7 days there is the release of prostaglandins and decrease in oestrogen and progesterone levels, 17 - 24 day there is building up of testosterone at the end of the cycle, 25 - 28 day there is a decrease of progesterone and oestrogen levels) which makes the skin of females prone for wrinkles and pigmentation
- **Water intake:** Drinking less water can make your eyes look sunken because it raises oxidative stress.
- **Screen timing:** The artificial light from the screen dries out the skin by stealing moisture and causing collagen breakdown.
- **Rasapradhanta:** Katu Rasa is Vata and Pitta Vardhaka, Kasaya rasa is Vata vardhaka and lavana rasa can cause

the body to retain fluid which in turn make the area around the eye prone to puffiness and discoloration

- **Work pattern:** Blood circulation in the eye area slows down when people are fatigued or stressed, allowing blood to pool and cause puffy eyes and dark circles also fatigued stress, anxiety causes increased MSH (Melanocyte stimulating hormone) secretion making people prone for periorbital hyperpigmentation¹⁰
- **Use of spectacles:** Dark circles under the can appear only when a person is wearing the wrong frame (a frame that is too tightly pressed against the skin slows down the lymph circulation around the eyes and triggers dark circles) In long run e. g nose pads resting around that area slows down the blood circulation over time leads to dark circles¹¹
- **Nidra:** Our bodies go through three unique stages during sleep that contributes to our overall wellbeing and nightly skin regeneration. The pituitary gland produces somatotropin, in the first three hours of sleep, which contributes to the maintenance of youthful and healthy skin. The hormone melatonin is produced during the next

two hours of sleep, which acts as an antioxidant to protect the skin from free radical damage. Your cortisol levels begin to drop along with your skin temperature during the final stage of sleep and as your skin cools down, your muscles relax, and collagen production increases

- **Habits:** The habit of having tea, coffee, and soft drinks will increase Pitta Dosha due to its Tikshna and Ushna Guna which will, in turn, increase the chances of periorbital hyperpigmentation
- **Use of cosmetics:** Some people may develop allergic reactions to makeup and develop dark circles as a result of irritation, rubbing, or scratching Rubbing can cause capillary damage and inflammation, which exacerbates dark circles, and some cosmetics contain salicylic acid,

which isn't sufficiently hydrating and dries out skin and causes collagen breakdown

- **Menstrual cycle:** 7 days - release of prostaglandins, decrease in oestrogen and progesterone, 17 - 24 day - testosterone builds up, 25 - 28 day - decrease of progesterone and oestrogen levels, Menopause – decrease collagen production, increased water loss, drop in oestrogen level makes skin prone for wrinkles & dark circles
- **Exposure to sun:** Overexposure to the sun causes melanocytes to mature abnormally, causes the breakdown of collagen and elastin at a higher rate than normal aging
- **Prakruti:** Subjects with Kapha Pitta Prakruti and Vata pitta prakruti were more prone to periorbital hyperpigmentation

PROBABLE SAMPRAPTI OF PERIORBITAL HYPERPIGMENTATION

<i>AHARAJA & VIHARJANIDANA</i>	
<i>(Lavana rasa sevana, drinking less water use of tea, coffee, cold drink Atapa sevana)</i>	<i>(Kashaya & Katu rasa sevana Eye strain, more screen time)</i>
<i>Increase in ushna guna of pitta vikruti of bhrajaka pitta</i>	<i>Soshana of kledata Vata vridhhi</i>

Discussion on intervention

Madhu Kumari lepa is a coined term for the combination of honey and aloe vera used as a folklore medicine in Periorbital hyperpigmentation where honey has to be applied for 15 minutes followed by application of Aloe vera pulp for 15 minutes.

Madhu - Madhura in rasa and has sheeta virya. It is Pitta rakta shamaka Sukshamarganusari, Yogavahi and varnya

Kumari - Snigdha guna and sheeta virya. It is Rasayani, Twagamayam, Vrishya, Bramhana. Thus considering the overall effect of Madhu Kumari lepa, by its Madhura, tikta, and kashaya rasa it does the Chedana of Prakupita (vitiated) vata and pitta and Upashamana i. e. it does not allow Utklesha of Dosha and maintains the equilibrium and hence pacifies pitta which is one of the main culprits in the causation of Periorbital hyperpigmentation. Snigdha guna act as Vata shamaka by maintaining the kledata in twak (trans - epidermal water balance) responsible for mardavata and varna prasadana, ruksha guna being the property of Agneya dravya is responsible for Prabha, Prakasha, and varna Sheeta virya is endowed with pittahara and rakta prasadana karma. Madhura vipaka by its Snigdha guna and Kapha vardhana karma is responsible for varna utkarsha. Thus, the combination is effective in achieving Samprapti Vighatana by reducing the prakupitta pitta and vata, thereby reducing Periorbital Hyperpigmentation.

Mode of action based on phytochemicals

MADHU

Depigmenting agent - Honey possesses inhibitory activity on tyrosinase (an enzyme that catalyzes dihydroxyphenylalanine (DOPA) in the pathway of melanin synthesis) due to the presence of polyphenols¹²

Moisturizing effect - the humectant feature is thought to be given by the presence of a high quantity of glucose and fructose, both of which can form hydrogen bridges with water, keeping moisture in the stratum corneum skin layer and providing a hydrating effect to the skin. Honey contains various amino acids and organic acids that can augment the effect of glucose and fructose

Emollient effect - Honey softens the skin and improves blood circulation by utilizing the osmotic force of sugar. It nourishes interior epithelial tissues while also stimulating surface circulation, and helps to avoid dry skin and wrinkles.

Antioxidant activity Honey's antioxidant properties are attributable to phenolic chemicals and flavonoids.

Minerals - honey contains only a little number of trace elements, they are highly bioavailable. Minerals from honey have been found to have 80–90 percent bioavailability.

Copper - helps to reduce the appearance of fine lines and wrinkles it stimulates dermal fibroblasts proliferation¹³, upregulates collagen (types 1, 2 and 5) and elastin fiber components (elastin, fibrillins production) by fibroblast¹⁴, serves as a cofactor of superoxidase dismutase¹⁵

Calcium and Magnesium Key regulator of epithelization (the process of covering denuded epithelial surface) regulates the differentiation of basal keratinocytes to corneocytes (terminally differentiated keratinocytes), it acts as a key modulator of directional locomotion of human keratinocytes helps in reducing scar^{16, 17}

Zinc Zinc stimulates keratinocyte proliferation¹⁶ and reduces skin penetration by UVB rays hence act as a barrier Vitamin C Vitamin C protects the skin from oxidative stress by

sequentially donating electrons to neutralize the free radicals.¹⁸ Vitamin C is necessary for collagen synthesis. Vitamin C interacts with copper ions at the active site of tyrosinase, inhibiting the enzyme's function and lowering melanin production.¹⁹

Vitamin E cause depigmentation by interfering with melanocyte membrane lipid peroxidation, increasing intracellular glutathione (antioxidant) concentration, and by inhibiting tyrosinase.²⁰

Vitamin B complex Thiamine is a precursor that aids in the regeneration of collagen in our skin. Riboflavin - plays a key part in collagen formation, enhances zinc absorption, and strengthens the skin's immune system to help it recover from UV exposure. Pantothenic acid act as a humectant and a skin soother. Pyridoxine is an antioxidant that protects cells from harm.

Aloe Vera

Healing properties Topical application of aloe vera, produces glucomannan, and gibberellin which interact with growth factor receptors on the fibroblast, stimulating its activity and proliferation, in turn significantly increases collagen synthesis.²¹ It also increases the degree of collagen cross-linking, resulting in increased scar tissue breaking strength.²²

Effect of Aloe vera on skin exposed to UV and gamma rays The exact role is uncertain, however, after applying aloe vera gel to the skin, an antioxidant protein called metallothionein is produced, which scavenges hydroxyl radicals and prevents the skin's superoxide dismutase and glutathione peroxidase from being suppressed²³

Moisturizing and anti - aging effect - Mucopolysaccharides present in aloe vera aid in the retention of moisture in the skin. Aloe encourages the production of collagen and elastin fibres in the skin, making it more elastic and wrinkle - free. The amino acids soften the skin cell, and zinc serves as an astringent to tighten pores.²⁴

Antioxidant effect Aloe vera gel antioxidant activity is due to the presence of glutathione peroxidase, superoxide dismutase enzymes, and a phenolic anti - oxidant. Saponins have antioxidant properties and protect the skin from UV damage by blocking extracellular matrix disintegration.²⁵

Depigmenting agent Aloesin inhibits tyrosinase by preventing tyrosine from being hydroxylated to 3, 4 - dihydroxyphenylalanine (DOPA) and DOPA from being oxidized to dopaquinone. It has also been reported to reduce melanin formation in melanocytes.²⁶ Aloin, a natural skin lightening agent derived from Aloe vera leaf extract, binds to the enzyme - substrate complex as well as the tyrosinase enzyme, inactivating it and resulting in skin whitening,²⁷

Vitamin Action

Retinol - promotes the growth of new skin cells when used topically, it stimulates collagen production and reduces wrinkles.²⁸

Folic acid It has antioxidant concentrations that work to minimize oxidative stress in the skin as well as neutralize

damaging free radicals. It helps help boost skin - barrier function, resulting in enhanced moisture.²⁹

Choline - Choline aids in the development of cell membranes and helps maintain adequate B vitamin levels in the skin, which aid in the production of collagen and elastin.

Vitamin 12 Vitamin B12 interacts with other B vitamins to maintain healthy skin color and controls the formation of melanin³⁰

Drug delivery action - Discussion on Probable mode of action of Madhu Kumari Lepa

Madhu Kumari lepa is both lipophilic and hydrophilic Madhu contains terpenes, terpenes are volatile compounds with molecular components composed of carbon, hydrogen, and oxygen atoms. Natural terpenes have shown improvement in permeation of both lipophilic and hydrophilic compounds Terpenes enhance skin penetration by acting on Stratum corneum intracellular lipid by extraction or by stratum corneum partitioning of the drug by modifying keratinized protein, by disturbing hydrogen bond connection of stratum corneum layer, or by inducing physiological reaction e. g vasodilatation Kumari (Aloe vera) contain Lignin a structural material of cellulose content which helps in penetration till cellular level, the nanoparticles derived from lignin are nontoxic and biodegradable deliver drugs in a regulated manner Lignin's molecular structure is similar to that of melanin, studies have shown that lignin peroxidase can enhance skin tone by lowering eumelanin. Saponin is another element in Aloe vera that acts as a natural cleansing agent both these elements working together in conjugation reach the cellular level by regulating acid - alkaline ph. levels of the skin and by dilating blood vessels and hence increased circulation. This makes the molecules penetrate the stratum corneum easily to reach the target. Hence, Madhu Kumari Lepa being both hydrophilic and lipophilic helps in drug penetration through the skin by modifying keratinized protein of stratum corneum and by disturbing hydrogen bond connection of Stratum corneum, it enhances skin tone by lowering eumelanin and reach to cellular level by regulating acid - alkaline ph which can be well correlated to pittahara and varnya karma and brings about the desired action of reducing Periorbital hyperpigmentation

7. Conclusion

- Periorbital hyperpigmentation is a cosmetic concern characterized by bilateral round or semi - circular homogeneous brown or dark brown pigmented macules in the periocular region.
- Due to various etiological factor there will be *vikruti* of *bhrajaka pitta* and *rukshata* of *twak* leads to increase in *vata dosha* which leads to Periorbital hyperpigmentation
- This study was aimed to evaluate the efficacy of *Madhu kumari lepa* (Group A - trial) and conventional topical cream (Group -B -control) in Periorbital hyperpigmentation
- Both intervention are found to be effective within the group with more percentage of improvement in Group A
- *Madhu Kumari lepa* is *Pitta hara* in nature and *varnya* by its *karma*. *Madhu Kumari lepa* and Conventional

topical cream are rich in antioxidants, contain phytochemicals which have action on any stage in the process of melanogenesis

- As etiologic factors are part of routine, *Lepa* can be used as part of *Dinachariya*, and benefit of *Madhu Kumari lepa* is that ingredients are easily available
- On comparing *Madhu Kumari lepa* and Conventional topical cream, both are effective in reducing Periorbital hyperpigmentation but *Madhu Kumari lepa* showed clinically sustained effect
- Thus, **null hypothesis (H₀) is accepted** - The efficacy of *Madhu Kumari lepa* is equivalent to that of Conventional topical cream in the management of Periorbital Hyperpigmentation.

References

- [1] Gendler EC. Treatment of periorbital hyperpigmentation *Aesthet Surg J.*2005; 25 (6): 618 - 24.
- [2] Agrawal S. Periorbital hyperpigmentation. Overcoming the challenges in the management. *Nepal Journal of Dermatology Venereology and Leprology.*2018; 16 (1): 2 - 11.
- [3] Sheth PB, Shah HA, Dave JN. Periorbital hyperpigmentation: A study of its prevalence, common factors, and its association with personal habits and other disorders. *Indian J Dermatol* 2014; 59: 151 - 7
- [4] Freitag FM, Cestari TF. What causes dark circles under the eyes? *J Cosmet Dermatol.*2007; 6: 211 - 5.
- [5] Sarkar R, Ranjan R, Garg VK, Sonthalia S, Bansal S, et al. Periorbital hyperpigmentation: A comprehensive review. *J Clin Aesthet Dermatol.*2016; 9 (1): 49 - 55.
- [6] Murthy S. K. R, Bhavaprakasa, Purvakhanda, Ch.6, Sh1 - 5, Varanasi: Chaukhamba krishnadas academy; 2004, p.485 - 9.
- [7] Samarghandian S, Farkhondeh T, Samini F. Honey and health: A review of recent clinical research. *Pharmacognosy Res.*2017 Apr - June; 9 (2): p121 - 7.
- [8] Sastry. J. L. N. Dravyaguna Vijnana, Kumari, Varanasi: Chaukhamba orientalia; 2008 (3), p.536 - 40.
- [9] Christian FC, Frohne F, Holtzel C. Herbal drugs and phytopharmaceuticals: med pharm scientific publishers.2010; 59 - 61.
- [10] Laura Geggel” Why do people get ‘bags’ Under their eyes? March 23, 2016 Available from URL: <https://www.livescience.com/32188-why-do-we-getbaggy-eyes.html>
- [11] Malakar S, Lahiri K, Banerjee U, Mondal S, Sarangi S. Periorbital melanosis isan extension of pigmentary demarcation line - F on face. *Indian J Dermatol Venereol Leprol* 2007; 73: 323 - 5.
- [12] Chang T - S. An updated review of tyrosinase inhibitors. *Int. J. Mol. Sci.*2009; 10: 2440 - 2475. doi: 10.3390/ijms10062440. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [13] Philips N, Hwang H, Chauhan S, Leonardi D, Gonzalez S. Stimulation of cell proliferation and expression of matrix metalloproteinase - 1 and interleukin - 8 genes in dermal fibroblasts by copper. *Connect. Tissue Res.*2010; 51: 224 - 9. [PubMed]
- [14] Philips N, Samuel P, Parakandi H, et al. Beneficial regulation of fibrillary collagens, heat shock protein - 47, elastin fiber components, transforming growth factor - beta 1, vascular endothelial growth factor and oxidative stress effects by copper in dermal fibroblasts. *Connect. Tissue Res.*2012; 53: 373 - 8 [PubMed]
- [15] Kobayashi T, Saito N, Takemori N, et al. Ultrastructural localization of superoxide dismutase in human skin. *Acta Derm. Venereol.*1993; 73: 41 - 5
- [16] Olivares C, Solano F. New insights into the active site structure and catalytic mechanism of tyrosinase and its related proteins. *Pigment Cell Melanoma Res.*2009; 22: 750 - 60. [PubMed] [Google Scholar]
- [17] Fang, K. S., Farboud, B., Nuccitelli, R. and Isseroff, R. and Isseroff, R. R. Migration of human keratinocytes in electric fields requires growth factors and extracellular calcium. *J Invest Dermatol.*111, 751 - 756 (1998) [Crossref] [PubMed]
- [18] Traikovich SS. Use of Topical Ascorbic acid and its effects on photodamaged skin topography. *Arch Otorhinol head Neck Surg.*1999; 125: 1091 - 8 [PubMed] [Google Scholar]
- [19] Dtaelos ZD. Skin lightening preparations and the hydroquinone controversy. *Dermatol Ther.*2007; 20: 308 - 13 [PubMed] [Google Scholar]
- [20] Badreshia –Bansal S, Draelos ZD. Insight into skin - lightening cosmeceuticals for women of color. *J Drugs Dermatol.*2007; 6: 32 - 9 [PubMed] [Google Scholar]
- [21] Chithra R Sajithlal GB, Chandrakasan G. Influence of aloe vera on collagen characteristics in healing dermal wounds in rats. *Mol Cell Biochem.*1998; 181: 71 - 6 [PubMed] [Google Scholar]
- [22] Heggors J, Kucukcelebi A, Listengarten D, Stabenau J, Ko F, Broemeling LD, et al. Beneficial effect of aloe on wound healing an excisional wound model. *J Altern Complement Med.*1996; 2: 271 - 7 [PubMed] [Google Scholar]
- [23] Byeon S, Pelley R, Ullrich SE, Waller TA, Bucana CD, Strickland FM. Aloe Barbadensis extracts reduce the production of interleukin - 10 after exposure to ultraviolet radiation. *J Invest Dermatol.*1988; 110: 811 - 7
- [24] West DP, Zhu YF. Evaluation of aloe vera gel gloves in the treatment of dry skin associated with occupational exposure. *Am J Infect Control.*2003; 21 - 40 - 2 [PubMed] [Google Scholar]
- [25] Langmead L., Makins R. J., Rampton D. S. Anti - inflammatory effects of aloe vera gel in human colorectal mucosa in vitro. *Aliment. Pharmacol. Ther.*2004; 19: 521–527. DOI: 10.1111/j.1365 - 2036.2004.01874. x. [PubMed] [CrossRef] [Google Scholar]
- [26] Ebanks JP, Wickett RR, Biossy RE. Mechanisms Regulating Skin Pigmentation: The Rise and Fall of Complexion Coloration. *Int J Mol Sci* 2009; 10: 4066 - 4087.
- [27] Elmets CA. Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. *J Am Acad Dermatol* 2001; 44 (3): 425 - 432.
- [28] Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol.*2002; 138 (11): 1462 - 1470. [PubMed]
- [29] Joshi, R. et al. Free radical scavenging behaviour of folic acid: evidence for possible antioxidant activity.

Free Radical Biology and Medicine 30.12, 1390 - 1399
(2001)

- [30] Gilliam JN, Cox AJ. Epidermal changes in vitamin B12 deficiency. Arch Dermatol.1973; 107: 231–6.
[PubMed] [Google Scholar]