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

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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 pitahara 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 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.3

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, ropana 6

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

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.

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

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 kumari lepa in periorbital hyper pigmentation
- To re - evaluate the effect of conventional topical cream (unshade 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

<table>
<thead>
<tr>
<th>Assessment / Follow up</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre – Study Assessment</td>
<td>0 day</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Assessment</td>
<td>10&lt;sup&gt;th&lt;/sup&gt; day</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Follow up</td>
<td>20&lt;sup&gt;th&lt;/sup&gt; day</td>
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<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Follow up</td>
<td>30&lt;sup&gt;th&lt;/sup&gt; day</td>
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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 0<sup>th</sup> day and 10<sup>th</sup> day
- Under eye scale score on 0<sup>th</sup> day and 20<sup>th</sup> day
- Under eye scale score on 0<sup>th</sup> day and 30<sup>th</sup> 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

<table>
<thead>
<tr>
<th>Between Groups</th>
<th>Results</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent t test Analysis</td>
<td>No significant differences found between the efficacies of Madhu Kumari lepa and Conventional topical cream</td>
<td>Both have Par (equal) results in reducing Periorbital Hyperpigmentation</td>
</tr>
<tr>
<td>On 10&lt;sup&gt;th&lt;/sup&gt; day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On 20&lt;sup&gt;th&lt;/sup&gt; day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On 30&lt;sup&gt;th&lt;/sup&gt; day</td>
<td></td>
<td></td>
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</tbody>
</table>

Overall Efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>% Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0&lt;sup&gt;th&lt;/sup&gt; day – 10&lt;sup&gt;th&lt;/sup&gt; day</td>
</tr>
<tr>
<td>Group A</td>
<td>23.80%</td>
</tr>
<tr>
<td>Group B</td>
<td>18.26%</td>
</tr>
</tbody>
</table>

Repeated measures of ANOVA - Within the Group A and B on 0<sup>th</sup>day, 10<sup>th</sup> day, 20<sup>th</sup> day, 30<sup>th</sup> day

<table>
<thead>
<tr>
<th>Under eye scale score</th>
<th>0&lt;sup&gt;th&lt;/sup&gt; DAY</th>
<th>10&lt;sup&gt;th&lt;/sup&gt; DAY</th>
<th>20&lt;sup&gt;th&lt;/sup&gt; DAY</th>
<th>30&lt;sup&gt;th&lt;/sup&gt; DAY</th>
<th>Repeated period ANOVA</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>5.25±1.372</td>
<td>4.00±1.214</td>
<td>4.40±1.429</td>
<td>4.65±1.387</td>
<td>P=0.000</td>
<td>Highly significant</td>
</tr>
<tr>
<td>Group B</td>
<td>5.20±1.005</td>
<td>4.25±1.118</td>
<td>4.55±1.146</td>
<td>5.00±1.124</td>
<td>P=0.000</td>
<td>Highly significant</td>
</tr>
</tbody>
</table>

ANALYSIS - Repeated measures of ANOVA

Within the Group A & Group B on 0<sup>th</sup> day, 10<sup>th</sup> day, 20<sup>th</sup> 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 testostrone 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 peri orbital hyperpigmentation.

- **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 circles.

- **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

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**PROBABLE SAMPRAPTI OF PERIORBITAL HYPERPIGMENTATION**

**AHAJA & VIHARJA NIDANA**

<table>
<thead>
<tr>
<th>(Lavana rasa sevana, drinking less water use of tea, coffee, cold drink)</th>
<th>(Kashaya &amp; Katu rasa sevana)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atapa sevana</td>
<td>Eye strain, more screen time</td>
</tr>
<tr>
<td>Increase in rehna guna of pitta</td>
<td>Soshana of kledata</td>
</tr>
<tr>
<td>vikruti of birajaka pitta</td>
<td>Vata vridhhi</td>
</tr>
</tbody>
</table>

**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 Sukshamaganusari, Yogavahi and varnya

Kumari - Snigdha guna and sheeta virya. It is Rasayani, Twagamayam, Vrishya, Brathamana. 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 Prahsa, 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 scar16, 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. 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.

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

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. It also increases the degree of collagen cross-linking, resulting in increased scar tissue breaking strength.

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 suppressed

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.

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.

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. 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.

Vitamin Action

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

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 melanin

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 pitthahara 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 periorcular region.
- Due to various etiological factor there will be vikruti of bhrjajaka 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

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