



Comparative Study of Arjun Twak Lepa and Arjun Twak Kukkutand Pottali in Management of Vyanga with Special Reference to Melasma

Priyanka Shelotkar^{1*}, Shweta Parwe² and Swapnil Borage³

¹Department of Kaumarbhritya, Mahatma Gandhi Ayurveda College, Hospital and Research Centre, Salod (H Wardha, Maharashtra. Datta Meghe Institute of Medical Sciences (DU), Nagpur, India.

²Department of Panchakarma, Mahatma Gandhi Ayurveda College, Hospital and Research Centre, Salod (H), Wardha, Maharashtra. Datta Meghe Institute of Medical Sciences (DU), Nagpur, India.

³Department of Shalakyatantra, Mahatma Gandhi Ayurveda College, Hospital and Research Centre, Salod (H), Wardha, Maharashtra. Datta Meghe Institute of Medical Sciences (DU), Nagpur, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i33B31813

Editor(s):

(1) Dr. Giuseppe Murdaca, University of Genoa, Italy.

Reviewers:

(1) Efrain Orlando Silva Vega, State University of Guayaquil, Ecuador.

(2) Katherin Jossenka Silva León, Ecuador.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/70578>

Original Research Article

Received 20 April 2021
Accepted 28 June 2021
Published 30 June 2021

ABSTRACT

Background: A person's beauty and self-confidence are both enhanced by healthy and glowing facial skin. A darkening of the skin caused by an excess of the pigment melanin in the skin is known as hyperpigmentation. Vyanga is a *Kshrudraroga* with appearance of *Niruja* (painless) and *Shavavarna Mandalas* (bluish-brownish) on the face. Melasma, one of the hyper pigmented disorders, can be compared to it based on clinical features. Whole raw egg/egg yolk alone/with herbs have shown very good results in tightening of skin, complexion and healing in skin disorders, when it is locally applied. So, in present study egg is used with *Arjun Twak Churna* in the form of *Pottali* in experimental group for better result in management of Vyanga.

Aim and Objectives: To study the effect of *Arjun Twak Kukkutand Pottali* on MSI (Melasma Severity Index) and to compare the effect of *Arjun Twak Kukkutand Pottali* and *Arjun Twak Lepa* on MSI.

Methodology: Total no. of 44 patients will be enrolled (22 in each group). In control group for a period of 21 days, *Arjun Twak Lepa* will be available for local use. While in experimental group, *ArjunTwak Kukkutand Pottali* will be given for local application for 21 days. The assessment will be done on 0 & 21st day.

Results: Changes will be observed as per subjective & objective parameters.

Conclusion: *ArjunTwak Kukkutand Pottali* will be more effective on MSI (Melasma Severity Index).

Keywords: *Arjun twak lepa; arjun twak kukkut and pottali; MSI (Melasma Severity Index) vyanga.*

1. INTRODUCTION

A person's beauty and self-confidence are both enhanced by healthy and glowing facial skin. Acne, hyperpigmentation, and other factors can affect the complexion and texture of the facial skin. Hyperpigmentation is described by darkening of the skin caused by an excess of the pigment melanin in the skin. Although it is common in middle age and beyond, it can be seen in much younger patients. It is common and usually harmless, but it causes discomfort to those who have it for cosmetic reasons. Hyper pigmentation presents no medical threat. Thus the condition deserves serious attention [1].

Vyanga is a *Kshrudraroga* with appearance of *Niruja* (painless) and *Shavavarna Mandalas* (bluish-brownish) on the face. When it comes to the face, it is one of the most widespread illnesses. Melasma, one of the hyper pigmented disorders, can be compared to it, based on its clinical features.

Melasma is an acquired skin pigmentation disorder that is additional prevalent in persons of Oriental, Hispanic, and Indo-Chinese descent and affects women far more frequently than men. Melasma, like other skin disorders, has a negative psychosocial effect that degrades one's quality of life and emotional well-being. To assess the severity of the disease and the efficacy of therapeutic options in Melasma, valid and reliable scoring systems are required. Furthermore, as with other diseases, not only should this scoring system be able to assess severity, but it should also be able to predict prognosis and help we choose the best treatment option [2].

In Ayurveda, very good medicines are available for skin diseases. Massage with oils, application of medicine pastes, and other procedures leave the skin smooth, soft, and glowing [3]. In addition, there is a description of bloodletting, as good therapy for skin diseases [4]. Drugs with *Kushthaghna*, *Kandughna*, *RakstaPrasadaka*, *Twak Prasadaka* and *Varnayakara* Properties aid

in the management of *Vyanga*, which balances the Doshas and aids in Rakstashoadhana (blood purification). And ultimately, can cause cutaneous depigmentation, which is the removal of blackish skin discoloration. *ArjunTwak Churna* has been chosen for research based on these considerations.

Another drug in trial group is raw egg. Whole raw egg/egg yolk alone/with herbs have shown very good results in tightening of skin, complexion and healing in skin disorders, when it is locally applied [5]. Intracellular & extra cellular glutathione content of egg white plays an important role in skin healing. In addition, the effects of anti-oxidants such as vitamin A, E, and C, as well as trace elements such as zinc, copper, and selenium, were discovered. It has previously been demonstrated that L-Argin present in eggs reduces inflammation, speeds up necrotic tissue cleansing, and accelerates epithelial cell growth with depigmentation [6].

Till today study on melasma including external application of egg is not carried out. So, in present study egg is used with *ArjunTwak Churna* in the form of *Pottali* in experimental group for better result in management of *Vyanga*.

1.1 Aim

Study the comparative effect of *ArjunaTwakLepa* and *ArjunaTwakKukkutandPottali* in *Vyanga* management, with a special focus on Melasma

2. OBJECTIVES

1. To study the effect of *ArjunaTwak Lepa* on MSI (Melasma Severity Index)
2. To compare the effect of *Arjun Twak Kukkutand Pottali and Arjun Twak Lepa* on MSI (Melasma Severity Index)

2.1 Case Definition

Diagnosed cases of *Vyanga*, with appearance of thin, *Niruja* (painless) and *Shavavarna Mandalas* (blackish/brownish patches) on face.

2.2 Research Question

Whether *Arjun Twak Kukkutanda Pottali* is more effective than *Arjun Twak Lepa* in *Vyanga* management, with a special focus on Melasma.

2.3 Hypothesis

Arjun Twak Kukkutanda Pottali is more effective than *Arjun Twak Lepa* in *Vyanga* management, with a special focus on Melasma.

2.4 Null Hypothesis

Arjun Twak Kukkutanda Pottali is not more effective than *Arjun Twak Lepa* in *Vyanga* management, with a special focus on Melasma.

3. MATERIAL AND METHODS

3.1 Selection of Materials

The raw material will be procured from reliable sources and will be authenticated by department of Dravyaguna MGAC & RC.

3.2 Preparation of Materials

- 1) *ArjunTwakLepa*
- 2) *ArjunTwakKukkutandPottali*

3.3 Main Ingredient with Procedure

ArjunTwakLepa– 5gm *ArjunTwak Churna* along with sufficient amount of Madhu to make Lepa. Apply Lepa on affected area once a day. After application leave it to dry. Then wash with Luke warm water.

Arjun Twak Kukkutand Pottali – 5gm *ArjunTwak Churna* along with 1 *Kukkutand* (Egg). Then *Pottali* will be prepared using cotton cloth. Applying *pottali* in circular manner on affected are once a day. After applying *Pottali*for 15 min, leave the face pack to dry. Then wash with Luke warm water.

Trial design– A randomized standard comparative clinical trial.

Study setting – The study will be conducted at MGACH & RC, Salod, Wardha.

3.4 Inclusion Criteria

1. Subjects irrespective of sex, religion, occupation and chronicity less than 5 years will be selected for the study.
2. For the study, subjects between the ages of 20 and 50 will be chosen.
3. Subjects with cardinal features of *Vyanga* includes thin, painless, blackish/brownish patch on the skin of the face.

3.5 Exclusion Criteria

1. Hyper pigmentation caused due to any known cases of systemic disease like Addison's disease, Cushing's syndrome.
2. Hyper pigmentation since birth like Neavus of ota.
3. Hyper pigmentation caused by tumors like malignant melanoma.
4. Patient suffering with systemic disorders like renal failure, hepatic disorder.

3.6 Withdrawal Criteria

1. If any type of side effect were observed during study.
2. If aggravation of symptoms occurred.
3. If patient is not willing to continue the treatment.

3.7 Interventions

The total duration of the intervention will be the same for both groups which will be for 21 days and fallow up will be on 15 days in both groups (Table 1).

3.8 Assessment Criteria [7]

Subjective and objective criteria will be used to evaluate the therapy's effectiveness.

Table. 1 Intervention of both groups

Objectives	Experimental Group: A	Control Group: B
Drug	<i>Arjun Twak Kukkutand Pottali</i>	<i>Arjun Twak Lepa</i>
Dose	5gm	5gm
Route of drug administration	Local	Local
Time of drug administration	Once daily	Once daily
Duration	21 days	21 days
Follow up Days	0, 21st	0, 21st
Pathya	Avoid direct sunlight	Avoid direct sunlight

3.9 Subjective Criteria

It includes itching and burning sensation.

Parameters	Grade
Itching	
No itching	0
Mild itching (occasional, does not disturb routine)	1
Moderate itching (frequent itching, disturbs routine activity but not sleep)	2
Severe itching (disturbs both routine and sleep)	3
Burning	
No burning	0
Mild burning (occasional, sensation mostly when exposed to sun)	1
Moderate burning (frequent burning which increases when exposed to sun)	2
Severe burning (continuous burning without sun exposure)	3

3.10 Objective Criteria

It includes skin/lesion color, texture (dry/oily), luster, number of lesions, size of lesions, darkness and photographs.

Parameters	Score
Skin texture (dryness)	
Absent	0
Mild (not seen but felt)	1
Moderate (stretching of the skin that a person feels)	2
Severe (visible dryness chapping of skin-hardness of skin)	3
Skin texture (oiliness)	
Absent	0
Mild (not seen with naked eye) oiliness felt by touch (no need to wash face frequently, only 1-2 times)	1
Moderate (visible on skin, need to wash face frequently)	2
Severe (excessive oiliness, formation of acne)	3
Skin luster	
Poor	1
Mild	2
Moderate	3
Good/radiant	4
Number of lesion	
1-2	1
3-4	2
5-6	3
>6	4
Size of lesion (in cm)	
0-2	1
3-4	2
5-6	3
>6	4

Note: When lesions or patches are multiple, the size of the largest lesion is taken into consideration

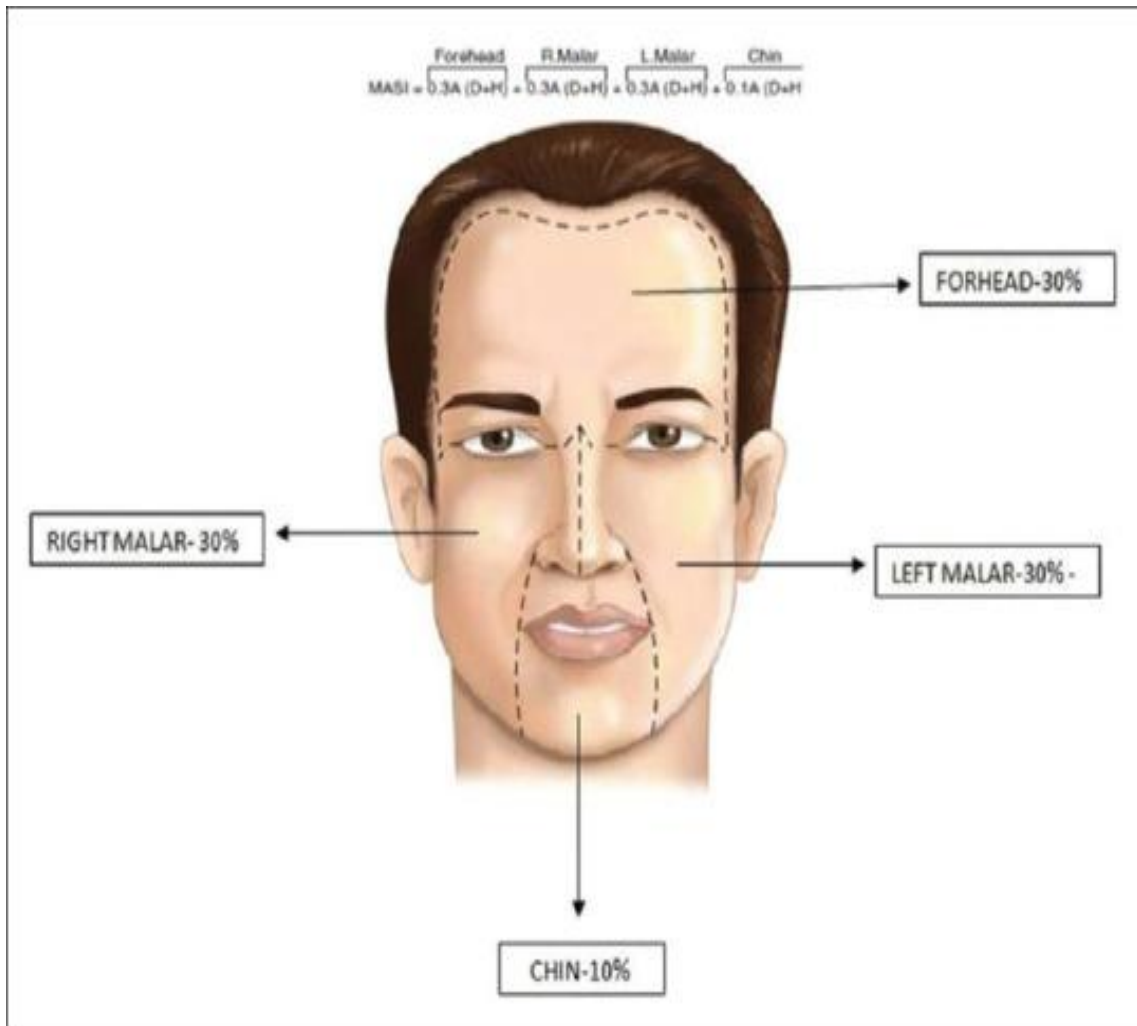


Fig. 1. Melasma area severity index score

Three parameters are used to calculate the melasma area severity index (MSAI) score:

Area (A), Darkness (D), and Homogeneity (H) of involvement where in forehead (f) constituents 30 %, right malar region (rm) 30%, left malar region (lm) 30% and chin (c) 10%. For each of the four facial areas, the MSAI score is calculated by multiplying the area of involvement's value by the sum of the severity ratings for darkness and homogeneity. The total score range is 0-48. Higher the score, higher is the severity.

The following formula will be used for calculation is:

$$\text{MSAI total score} = 0.3A (f) [D (f) + H (f)] + 0.3 A (lm) [D (lm) + H (lm)] + 0.3A (rm) [D (rm) + H (rm)] + 0.1 A (c) + H (c) [D (c) + H (c)].$$

Grading for parameters of Melasma Area Severity Index Score.

Parameters	Score
The area of involvement (%)	
No involvement	0
0-9	1
10-29	2
30-49	3
50-69	4
70-89	5
90-100	6
Darkness	
Absent	0
Slight	1
Mild	2
Marked	3
Maximum	4
Homogeneity	
Absent	0
Slight	1
Mild	2
Marked	3
Maximum	4

Overall Assessment

The following criteria will be used to make an overall assessment:

CD – Clinically deteriorated that is, increase in severity score against initial score

CS – Clinically stable that is, severity of score remains same as against initial score

CI-1 – Clinically improvement mild that is, one grade reduction against initial score

CI-2 – Clinically moderate that is, two grade reduction against initial score

CI – 3 – Clinically good that is, three grade reduction against initial score

3.11 Criteria for Discontinuing or Modifying Allocated Interventions

The subject will be withdrawn from the study if any untoward incidence, features of drug sensitivity or any other disease or problem arises, the subject will be offered free treatment till the problem subsides.

Follow up - 0, 21st, 15th day follow up will be taken.

MSI Score	0 day	15 th day	21 st day
-----------	-------	----------------------	----------------------

Primary outcome – We will see the effect of *ArjunTwakKukkutandPottali* on itching, burning, skin/lesion color, texture (dry/oily), luster, number of lesions, size of lesions and darkness.

Secondary outcome - We will see the effect of *ArjunTwakKukkutandPottali* on Melasma area severity index score.

Statistical analysis - The data will be analyzed by using 'Wilcoxon's test.

Time duration till following up – The patient will be followed up during treatment for 21 days.

Schedule of enrollment or intervention - *ArjunTwakKukkutandPottali* for local application will be given from 0 to 21 days.

Recruitment – Total 44 (22 in each group) [8] patients will be selected by strait forward arbitrary resting lottery strategy, and Principle Investigator will assign and enlist the patient.

Methods –Data collection, management and analysis.

Data collection method –Will be done as per assessment criteria.

Objective criteria– It includes skin/lesion color, texture (dry/oily), luster, number of lesions, size of lesions and darkness and photographs &melasma severity index score.

Data management –The information passage coding will be finished by principle investigator.

Dissemination policy – The information will be dispersed by paper distribution. Creation qualification rules and any proposed utilization of expert scholars.

Informed consent material –With all the data models assent structure and other related documentation will be given to members.

4. DISCUSSION

The beauty of a person's face is enhanced by a smooth and glowing complexion, which also boosts self-confidence. In a general dermatology clinic, acquired hyperpigmentation disorders of the skin are among the most common complaints. Melasma is known to have a negative impact on patients' emotional well-being and social lives, as well as a significant influence on the quality of life. Melasma affects the skin and reduces the glowing complexion of the face. Despite the advent of powerful pigment-targeting lasers, the treatment for melisma remains challenging. It should not be dismissed as simply a cosmetic entity because it often evokes emotional distress. In addition, stigma may be associated with melasma, particularly in Asian cultures. Melasma is a reverting hyper melanosis characterized by sun-exposed areas of the face, neck, and forearms have hyper pigmented patches. It is a chronic, acquired cutaneous hyper melanosis. UV (ultraviolet) radiation exposure is thought to be a key factor in its development.

This condition is known in Ayurveda as *Vyanga*, and it is caused by *Vata Pitta Dosh*a as well as *Manasik Nidan* (psychological etiological factors) such as *Krodha* (Anger), *Shoka* (Sorrow) and *Ayasa* (Mental exertion) are the main culprits [9]. Treatment modalities and other strategies for hyperpigmentation are typically unsatisfactory because it exhibits alleviation and cessation due

to a variation of influencing elements such as frequent exposure to UV rays, pollution, stress, and hormonal fluctuations. The usage of topical steroids in the treatment of Melasma has been documented in modern medicine. However, there are some side effects to topical steroids, such as irritation and rashes. As a result, better management methods must be sought.

Arjuna Twak has *Rakta Prasadak* (blood soother), *Twakprasadak* (Skin soother) and *Varnyakar* (Enhancing complexion) properties. They aid in the management of *Vyanga*, as well as pacifying aggregated *Doshas* (Body Humors) and assisting in *Rakta shodhana* (Blood purification or detoxification). Another drug of trial group is Egg white. Raw egg has some properties which shows good results on skin, when it is locally applied. The glutathione content of egg white, both intracellular and extracellular, plays an important role in skin healing. In addition, the effects of anti-oxidants such as vitamin A, E, and C, as well as trace elements such as zinc, copper, and selenium, were discovered. It has previously been demonstrated that L-Argin present in eggs reduces inflammation, speeds up necrotic tissue cleansing, and accelerates epithelial cell proliferation with depigmentation. [10].

Many studies have been conducted on the management of melasma, but none have been conducted on the effect of local application of raw egg in the management of melasma. Hence, combined effect of *Arjuna Twak churna* & Egg will give good result in management of *Vyanga*.

There are some studies which have been conducted in regards with epidemiology, assessment criteria, management & other interventions of Melasma in modern science & as well as in Ayurveda. Handel AC, reviewed clinical & epidemiological aspect of melasma [11]. Angadi SS, studied management of *Vyanga* with *Arjuna Twak Lepa* locally and *Panchanimba Churna* orally. It was comparative study where *ArjunaTwakLepa* was given for local application in one group & *ArjunaTwakLepa* locally and *Panchanimba Churna* orally in another group. Both trial drugs showed encouraging results. *ArjunaTwakLepa* showed no skin reactions and had better results in group B on hyperpigmentation of patches, which was seen in *Vyanga* cases. Here in present study standard group is having same intervention i.e. *Arjun Twak Lepa*. Shreya US, has given a treatment protocol in her case study for facial melanosis. Singh R

evaluated efficacy of *Pralepa* of *Ficus Bengalensis* and *Ervum lens* in *Vyanga* (Dark spots on face). The combination of *Vat* (*Ficus Bengalensis* Linn) and *Masur* (*Ervum lens* Linn) to cure *Vyanga* is cited in many classical text. This combination is not only good for *vyanga* but also for glaring appearance of skin [12]. Rajaratnam R, evaluated interventions for *Melasma* [13]. Mapari et al, evaluated efficacy of *Vatankuradi Lepa* in the management of *Vyanga* w.r.t. *Melasma*. The number of skin lesion were statistically was not significant but effect of medication on *MSAI* score was significant, thus providing its efficacy [14]. Mundhe SS, studied effect of *VarunTwakLepa* in management of *Vyanga*. Here progress of *Melasma Severity Index* score indicated that *Varun Twak Lepa* is found to be efficient in reducing the severity in pigmentation. As per types *Vatun Twak Lepa* is more efficient in epidermal [15]. Wake S et al, studied comparative effect of *Ingudi Phalamajja Lepa* and *Ananatamul* Ghana in management of *Vyanga* (*Melasma*) [16].

There are some studies showed effects of local application of egg. Pieroni A at el, studied Ethnopharmacognostic survey on the natural ingredients used in folk cosmetics, cosmeceuticals and remedies for healing skin diseases in the inland marches, Central-Eastern Italy. Here they used raw egg as folk medicine in skin and hair diseases [17]. The combination of red cabbage and egg white has a significant effect on the healing of second-degree burn wounds, with the treated group experiencing faster repair processing, 100% recovery, or fewer scars according to a study of Hassanzadeh et al [18]. Another study by Hassanzadeh et al. discovered that the egg yolk and silver sulfadiazine group healed wounds faster than the negative control group [19]. Jensen S at el, published study on reduction of facial wrinkles by hydrolyzed water-soluble egg membrane associated with reduction of free radicle stress and support of matrix production by dermal fibroblasts. The topical use of water soluble egg membrane on facial skin significantly reduced the wrinkle depth by protection from free radicle damage at cellular level and induction of several antioxidants response elements, combined with stimulation of human dermal fibroblasts to secret high level of matrix components [20, 21].

Strength – If *Arjun Twak Kukkutand Pottali* works, it will be give the best equal methodology for management of *Vyanga*.

5. LIMITATIONS

Sample size is small, for better results it can be increased.

6. CONCLUSION

Many studies have been conducted on management of *Melasma* but study on effect of local application of egg on *Melasma*, not yet conducted. *Arjun Twak Kukkutand Pottali* will be more effective than *Arjun Twak Lepa* on subjective & objective parameters.

CONSENT OR ASSET

The made consent will be taken from the patient before starting the assessment. During the investigation, the classification of every patient will be kept up.

ETHICS AND DISCUSSION

Research ethics approval; approval from the research ethics committee has taken. Ref.No. MGACHRC/IEC/February-2021/178.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Shreya US, Jayant SH, Umesh VS. Effective Ayurvedic Treatment in Facial Melanosis – A Case Study IAMJ: 2015;3(2):651.
2. Majid I, Haq I, Imran S, Keen A, Aziz K, Arif T. Proposing melasma severity index: A new, more practical, office-based scoring system for assessing the severity of melasma. Indian journal of dermatology. 2016;61(1):39.
3. Yogaratnakara Kshudra Roga Chikitsa. In: Bhisagratna Brahma Shankar Shastri., editor. Chaukhamba Sanskrit Sansthan, Varanasi. 8th ed. 2004;283.
4. Sushruta, Sushruta Samhita, Chikitsa Sthana. *Kshudraroga* Chikitsa Adhyaya, 20/33. In: KavirajAmbikadattaShastri., editor. Chaukhamba Sanskrit Sansthan, Varanasi. 14th ed. 2003;94.
5. Abbasi AM, Khan MA, Ahmad M, Zafar M, Jahan S, Sultana S. Ethnopharmacological application of medicinal plants to cure skin

- diseases and in folk cosmetics among the tribal communities of North-West Frontier Province, Pakistan. *Journal of ethnopharmacology*. 2010;128(2):322-35..
6. Angadi SS, Gowda ST. Management of *Vyanga* (facial melanosis) with *ArjunaTwakLepa* and *Panchanimba Churna*. *Ayu*. 2014;35(1):50.
 7. Pallavi G, Gupta KV, Shreevathsa M, Chate VA, Balakrishna DL. Clinical evaluation of *VarnyaGanaLepa* in *Vyanga* (melasma). *Ayu*. 2015;36(2):151.
 8. Kadam P, Bhalerao S. Sample size calculation. *International journal of Ayurveda research*. 2010;1(1):55.
 9. Acharya YT, editor. 8th ed. Ch 13, Ver 45-46. Varanasi: Chaukhamba Orientalia; 2005. *Sushruta Samhita of Sushruta, Nidana Sthana*; 324.
 10. Jahani S, Ashrafizadeh H, Babai K, Siahpoosh A, Cheraghian B. Effect of ointment-based egg white on healing of second-degree wound in burn patients: a triple-blind randomized clinical trial study. *Avicenna journal of phytomedicine*. 2019;9(3):260.
 11. Handel AC, Miot LD, Miot HA. Melasma: a clinical and epidemiological review. *Anaisbrasileiros de dermatologia*. 2014;89(5):771-82.
 12. Singh R, Gaur DS, Dadhich M. Clinical evaluation of *FicusBengalensis* Linn and *Ervum Lens* Linn wsr to efficacy of their *pralepa* in *Vyanga* (Dark spots on face). *Research and Education in Indian Medicine*. 2011;17(1-2):27.
 13. Mapari P, Thote A, Manu R. Clinical evaluation of efficacy of *Vatankuradi Lepa* in the Management of *Vyangaw.s.r.* to Melasma. *World Journal of Pharmaceutical and Medical Research*. 2019;5(7):310-314
 14. Rajaratnam R, Halpern J, Salim A, Emmett C. Interventions for melasma. *Cochrane database of systematic reviews*. 2010;(7).
 15. Mundhe SS, Ade V. Study on the Effect of *VarunTwakLepa* in Management of *Vyanga*. *International Journal of Ayurvedic Medicine*. 11(2):241-8.
 16. Wake S, Kuchewar V, Hagone P. A Comparative Study of *IngudiphalamajjaLepa* and *AnanatmulGhan* in The Management of *Vyanga* (Melasma). *International Journal of Ayurvedic Medicine*. 11(2):331-6.
 17. Pieroni A, Quave CL, Villanelli ML, Mangino P, Sabbatini G, Santini L, Boccetti T, Profili M, Ciccioli T, Rampa LG, Antonini G. Ethnopharmacognostic survey on the natural ingredients used in folk cosmetics, cosmeceuticals and remedies for healing skin diseases in the inland Marches, Central-Eastern Italy. *Journal of Ethnopharmacology*. 2004;91(2-3):331-44.
 18. Ali Say. The impact of medication quality on patient rehospitalization rate. *International Journal of Respiratory Care*. 2019;15(1):12-14.
 19. Ahmed N. Public health outcome framework application on obesity patients. *International Journal of Respiratory Care*. 2019;15(1):15-18.
 20. Hasanzadeh G, Mehdikhanloo N. The effect of compound of *Brassica Oleracea L.* and egg-white on burn wound healing in rat. *J SabzevarUniv Med Sci*, 1983;11(4 (34)):6-12.
 21. Hasanzadeh G, Nouri A, Hajiabadi M, Soltan K, Javadi A. The effect of egg yolk on burn wound healing in Rats. *J GorganUniv Med Sci*. 2005;7: 6-10.

© 2021 Shelotkar et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:

<http://www.sdiarticle4.com/review-history/70578>