

## **Evaluation of efficacy and safety of Clarina cream in newly diagnosed and previously treated cases of acne vulgaris**

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### **ABSTRACT**

*Acne is a common disease of the pilosebaceous units of the skin and topical therapy is recommended for the management of acne with comedolytic, anti-inflammatory agents, along with antimicrobials. However, topical application of these drugs leads to frequent adverse effects and also, there is an emergence of antibiotic resistance by *Propionibacterium acnes*. Furthermore, systemic antimicrobial usage has been causally associated with various adverse events. Clarina cream is a polyherbal formulation and contains extracts of *Aloe barbadensis*, *Prunus amygdalus*, *Alternanthera sessilis* and *Rubia cordifolia*, and the present study was planned to evaluate the efficacy and safety of Clarina cream in management of acne vulgaris.*

*This study was an open, non-comparative clinical trial conducted at the Department of Dermatology of V. S. Medical College, Ahmedabad, from January to April 2002. Twenty eight patients of both sexes were included in the study. Children below 18 years of age, patients with preexisting systemic disease necessitating long-term medications, genetic and endocrinal disorders and those who refused to give informed consent were excluded from the study. Pregnant and lactating women were also excluded from the study. A baseline history was obtained in order to determine the patient's eligibility for enrolment in the trial. Thereafter all patients underwent a clinical examination and thorough skin examination was done. All patients were advised to apply Clarina cream topically over the lesions, twice a day for a period of 6 weeks. All patients were followed up every two weeks and during each follow-up visit, local skin examination was done. The predefined primary outcome measures were reduction in number of blackheads, whiteheads, inflamed pustules and overall inflammation along with increase in exfoliation, overall moisturizing and soothing effects and healing without scar formation. The predefined secondary outcome measures were incidence of adverse events and compliance to the treatment. Statistical analysis was done according to intention-to-treat principles.*

*This study observed significant improvement in the mean scores for reduction in number of blackheads, whiteheads, inflamed pustules and overall inflammation. In addition, there was significantly better exfoliation, moisturizing and soothing effects, along with significant improvement in healing without scar formation. The overall response to the treatment also recorded a significant improvement from the second week onwards. There were no clinically significant short- and long-term adverse reactions (either reported or observed), during the entire period of study and excellent patient compliance to Clarina cream was also observed. Based on these observations, it may be concluded that Clarina cream is clinically effective and safe for short- and long-term usage in acne vulgaris.*

## **INTRODUCTION**

Acne is a common disease of the pilosebaceous units of the skin and acne is an end result of the interplay of multiple factors. Excessive sebum production secondary to sebaceous gland hyperplasia is the first abnormality to occur<sup>1</sup>. Subsequent hyperkeratinization of the hair follicle prevents normal shedding of the follicular keratinocytes, which then obstruct the follicle and form an inapparent microcomedo<sup>2</sup>. Lipids and cellular debris soon accumulate within the blocked follicle and this microenvironment encourages colonization of *Propionibacterium acnes*, which provokes an immune response through the production of numerous inflammatory chemomediators. Inflammation is further enhanced by follicular rupture and subsequent leakage of lipids, bacteria, and fatty acids into the dermis. The clinical diagnosis of acne is based on the history and a physical examination. Acne most commonly develops in areas with the greatest concentration of sebaceous glands, which include the face, neck, chest, upper arms, and back<sup>3</sup>.

Topical therapy is recommended for the management of acne (especially for non-inflammatory comedones and mild to moderate inflammatory acne) and comedolytic, anti-inflammatory agents, alongwith antimicrobials are preferred drugs. Tretinoin is the most effective available topical comedolytic agent, but topical application leads to frequent erythema, peeling, and burning of the skin. During the past few decades, many reports have documented an emergence of antibiotic resistance by *Propionibacterium acnes* during treatment of acne<sup>4,6</sup>. Furthermore, systemic antimicrobial usage has been causally associated with various short-term and long-term adverse events<sup>7</sup>.

Clarina cream is a polyherbal formulation and contains extracts of *Aloe barbadensis*, *Prunus amygdalus*, *Alternanthera sessilis*, and *Rubia cordifolia*. Clarina cream was found to be beneficial in topical treatment of acne vulgaris, in various clinical trials<sup>8,9</sup>. The present study was planned to evaluate the efficacy and safety of Clarina cream in management of acne vulgaris.

## **MATERIAL AND METHODS**

### **Aim of the study**

This study was aimed to evaluate the clinical efficacy, short- and long-term safety of Clarina cream in newly diagnosed and previously treated cases of acne vulgaris.

### **Study design**

This study was an open, non-comparative clinical trial conducted at Department of Dermatology of V. S. Medical College, Ahmedabad, from January to April 2002, as per the ethical guidelines of the Declaration of Helsinki. The study protocol, case report forms (CRFs), regulatory clearance documents, product-related information and informed consent forms (in English, Hindi and Gujrathi) were submitted to the Institutional Ethics Committee and approved by the same.

### **Inclusion criteria**

Twenty-eight patients of both sexes, of the out-patient clinic of the Department of Dermatology of V. S. Medical College, Ahmedabad, were included in the study. A written informed consent was obtained from all patients.

### **Exclusion criteria**

Children below eighteen years of age, patients with preexisting systemic disease necessitating long-term medications, genetic and endocrinal disorders and those who refused to give

informed consent, were excluded from the study. Pregnant the lactating women were also excluded from the study.

### **Study procedures**

A baseline history was obtained in order to determine the patient's eligibility for enrolment in the trial. The baseline assessment included personal data, a description of symptoms and details of past medical history (family history of acne, history of possible exacerbating factor/s, etc.). Thereafter all patients underwent a clinical examination and thorough skin examination was done for presence of black and white heads, inflamed papules and pustules, and cysts and nodules.

Patients were advised to apply Clarina cream topically over the lesions, twice a day for a period of 6 weeks. Patients were followed up every two weeks and during each follow-up visit, local skin examination was done and observations recorded in the structured case record sheet. All patients were reviewed clinically at the end of 6 weeks.

### **Primary and secondary outcome measures**

The predefined primary outcome measures were reduction in number of blackheads and whiteheads, inflamed pustules and overall inflammation along with increase in exfoliation, overall moisturizing and soothing effect and healing without scar formation. The predefined secondary outcome measures were incidence of adverse events and compliance to treatment.

### **Adverse events**

All local and systemic adverse events, reported or observed by patients were recorded with information about severity, time of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication was predefined as "*Unrelated*" (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), "*Possible*" (follows a known response pattern to the suspected drug, but could have been produced by the patient's clinical state or other modes of therapy administered to the patient), and "*Probable*" (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient's clinical state).

Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

### **Statistical analysis**

Statistical analysis was done according to intention-to-treat principles. Changes in various parameters from baseline values and values after the 2, 4 and 6 weeks were analyzed by "*Repeated Measures ANOVA test*", followed by "*Bonferroni's Multiple Comparison Test*". The changes in the values, before the initiation of study and at the end of the study were analyzed by "*Paired t test*". The minimum level of significance was fixed at 99% confidence limit and a 2-sided p value of <0.0001 was considered significant. The values are expressed in the sequence as: mean score (M) at 2, 4 and 6 weeks, standard deviation (SD) at baseline, 2, 4 and 6 weeks, standard error of mean (SEM) at 2, 4 and 6 weeks, lower 99% confidence interval (CI) of mean at 2, 4 and 6 weeks, upper 99% confidence interval (CI) of mean at 2, 4 and 6 weeks and F value, squared R value, p value, significant (S). In all graphs, the baseline value is 0.00.

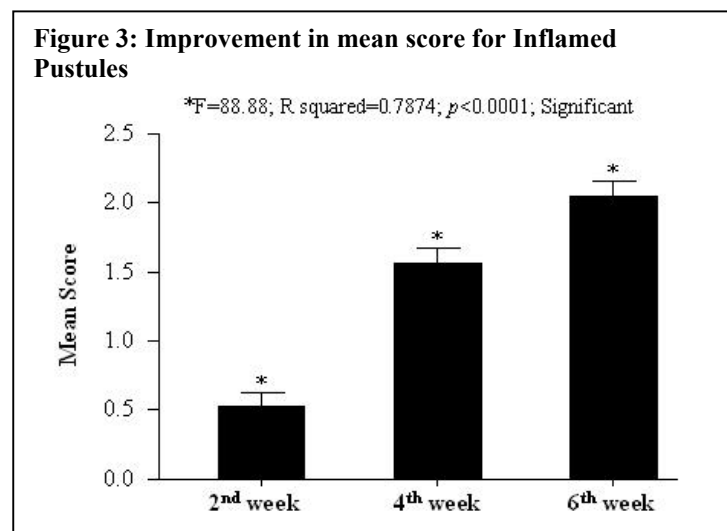
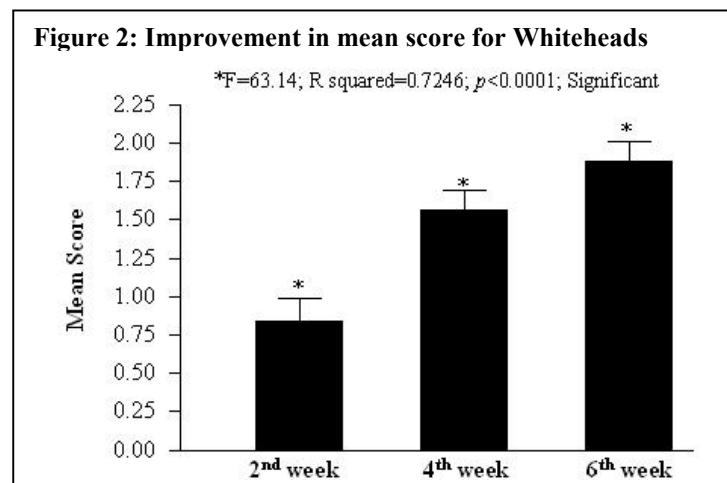
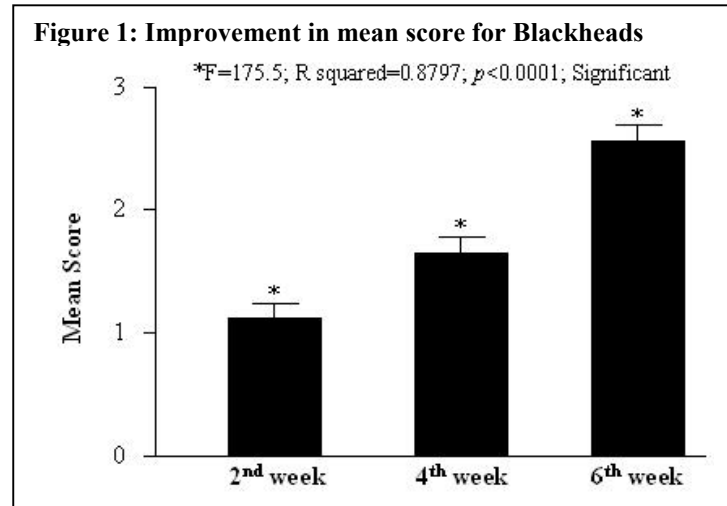
## RESULTS

Twenty eight patients were included in this study and 3 patients were lost to follow up. The age range was 14-25 years (M=18.20, SD=3.202, SEM=0.6403, lower 99% CI of mean=16.41, upper 99% CI of mean=19.99). There was a female preponderance in the study and total 8 (32%) males and 17 (68%) females were included in the study.

It was observed that from second week onwards there was significant improvement in the mean score for reduction in number of blackheads, when compared to the baseline score (M=1.120, 1.640 and 2.560, SD=0.6000, 0.7000 and 0.7118, SEM=0.1200, 0.1400 and 0.1424, lower 99% CI of mean=0.7844, 1.248 and 2.162, upper 99% CI of mean=1.456, 2.032 and 2.958, F=175.5, R squared=0.8797,  $p<0.0001$ , S) (Figure 1). There was

also a significant improvement in the mean score for reduction in number of whiteheads when compared to the baseline score (M=0.8400, 1.560 and 1.880, SD=0.7461, 0.6506 and 0.6658, SEM=0.1492, 0.1301 and 0.1332, lower 99% CI of mean=0.5320, 1.291 and 1.605, upper 99% CI of mean=1.148, 1.829 and 2.155, F=63.14, R squared=0.7246,  $p<0.0001$ , S) (Figure 2).

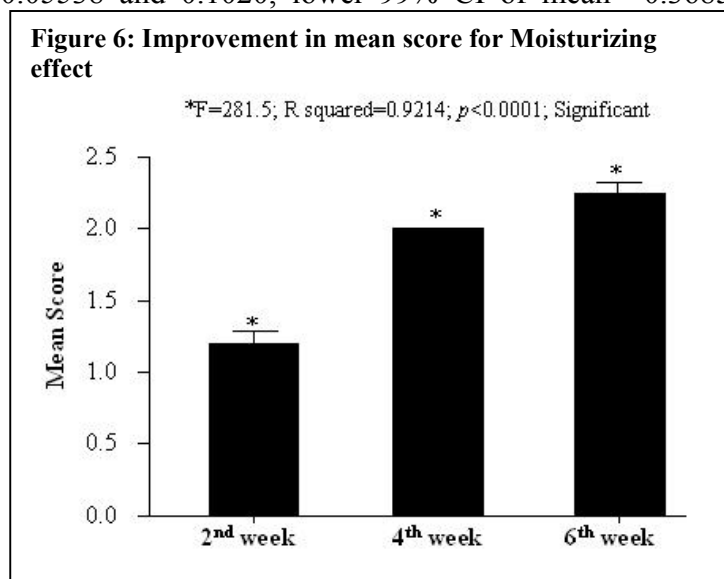
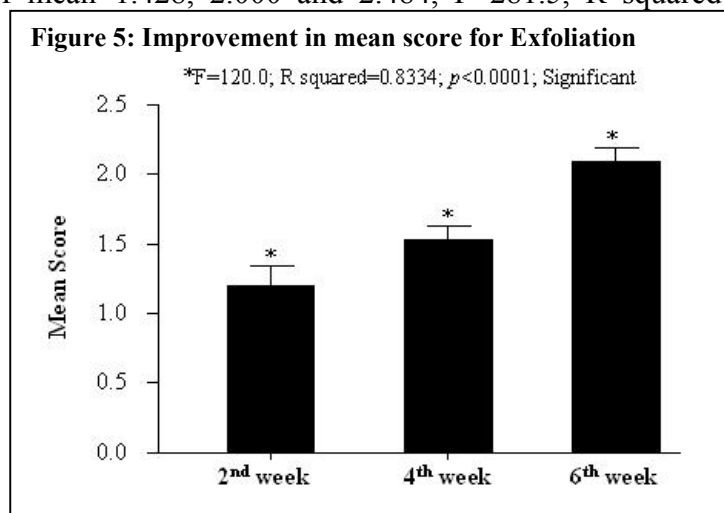
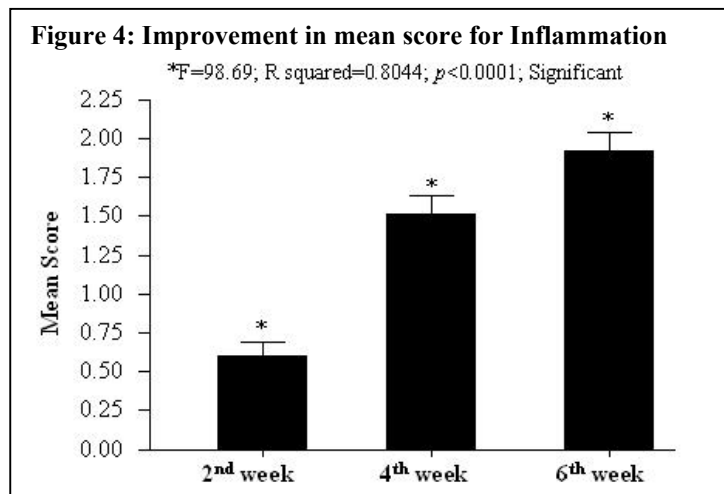
The mean score for reduction in number of inflamed pustules also improved, when compared to the baseline score (M=0.5200, 1.560 and 2.040, SD=0.5099, 0.5831 and 0.6110, SEM=0.1020, 0.1166 and 0.1222, lower 99% CI of mean=0.3095, 1.319 and 1.788, upper 99% CI of mean=0.7305, 1.801 and 2.292, F=88.88, R squared=0.7874,  $p<0.0001$ , S) (Figure 3). The score for overall inflammation, as judged clinically was also significantly improved when compared to the baseline score (M=0.6000, 1.520 and 1.920, SD=0.5000, 0.5099 and 0.5715, SEM=0.1000, 0.1020 and 0.1143, lower 99% CI of mean=0.3936, 1.310 and 1.684, upper 99% CI of mean=0.8064, 1.730 and 2.156, F=98.69, R



squared=0.8044,  $p<0.0001$ , S) (Figure 4). Similarly the mean score for exfoliation also showed significant improvement when compared to the baseline score (M=1.200, 1.520 and 2.080, SD=0.6455, 0.5099 and 0.4933, SEM=0.1291, 0.1020 and 0.09866, lower 99% CI of mean=0.8389, 1.235 and 1.804, upper 99% CI of mean=1.561, 1.805 and 2.356, F=120.0, R squared=0.8334,  $p<0.0001$ , S) (Figure 5).

There was a significantly better moisturizing effect from the second week onwards, as compared to baseline score (M=1.200, 2.000 and 2.240, SD=0.4082, 0.0 and 0.4359, SEM=0.08165, 0.0 and 0.08718, lower 99% CI of mean=0.9716, 2.000 and 1.996, upper 99% CI of mean=1.428, 2.000 and 2.484, F=281.5, R squared=0.9214,  $p<0.0001$ , S) (Figure 6). In addition, the soothing effect was also observed to improve significantly when compared to the baseline score (M=1.200, 1.440 and 2.280, SD=0.4082 and 0.5066 and 0.4583, SEM=0.08165, 0.1013 and 0.09165, F=136.0, R squared=0.8500,  $p<0.0001$ , S) (Figure 7). There was significant improvement in healing without scar formation when compared to the baseline score (M=0.6800, 1.080 and 1.520, SD=0.5568, 0.2769 and 0.5099, SEM=0.1114, 0.05538 and 0.1020, lower 99% CI of mean= 0.3685, 0.9251 and 1.235, upper 99% CI of mean=0.9915, 1.235 and 1.805, F=24.90, R squared=0.5092,  $p<0.0001$ , S) (Figure 8).

The overall response to the drug treatment also recorded a significant improvement from second week onwards, when compared to the baseline score (M=0.8800, 1.560 and 2.560, SD=0.3317, 0.5066 and 0.5066, SEM=0.06633, 0.1013 and 0.1013, lower 99% CI of mean=0.6945 and 1.277 and 2.277, upper 99% CI of mean=1.066, 1.843 and 2.843, F=249.0, R squared=0.9121,  $p<0.0001$ , S) (Figure 9).



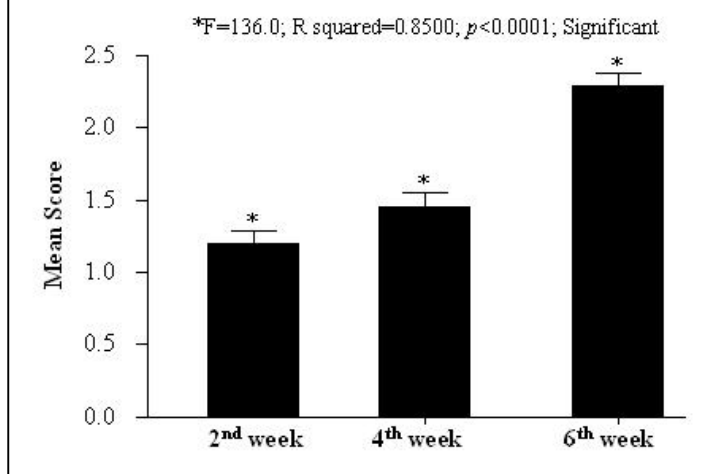
There were no clinically significant short- and long-term adverse reactions (either reported or observed), during the entire period of the study and excellent patient compliance to Clarina cream was also observed.

## DISCUSSION

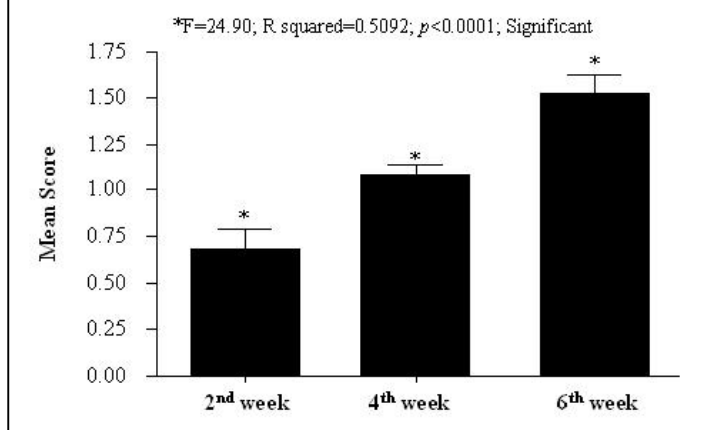
Acne vulgaris is a skin disorder with initial formation of microscopic microcomedo, which evolve into visible open comedones ("blackheads") or closed comedones ("whiteheads"). Subsequently, inflammatory papules, pustules and nodules also develop (nodulocystic acne consists of pustular lesions larger than 0.5 cm) and there may be presence of excoriations, post-inflammatory hyperpigmentation and scars<sup>10</sup>.

Acne may be triggered or worsened by external factors such as mechanical obstruction (shirt collars), occupational exposures or medications. The most commonly involved drugs are: anabolic steroids, corticosteroids, corticotropin, isoniazid, lithium, phenytoin, azathioprine, cyclosporine, phenobarbital, quinidine, tetracycline and vitamins (B1, B6, B12 and D2). Cosmetics and emollients may occlude follicles and cause an acneiform eruption. Topical corticosteroids may produce perioral dermatitis, a localized erythematous papular or pustular eruption<sup>11</sup>. Endocrine causes of acne include Cushing's syndrome, polycystic ovary syndrome and congenital adrenal hyperplasia. Clinical clues to possible hyperandrogenism in women include dysmenorrhea, virilization (hirsutism, clitoromegaly and temporal balding) and severe acne<sup>12</sup>.

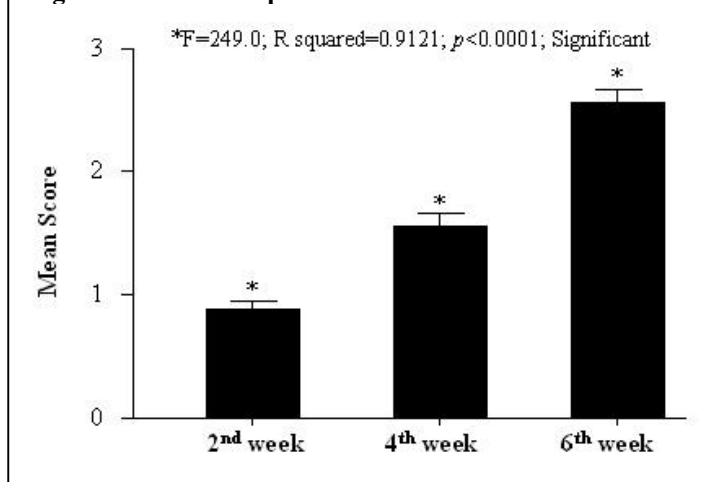
**Figure 7: Improvement in mean score for Soothing and smoothening effect**



**Figure 8: Improvement in mean score for Healing without scar formation**



**Figure 9: Overall response to Clarina treatment**



As per the guidelines of The American Academy of Dermatology, primary acne vulgaris is classified into mild, moderate and severe grades. Mild acne is characterized by the presence of few to several papules and pustules (without nodules). Patients with moderate acne have

too many papules and pustules (along with a few to several nodules) and with severe acne, patients have numerous or extensive papules and pustules (as well as many nodules). Acne is also classified by lesion type as comedonal, papulopustular and nodulocystic<sup>13</sup>.

The management of acne varies as per the severity and type of acne. Mild acne is generally responsive to aggressive topical treatment by an antibacterial and a comedolytic agent. Topical erythromycin and clindamycin are commonly used antibacterial agents. Benzoyl peroxide is the most commonly used comedolytic agent, but the major disadvantage is the resultant dermal irritation. Azelaic acid causes dermal hypo-pigmentation in few patients, but in dark-skinned patients it causes hyper-pigmentation, which remains for weeks or months<sup>14,15</sup>. Topical retinoids inhibit formation of comedones, however, dermal irritation is the major drawback of topical retinoids. Patients with atopic diseases may not tolerate topical retinoids due to their inherently irritable skin. Teratogenicity is the most dangerous adverse effect of topical retinoids and two means of birth control methods (one must be hormonal) are critical for all fertile women taking the retinoids to prevent pregnancy<sup>16,17</sup>.

Resistant acne or nodular lesions typically require oral antibiotics. Oral erythromycin used to be a common treatment for acne, but the emergence of antimicrobial resistance has greatly limited its utility. Although oral clindamycin improves inflammatory acne, its use has been virtually abandoned because of its association with pseudomembranous colitis<sup>18-20</sup>. Hepatitis, serum sickness like reactions, lupus erythematosus, vestibular disturbances (dizziness, vertigo and ataxia) and dermal discolorations has been associated with use of the tetracyclines. Though co-trimoxazole is effective in treating inflammatory acne, the potential for serious, side effects (hypersensitivity reactions like toxic epidermal necrolysis and bone-marrow suppression) limits its use to patients who have responded inadequately to the commonly used oral antimicrobials<sup>21</sup>.

This study observed significant improvement in the mean scores for reduction in number of blackheads, whiteheads, inflamed pustules and overall inflammation. In addition, there was significantly better exfoliation, moisturizing effect and soothing effect, alongwith significant improvement in healing without scar formation. The overall response to the treatment was also recorded a significant improvement from second week onwards. There were no clinically significant short- and long-term adverse reactions (either reported or observed), during the entire period of the study. This favourable improvement in acne by Clarina cream might be due to synergistic actions of its ingredients.

*Aloe vera* has been evaluated for its anti-inflammatory activity by various researchers. Heggors *et al.* demonstrated that the extracts of *Aloe vera* gel have anti-inflammatory activity and suggested its inhibitory action on the arachidonic acid pathway via cyclooxygenase<sup>22</sup>. Davis *et al.* demonstrated that, *Aloe vera* blocks wound-healing suppression of hydrocortisone acetate and this response due to growth factors in *Aloe vera* masked wound-healing inhibitors such as sterols and certain amino acids<sup>23,24</sup>.

When applied topically, *Aloe vera* plays an important role in the wound-healing process. Choi *et al.* isolated and characterized a glycoprotein fraction (G1G1M1DI2) from *Aloe vera*, which was demonstrated effective in wound healing, and the proposed action was via cell proliferation and migration. This effect of G1G1M1DI2 on cell migration was confirmed on a monolayer of human keratinocytes and when this fraction was tested on a raft culture, it stimulated the formation of epidermal tissue. Furthermore, proliferation markers (epidermal growth factor receptor, fibronectin receptor, fibronectin, keratin 5/14 and keratin 1/10) were markedly expressed at the immunohistochemical level<sup>25</sup>.

Chithra *et al.* studied the influence of *Aloe vera* on the glycosaminoglycan (GAG) components of the matrix in a healing wound and levels of the glycohydrolases were elevated on treatment with *Aloe vera*, indicating increased turnover of the matrix. Both topical and oral treatments with *Aloe vera* were found to have a positive influence on the synthesis of GAGs and thereby beneficial in wound healing<sup>26,27</sup>.

A basic peroxidase (EC 1.11.1.7) has been identified from *Aloe vera* and it was observed that, when applied topically, *Aloe vera* peroxidase might scavenge H<sub>2</sub>O<sub>2</sub> in skin surface<sup>28</sup>. Heggers *et al.* observed that *Aloe vera* expedites wound contraction and neutralizes the wound-retardant effect due to increased collagen activity, enhanced by a lectin, that consequently improves collagen matrix and enhances breaking strength<sup>29</sup>.

*Prunus amygdalus* is known to exert a cooling action on inflamed wounds<sup>30</sup>. *Alternanthera sessilis* contains very high amounts of carotene, which is a potent antioxidant<sup>31</sup>. The extract of *Rubia cordifolia* has been shown to possess significant inhibitory properties in experimentally-induced lipid peroxidation<sup>32</sup>.

## CONCLUSION

This study observed significant improvement in formation of blackheads, whiteheads, reduction in number of inflamed pustules and overall inflammation. In addition, there was significantly better exfoliation, better moisturizing and soothing effects, along with significant improvement in healing without scar formation. There were no clinically significant short- and long-term adverse reactions during the entire period of the study. Based on these observations, it may be concluded that Clarina cream is clinically effective and safe for short- and long-term usage, in acne vulgaris.

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