

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

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INTRODUCTION

Acne vulgaris is an extremely common skin disorder, affecting virtually all adolescents and adults at some time in their lives. Although the overall health is not impaired, acne is not a trivial disease, as it can produce cutaneous and emotional scars that last a lifetime¹⁻³. Numerous psychological problems stem from acne, some even resulting in decreased employability in adulthood⁴.

The etiology of acne is multifactorial and according to the severity of inflammation, acne can be classified into purely comedonal (non-inflammatory acne), mildly papular, scarring papular and scarring nodular acne. Clinically, the peak incidence of acne is evident during the teen years, but a significant chunk of men and women between 20-40 years of age, also suffer from acne vulgaris^{5,6}.

Topical therapy is advocated for the management of acne, especially for patients with non-inflammatory comedones and mild to moderate inflammatory acne. Comedolytic and anti-inflammatory agents, along with antimicrobials, are generally preferred in topical treatment of acne.

Tretinoin is the most effective available topical comedolytic agent, but topical application may lead to 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 acne⁷⁻⁹. Furthermore, systemic antimicrobials used in the treatment of acne have been causally associated with various short- and long-term adverse effects¹⁰.

Clarina cream, a polyherbal formulation containing extracts of *Aloe barbadensis*, *Prunus amygdalus*, *Alternanthera sessilis*, and *Rubia cordifolia*, was found to be beneficial in topical treatment of acne vulgaris¹¹. 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, and 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 the Department of Dermatology approved by the Institutional Ethics Committee of L.T.M.M. College & L.T.M.G. Hospital, Sion, Mumbai, India.

Inclusion criteria

Fifty patients, of both sexes, attending the out-patient clinic, of the Department of Dermatology of L.T.M.M. College & L.T.M.G. Hospital, Sion, Mumbai, 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, a with genetic and endocrinal disorders as those who refused to give informed consent, were excluded from the study. Pregnant and 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 factors, etc). Thereafter all patients underwent a clinical examination and a thorough skin examination for presence of black and white heads, inflamed papules and pustules, cysts and nodules.

All patients were advised to apply Clarina cream 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 and observations recorded in the structured case record sheet. All patients were reviewed at the end of 6 weeks.

Primary and secondary outcome measures

The predefined primary outcome measures were the control of local inflammation (erythema and telangiectasia), reduction in facial oiliness, number of papules and pustules, new comedone (black and white) formation, and soothed skin (reduction in burning and itching sensation). The predefined secondary outcome measures were reduction in formation of nodules and cysts, healing without scar formation, incidence of adverse events and compliance to treatment.

Adverse events

All local and systemic adverse events regarding the study drug reported or observed by patients, were recorded with information about severity, time of onset, duration and action taken. 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.

Statistical analysis

An analysis was done according to intention-to-treat principles. Changes in various parameters from baseline values to the values after 6th week were analyzed by using "paired 't' test". The minimum level of significance was fixed at 95% confidence limit and a 2-sided *p* value of <0.05 was considered significant.

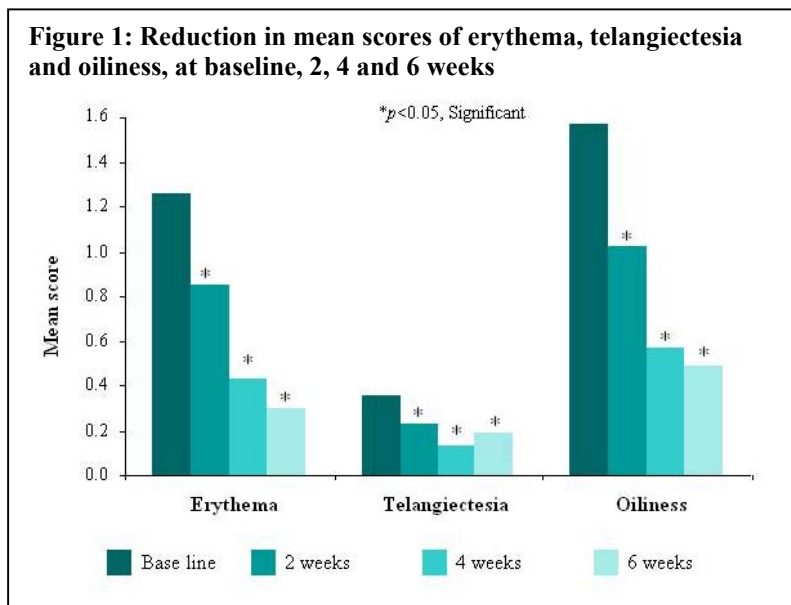
RESULTS

Fifty patients in the age range of 14 to 32 years (mean \pm SD: 19.55 \pm 3.69 years) were included in this study. There were 23 (46%) males and 27 (54%) females in the study. There was excellent compliance for the treatment and no dropouts.

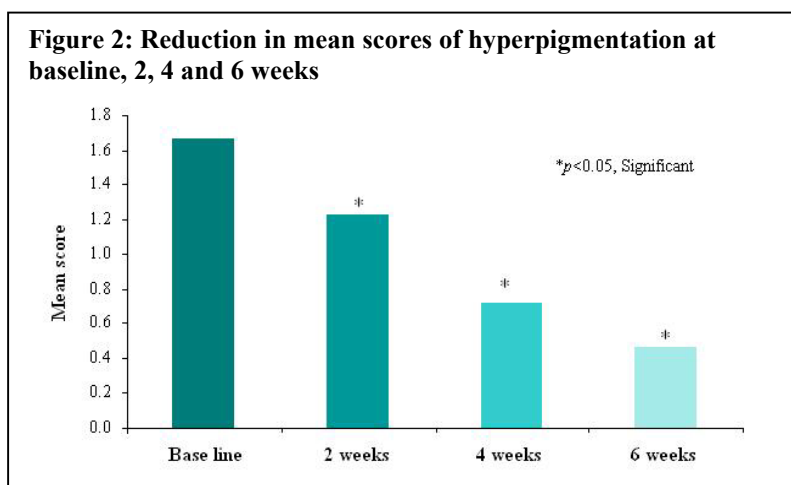
Thirty-one (62%) patients had a family history of acne and the mean duration of acne was 3.19 years. Forty-two (84%) patients had a past history of topical treatment and 12 (24%) had a past history of systemic medications for acne.

Thirty six patients in this study correlated sunlight as the exacerbating factor, while, 11 (40.7%) females had observed premenstrual flare of acne. Eight (16%) patients linked mental stress and 4 (8%) patients linked cosmetics as the exacerbating factors for acne. On clinical examination, it was observed that dandruff was a major common finding in 34 (68%) patients.

It was observed that from the second week onwards, there were significant improvement in the mean score of signs and symptoms as evaluated by erythema, telangiectesia and oiliness of the facial skin. The mean baseline score for erythema significantly reduced from 1.26 ± 1.10 to 0.85 ± 0.78 , 0.43 ± 0.58 and 0.30 ± 0.46 at the end of 2, 4 and 6 weeks, respectively. The mean baseline score for telangiectesia significantly reduced from 0.36 ± 0.70 to 0.23 ± 0.52 , 0.13 ± 0.34 and 0.19 ± 0.45 at the end of 2, 4 and 6 weeks, respectively. The mean baseline score for oiliness significantly reduced from 1.57 ± 0.68 to 1.02 ± 0.57 , 0.57 ± 0.50 and 0.49 ± 0.55 at end of 2, 4 and 6 weeks, respectively (Figure 1).



The mean baseline score of hyper-pigmentation 1.66 ± 0.92 significantly reduced to 1.23 ± 0.67 , 0.72 ± 0.58 and 0.47 ± 0.55 at the end of 2, 4 and 6 weeks, respectively. There was no significant change in patients of hypopigmentation (Figure 2).



All included patients reported a significant symptomatic improvement. The burning sensation reduced significantly from the mean baseline score of 0.43 ± 0.65 to 0.19 ± 0.45 , 0.17 ± 0.38 and 0.09 ± 0.28 at the end of 2, 4 and 6 weeks, respectively. The itching sensation reduced significantly from the mean baseline score of 0.49 ± 0.59 to 0.28 ± 0.45 , 0.15 ± 0.36 , and 0.02 ± 0.15 at the end of 2, 4 and 6 weeks, respectively (Figure 3).

There was significant reduction in papules and pustules after the treatment. Papules reduced significantly from the mean baseline score of 18.73 ± 7.29 to 14.64 ± 8.34 , 9.91 ± 7.30 and 5.80 ± 6.50 at the end of 2, 4 and 6 weeks, respectively. Pustules reduced significantly from the mean baseline score of 3.80 ± 3.48 to 1.84 ± 1.91 , 1.04 ± 1.54 and 0.33 ± 0.77 at the end of 2, 4 and 6 weeks, respectively (Figure 4).

There was significant reduction in black and white comedones after treatment. Black comedones reduced significantly from the mean baseline score of 11.91 ± 8.01 to 8.29 ± 6.85 , 4.18 ± 4.17 and 2.02 ± 3.16 at the end of 2, 4 and 6 weeks, respectively. White comedones reduced significantly from the mean baseline score of 7.72 ± 6.02 to 5.07 ± 5.19 , 2.56 ± 3.82 and 1.38 ± 3.73 at the end of 2, 4 and 6 weeks, respectively (Figure 5).

There were significant reduction nodules, cysts and scars after treatment. Nodules reduced significantly from the mean baseline score of 0.60 ± 1.12 to 0.31 ± 0.76 , 0.20 ± 0.59 and 0.07 ± 0.33 at the end of 2, 4 and 6 weeks, respectively. Scars reduced from the mean baseline score of 3.66 ± 7.19 to 3.40 ± 7.43 at the end of the study period. The study also observed total elimination of cysts at the end of the study period (Figure 6).

In the subjective evaluation of efficacy of treatment, 4 (8%) patients rated the treatment as excellent, 32 (64%) as good, and 11 (22%) as fair. In the subjective evaluation of treatment tolerability, 40 (80%) patients rated the treatment as good and 10 (20%) as fair.

DISCUSSION

Acne vulgaris has a multifactorial etiology and is influenced by keratinization, hormonal function, resident

Figure 3: Reduction in mean scores of burning sensation and itching sensation at baseline, 2, 4 and 6 weeks

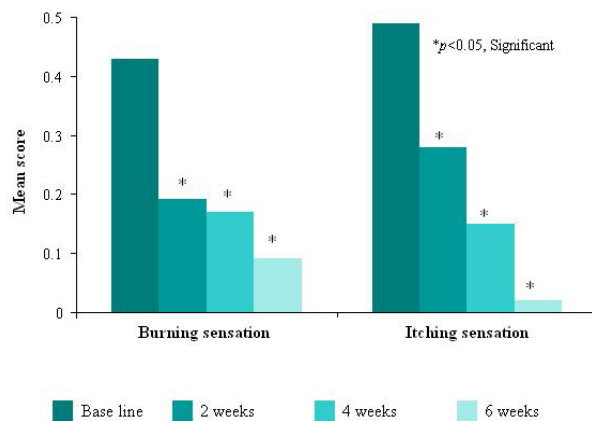


Figure 4: Reduction in mean scores of papules and pustules at baseline, 2, 4 and 6 weeks

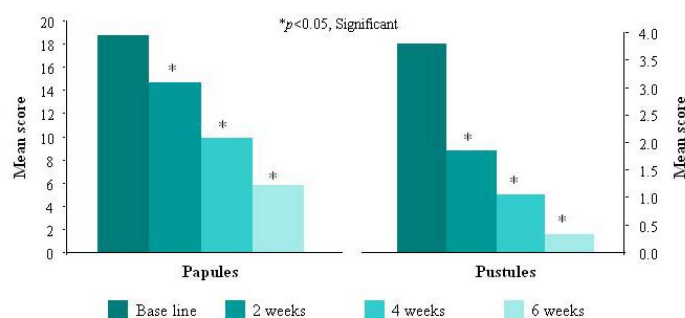
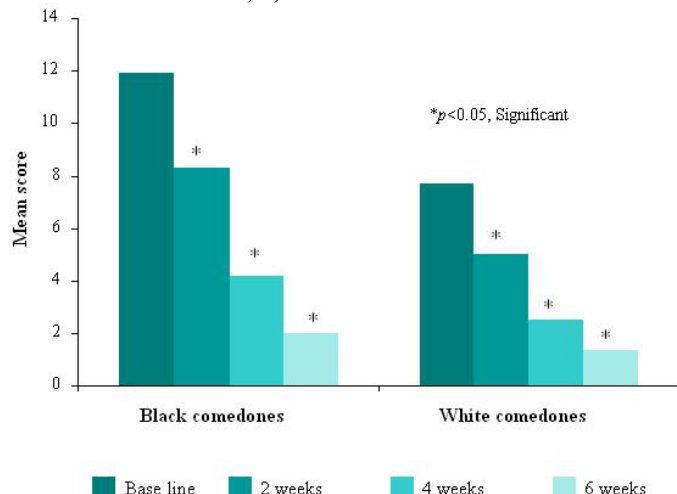


Figure 5: Reduction in mean scores of black and white comedones at baseline, 2, 4 and 6 weeks



bacterial flora and immune status of a person. The disease is limited to pilosebaceous follicles of the head and upper trunk, as the sebaceous glands in these regions are comparatively more active. The sebum production is androgen mediated and the sebum is composed of triglycerides, cholesterol esters, waxes and fatty acids. After puberty, androgen production is increased and it stimulates

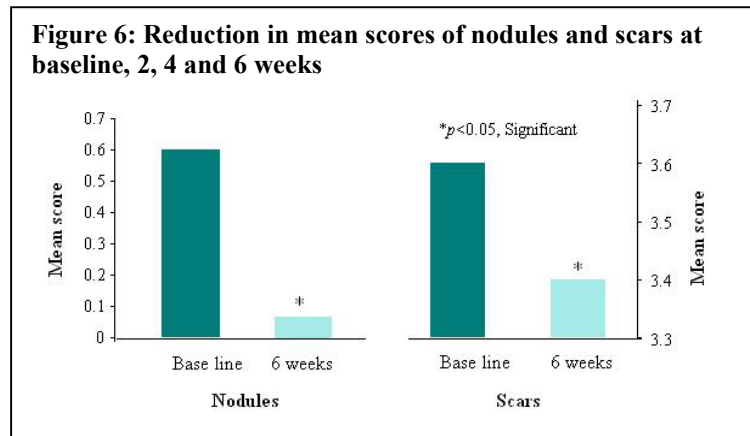
sebaceous follicles to secrete sebum. Paradoxically, androgen levels do not correlate with acne severity among people with acne¹². Sebum is an excellent growth medium for *Propionibacterium acnes*¹³. It has been documented that people with acne have a higher rate of sebum production than unaffected individuals. Moreover, the severity of acne is generally proportional to the amount of sebum production¹⁴.

The primary acne lesion is the “blackhead”, also referred as a microcomedo, which is an impaction formed in the distended pilosebaceous follicle by improperly desquamated keratinocytes and sebum. The stimulus for comedogenesis is uncertain; melanin imparts black color to open comedones, commonly referred to as “blackheads”, which seldom become inflamed. Closed comedones commonly referred to as “whiteheads” block the pilosebaceous canal, which encourages anaerobic bacterial growth. *Propionibacterium acnes* are a commensal of the normal dermal microbial resident flora and are incapable of tissue invasion or serious infection. *Propionibacterium acnes* fuels inflammatory process by lipase secretion, which leads to lysis of triglycerides and free fatty acids that in turn fuels local dermal irritation. *Propionibacterium acnes* acts as inflammatory stimulus by producing neutrophil chemoattractants and activating the complement system. As a consequence, there is formation of papules, pustules, nodules or cysts^{6,15}.

Non-inflammatory acne is one of the mildest forms of disease, but can be the hardest to treat. Topical retinoids, when applied daily, inhibit formation of comedones and are effective in clearing comedonal acne within few months. The major drawback of topical retinoids is dermal irritation and patients with atopic disease may not tolerate topical retinoids due to their inherently irritable skin. The most important adverse effect of topical retinoids is teratogenicity and all fertile women taking the drug, would take birth control measures to avoid pregnancy during the treatment period.^{6,16-18}

Mild papulo-pustular acne rarely results in scarring and is 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^{6,19,20}.

Acne that is resistant to topical treatment or that manifests as scarring or nodular lesions typically requires 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 colitis²⁰⁻²³. Hepatitis, reactions resembling serum sickness, lupus erythematosus, vestibular disturbances (dizziness, vertigo and ataxia) and blue-gray discolorations of the skin have also been reported in association with use of the tetracyclines^{24,25}. Though co-trimoxazole is effective in treating inflammatory acne, the potential for serious side effects (hypersensitivity reactions like toxic epidermal necrolysis, bone-marrow suppression) limits its use to patients who have responded inadequately to commonly used oral antimicrobials²⁴.

Hormonal treatment improves acne by decreasing androgen-induced sebum production. Acne resistant to treatment (especially in a woman with irregular menses) should be investigated for total and free testosterone levels and dehydroepiandrosterone sulfate quantification^{6,26}. Hormonal therapy may be beneficial for women with significant hormonal influence (inadequate response to other acne treatments, acne that begins or worsens in adulthood, premenstrual flares of acne, excessive facial oiliness and acne accompanied by mild to moderate hirsutism), however, long-term side effects have limited their use⁶.

As mentioned above, the current available options in the management of acne are associated with various short- and long-term adverse events and this trial was planned to evaluate the efficacy and safety of a polyherbal topical cream in acne. This study observed that from second week onwards there were significant reductions in erythema, telangiectasia, skin oiliness, and hyper-pigmentation, and there was symptomatic improvement in all patients. There was also significant reduction in the mean number of papules, pustules, black, and white comedones, nodules, cysts and scars at the end of the study. The favourable improvement in acne by Clarina cream might be due to the 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 cyclooxygenase²⁷. Davis *et al.* demonstrated that *Aloe vera* blocks wound-healing suppression of hydrocortisone acetate and this response was due to growth factors in *Aloe vera* that masked wound-healing inhibitors such as sterols and certain amino acids^{28,29}.

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, with 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 level³⁰. Chithra *et al.* studied the influence of *Aloe vera* on the glycosaminoglycan (GAG) components of the matrix in a healing wound, levels of glycohydrolases were elevated on treatment with *Aloe vera*, indicating increased turnover of the matrix. Both topical and oral treatments with *Aloe vera* have a positive influence on the synthesis of GAGs to beneficially modulate wound healing^{31,32}. A basic peroxidase (EC 1.11.1.7) has been identified in the *Aloe vera* and it was observed that when applied topically, *Aloe vera* peroxidase might scavenge H₂O₂ on the skin surface^{33,34}. Heggors *et al.* observed that *Aloe vera* expedites wound contraction and neutralizes wound retardant effect and this effect appears to be due to increased collagen activity, enhanced by a lectin, consequently improving the collagen matrix and enhancing breaking strength^{27,35}.

Prunus amygdalus is known to exert a cooling action on inflamed wounds³⁶. *Alternanthera sessilis* contains very high amounts of carotene, a potent antioxidant³⁷. The extract of *Rubia cordifolia* has been shown to possess significant inhibitory properties in experimentally-induced lipid peroxidation³⁸.

There were no short- or long-term adverse events reported or observed during the entire study period and the study also observed excellent compliance to Clarina cream.

CONCLUSION

Acne vulgaris, a common skin disorder, is not a trivial disease, as it can produce cutaneous and emotional scars that last for a lifetime. Topical therapy is advocated for patients with non-inflammatory comedones and mild to moderate inflammatory acne. Comedolytic and anti-inflammatory agents, along with antimicrobials are generally preferred, in the topical treatment of acne. The emergence of antibiotic resistance and associated risk of short- and long-term adverse effects questions its advocacy in the management of acne.

In this study, it was observed that use of Clarina cream was associated with significant reduction in erythema, telangiectesia, skin oiliness, hyper-pigmentation, papules, pustules, black and white comedones, nodules, cysts and scars, and there was excellent compliance for Clarina. Based on these observations, it may be concluded that Clarina cream is clinically effective and safe for long term usage, in newly diagnosed and previously treated cases of acne vulgaris.

REFERENCES

1. Webster G F. Inflammation in acne vulgaris, *J. Am. Acad. Derm.* 1995; 33: 247-253.
2. Kligman AM. An overview of acne. *J. Invest. Derm.* 1974; 62: 268-287.
3. Koo J. The psychosocial impact of acne: Patient's perceptions. *J. Am. Acad. Dermatol.* 1995; 32: S26-S30.
4. Cunliffe WJ. Acne and unemployment. *Br. J. Derm.* 1984; 115: 386.
5. Cunliffe WJ and Gould DJ. Prevalence of facial acne in late adolescence and in adults. *Br. J. Dermatol.* 1979; 1: 1109-1110.
6. Webster and Guy F. Acne vulgaris. *Br. Med. J.* 2002; 325(7362): 475-479.
7. Eady EA, Farmery MR, Ross JI, Cove JH and Cunliffe WJ. Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. *Br. J. Dermatol.* 1994; 131: 331-336.
8. Eady EA. Bacterial resistance in acne. *Dermatology* 1998; 196(1): 59-66.
9. Leyden JJ, McGinley KJ, Cavalieri S, Webster GF, Mills OH and Kligman AM. Propionibacterium acnes resistance to antibiotics in acne patients. *J. Am. Acad. Derm.* 1983; 8: 41-45.
10. Reisner RM. Antibiotic and anti-inflammatory therapy of acne. *Dermatol. Clin.* 1983; 1: 385-397.
11. Gopal M G and Farahana B. Effectiveness of herbal medications in the treatment of acne vulgaris – A pilot study. *The Indian Practitioner* 2001; 54 (10): 723.
12. Levell MJ, Cawood ML, Burke B and Cunliffe WJ. Acne is not associated with abnormal plasma androgens. *Br. J. Derm.* 1989; 120: 649-654.
13. Rothman KF and Lucky AW. Acne vulgaris. *Adv. Dermatol.* 1993; 8: 347-374.

14. Pochi PE and Strauss JS. Endocrinologic control of the development and activity of the human sebaceous gland. *J. Invest. Dermatol.* 1964; 43: 383-388.
15. Leyden JJ. The evolving role of Propionibacterium acnes in acne. *Semin. Cutan. Med. Surg.* 2001; 20: 139-143.
16. Shalita AR. The integral role of topical and oral retinoids in the early treatment of acne. *J. Eur. Acad. Dermatol. Venereol.* 2001; 15(Suppl 3): 43-49.
17. Sykes N and Webster GF. Therapeutic advances in the treatment of acne vulgaris. *Drugs* 1994; 48: 59-70.
18. McClane J. Analysis of common side effects of isotretinoin. *J. Am. Acad. Dermatol.* 2001; 45: S188-S194.
19. Leyden JJ, Shalita AR, Saatjian GD and Sefton J. Erythromycin 2% gel in comparison with clindamycin phosphate 1% solution in acne vulgaris. *J. Am. Acad. Derm.* 1987; 16: 822-827.
20. Webster GF. Acne and rosacea. *Med. Clin. North Am.* 1998; 82: 1145-1154.
21. Gammon WR, Meyer C, Lantis S, *et al.*, Comparative efficacy of oral erythromycin versus oral tetracycline in the treatment of acne vulgaris: A double-blind study. *J. Am. Acad. Dermatol.* 1986; 14: 183-186.
22. Eady EA, Cove JH, Holland KT, *et al.* Erythromycin resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. *Br. J. Dermatol.* 1989; 121: 51-57.
23. Poulos ET and Tedesco FJ. Acne vulgaris: double-blind trial comparing tetracycline and clindamycin. *Arch. Dermatol.* 1976; 12: 974-976.
24. Hersle K. Trimethoprim-sulphamethoxazole in acne vulgaris: A double-blind study. *Dermatologica* 1972; 145:187-191.
25. Gough A, Chapman S and Wagstaff K. Minocycline induced autoimmune hepatitis and systemic lupus erythematosus like syndrome, *BJM* 1996; 312: 369-372.
26. Thiboutot D. New treatments and therapeutic strategies for acne. *Arch. Fam. Med.* 2000; 9: 179-187.
27. Heggors JP, Kucukcelebi A, Listengarten D, Stabenau J, Ko F, Broemeling LD, Robson MC and Winters WD. Beneficial effect of Aloe on wound healing in an excisional wound model. *J. Altern. Complement. Med.* 1996; 2(2): 271-277.
28. Davis RH, Di Donato JJ, Johnson RW and Stewart CB. *Aloe vera*, hydrocortisone, and sterol influence on wound tensile strength and anti-inflammation. *J. Am. Podiatr. Med. Assoc.* 1994; 84(12): 614-621.
29. Hutter JA, Salman M, Stavinoha WB, Satsangi N, Williams RF, Streeper RT and Weintraub ST. Anti-inflammatory C-glucosyl chromone from *Aloe barbadensis*. *J. Natural Products* 1996; 59(5): 541-543.
30. Choi SW, Son BW, Son YS, Park YI, Lee SK and Chung MH. The wound-healing effect of a glycoprotein fraction isolated from aloe vera. *Br. J. Dermatol.* 2001; 145(4): 535-545.
31. Chithra P, Sajithlal GB and Gowri Chandrakasan. Influence of *Aloe vera* on the glycosaminoglycans in the matrix of healing dermal wounds in rats. *J. Ethnopharmacol.* 1998; 59(3): 179-186.
32. Reynolds T and Dweckb AC. *Aloe vera* leaf gel: A review update. *J. Ethnopharmacol.* 1999; 68(1-3): 3-37.

33. Esteban A, Zapata JM, Casano L, Martin M and Sabater B. Peroxidase activity in Aloe barbadensis commercial gel: probable role in skin protection. *Planta Med.* 2000; 66(8): 724-727.
34. Vazquez B, Avila G, Segura D and Escalante B. Anti-inflammatory activity of extracts from Aloe vera gel. *J. Ethnopharmacol.* 1996; 55(1): 69-75.
35. Visuthikosol V, Chowchuen B, Sukwanarat Y, Sriurairatana S and Boonpucknavig V. Effect of Aloe vera gel to healing of burn wound a clinical and histologic study. *J. Med. Assoc. Thai.* 1995; 78(8): 403-409.
36. Nadkarni KM. Indian Materia Medica, 3rd Edition, Bombay Popular Prakashan, Bombay, India. 1996; 2: 103-107.
37. Devadas Rajammal P., Chandrasekhar U., Premakumari S., *et al.*, Consumption pattern of carotene rich foods and development of a year calendar. *Biomed. Environ. Sci.* 1996; 9(2-3): 213-222.
38. Tripathi YB and Sharma M. The interaction of Rubia cordifolia with iron redox status: A mechanistic aspect in free radical reactions. *Phytomedicine* 1999; 6(1): 51-57.