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# EFFECTIVENESS OF ZINC SUPPLEMENTATION WITH TOPICAL RETINOIDS IN ACNE VULGARIS PATIENTS: A RANDOMIZED, DOUBLE- BLIND, PLACEBO-CONTROLLED TRIAL

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## ABSTRACT

**Background:** The investigation of combining zinc supplementation with topical retinoids represents a promising avenue in the pursuit of effective acne vulgaris management. By addressing multiple aspects of acne pathogenesis simultaneously and potentially reducing the adverse effects of retinoid treatment, this approach could offer a well-rounded and enhanced therapeutic strategy for individuals burdened by this dermatological condition. **Objective:** To evaluate the additional benefit in reducing symptoms by supplementation of oral zinc with topical retinoids treated acne vulgaris patients. **Method:** This randomized, double-blind, placebo-controlled trial was conducted at Bangabandhu Sheikh Mujib Medical University's Pharmacology and Dermatology and Venereology Department from March 2020 to January 2022 (with enrollment starting in April 2021). The study involved 122 newly diagnosed mild and moderate acne vulgaris (AV) patients treated with 20 mg tablet of zinc sulphate or 20mg of placebo tablet with topical retinoids. Nine patients dropped out due to various reasons, leaving 113 participants for per-protocol (PP) analysis. The study comprised baseline and after 8-week follow-up visits, evaluating GAGS acne severity scores and evaluate the appearance of the adverse effect. **Results:** Initially, both control and intervention arms had similar GAGS scores (around 16), with no significant difference. After 8 weeks, the control arm's GAGS score decreased to about 15, while the intervention arm showed a significant drop to around 12 ($p=0.004$). Both groups had notable reductions from their baseline scores ($p<0.05$). There were no significant differences in side effects (abdominal discomfort, nausea, vomiting, and diarrhea) between the two arms. **Conclusion:** Incorporating the findings from various studies, it is evident that the effectiveness of combining zinc supplementation with topical retinoids in the treatment of acne vulgaris is influenced by multiple factors, including patient characteristics, formulations used, and treatment duration. While some studies present conflicting results, a general trend towards enhanced clinical outcomes with combination therapy is observed. The synergy between zinc's anti-inflammatory, sebum-regulating, and immunomodulatory properties and retinoids' comedolytic and anti-inflammatory effects offers a promising avenue for improved acne management. This trial was registered in ClinicalTrials.gov with the trial ID number NCT04899843.

**KEYWORDS:** Zinc Supplementation, Topical Retinoids, Acne Vulgaris Patients, GAGS score.

## INTRODUCTION

Acne vulgaris, a common dermatological condition, affects individuals across various age groups, causing not only physical discomfort but also psychological distress due to its visible nature. The multifactorial nature of acne involves factors such as sebum production, inflammation, follicular hyperkeratinization, and the colonization of Propionibacterium acnes. As a result, acne treatment approaches often aim to address multiple aspects of its pathogenesis.

Zinc, an essential trace element, has garnered attention for its potential role in acne management. It exerts anti-inflammatory, antioxidant, and immunomodulatory effects, all of which can contribute to reducing the severity of acne lesions. Furthermore, zinc has been found to regulate sebum production and inhibit the

growth of Propionibacterium acnes, making it a promising adjunctive therapy for acne vulgaris.[1-6]

Retinoids, on the other hand, are well-established in acne treatment due to their comedolytic and anti-inflammatory properties. Topical retinoids normalize follicular keratinization, effectively unclogging pores and preventing the formation of comedones. Additionally, they possess potent anti-inflammatory effects, reducing the redness and swelling associated with acne lesions. Despite their efficacy, retinoid use can be associated with skin irritation and dryness, which can lead to reduced adherence to treatment.[7-9]

Given the individual merits of both zinc and retinoids in managing acne vulgaris, researchers and clinicians have explored the potential benefits of combining these therapies. The rationale behind this approach lies in the possibility of achieving a synergistic effect, where the anti-inflammatory, sebum-regulating, and antimicrobial properties of zinc supplement and the comedolytic and anti-inflammatory actions of retinoids. This combination holds the promise of not only enhancing the overall efficacy of treatment but also mitigating potential side effects associated with retinoid use.[9-10]

This paper aims to review and consolidate the existing body of knowledge regarding the effectiveness of zinc supplementation when used in conjunction with topical retinoids in the management of acne vulgaris. By examining the individual contributions of these two therapeutic agents and their potential synergistic effects, we seek to provide a comprehensive understanding of the clinical implications of this combination therapy. Furthermore, a thorough analysis of available studies will shed light on the optimal dosages, formulations, and patient profiles that could benefit the most from this combined approach.

## OBJECTIVE

To evaluate the additional benefit in reducing symptoms by supplementation of oral zinc with topical retinoids treated acne vulgaris patients.

## METHODOLOGY

### Type & Place of the Study

The study is a randomized, double-blind, placebo-controlled trial. This means that it involved random assignment of participants, double-blind procedures to ensure unbiased results, and the use of a placebo group as a control. The research was conducted in the Department of Pharmacology and Department of Dermatology and Venereology at Bangabandhu Sheikh Mujib Medical University.

### Duration of the Study

The study took place from March 2020 to January 2022. Actual enrollment began in April 2021 after approval from the Institutional Review Board (IRB).

### Study Population

The study focused on newly diagnosed mild and moderate acne vulgaris (AV) patients treated with topical retinoids.

### Sample Size

The sample size was determined based on a formula, resulting in 56 participants in each arm, with a 10% dropout rate, leading to a final sample size of 61 in each arm. A consecutive sampling procedure was used to select 122 patients who met the inclusion and exclusion criteria.

### Randomization

After completing screening and baseline measurements, participants were randomly assigned to one of two arms: (i) 20 mg zinc sulphate tablet or (ii) 20 mg placebo tablet for 8 weeks. Treatment assignment was done by online graph pad software using a computer from the website (http://www.graphpad.com/quickcales/ranMenu) which automatically generated two distinct sets of random numbers after giving necessary inputs, by one senior faculty member from department of Microbiology BSMMU. All subjects and investigators were blind to the treatment condition and remained blinded until unblinding the codes during data analysis.

### Intervention schedule

Patients were instructed to take 20 mg zinc sulphate or 20 mg placebo tablet: 1 tablet twice daily after meals for 8 weeks along with topical retinoids given by the Dermatologist. Patients were scheduled for assessments at the end of 8 weeks of the treatment. Zinc or placebo tablets were provided free of charge.

### Intervention protocol

Throughout the treatment, patients were not instructed to change their food, physical activity habits, or prescription medicine usage habits. They were also told not to use any zinc-containing dietary supplements while participating in the experiment. Regular intake of medicine was confirmed over the telephone by an audio call or text message, pill count, and compliance sheet. Adverse effects were evaluated by a pre-formed checklist, and patients were asked over the phone to report any unwanted effects after medicine administration during the trial period while on the treatment.

### Patient Assessment Tools

Assessment tools included a questionnaire for socio-demographic data and the Global Acne Grading System (GAGS) to evaluate acne severity.[11]

### Outcome Measures

The primary outcome measure was the assessment of acne vulgaris severity using GAGS, while secondary outcomes included measuring and evaluating adverse effects.

**Inclusion and Exclusion Criteria**

The study included newly diagnosed mild and moderate AV patients aged 11-35 years, of both genders, meeting specific criteria. Exclusion criteria included various factors like cosmetic-induced acne, oral contraceptive pill use, pregnancy, and lactation.

**Study Procedure**

The study procedure involved the procurement, packaging, storage, randomization, blinding, and allocation concealment of medications. Patients were enrolled, provided treatment, and assessed over a specified duration.

**Data Collection Procedure**

The study followed CONSORT principles for data collection, involving detailed explanations, informed consent, and recording demographic information. Patients were assessed by GAGS score at baseline and after 8 weeks.

**Documentation of Follow-up Visit**

All patient data, including questionnaires, prescriptions were meticulously documented.

**Data Interpretation**

After unblinding, data were divided into two arms, and statistical analysis was performed using various tests, including chi-square, t-tests, and two proportion Z test with a significance threshold of $p \leq 0.05$.

**RESULTS**

According to the Consolidated Standards of Reporting Trials (CONSORT) principle, total one hundred and twenty-two (122) patients were enrolled based on the study's eligibility criteria. Of which, sixty- one (61) patients received a placebo, and sixty-one (61) patients received an intervention. A total of six (6) patients from the control arm and three (3) patients from the intervention arm dropped out from the study. So fifty-five (55) patients from the control arm and fifty-eight (58) patients from the intervention arm completed the study.

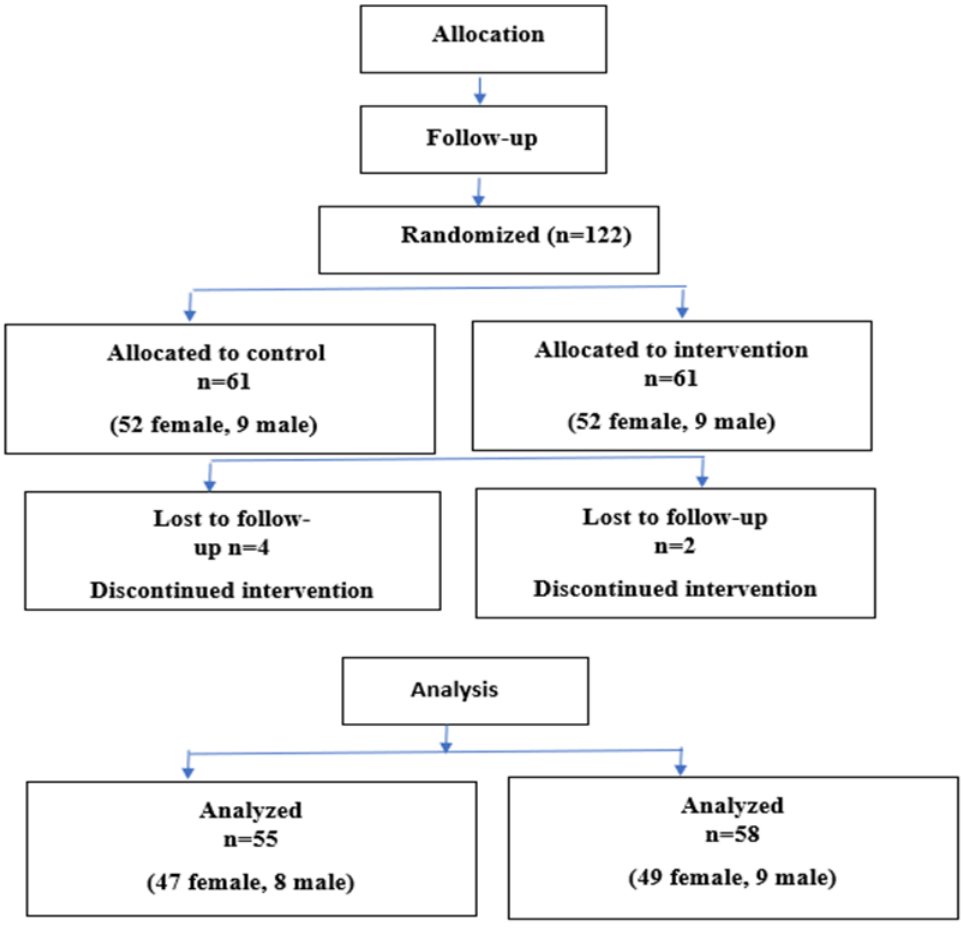


**Figure I: Flowchart of Consolidated Standards of Reporting Trials (CONSORT).**

Table I shows the age and BMI of patients. There was no significant difference between arms in age and BMI. The patient's age was (20.57± 4.45; range 13-35 years) in the control arm. At the same time, the age of the patients in the intervention arm was (20.52 ± 4.69; range 13-30 years). The difference was not statistically significant (P

= 0.95). The patient's BMI was (22.67 ± 3.76; range 16.2-33.9) in the control arm. At the same time, the BMI of the patients in the intervention arm was (22.43 ± 2.99; range 16.3-32.8). The difference was not statistically significant (P=0.69).

**Table I: Demographic Characteristics (Age and BMI) of the Patients at the Time of Enrolment (Baseline).**

| Variables | | Control (n=61) | Intervention (n=61) | P-value |
|---|---|---|---|---|
| Age (years) | Mean ± SD | 20.57 ± 4.45 | 20.52 ± 4.69 | 0.95 |
| | Range | 13-35 | 13-30 | |
| BMI (kg/m2 ) | Mean ± SD | 22.67 ± 3.76 | 22.43 ± 2.99 | 0.69 |
| | Range | 16.2-33.9 | 16.3-32.8 | |

Unpaired t-test was done

Table II shows the gender of patients. 14.75% (9/61) patients were male in the control arm, and 85.24% (52/61) were female. While in the intervention arm, 14.75% (9/61) patients were male, and 85.24% (52/61) were female. The difference was not significant (P = 1).

**Table II: Demographic Characteristics (Gender) of the Patients at the Time of Enrolment (Baseline)**

| Variables | control (n=61) | Intervention (n=61) | P-value |
|---|---|---|---|
| Male | 9 (14.75%) | 9 (14.75%) | |
| Female | 52 (85.24%) | 52 (85.24%) | 1 |

Chi-square (x2) test was done Significant P-value < 0.05

Table III shows, at baseline, the GAGS score was 16.07 ± 6.54 (range 6- 29) in the control arm compared to 16.74 ± 6.09 (range 8-29) in the intervention arm. The difference between the GAGS score of the control and intervention arm was not statistically significant (P = 0.57). On assessment after 8 weeks, the GAGS score was 15.27 ± 6.32 (range 6-29) in the control arm compared to 12.03 ± 5.39 (range 4-20) in the intervention arm. The GAGS score of the intervention arm was significantly (P = 0.00) lower than that of the control arm. After 8 weeks, the GAGS score significantly decreased (P = 0.00) from the baseline control and intervention arm.

**Table-III: Comparison of GAGS Score Between Control and Intervention Arms (at Baseline and After 8 Weeks of Treatment)**

| | | | GAGS Score | |
|---|---|---|---|---|
| | | Control (n=55) | Intervention (n=58) | P-value[a] |
| Baseline | Mean ± SD | 16.07 ± 6.54 | 16.74 ± 6.09 | 0.575 |
| | Range | 6-29 | 8-29 | |
| After 8 weeks | Mean ± SD | 15.27 ± 6.32 | 12.03 ± 5.39 | 0.004 |
| | Range | 6-29 | 4-20 | |
| P-value[b] | | 0.000 | 0.000 | |

aUnpaired t-test was done bPaired t-test was done Significant P-value < 0.05

Figure-II shows the GAGS score (mean ± SD) in the control and intervention arms at baseline and after 8 weeks of treatment. Here blue bar indicates baseline, and red suggest after 8 weeks of treatment.

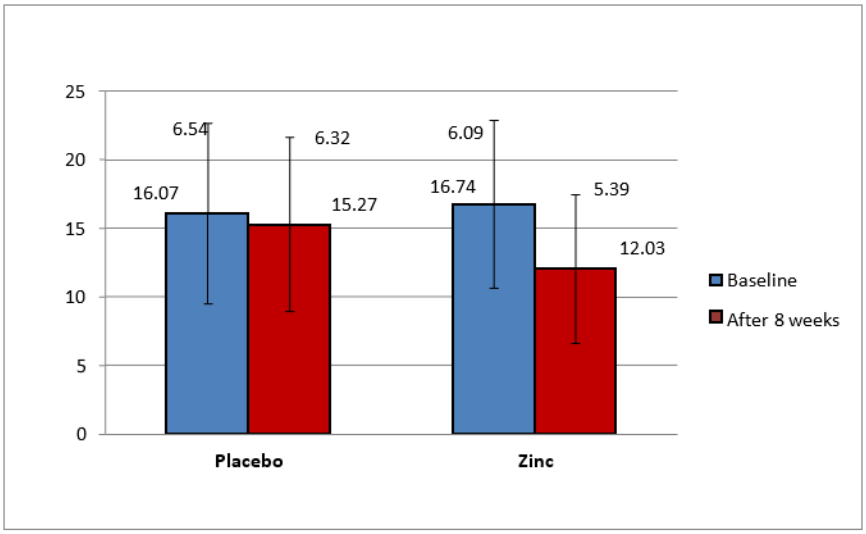


**Figure II: Comparison of GAGS Score Between Control and Intervention Arms (at Baseline and After 8 Weeks of Treatment).**

Table-IV shows adverse effects in both arms of placebo and zinc sulphate. There was no significant difference in abdominal discomfort, nausea, vomiting and diarrhea between control and intervention arm (P = 0.56, P = 0.68, P = 0.74 and P = 0.58 respectively).

**Table IV: Adverse Effects in the Control and Intervention Arms During Treatment.**

| Adverse Effects | Control (n=55) | Intervention (n=58) | P-value[a] |
|---|---|---|---|
| Abdominal Discomfort | 4/55 (7.27%) | 6/58 (10.34%) | 0.568 |
| Nausea | 2/55 (3.63%) | 3/58 (5.17%) | 0.689 |
| Vomiting | 3/55 (5.45%) | 4/58 (6.89%) | 0.748 |
| Diarrhea | 1/55 (1.81%) | 2/58 (3.44%) | 0.589 |

a Two proportion Z test was done Significant P-value < 0.05

## DISCUSSION

Acne is the eighth most prevalent disease globally, and it is estimated that 9.4% of the global population is affected by acne vulgaris.[12] Acne vulgaris is the most common cutaneous disorder affecting adolescents and young adults.

The combined use of zinc supplementation and topical retinoids in the treatment of acne vulgaris has garnered significant interest in recent years, with several studies examining the potential synergistic effects and clinical outcomes. This section discusses key findings from various studies that shed light on the effectiveness of this combination therapy.

In our study, daily supplementation of 20 mg of zinc sulphate for 8 weeks, the acne severity score (GAGS score) significantly decreased from the baseline in the intervention arm. Which was quite similar to our study where, one study revealed the maximum acne severity score reduction was observed after 3 to 6 weeks of supplementation with zinc sulphate.[13] Another trial found a significant decrease in papules, infiltrates, and cysts after 12 weeks of zinc supplementation.[14] However, other study reported no difference between the zinc supplementation and control groups. Perhaps improvement was not significant because of a limited number of patients.[15]

Besides that, in a randomized controlled trial reported that, patients with moderate to severe acne were divided into three groups: one receiving topical retinoid therapy alone, another receiving oral zinc supplementation alone, and a third receiving a combination of both. The results demonstrated that the combination group exhibited a more rapid reduction in lesion count, decreased sebum production, and improved overall skin appearance compared to the monotherapy groups. This suggests that the combination of zinc supplementation and retinoid treatment could lead to enhanced and faster clinical improvement.[9]

Conversely, a another study produced contrasting results. The researchers evaluated the effects of zinc supplementation in patients who were already undergoing retinoid therapy. Surprisingly, the group receiving zinc supplementation alongside retinoids showed no significant difference in lesion reduction compared to the group receiving retinoids alone. However, subgroup analysis indicated that patients with lower baseline zinc levels experienced more pronounced benefits from the combination therapy.[10] This highlights

the potential role of individual patient characteristics in influencing treatment outcomes.

A meta-analysis by pooled data from multiple studies to provide a comprehensive overview of the effectiveness of zinc and retinoid combination therapy. The analysis indicated that while there is considerable heterogeneity in study designs and outcomes, an overall positive trend in favor of combination therapy is observed. The meta-analysis also suggested that the optimal outcome might be achieved when specific zinc formulations and retinoid concentrations are used, emphasizing the importance of formulation considerations in this combination approach.[4]

The current study observed most of the adverse effects are gastrointestinal in both intervention and control arms; however, those were not severe enough to discontinue the treatment, and there was no significant difference. Similarly, several studies reported adverse effects, predominantly gastrointestinal, and few patients discontinued the study due to gastrointestinal symptoms.[16][17][14] Whereas other study found no serious side effects after zinc supplementation.[18]

## CONCLUSION

Incorporating the findings from various studies, it is evident that the effectiveness of combining zinc supplementation with topical retinoids in the treatment of acne vulgaris is influenced by multiple factors, including patient characteristics, formulations used, and treatment duration. While some studies present conflicting results, a general trend towards enhanced clinical outcomes with combination therapy is observed. The synergy between zinc's anti-inflammatory, sebum-regulating, and immunomodulatory properties and retinoids' comedolytic and anti-inflammatory effects offers a promising avenue for improved acne management. However, further well-designed randomized controlled trials with standardized protocols and larger sample sizes are needed to provide more definitive conclusions and to refine the optimal parameters for this combined approach.

## REFERENCE


1. Agak, G.W., Qin, M., Nobe, J., Kim, M.H., Krutzik, S.R., Tristan, G.R., Elashoff, D., Garban, H.J. and Kim, J., Propionibacterium acnes induces an IL-17 response in acne vulgaris that is regulated by vitamin A and vitamin D. Journal of Investigative Dermatology, 2014; 134: 366-373.
2. Amer, M., Bahgat, M.R., Tosson, Z., Mowla, M.Y.A. and Amer, K., Serum zinc in acne vulgaris. International Journal of Dermatology, 1982; 21: 481-484.
3. Arora, P.N., Dhillon, K.S., Rajan, S.R., Sayal, S.K. and Das, A.L., Serum zinc levels in cutaneous disorders. Medical Journal Armed Forces India, 2002; 58: 304-306.
4. Baer, M.T. and King, J.C., Tissue zinc levels and zinc excretion during experimental zinc depletion in young men. The American Journal of Clinical Nutrition, 1984; 39: 556-570.
5. Bojar, R.A., Eady, B., Jones, C.E., Cunijffh, W. and Holland, K.T., Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc. British Journal of Dermatology, 1994; 130: 329-336.
6. Borgia, F., Cannavo, S., Guarneri, F., Cannavo, S.P., Vaccaro, M. and Guarneri, B., Correlation between endocrinological parameters and acne severity in adult women. Acta Dermatovenereologica-Stockholm, 2004; 84: 201-204.
7. Brown, K.H., Rivera, J.A., Bhutta, Z., Gibson, R.S., King, J.C., Lonnerdal, B., Ruel, M.T., Sandtrom, B., Wasantwisut, E., Hotz, C. and International Zinc Nutrition Consultative Group (IZiNCG, International Zinc Nutrition Consultative Group (IZiNCG) technical document# 1. Assessment of the risk of zinc deficiency in populations and options for its control. Food and Nutrition Bulletin, 2004; 25: S99-S203.
8. Burke, B.M. and Cunliffe, W.J., The assessment of acne vulgaris—the Leeds technique. British Journal of Dermatology, 1984; 111: 83-92.
9. Burris, J., Rietkerk, W. and Woolf, K., Relationships of self- reported dietary factors and perceived acne severity in a cohort of New York young adults. Journal of the Academy of Nutrition and Dietetics, 2014; 114: 384-392.
10. Butool, F., Rekha, C. and Rao, A.G., Clinical study on serum zinc levels in patients with acne vulgaris. Asian Journal of Research in Chemistry, 2013; 6: 464-466.
11. Doshi, A., Zaheer, A. and Stiller, M.J., A comparison of current acne grading systems and proposal of a novel system. International Journal of Dermatology, 1997; 36: 416-418.
12. Hay, R.J., Johns, N.E., Williams, H.C., Bolliger, I.W., Dellavalle, R.P., Margolis, D.J., Marks, R., Naldi, L., Weinstock, M.A., Wulf, S.K. and Michaud, C., The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. Journal of Investigative Dermatology, 2014; 134: 1527-1534.
13. Thomas, J., Role of zinc in acne: a study of 77 patients. International Journal of Research in Dermatology, 2018; 4: 1-5.
14. Verma, K.C., Saini, A.S. and Dhamija, S.K., Oral zinc sulphate therapy in acne vulgaris: a double-blind trial. Acta Dermato- Venereologica, 1980; 60: 337-340.
15. Weismann, K., Wadskov, S. and Sondergaard, J., Oral zinc sulphate therapy for acne vulgaris. Acta Dermato-Venereologica, 1977; 57: 357-360.
16. Dreno, B., Moyse, D., Alirezai, M., Amblard, P., Auffret, N., Beylot, C., Bodokh, I., Chivot, M., Daniel, F., Humbert, P. and Meynadier, J., Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in

the treatment of inflammatory acne vulgaris. Dermatology, 2001; 203: 135-140.
17. Hillstrom, L., Pettersson, L., Hellbe, L., Kjellin, A., Leczinsky, C.G. and Nordwall, C., Comparison of oral treatment with zinc sulphate and placebo in acne vulgaris. British Journal of Dermatology, 1977; 97: 679-684.
18. Michaelsson, G., Juhlin, L. and Vahlquist, A., Effects of oral zinc and vitamin A in acne. Archives of Dermatology, 1977; 113: 31-36.