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A RANDOMIZED CLINICAL STUDY OF POMEWHITE®: EFFECTS ON ACNE, SKIN MICROBIOTA, AND OXIDATIVE STRESS

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Abstract *This clinical study evaluates the therapeutic potential of POMEWHITE®, a novel pomegranate-derived food supplement, in improving skin health and alleviating acne-related symptoms. Conducted over eight weeks, the trial involved 100 participants with moderate to severe acne and 20 healthy controls. Participants were randomly assigned to placebo (rice powder) or POMEWHITE® supplementation at 150 mg/day or 300 mg/day. Primary outcomes included acne lesion count, bacterial colony composition, and inflammation severity, while secondary outcomes assessed skin brightness, fine lines, antioxidative enzyme activity, and participant satisfaction. Results showed that eight weeks of POMEWHITE® intake, particularly at 300 mg/day, significantly reduced P. acnes colonies and increased beneficial skin flora. There was a notable decrease in lipase activity, contributing to reduced sebum production. Visual analogue scores and dermatologist-graded acne severity scales demonstrated substantial improvements in treated groups compared to placebo. Additionally, POMEWHITE® significantly improved antioxidant defenses by lowering superoxide dismutase (SOD) and increasing glucose-6-phosphate dehydrogenase (G6PD) levels. Inflammatory markers IL-4 and IFN-γ also showed favorable modulation, reflecting reduced skin inflammation. Tyrosinase activity inhibition and improvements in fine lines and wrinkles further highlighted the supplement's anti-aging and skin-brightening potential. These findings suggest that POMEWHITE® is a safe and effective nutraceutical intervention for acne management. Its ability to restore microbiome balance, reduce oxidative stress and inflammation, and enhance skin appearance positions it as a promising alternative or adjunct to conventional acne therapies.*

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Keywords: *Acne vulgaris; microbiota; white pomegranate; prebiotic; antioxidant; tyrosinase*

Introduction

Acne vulgaris is one of the most prevalent chronic inflammatory skin conditions, impacting approximately 650 million people worldwide. It predominantly affects adolescents but persists into adulthood in many cases, with varying severity (Ak, 2019; Alsaadoon et al., 2024). The pathogenesis of acne involves a complex interplay of factors including excess sebum production, abnormal keratinization of hair follicles, bacterial colonization, and inflammation (Bharti and Vadlamudi, 2021). These processes lead to the formation of comedones, papules, pustules, and, in severe cases, nodules and cysts. While conventional treatments such as retinoids, antibiotics, hormonal therapy, and benzoyl peroxide are effective to varying degrees, they often pose risks of side effects, resistance development, and long-term skin barrier disruption (Gollnick, 2003; Kim and Kim, 2024). In recent years, a paradigm shift in acne management has emerged with increasing interest in the role of the skin microbiome and the therapeutic potential of nutraceuticals (Lee et al., 2019; Niedźwiedzka et al., 2024). Natural products with antioxidant, anti-inflammatory, and antimicrobial properties are being explored as viable alternatives or adjuncts to traditional therapies (Sychrová et al., 2020). Among these, pomegranate (*Punica granatum*), particularly its less pigmented white variant, has drawn attention due to its rich content of bioactive compounds like polyphenols, ellagitannins, and prebiotics. Unlike red pomegranate, white pomegranate lacks anthocyanins and instead accumulates upstream flavonoid intermediates such as proanthocyanidins, which have demonstrated potent antioxidant and anti-inflammatory effects (Ben-Simhon et al., 2015; Mphahlele et al., 2014; Pirzadeh et al., 2021).

POMEWHITE®, a standardized food supplement derived from white pomegranate, is formulated to

support skin health by modulating the microbiota, reducing oxidative stress, and improving dermal inflammation. It is hypothesized that the supplement's prebiotic-rich matrix can promote the growth of beneficial skin flora while suppressing pathogenic bacteria. In addition, its influence on oxidative and inflammatory markers may contribute to reduced acne severity and improved skin texture. This clinical trial investigates the impact of POMEWHITE® at two daily doses (150 mg and 300 mg) over eight weeks, evaluating parameters including acne lesion counts, microbial colony distribution, antioxidant enzyme levels, inflammatory cytokines, tyrosinase activity, and participant satisfaction. By addressing both the microbial and biochemical contributors to acne, this study aims to establish POMEWHITE® as a safe, effective, and multifaceted option in holistic dermatologic care.

METHODOLOGY

Trial period and approval

The study began on September 1, 2021, after receiving the products on August 1, 2021, and concluded on October 27, 2021. The study was approved by the ethical committee of the skincare laboratory Greenacre FZCO.

Assessment criteria

The primary outcome measures included bacterial index (probiotic/normal flora and acne-causing bacteria colony count) and acne lesion counts (total, inflammatory, and non-inflammatory), evaluated through inflammation and severity indices based on lesion number, diameter, and depth. Secondary outcome measures included skin biophysical parameters, assessed at baseline, week 4, and week 8.

Secondary criteria

Clinical evaluations were conducted at baseline, week 4, and week 8, focusing on fine lines, wrinkles, and overall skin brightening. These were assessed using DSLR images scored on a scale of 1–8 by experts. Additional analyses included brightening and anti-aging effects, stress and inflammatory marker reduction, and responses from a subjective evaluation questionnaire.

Principles and measurement instruments

Bacterial index and acne lesion counts were evaluated clinically, while severity was graded by dermatologists. Fine lines, wrinkles, and skin brightness were scored using Griffith's scale and ImageJ software. The study was conducted at three time points: baseline, week 4, and week 8.

Subjective evaluation questionnaire

Participants completed a questionnaire at the end of the study to assess their experience with the products and their likelihood of future use.

Subject selection

The study included 100 participants with moderate to severe acne and 20 healthy control subjects, all of whom had not used any antibiotics or medications 2–3 months before the study. Inclusion criteria included acne grading, presence of fine lines/wrinkles, healthy diet, and no prior treatments. Control participants were untreated and classified as having clear or almost clear skin by dermatologists.

Inclusion criteria

General criteria
Healthy subject
The subject has given his/her informed, written consent.
Cooperative subject, aware of the necessity and duration of controls so that perfect adhesion to the protocol established by the clinical trial center could have been expected.
Specific criteria
Sex: men and women
Age: between 20 and 45.
The person agrees not to change their alimentation habits.
Person with type 3,4 or 5 skin type on the face (normal persons with type 1 or 2 skin type)
For women with substitutive hormonal treatment: stabilized treatment for 12 months and more.
For women of age for procreation: use an efficient method of contraception 12 weeks before the beginning of the study, during the study, and 4 weeks after the end of the study.

Exclusion criteria

Pregnant or nursing woman or woman planning to get pregnant during the study.
Cutaneous pathology on the studied zone (eczema, etc).
The use of topical or systemic treatment during the previous weeks is liable to interfere with the assessment of the acceptability of the studied product.
Taking a food supplement two months before the study.
All medical treatments are taken continually 7 days before the beginning of the study.
All medical treatments taken during 2 weeks and more continue the month before the beginning of the study.
A person enrolled in another clinical trial during the study period.
Known allergy to a constituent.
Severe chronic or acute problems to health

Compliance assessment and restrictions during the study

Participants who significantly deviated from the protocol were excluded, while minor deviations led to warnings. Only the study products and usual facial cleansers were allowed; no additional skin treatments were permitted during the study.

Assessment of Vital Functions

Vital parameters, including shock index, vitamin D, glucose, bilirubin, ALP, hepatitis B and C, heart rate, and blood pressure, were recorded at baseline, week 4, and week 8. These tests were performed in certified diagnostic labs.

Treatment Groups

Volunteers were divided into five groups excluding the normal ones. These groups' details are given in the table 1 below:

Table 1. Volunteers groups

No	Abbreviation	Group name	Number at week 0	Number at week 8
1	Normal	Persons with skin types 1 and 2	26	20
2	Untreated	Acne Skin types 3, 4, and 5 with no treatment	24	20
3	T-Plac-150mg/day	Acne skin: Treatment with rice powder 150mg/day	28	20
4	T- POME-150mg/day	Acne skin: Treatment with POMWHITE 150mg/day	27	20
5	T-Plac-300 mg/day	Acne skin: Treatment with rice powder 300mg/day	20	20
6	T- POME-300mg/day	Acne skin: Treatment with POMWHITE 300mg/day	22	20

At the end of the treatment data in each group was restricted to 20 volunteers in each group. This reduction was because 20 is the lowest number of respondents in some groups.

Trial Schedule

Participants were randomly assigned to receive either a placebo (rice powder capsules) or POMEWHITE® capsules (150mg/day or 300mg/day for 8 weeks). Clinical assessments and lab tests, including blood sampling, microbiota culturing, and ELISA, were conducted at baseline, week 4, and week 8.

Assessment of skin health

Skin assessments focused on wrinkles, fine lines, and brightening using Griffith's scale. Acne grading, lesion counts, and microbiota sampling were conducted with standardized swabbing protocols. Samples were cultured in diagnostic labs. A visual analogue scale (VAS) was used to measure satisfaction from 1 to 10.

Estimation of anti-oxidative enzymes

Normally, the production of free radicals is slow and they are removed by the antioxidant enzymes existing in the cell. The first line of defense from ROS includes antioxidant enzymes including Superoxide dismutase (SOD) and glucose-6-phosphate dehydrogenase (G6PD).

Estimation of superoxide dismutase (SOD)

For the evaluation of SOD in pre-treated and post-treated groups of POMEWHITE® capsules, the harvested serum was used, and SOD estimation was done via kit according to the manufacturer's protocol (Sigma Aldrich). The results were measured in units/ml of serum.

Estimation of glucose-6-phosphate dehydrogenase (G6PD)

G6PD in pre-treated and post-treated groups of POMEWHITE® capsules was estimated by using the blood of volunteers taken in EDTA-containing tubes, and G6PD estimation was done via kit according to the manufacturer's protocol (Sigma Aldrich). The test results were measured as units per gram of hemoglobin.

Enzyme Linked Immunosorbant assay (ELISA)

Solid phase sandwich ELISA was implemented for IL-4 (inflammation) and INF-γ (inflammation) by the previously reported Wajid et al, (Wajid et al., 2015) method with slight modifications.

Lipase activity

Lipase activity was done by using the serum lipase estimation kit. This test was done as more lipase in serum can cause more free fatty acids present in the blood, thus promoting acne-like problems.

Tyrosinase assay

Tyrosinase activity was calculated by the method of Chan, Kim et al. with some modifications (Chan et al., 2011). This test evaluates the potential of POMEWHITE® for skin brightening. Tyrosinase is a copper-containing enzyme present in plant and animal tissues that catalyzes the production of melanin and other pigments from tyrosine by oxidation. So this test evaluates the melanin production.

Statistical analysis

All data of experimental groups was expressed as mean ± SEM in triplicate experiments. For statistical analysis, group means were compared by one-way ANOVA and Bonferroni's test was used to identify differences between groups. Quantitative data obtained from different experimental groups was statistically analyzed via graph pad software by using two-way ANOVA. A p-value less than 0.05 was considered significant from statistical analysis. The level of significance of the p-value within a group was determined by asterisks (*/ **/***). One asterisk (*) indicated a low level of significance, and two asterisks (**) indicated a moderate level of significance. Three asterisks (***) indicated a high level of significance. Moreover, α and β also showed a significant level of the p-value between different groups. Specifications of the significant signs are given in the table 2 below.

Table 2. Group comparisons

Intra-group comparison denoted by *
Significant comparison of zero-week untreated group with treatment and placebo groups of zero-week
Significant comparison of 4-week untreated group with treatment and placebo groups of 4-week
Significant comparison of 8-week untreated group with treatment and placebo groups of 8-week
Inter-group comparison denoted by α and β
α symbolized a significant comparison of zero-week treatment group (150mg/day) with treatment groups (150mg/day) of 4 and 8 weeks
β symbolized a significant comparison of zero-week treatment group (300mg/day) with treatment groups (300mg/day) of 4 and 8 weeks

Results

Evaluation of POMEWHITE® Intake on the vital functions of the volunteers

To assess the impact of POMEWHITE® at two concentrations (150mg/day and 300mg/day) on vital biological functions, several parameters were evaluated in all participant groups. These included serum bilirubin (direct and total), alkaline phosphatase (ALP), vitamin D levels, random glucose levels (RGL), and shock index (SI). Direct and total bilirubin concentrations were measured to examine hepatic function. As shown in Figures 1a and 1b, no significant differences were observed between untreated and treated groups. All values remained within the normal range, indicating no hepatic stress due to the supplement. Serum ALP levels, assessed at baseline, week 4, and week 8, also remained within the normal range across all groups. Figure 1c demonstrates that POMEWHITE® intake had no notable impact on ALP levels. Vitamin D levels were monitored to evaluate any potential changes in nutritional status. Figure 1d shows that vitamin D levels remained stable and comparable among all groups throughout the study period, indicating that POMEWHITE® did not affect vitamin D metabolism. Random glucose levels were consistent across all groups at weeks 0, 4, and 8. Figure 1e reflects no significant fluctuations, suggesting that glucose regulation was unaffected by POMEWHITE® supplementation. Lastly, the shock index (SI), calculated from heart rate and systolic blood pressure, remained unchanged during the study, as shown in Figure 1f. This indicates that cardiovascular stability was maintained across all groups, with or without supplementation.

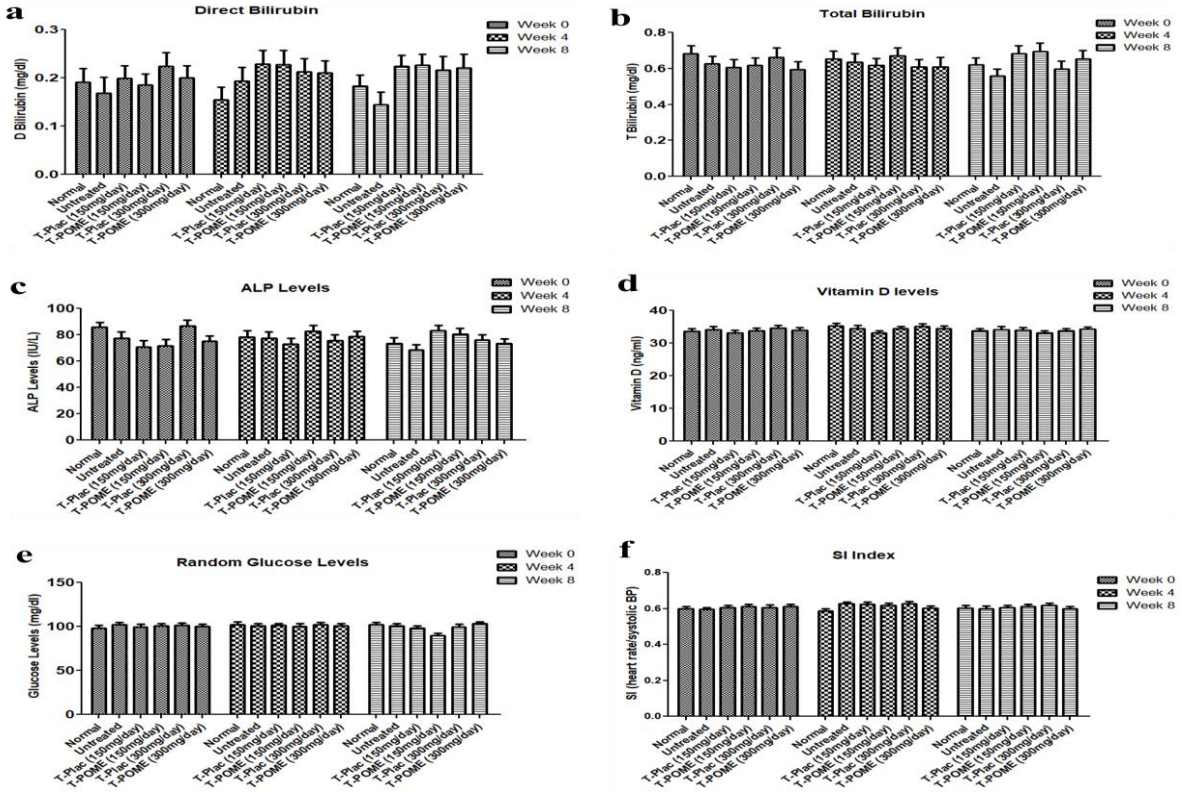

Figure 1. Vital biological function parameters were measured in all participants at baseline (week 0), week 4, and week 8. The *normal group* includes healthy individuals with Fitzpatrick skin types I or II, while all other groups consist of individuals with skin types III, IV, or V. These groups include the *untreated group* (no treatment), *T-Plac (150 mg/day),* and *T-Plac (300 mg/day)* (participants treated with rice powder at respective doses), and *T-POME*

(150 mg/day) and *T-POME (300 mg/day)* (participants treated with POMEWHITE® at respective doses). Subfigures represent the following parameters: (a) hepatic direct bilirubin concentration, (b) total bilirubin concentration, (c) alkaline phosphatase (ALP) levels, (d) vitamin D levels, (e) random glucose levels (RGL), and (f) shock index (SI), calculated as heart rate divided by systolic blood pressure (HR/SBP).

POMEWHITE® food supplement decreases skin acne

Skin Microbiota assessments

The colony count of skin microbiota was estimated by using swabbing and culturing of bacteria to evaluate the POMEWHITE® effects for the reduction of acne-producing bacteria *Propionibacterium acnes* and some other pathogens along with supporting the growth of probiotic and normal skin flora including *Staphylococcus epidermidis, Streptococcus salivarius, lactobacilli, bifidobacterium, and enterococci.* Culturing was done from week zero, four, and eight samples, and results were obtained after 48 hours of culturing. The graph (Figure 2a) reveals that at week zero number of acne-producing bacteria colonies was higher in volunteers as compared to normal controls. On week four post-POMEWHITE® treatment (Figure 2b), the acne-producing bacteria started decreasing in number, and probiotic colonies started increasing in acne patients. Eight weeks of intake of POMEWHITE® (Figure 2c) at 300mg/day dose resulted in a significant decline in acne-producing bacteria colonies compared to the untreated group, where a significant increase in probiotic/normal flora was observed. Additionally, 300 mg/day dosage of POMEWHITE® was more effective in decreasing the acne flora and increasing probiotics than 150mg/day consumption of the supplement for 8 weeks.

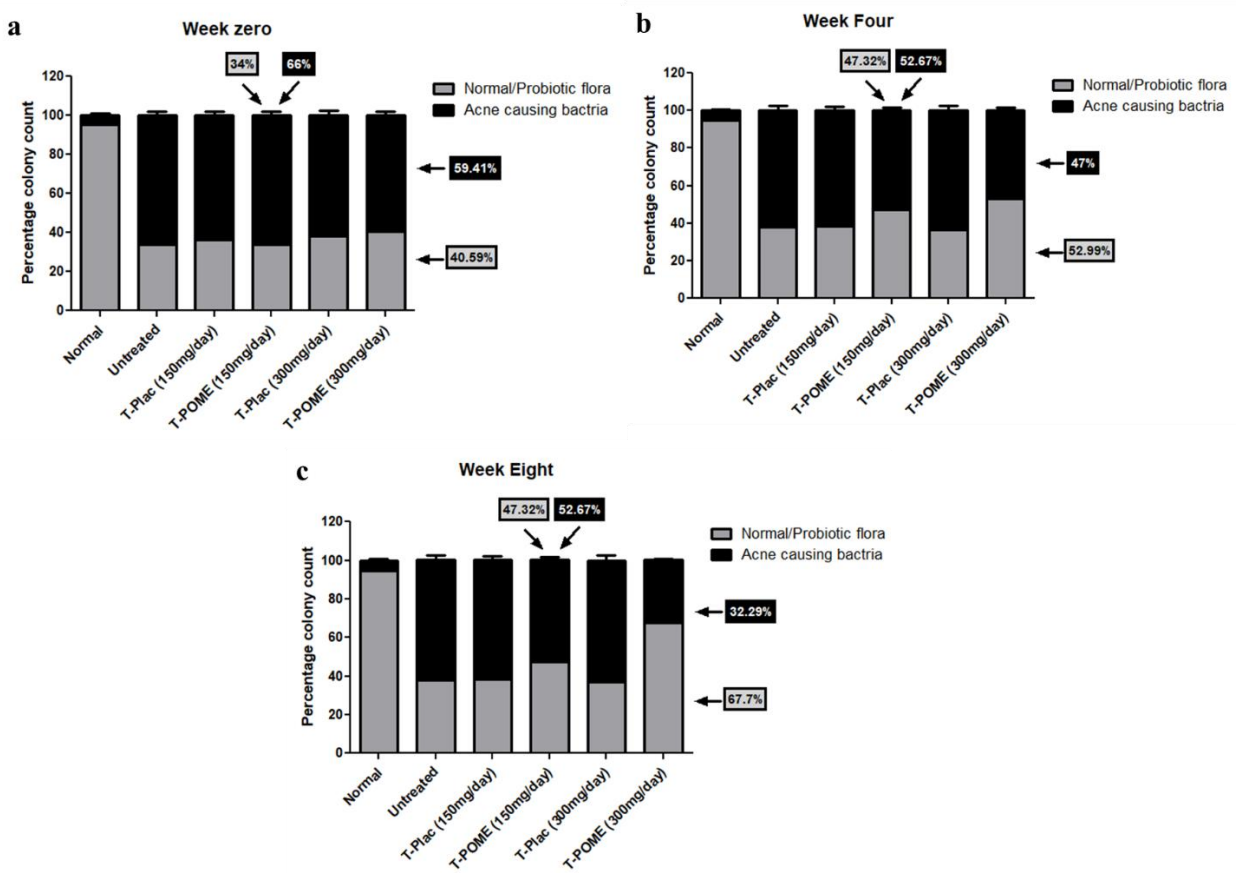

Figure 2: Relative percentage analysis of skin microbiota colony counts was conducted at three time points across different experimental groups. The *normal group* includes microbiota from healthy individuals with Fitzpatrick skin types I or II, while the other groups include individuals with skin types III, IV, or V. These consist of the *untreated group* (no treatment), *T-Plac (150 mg/day)* and *T-Plac (300 mg/day)* (treated with rice powder), and *T-POME (150 mg/day)* and *T-POME (300 mg/day)* (treated with POMEWHITE®). Subfigures represent data from (a) week 0, (b) week 4, and (c) week 8.

Decline in lipase activity

Levels of enzyme lipase were estimated by using a biochemical kit to evaluate the POMEWHITE® effects for the reduction of lipase in the blood which in turn reduces the oil production in the skin further leading to a reduction of the production of acne. The graph (Figure 3) reveals that eight weeks of intake of POMEWHITE® at 300mg/day dose results in a significant decline in lipase expression levels

compared to the untreated group, where up-regulated levels can be seen. Additionally, 300 mg/day dosage of POMEWHITE® was more effective in decreasing the lipase levels than 150mg/day consumption of the supplement for 8 weeks. Relative percentage analysis further strengthened this fact that the T- POME (300mg/day, 8 weeks) group exhibited strong anti-lipase activity hereby reducing the lipase activity and taking it closer to that of normal group levels. No significant change was seen in lipase expression in vehicle rice powder group participants.

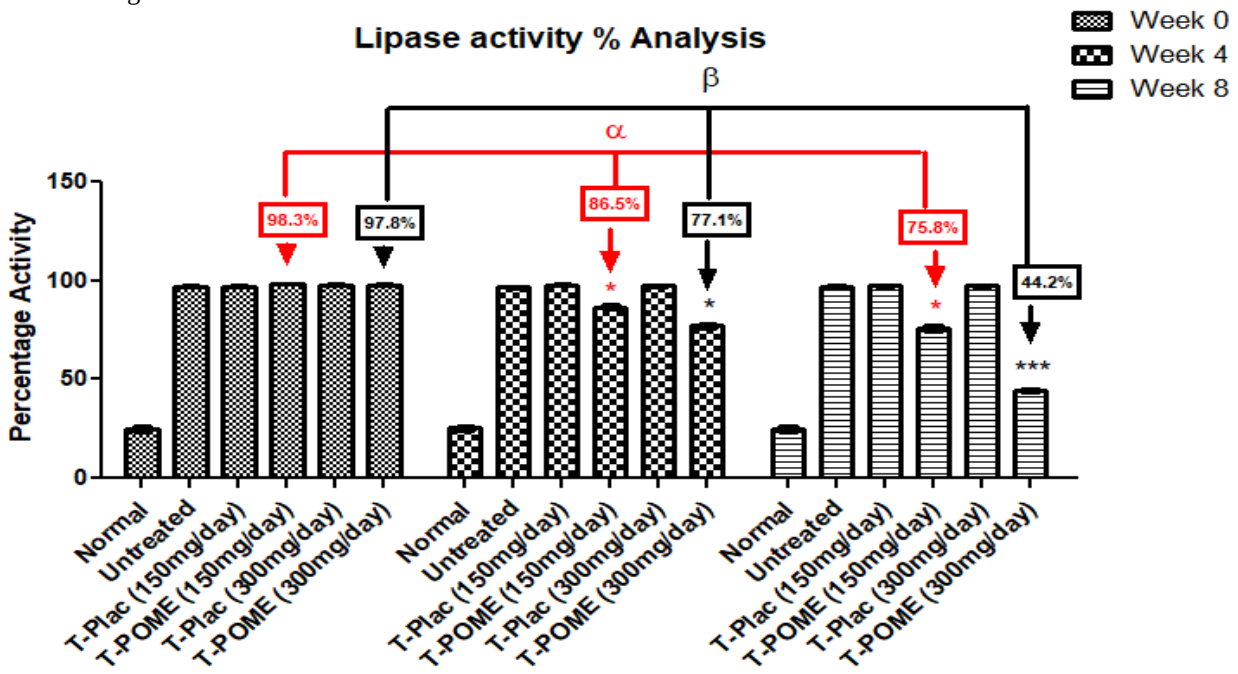

Figure 3. Percentage analysis of lipase activity: Lipase levels were determined in all subjects at weeks zero, 4, and 8 via biochemical assay. Relative percentage analysis of Lipase among different experimental groups was estimated. The normal group indicates healthy persons with skin type 1 and 2, the untreated group includes persons with Skin type 3-5 with no treatment, T-Plac (150mg/day) group includes persons skin type 3-5 treated with rice powder 150mg/day, T- POME (150mg/day) includes participants skin type 3-5 treated with POMEWHITE® 150mg/day, T-Plac (300mg/day) represents participants skin type 3-5 treated with rice powder 300mg/day and T- POME (300mg/day) includes participants skin type 3-5 treated with POMEWHITE® 300mg/day. Values were expressed as ±SEM. ($p<0.05$ consider as significant) (* shows the significant difference between treated groups and untreated control of same week) (α indicates the significance of 150mg/day groups of 4 and 8 weeks vs. zero weeks) (β indicates the significance of 300mg/day groups of 4 and 8 weeks vs. zero weeks).

Visual Analogue and Morphological quantification of skin acne

Each participant's satisfaction with the treatment was measured using a visual analogue scale (VAS) of 1 (completely unsatisfied) to 10 (completely satisfied). The graph (Figure 4a) reveals that eight weeks of intake of POMEWHITE® at 300mg/day dose results in a significant improvement in the overall well-being of the skin as compared to the untreated group, where an unsatisfied index is high among the participants. Additionally, a 300 mg/day dosage of POMEWHITE® was more effective in decreasing acne levels and improving skin than 150 mg/day consumption of the supplement for 8 weeks. Relative percentage analysis (Figure 4b) further strengthens this fact that the T- POME (300mg/day, 8 weeks) group displays a strong satisfactory index to participants. Evaluation of acne reduction of skin in pre-treatment and post-treatment groups of POMEWHITE® was done by quantification of pre-treatment and post-treatment face images with the help of Image J software. Figure 4c shows a visible decrease in acne levels of the skin after an 8-week intake of POMEWHITE® at a dose of 300mg/day for 8 weeks. The graphs further indicate that, at the 8th-week post-POMEWHITE® oral intake of 300mg/day, an apparent decrease with a numerical scale value (calculated by a dermatologist) of acne was observed as compared to before the treatment group. Moreover, the graph of relative percentage (Figure 4d) analysis extracted from the numerical scale value for acne reduction also reveals that levels of acne are markedly reduced after 300mg/day treatment for 8 weeks compared to all other groups.

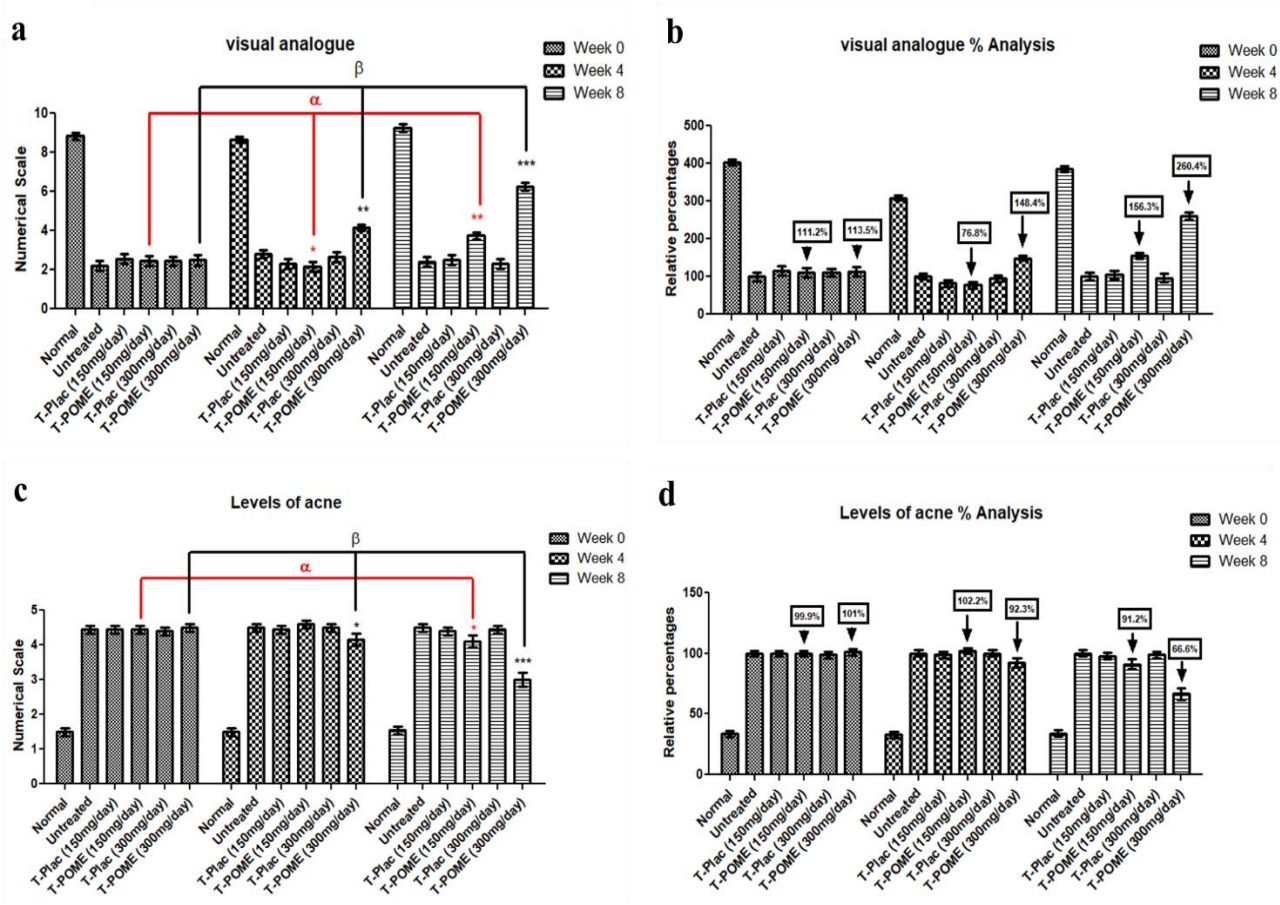

Figure 4. Evaluation of participant outcomes was conducted using (a, b) visual analogue scores based on volunteers' self-assessment of satisfaction and (c, d) numerical acne scores assessed by dermatologists. Measurements were taken at weeks 0, 4, and 8. The normal group includes healthy individuals with Fitzpatrick skin types I and II, while all other groups include individuals with skin types III–V: the untreated group received no intervention, T-Plac (150 mg/day) and T-Plac (300 mg/day) groups received rice powder, and T-POME (150 mg/day) and T-POME (300 mg/day) groups were administered POMEWHITE®. Values are presented as mean ± SEM. A p-value < 0.05 was considered statistically significant. Asterisks (*) denote significant differences between treated groups and the untreated control within the same week; α indicates the significance of 150 mg/day groups at weeks 4 and 8 compared to baseline; β indicates the same for 300 mg/day groups.5.3. Effect of POMEWHITE® food supplement on the skin stress.

POMEWHITE® curtails anti-oxidative enzymes

Superoxide dismutase is increased by skin stress. SOD levels were assessed in all participant groups at days zero (week 0), 28 (week 4), and 56 (week 8) for evaluation of the POMEWHITE® effects for the reduction of superoxide ions. The graphs in Figure 5a and b show that in the untreated groups, SOD levels were significantly increased. Additionally, the graph also indicates that POMEWHITE® at a dose of 300mg/day post-eight-weeks intake reduces the SOD levels to a considerable extent compared to the 150mg/day dose of POMEWHITE®. Furthermore, the levels of SOD for the T- POME (300mg/day) group are nearly similar to that of normal group participants. No effect of vehicle rice powder on SOD levels was observed. Relative percentage analysis also reveals that approximately a 25% decrease was observed in the week 8 post-treated (300mg/day) group compared with week 0. G6PD is decreased by reactive oxygen species (ROS). G6PD levels were assessed in all participant groups at days zero (week 0), 28 (week 4), and 56 (week 8) for evaluation of the POMEWHITE® effects for the reduction of ROS and improvement of antioxidative enzymes like G6PD. The graphs in Figure 5c and d show that in the untreated groups, G6PD levels were significantly decreased. Additionally, the graph also indicates that POMEWHITE® at a dose of 300mg/day post-eight-week intake augments the G6PD levels to a considerable extent compared to the 150mg/day dose of POMEWHITE®. Furthermore, the levels of G6PD for the T- POME (300mg/day) group are nearly similar to that of normal group participants. No effect of vehicle rice powder on G6PD levels was observed. Relative percentage analysis also reveals that approximately 3 times increase was observed in week 8 post-treated (300mg/day) group compared with week 0.

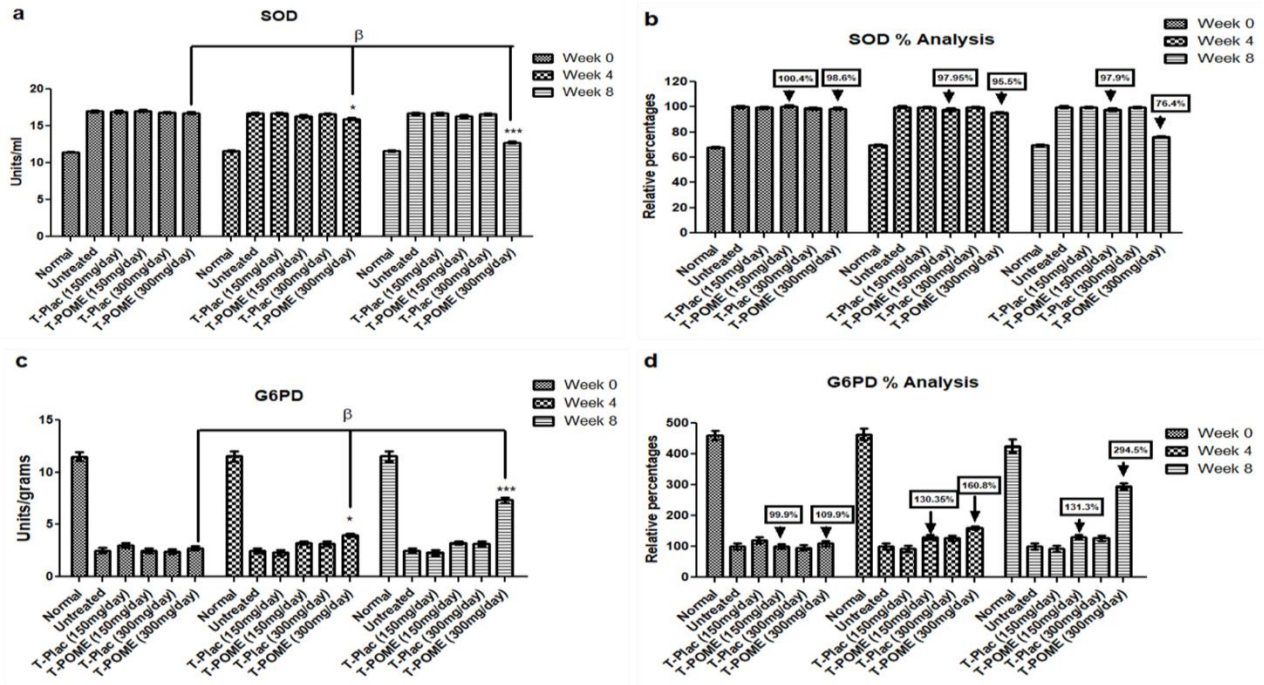

Figure 5: Assessment of oxidative stress levels in the skin was conducted by measuring (a, b) superoxide dismutase (SOD) and (c, d) glucose-6-phosphate dehydrogenase (G6PD) levels across all participant groups at weeks 0, 4, and 8. The normal group comprises healthy individuals with skin types I and II, while all other groups include individuals with skin types III–V: the untreated group received no intervention, T-Plac (150 mg/day) and T-Plac (300 mg/day) groups were given rice powder, and T-POME (150 mg/day) and T-POME (300 mg/day) groups received POMEWHITE®. Data are expressed as mean ± SEM. A p-value < 0.05 was considered statistically significant. Asterisks (*) indicate significant differences between treated groups and the untreated control within the same week; α indicates significance for 150 mg/day groups at weeks 4 and 8 compared to baseline; β indicates the same for 300 mg/day groups.

Effect of POMEWHITE® food supplement for Inhibition of tyrosinase activity

Evaluation of lightening of skin tone in pre-treatment and post-treatment groups of POMEWHITE® was done by percentage activity analysis of enzyme tyrosinase in pre-treatment and post-treatment groups. Figure 4 shows a visible increase in tyrosinase inhibition that further resulted in lightening the skin tone after an 8-week intake of POMEWHITE® at a dose of 300mg/day. The graphs in Figure 6 also indicate that, at the 8th-week post-POMEWHITE® oral intake of 300 mg/day, an apparent increase in percentage activity of inhibition of tyrosinase was observed as compared to placebo and untreated groups.

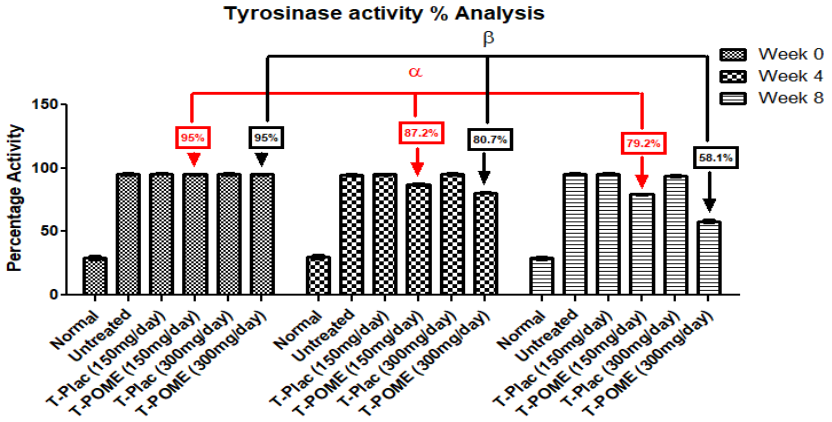

Figure 6. Tyrosinase activity after POMEWHITE® treatment. Percentage analysis of tyrosinase activity clearly shows tyrosinase inhibition in POMEWHITE® 300mg/day 8 weeks group. The normal group indicates healthy persons with skin type 1 and 2, the untreated group includes persons with Skin type 3-5 with no treatment, T-Plac (150mg/day) group includes persons skin type 3-5 treated with rice powder 150mg/day, T- POME (150mg/day)

includes participants skin type 3-5 treated with POMEWHITE® 150mg/day, T-Plac (300mg/day) represents participants skin type 3-5 treated with rice powder 300mg/day and T- POME (300mg/day) includes participants skin type 3-5 treated with POMEWHITE® 300mg/day. Values were expressed as ±SEM. ($p<0.05$ consider as significant) (* shows the significant difference between treated groups and untreated control of same week) (α indicates the significance of 150mg/day groups of 4 and 8 weeks vs. zero weeks) (β indicates the significance of 300mg/day groups of 4 and 8 weeks vs. zero weeks).

Anti-aging effects of POMEWHITE® by reduction of fine lines and wrinkles

The expert performed a clinical evaluation of the face and hands. At 0, 4, and 8 weeks, fine lines and wrinkles were assessed on the faces of volunteers. Fine lines and wrinkles have been evaluated using the numeric scale of Griffith. The scale is between 1 and 8, where 1 is without wrinkles, and 8 is the worst wrinkled skin. In Figure 7a, the graph indicates that a seeming reduction in the face's fine lines and wrinkles at 8th weeks after POMEWHITE® (300mg/day) oral consumption was observed in comparison with the untreated group. Placebo intake does not affect volunteers' facial lines or wrinkles. Graph 7b indicates the relative percentage analysis of reduction in fine lines and wrinkles in the POMEWHITE® post-treated group (300mg/day, 8 weeks) as compared to other groups. Relative percentage analysis also reveals that approximately a 45% decrease in fine-lines and wrinkles was observed in week 8 post-treated (300mg/day) group compared with week 0.

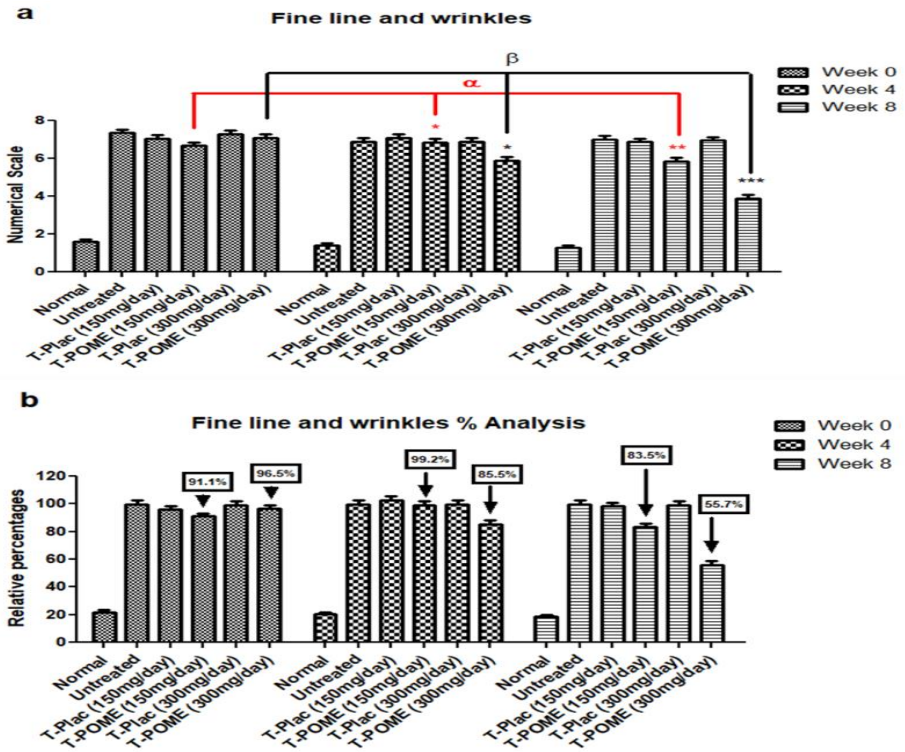

Figure 7. Clinical assessment of skin fine lines and wrinkles: a**)** Fine lines and wrinkles were assessed in all-participants groups at 0, 4, and 8 weeks according to a numerical scale to estimate the anti-aging effects of POMEWHITE®. **b)** Relative percentage analysis of fine lines and wrinkles among different experimental groups. The normal group indicates healthy persons with skin type 1 and 2, the untreated group includes persons with Skin type 3-5 with no treatment, T-Plac (150mg/day) group includes persons skin type 3-5 treated with rice powder 150mg/day, T- POME (150mg/day) includes participants skin type 3-5 treated with POMEWHITE® 150mg/day, T-Plac (300mg/day) represents participants skin type 3-5 treated with rice powder 300mg/day and T- POME (300mg/day) includes participants skin type 3-5 treated with POMEWHITE® 300mg/day. Values were expressed as ±SEM. ($p<0.05$ consider as significant) (* shows the significant difference between treated groups and untreated control of same week) (α indicates the significance of 150mg/day groups of 4 and 8 weeks vs. zero weeks) (β indicates the significance of 300mg/day groups of 4 and 8 weeks vs. zero weeks).

POMEWHITE® food supplement lessens skin inflammation

Levels of IL-4 were estimated by using ELISA to evaluate the POMEWHITE® effects for the reduction of inflammation of the skin. The graph (Figure 8a) reveals that eight weeks of intake of POMEWHITE® at 300mg/day dose results in a significant decline in IL-4 expression levels compared to the untreated group, where an upsurge in levels can be seen.

Additionally, a 300 mg/day dosage of POMEWHITE® was more effective in decreasing the IL-4 levels than 150mg/day consumption of the supplement for 8 weeks. Relative percentage analysis (Figure 8b) further strengthens this fact that IL-4 levels in the T- POME (300mg/day) group are similar to that of normal group levels. No alteration was seen in IL-4 expression in vehicle rice powder group participants. Relative percentage analysis also reveals that approximately a 52% decrease in IL-4 was observed in the week 8 post-treated (300mg/day) group compared with week 0. IFN-γ is an anti-inflammatory marker. Evaluation of the IFN-γ was done in all participants at 0, 4, and 8 weeks to check the effect of a POMEWHITE® for inflammation reduction. The graph (Figure 8c) indicates that 300mg/day dosage of POMEWHITE® for 8 weeks was more effective in improving IFN-γ as compared to POMEWHITE® at 150mg/day dosage. Whereas low levels of IFN-γ were observed in the untreated group. Moreover, relative percentage analysis (Figure 8d) reveals that the levels of IFN-γ in the T- POME (300mg/day) group are non-significantly different from the normal groups, while rice powder intake has no impact on IFN-γ levels. Relative percentage analysis also reveals that approximately 3 times improvement in IFN-γ levels was observed in the week 8 post-treated (300mg/day) group compared with week 0. This will decrease the inflammation of the lesion to a significant extent.

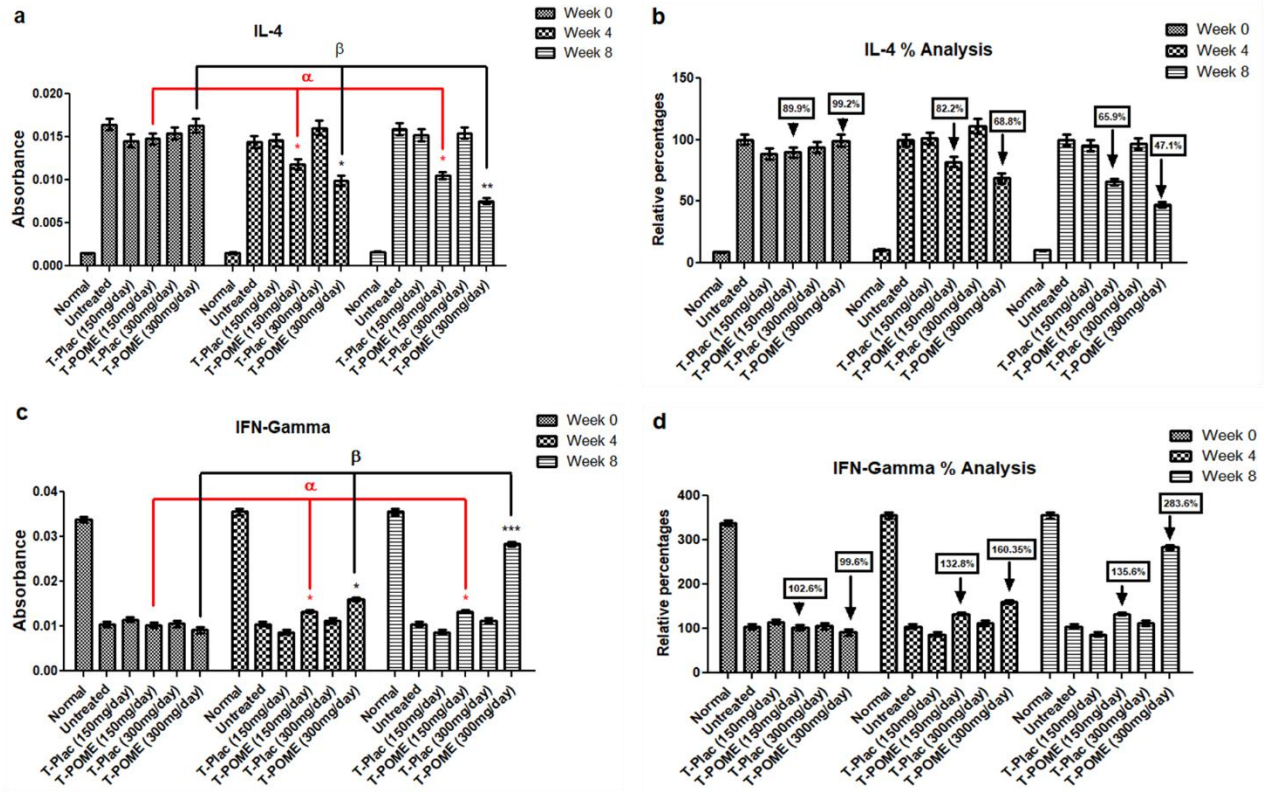

Figure 8. Clinical evaluation of skin inflammation was assessed by measuring (a, b) IL-4 and (c, d) IFN-γ levels in all participant groups at weeks 0, 4, and 8 using ELISA assays. The *normal group* includes healthy individuals with skin types I and II, while all other groups include individuals with skin types III–V: the *untreated group* received no treatment, *T-Plac (150 mg/day)* and *T-Plac (300 mg/day)* groups received rice powder, and *T-POME (150 mg/day)* and *T-POME (300 mg/day)* groups were treated with POMEWHITE®. Data are presented as mean ± SEM. Statistical significance was considered at $p < 0.05$. Asterisks (*) indicate significant differences between treated groups and the untreated control of the same week; α denotes the significance of 150 mg/day groups at weeks 4 and 8 compared to baseline; β denotes the same for 300 mg/day groups.

Discussion

Fruit color mutations are important for the genes involved in the biosynthetic pathways of flavonoids. Structural and regulatory mutations may produce missing or diminished pigmentation in fruit (Kotepong et al., 2011). One research has shown that in the fruit skins of the white pomegranate, no anthocyanins were detected whose unique formula could be found in POMEWHITE®. Expression profiling showed that other than anthocyanin synthase biosynthesis, other genes showed significant expression levels in white pomegranate. The inhibition or restricted production of anthocyanin synthase is one potential cause of the loss of anthocyanin in white pomegranate (Zhao et al., 2015). The indication that the "white" anthocyanine less phénotype of pomegranate, might result in lower expression of its genetic pathway for color production (Ben-Simhon et al., 2015) anticipated that flavonoids that are upstream intermediates of that pathway would accumulate including proanthocyanins.

Probiotics are live microorganisms that provide a health benefit to the host. During the past few decades, there has been renewed interest in probiotics not only regarding digestive health but also in the management of inflammatory diseases. Most commonly formulated as fermentation products, probiotics counter pathogenic bacteria (Kober and Bowe, 2015). Through basic science and animal and human clinical trials, the evidence is growing for the use of probiotics in the treatment of acne. Acne formation is dependent upon several processes, including follicular hyperkeratinization, excess sebum production, Propionibacterium acnes colonization, and an inflammatory cascade (Nole et al., 2014). POMEWHITE® has enhanced prebiotic content that can also support the growth of probiotics as shown by the results and inhibits the growth *p. acnes*. At the basic science level, probiotics have been shown to directly inhibit P. acnes through the production of antibacterial proteins.

More recent studies evaluating the role of oral probiotics on acne have largely been published in foreign journals (Kober and Bowe, 2015). POMEWHITE® further minimizes acne by decreasing lipase activity. POMEWHITE® has its effects for the reduction of lipase in the blood which in turn reduces the oil production in the skin further leading to a reduction of the production of acne. Relative percentage analysis strengthens this fact that the T- POME (300 mg/day, 8 weeks) group exhibits strong anti-lipase activity hereby reducing the lipase activity and taking it closer to that of normal group levels. Tyrosinase is an enzyme that controls the melanogenesis (Wood et al., 1995). POMEWHITE® post-treated group exhibits a low percentage activity of tyrosinase showing the inhibition of enzymes thus decreasing the melanin content in the skin and once the melanin is decreased, the skin becomes whitened. Many shreds of evidence suggest that human skin microbiota help combat pathogenic microorganisms and retain microbiome homeostasis (Wang et al., 2014). POMEWHITE® pomegranate could potentially increase the growth of probiotics present in the skin. This property is imparted by the presence of more prebiotics in AL pomegranate (Li et al., 2015). Healthy, normal skin exhibits a slightly acidic pH in the range of 4.2-5.6, which aids in the prevention of pathogenic bacterial colonization, regulation of enzyme activity, and maintenance of a moisture-rich environment (Mauro, 2006); however, after the age of 70, the pH of the skin rises significantly, stimulating protease activity (Hachem et al., 2003). Probiotic metabolism frequently produces acidic molecules, lowering the pH of the surrounding environment (Cinque et al., 2010), as seen with Lactobacilli producing free fatty acids (FFAs) and conjugated linoleic acid (CLA) during the fermentation process (Yadav et al., 2007). Theoretically, therefore, the use of probiotics may work to restore the normal skin pH and consequently return protease activity levels closer to those seen in young, healthy skin. This shows the probiotic increase due to POMEWHITE® administration could potentially have anti-aging effects. A recent clinical trial demonstrated that oral antibiotics and probiotics might provide synergistic benefits, specifically for inflammatory acne (Jung et al., 2013). Several strains of Lactobacillus also demonstrate anti-inflammatory properties (Kober and Bowe, 2015). Probiotics also inhibited spontaneous and stress-induced reactive oxygen species (ROS) formation (Benson et al., 2012; Jensen et al., 2010). We are well aware that ROS and oxidative stress play a role in acne, making probiotics an intriguing finding with potential benefits for the acne patient (Bowe and Logan, 2010). Prebiotics from POMEWHITE® increase probiotics which in turn lessens ROS.

Conclusion

The unique natural formula of POMEWHITE® augments the increase of probiotics levels in acne-damaged skin not only eliminating acne but also contributing to repairing the damaged skin and enhancing the skin tone. POMEWHITE® further minimizes acne by decreasing lipase activity. POMEWHITE® treatment group expresses low levels of ROS and inflammation making POMEWHITE® a potential option for the treatment of inflammation due to acne damage and improving skin health.

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Declarations

Authors' Contributions

H.M designed the study and collected the literature, S.J.A performed the statistical analysis, wrote the protocol, A.S wrote the first draft of the manuscript, A.A.S, and B.A has done the analyses of the study and proofread the manuscript draft. All authors read and approved the final manuscript.

Conflict of Interest

The authors have declared no conflict of interest.

Declaration of Interest Statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

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Ethics approval and consent to participate

Not applicable

Consent for Publication

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