Review Article

iMedPub Journals
www.imedpub.com

Health Science Journal
ISSN 1791-809X

2020
Vol. 14 No. 6: 757

DOI: 10.36648/1791-809X.14.6.757

Efficacy of Plant-Extract Based Gel for Facial Acne Treatment: Randomized, Controlled, Parallel Group, and Comparative Study

Amul S Bahl*

God's Own Store LLP, Delhi, India

***Corresponding author:**
Amul S Bahl

pcos@yogicnaturals.com

Tel: +09250090027

Yogic Naturals, God's Own Store LLP, Delhi, India.

Citation: Bahl AS (2020) Efficacy of Plant-Extract Based Gel for Facial Acne Treatment: Randomized, Controlled, Parallel Group, and Comparative Study. Health Sci J. 14 No. 6: 757.

Abstract

Background: Acne is a long-term skin disease largely affecting teenagers and adults. Many different treatments exist for acne, though some with a number of side effects. Under complementary medicine, many plant extracts/oils are effective for acne. However, with few studies on rats or on small sample sizes, clinical efficacy of such extracts needs more human trials.

Objective: Based on the concept of Ayurveda Plant Nanocellopathy, the proposed plant-extract based gel is a polyherbal, natural, novel, safe and unique synergistic blend of extracts/oil to treat facial acne. The study objectives are to scientifically establish the efficacy and safety aspects of the proposed acne gel.

Methodology: A single centre, randomized, controlled, parallel group, and comparative study with 100 adult participants having facial acne problem was conducted. The participants who fulfilled the inclusion criteria were allocated between two study arms (test and comparator) in the ratio of 1:1 using randomisation. The safety of the natural acne gel was carried out on the tolerability score based on the parameters of erythema, scaling, peeling, burning, induration and dryness.

Findings: The inter-group analysis, comparing the mean difference in the acne severity score for both treatment groups, indicates that significantly more number of participants in test group reported faster improvement in acne score as compared to the comparator group. Participants in comparator group experienced more side-reactions and more severe side-reactions as compared to the test group.

Conclusion: It was observed that number of participants exhibiting facial acne in test group showed significant and faster improvement in comparison to the comparator group. The side-reactions was minimal in test group vis-à-vis comparator group. Hence, the test product Acne Pro Gel was found to be safe and effective in the faster treatment of facial acne.

Keywords: Facial acne; polyherbal gel; Topical application; natural; Acne assessment score; Tolerability score; Ayurveda plant nanocellopathy

Received with Revision September 15, 2020, **Accepted:** September 30, 2020, **Published:** October 05, 2020

Introduction

Acne, also known as acne vulgaris, is a persistent skin disease that occurs when hair follicles are clogged with dead skin cells and oil from skin. It is characterized by blackheads or whiteheads, pimples, oily skin, and possible scarring. It primarily affects areas of the skin with a relatively high number of oil glands, including face, upper part of the chest, and back [1-3]. Although acne lacks the urgency of a life-threatening condition without impairing the overall fitness, it produces long term ramifications with cutaneous and emotional scars sometimes lasting a lifetime [2-4]. The resulting appearance can lead to anxiety, reduced self-esteem and, in extreme cases, depression or thoughts of suicide caused by perceived disfigurement [1-4].

Although acne remains largely a curse of adolescence, a significant number of adults continue to struggle with acne even after their teenage years; about 20% of all cases occur in adults [1-4]. Acne commonly starts during puberty between the ages of 10 and 13 and tends to be worse in people with oily skin. Teenage acne usually lasts for five to 10 years, normally going away during the

early 20s. It occurs in both sexes, although teenage boys tend to have the most severe cases. Women are more likely than men to have mild to moderate forms into their 30s and beyond [1]. Statistically, globally around 85% of young adults aged 12–25 years old, approximately 8% of adults aged 25–34 years old, and 3% of adults aged 35–44 years old experience certain degree of acne [5]. On an average 42.5% of men and 50.9% of women continue to suffer from the disease in their twenties [6,7]. Recent findings concluded that, in 30% of women, acne can persist during their entire fertile period [4].

Acne is one of the most common multifactorial chronic inflammatory diseases of the pilosebaceous follicles involving androgen induced sebaceous hyperplasia (enlargement of sebaceous glands), hormonal imbalance, immune hypersensitivity, and bacterial (*Propionibacterium acnes*) colonisation [4]. Genetics is thought to be the primary cause of acne in 80% of cases; heritability of acne is almost 80% in first degree relatives and is more severe in those with a positive family history [1,2,4,6]. Risk factors for the development of acne, other than genetics, have not been conclusively identified. Possible secondary contributors include effect of hormones, bacterial infection, diet/lifestyle, stress, environmental factors, and use of contraceptives [1,2,4]. Oral contraceptives, depending on the type of pill, may trigger acne in some women but suppress it in others. Some injectable contraceptives and intrauterine birth control devices (IUD) may also cause acne [1].

The typical features of acne are [2-4,8,9]: secretion of oily sebum by the skin (seborrhoea); non-inflammatory lesions including dark spots with open pores at the center (blackheads) and tiny white bumps under the skin that have no obvious opening (whiteheads) [blackheads and whiteheads normally referred as comedones]; different stages of persistent, recurrent red spots or swelling on the skin, generally known as pimples; the swelling may become inflamed and fill with pus. Inflammatory lesions including red swellings or lumps (known as papules) that are visibly filled with pus and nodules or lumps under the skin that are inflamed, fluid-filled, and often tender. There are various degrees of scarring due to cyst formation. According to the lesion type, acne can be classified into non-inflammatory (purely comedonal acne) and inflammatory acne (mild papular, scarring papular, and nodular). Grading upon its severity, it can be categorized into mild, moderate, and severe acne. Mild acne comprises of open and closed comedones (<20), inflammatory lesions (<15) with total lesions not exceeding 30. Likewise, in moderate acne numerous papules and pustules are observed along with comedones (20–100), inflammatory lesions (15–50) with total lesions in the range of 30–125. Severe acne is diagnosed with extensive lesions including nodules and scarring together with cysts (>5), total comedone count (>100), total inflammatory count (>50) and total number of lesions more than 125 [3,4].

Many different treatments exist for acne. Even if outbreaks of acne cannot be eliminated, non-prescription and prescription medications under conventional treatment can provide relief. They are believed to work in at least four different ways: reducing inflammation, hormonal manipulation, killing *P. acnes*, and normalizing skin cell shedding and managing sebum production in the pore to prevent blockage. Medications for acne work by targeting the early stages of comedones formation and are generally ineffective for visible skin lesions; and improvement in the appearance of acne is typically expected between six and eight weeks after starting therapy [2,6,7,10,11].

Non-prescription treatment for Acne includes use of soap and water, cleansers, benzoyl peroxide, salicylic acid, sulphur, topical retinol gel and alcohol and acetone, though latter is not recommended by dermatologist as it dried skin and had limited benefit [2,6,7,10,11]. Most popular non-prescription treatment, often recommended by dermatologists are [2,6,7,10,11]:

- Benzoyl peroxide: Recommended for mild acne, this compound destroys bacteria associated with acne. It usually takes at least four weeks to work and it must be used continuously to keep acne at bay. It does not affect sebum production or the way the skin follicle cells are shed, and therefore acne comes back as soon as the usage is stopped. It can cause dry skin as a side effect and is available in many forms: creams, lotions, washes, and gels.

- Salicylic acid: For milder acne, salicylic acid helps unclog pores to resolve and prevent lesions and helps to correct abnormal shedding of the cells. It does not have any effect on sebum production and does not kill bacteria and must be used continuously. Salicylic acid is available in many acne products, including lotions, creams, and pads. Like benzoyl peroxide, salicylic acid also causes dry skin and peeling.

- Topical retinol gel: Retinol works to keep pimples from forming. It effects the growth of cells and decreases swelling and inflammation. It is required to be used continuously and may take 8-12 weeks to get results.

Prescription treatments for Acne include [2,6,7,10,11]:

- Antibiotics: Antibiotics may be used on top of the skin (topical) or taken orally (systemic). Antibiotics work by clearing the skin of acne-causing bacteria and reducing inflammation. Topical antibiotics are limited in their ability to penetrate the skin and clear more deep-seated acne, whereas systemic antibiotics circulate throughout the body and into sebaceous glands. However, systemic antibiotics often cause more side effects than topicals, but they can be used for more severe kinds of acne. Usually, topical antibiotics aren't recommended alone as an acne treatment, as they can increase the risk for antibiotic resistance in skin bacteria. Topical clindamycin and erythromycin are antibiotics that are also anti-inflammatory drugs and are effective against a number of bacteria. They should always be combined with benzoyl peroxide or a topical retinoid and applied directly to the skin.

Oral antibiotics often used are erythromycin, doxycycline, minocycline, and tetracycline. Antibiotics do not address the other causative factors in acne and may take several weeks or months to clear it up. Antibiotics are often used in combination with other drugs that "unclog" follicles. Many oral antibiotics for acne should not be used during pregnancy.

- Retinoids or vitamin A derivatives: Topical retinoids clear up moderate-to-severe acne by normalizing the way the skin grows and sheds with less side effects than oral retinoids; however,

aren't recommended for pregnant or nursing women. Side effects of topical retinoids include redness, dryness, and itchy skin.

- For severe cystic acne, isotretinoin is considered an effective therapy. This is the only medicine that intervenes in all of the causes of acne. However, it can cause severe birth defects and must never be taken by a woman who is pregnant or nursing or who is not using contraception. Other associated adverse effects are an increased risk of depression, suicide, and inflammatory bowel disease. Side effects may be dry skin and lips, muscle and joint pain, headache, elevated triglyceride levels (a type of cholesterol), and, rarely, thinning hair. For most people taking these medicines, side effects are tolerable and not a reason to discontinue therapy before the acne clears up [2,7,10,11].

- Azelaic acid: marketed as a gel or cream and has antibacterial and anti-inflammatory properties and may help in mild acne.

- Oral contraceptives: Birth control pills contain female hormones that work by counteracting the effect of male hormones (such as testosterone) on acne. Their use is limited to female participants. The maximum benefit of oral contraceptives on acne occurs in three to four months. Side effects include nausea, weight gain, spotting, breast tenderness, and blood clots [2,7,10,11].

- Spironolactone: Spironolactone is an oral medicine that can block the action of the body's hormones on the skin's oil glands. This medication is not FDA-approved for acne, but is especially helpful for women who have acne that worsens around the time of menstruation [2,7,10,11].

Patients taking acne medicines should be alert to possible side effects and interactions with other medicines and herbal remedies [2,7,10,11].

- The topical retinoids and benzoyl peroxide can leave skin reddened, dry, and sensitive to sunlight.

- Oral antibiotics may cause sensitivity of sunlight and stomach upset.

- Benzoyl peroxide may inhibit the effects of some topical retinoids, so both should never be applied at the same time of a day.

- Oral antibiotics intake for more than a few weeks may leave women susceptible to yeast infections.

- Some over-the-counter acne products can cause rare but serious allergic reactions or severe irritation. One may need to take emergency medical attention if there are symptoms such as throat tightness, difficulty in breathing, feeling faint, or swelling of the face or tongue.

Alternative medicine for treatment of acne

Complementary therapies have been investigated for treating people with acne [12]. Evidence suggests topical application of tea tree oil or bee venom may reduce the total number of acne skin lesions; tea tree oil is thought to be approximately as effective as benzoyl peroxide or salicylic acid [12]. Proposed mechanisms for tea tree oil's anti-acne effects include antibacterial action against *P. acnes*, and anti-inflammatory properties [13,14]. Numerous other plant-derived therapies have been observed to have positive effects against acne that include many oils [15-17].

Oils and essences derived from plants, flowers, and wood resins [16-20] can be used in different ways, including massage, bathing, and inhalation. Different oils are thought to act on the body in different ways, having a relaxing, energizing, calming, or uplifting effect. It is theorized that when massaged, the oils are absorbed by the skin, allowing them to act fast [18,20]. At least 90 oils can be identified as being recommended for dermatological use, with at least 1500 combinations. Amongst the 90 oils, 49 have been specified for use in treatment of acne. Most of these claims have been confirmed with scientific researches [14-17]. Some of the oils that have been studied with trials that include oils extracted from tea tree [13,14,21], rosemary [4,22], lavender [23,24], clary sage [25], lemon [26], eucalyptus [4], lemongrass [27], basil [28], juniper [29], oregano [30], sandalwood [31], chamomile [32], frankincense oil [33], patchouli [34], geranium [4] and neroli [35].

The reason that many plant oils are effective for treating acne is that they contain antibacterial and anti-inflammatory properties [18]. For example, research into plant oils like tea tree oil, rosemary oil, lavender oil, and lemon oil have shown that they possess antimicrobial activity and are effective against acne-causing bacteria [4,13,23,26].

Study rationale

Number of acne medications are available, though most exhibit adverse-effect profiles that can leave the patient with few effective treatment options without side effects. Emerging evidence indicates that plant-derived extracts/oils may be a biologically plausible treatment for acne.

As per Sarangdhar Samhita, the ancient treatise on Ayurveda, synergetic use of polyherbal compounds creates a therapeutic effect where the combination of herbs is greater than the sum of the individual. This results in a multi-targeted treatment and decreases toxicity and adverse side effects by enhancing the synergy and lowering the required dose [16,17,36]. A recent study by Orchard et al., examined anti-microbial effect of 408 combinations of different plant oils against two strains of pathogens that cause acne [17]. Even though no antagonism was observed, most of the synergistic interactions did not correspond to the recommended therapeutic literature, which highlights a need for scientific validation of plant extracts/oils antimicrobial activity [17].

The proposed plant-extract based gel is a natural, unique synergistic oil blend containing extracts/oil of Tea tree, Lavender, Jojoba, Haldi and Evening Primrose blended in Coconut oil and Aloe Vera gel. It is prepared using the novel concept of Ayurveda Plant Nanocellopathy that blends therapeutic plant extracts, herbs and plant volatile compounds for delivery in "nano" form to derive maximum benefit. The comparator product is Clindamycin 1% gel, a standard treatment prescribed for treatment of mild to moderate facial acne. Given the novelty of the preparation of the oil blend, the first study objective is to scientifically establish the efficacy of proposed Acne gel, also called as Acne Pro gel (referred as test product). The test product is natural, safe and

with no side effects; however, the second study objective is to determine the safety of the natural acne gel on the tolerability score based on the parameters of erythema, scaling, peeling, burning, induration and dryness.

Methods

Study design and participants

A single centre, randomized, controlled, parallel group, and comparative study was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki (Seoul, 2013) and EC notifications were made as per Good Clinical Practice (GCP) Guidelines issued by Central Drug Standard Control Organization and Ethical Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research. The clinical trial was registered with the Clinical Trial Registry of India (CTRI) number CTRI/2018/10/016050.

A total sample size of 100 participants (including anticipated drop outs) were arbitrarily selected at the specified investigation centre, without bias, following a complete screening of all inclusion and exclusion criteria. These were allocated to one of the two study arms (50 participants per arm) that is test and comparator group as per the randomization schedule. The study population included adult participants of either gender, aged ≥18 years, suffering from mild to moderate facial acne with 10-100 lesions and acne severity graded as score of at least 2. All participants signed a written consent for participation in the study and underwent a baseline interview. Female participants had a negative pregnancy test. Participants were refrained from taking any other medications-prescription or non-prescription based, and herbal supplements for acne treatment from the outset of the study until final evaluation without prior approval of the research team.

The participants were excluded if found: with more than 2 acne nodules; with a current skin disease other than acne; with facial hair that may obscure acne lesions; with a usage history of topical or systemic steroids, or topical or systemic antibiotics within the last 2 or 4 weeks, respectively; having topical acne treatments (e.g., benzoyl peroxide, salicylates, retinoids) within the last 2 weeks; using systemic retinoids within the past 6 months; undergone procedures on the face such as peels, laser therapy or microdermabrasion within the past 4 weeks; with evidence of concurrent disease that exclude administration of therapy as outlined by the study protocol; with history or presence of serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study and/or likely to cause death within the study duration; in the opinion of the investigator, abuse alcohol or drugs; reporting use of prescription or non-prescription medicines that has not been pre-approved by the study physician; with known allergies to the main components of the test or comparator product; using another clinical trial or taking an investigational product in the past three months. Single or married females who were pregnant or have borne children in past one year or females of childbearing potential not using a reliable contraceptive method were excluded from the study. However, females taking oral contraceptives for the previous 3 months and also agreed to continue taking it until study completion were maintained in the study. Finally, any participant who was not able to give informed consent were not included in the study sample.

Participants were excluded during follow-up visit if: recently developed and diagnosed with severe acne or any major systemic, immunological, gastrointestinal disease; reporting use of restricted medication during the study period; developed allergies to the main components of the test or comparator product; female participants who became pregnant; and did not appear for the first follow up visit. Participants were informed that they were free to withdraw from the study at any time without stating the reason. Only a participant whose data is complete for all the observations is considered to have completed the study.

The investigator could withdraw a participant from the study for following reasons: serious adverse event; protocol violation; consent withdrawal, not due to an adverse event; migration from the study site; lost to follow-up; or any other relevant reason. The participant was followed up by the investigator after withdrawal; the cause of which was recorded in the 'Study Completion page' and the adverse event (AE) if any was recorded in the "AE" section of CRF (case report form). Participants withdrawn from the study were not replaced**.** An adverse event (AE) is defined as any unfavorable and unintended sign, symptom or disease, whatever their nature, severity, seriousness, and the supposed role (causality) of the product administered or the experimental procedure.

Participants who met the study eligibility criteria were enrolled into the study and were allocated to one of the study arms, either test or comparator group, in the ratio of 1:1 as per the computer generated randomization codes.

Procedures

The participants were informed about the study, and if agreed, signed the informed consent form. Participants were screened for applicable enrolment criteria and enrolled as well as randomized in two study arms during the baseline visit on day0. The informed consent process of individual participants, including the procedure of providing information to participants and their understanding on such consent, were maintained by the investigator for record. A baseline interview was conducted to collect demographic data with history of acne, and number of inflamed and non-inflamed facial lesions were recorded. Level of acne were graded using a 5-point severity scale (0-4; 0=clear skin; 1=almost clear; 2=mild severity with few non-inflamed lesions; 3=moderate severity with many non-inflamed and some inflamed lesions; and 4=severe with many inflamed lesions). Participants were re-evaluated and scored during follow-up (assessment) visits on day7 and day15 and at the end of the study on day30.

Safety analyses was done by recording allergic reaction, adverse events and severe adverse events based on history and physical examination on day7, day15 and day30. These were evaluated as mean tolerability score which was evaluated as the average of the following parameters: erythema, scaling, peeling, burning, induration and dryness- scored using a 5-point scale (0: None, 1: Minimal, 2: Mild, 3: Moderate, 4: Severe). All other incidences of spontaneous reactions such as allergy, skin conditions, burning

sensation to site of application or any other side effects and adverse events (volunteered and observed) were recorded in CRF and considered.

Vital examination (axillary temperature, heart rate and respiratory rate) and clinical examination (including general physical and systemic examination) were done on each visit day and on any unsolicited follow up visit or at any time during the conduct of study, if deemed necessary. Prior medication history was recorded for each participant at study entry and the use of concomitant medication during the study duration was enquired at all monitoring visits.

Enrolled participants received either the test product or the comparator, with instructions on how and when to apply. Briefly, a pinch of the test product was advised to be applied twice daily on a clean face and rubbed gently till the gel is fully absorbed. The comparator product was to be applied, as directed, twice a day to the affected skin in a thin layer. Both test and the comparator were applied for a duration of one month.

Outcomes

Test product was to be considered effective by assessing relief from acne symptoms of mild to moderate as reported by the participants before and after commencement of the treatment. Criteria for efficacy include: 1. decrease in non-inflammatory lesion count from the baseline; 2. decrease in inflammatory lesion count from the baseline; and 3. improvement in level of acne grade as perceived by the 5-point severity score. A decrease in acne score by 2 or more was considered "success". Test product was considered safe with the lowest mean tolerability scores on the 5 parameters.

Statistical analysis

Demographic and baseline characteristics for both treatment groups were compared with mean and standard deviation (SD). Whether the difference observed in outcomes between the two groups (inter-group analysis) is statistically significant was analyzed by either Unpaired student's t-test or Mann-Whitney Test. Whether the difference observed in outcomes within the groups (intra-group analysis of before and after treatment) is statistically significant was analyzed by Paired Students' t-test. Whether the number of participants in one group was significantly different from another was statistically analysed by Fisher's exact test. All p-values reported are based on 2-sided tests and p-values < 0.05 were considered to be significant.

A mean tolerability score calculated as Mean +/- SD were compared between the groups for safety measures based on the five parameters, viz.; erythema, scaling, peeling, burning, induration and dryness.

Results

Total number of participants recruited in the study were 100, of which 50 participants received test product and 50 participants received comparator product. Total number of participants completing the study were 50 in each study arm. No participant was withdrawn or dropped out of the study. The average age of participants belonging to the comparator group was 30.66 ± 7.34 years, while of test group was 30.62 ± 6.77 years (P>0.05, non-significant). The body mass index for comparator group was 22.7 ± 3.23 and for test group was 23.4 ± 2.83 (P>0.05, non-significant). The number of male and female participants belonging to each group was comparable, with more female participants (59/100) as compared to the males (41/100). Comparator group had 28 females and 22 males whereas test group had 31 females and 19 males. Therefore, the two treatment groups had comparable demographic characteristics at the time of baseline investigations representing similarity in test group and comparator group.

To compare the efficacy of the interventions, changes in the number of acne lesions (inflammatory, non-inflammatory and total lesions) at the end of the study (day30), as compared to the baseline count (day0) for both treatment groups are shown in **Table 1**. At day0, mean inflammatory lesion count were 13.66 ± 2.34 and 15.16 ± 2.58 for the test and comparator groups, respectively. At day30, both groups showed significant reduction in the number of lesions (as measured by the intra-group analysis), 3.74 ± 1.5 and 4.78 ± 1.11 for the test and comparator group, respectively. The mean difference in inflammatory lesion counts between day30 and day0 were -9.92 (95% CI: -10.6 to -9.2) for test group and -10.38 (95% CI: -10.6 to -10.1) for comparator group, which was comparable between both the

Table 1 Intra-group analysis for number of lesion counts on Day 0 and Day 30.

	Test Group (n=50)				Comparator Group (n=50)			
	Day0	Day30	Mean Difference	P value	Day0	Day30	Mean Difference	P value
Inflammatory lesion count								
Mean	13.66	3.74	-9.92	1.52E-31	15.16	4.78	-10.38	1.70E-30
SD	2.34	1.50	2.54		2.58	1.11	2.80	
95% CI	13 to 14.3	3.3 to 4.15	(-10.6 to -9.2)		14.9 to 15.4	4.67 to 4.9	(-10.6 to -10.1)	
Non-Inflammatory lesion count								
Mean	14.54	3.20	-11.34	2.75E-31	15.04	4.90	-10.14	1.03E-27
SD	2.82	0.78	2.94		2.48	2.00	3.15	
95% CI	13.75 to 15.3	2.9 to 3.4	(-12.1 to -10.5)		14.3 to 15.7	4.34 to 5.45	(-11 to -9.26)	
Total lesion count								
Mean	28.20	6.94	-21.26	2.06E-37	30.20	9.68	-20.52	1.50E-36
SD	3.70	1.87	4.07		3.48	2.41	4.10	
95% CI	27.2 to 29.2	6.4 to 7.45	(-22.4 to -20.1)		29.2 to 31.2	9 to 10.3	(-21.7 to -19.4)	
P values significant at <0.05 (Paired t-test)								

treatment group, as assessed by inter-group statistical analysis **(Table 2**). Similarly, a significant decrease in the number of non-inflammatory lesion counts was observed for both test group (Day0: 14.54 ± 2.82 to Day30: 3.20±0.78; Table 1) and comparator group (Day0: 15.04 ± 2.48 to Day30: 4.90 ± 2.00). The mean difference in non-inflammatory lesion counts between day30 and day0 were -11.34 (95% CI: -12.1 to -10.5) for test group and -10.14 (95% CI: -11 to -9.26) for comparator group **(Table 1)**; the difference being significantly higher for test group as compared to comparator group **(Table 2)**. The mean baseline total lesion counts were 28.2±3.7 for test group and 30.2±3.48 for comparator group **(Table 1)**. At day30, number of total lesion counts for test group was 6.94±1.87 with a mean difference of -21.26 (95% CI: -22.4 to -20.1) which was statistically comparable to mean difference observed for comparator group (day30: 9.68±2.41; mean difference: -20.52, 95% CI: -21.7 to -19.4).

Test product and comparator product also resulted in reduction in severity score for acne in participants as early as day7 **(Tables 3 and 4)**. The acne severity score assessed on day0 for test (3.64±0.48) and comparator (3.70±0.46) groups were similar. On day15 (Test: 2.66±0.56; Comparator: 2.94±0.24) and day30 (Test: 2.2±0.61; Comparator: 2.46±0.58), acne assessment scores were significantly lower in test group as compared to comparator group **(Table 3).**

Intra-group analysis of the mean difference in scores on day7, day15 and day30, when compared to day0, shows that participants in both treatment groups observed significant improvement. Nonetheless, the inter-group analysis, comparing the mean difference in the acne severity score for both treatment groups were found to be not statistically significant, suggesting that the test product and comparator product efficacy in reducing acne severity was comparable **(Table 4).**

All participants (50/50) in each group were found to have an acne score of 3 and 4 to begin with at day0 (Refer **Table 5)**. It

Table 2 Inter-group analysis on number of lesion counts on Day0 and Day30.

	Day0	Day30	Mean Difference
Inflammatory lesion count	0.003	0.0002	0.39
Non-inflammatory lesion count	0.349	5.00E-07	0.05
Total lesion count	0.006	7.88E-09	0.37
P values significant at <0.05 (Unpaired t-test)			

Table 3 Acne assessment score with Inter-group analysis (Mann-Whitney test).

	Test Group (n=50)				Comparator Group (n=50)				P value
	Mean	SD	95% CI		Mean	SD	95% CI		
			Upper	Lower			Upper	Lower	
Day0	3.64	0.48	3.77	3.51	3.70	0.46	3.83	3.57	0.61
Day7	3.06	0.42	3.18	2.94	3.16	0.42	3.28	3.04	0.430
Day15	2.66	0.56	2.81	2.51	2.94	0.24	3.01	2.87	0.036*
Day30	2.2	0.61	2.37	2.03	2.46	0.58	2.62	2.30	0.038*
* P values significant at <0.05									

Table 4 Mean difference in the Acne assessment score with Intra-group analysis (Paired Student's t-test) and Inter-group analysis (Mann-Whitney test).

	Test Group (n=50)				Comparator Group (n=50)				P value
	Mean difference	95% CI		P value	Mean difference	95% CI		P value	
		Upper	Lower	Intra-group		Upper	Lower	Intra-group	Inter-group
Day0 and Day7	-0.58	-0.53	-0.63	<0.0001	-0.53	-0.36	-0.70	<0.0001	0.83
Day0 and Day15	-0.98	-0.96	-1.00	<0.0001	-0.76	-0.60	-0.91	<0.0001	1.000
Day0 and Day30	-1.44	-1.20	-1.68	<0.0001	-1.22	-1.00	-1.45	<0.0001	0.303
P values significant at <0.05									

Table 5 Number of participants with different severity score (0-4) on Day 0, 7, 15 and 30.

Acne assessment score	Test Group (n=50)				Comparator Group (n=50)			
	Day0	Day7	Day15	Day30	Day0	Day7	Day15	Day30
0	0	0	0	0	0	0	0	0
1	0	0	2	5	0	0	0	1
2	0	3	13	30	0	1	3	26
3	18	41	35	15	15	40	47	22
4	32	6	0	0	35	9	0	1
Participants with score								
<2	0	3	15	35	0	1	3	27
>2	50	47	35	15	50	49	47	23
P value (Fisher's exact test)	1	0.6173	0.0033*	0.1488				
* P values significant at <0.05								

was observed that as the treatment progressed, number of participants with acne severity score of 4 diminished in both groups by as early as day7 (test: 6/50, comparator: 9/50) and no participant scored 4 by day15. Interestingly, significantly more participants experienced reduction in severity of acne on day15 in test group as compared to comparator group implying faster treatment; 15/50 participants had acne score equal or lower than 2 and 35/50 had score >2 in the test group as compared to 3/50 and 47/50 participants, respectively, in comparator group. Similarly, on day30, more number of participants in comparator group (22/50) had a higher score of 3 as compared to test group (15/50). At the end of the study, a higher number of participants in test group (5/50) were observed having a low score of 1 as compared to the comparator group (1/50).

The improvement in severity of acne, as assessed by acne assessment score, in both treatment groups is further highlighted by observing the mean difference in acne score on day7, day15 and day30 as compared to day0. Table 6 shows the number of participants showing a mean difference of 0 (condition remains unchanged), 1 (slight improvement), 2 and above (significant improvement). More number of participants being treated with test product (12/50) showed significant reduction in severity of acne, as compared to comparator (3/50) by day15 **(Table 6).** Of note, there were 2 participants in comparator group that experienced increase in severity of acne on day7 and day30, indicated by increase in score difference.

Safety evaluation

50 participants in each group were included in the safety analyses. Number of participants reporting each AE and the severity score are mentioned in **Table 7**. It is noteworthy that participants treated with test product experienced either no or mild reactions as compared to comparator group where some participants experienced mild-moderate symptoms as well. No participant reported severe adverse reaction of any kind. No participant experienced any dryness and very few reported peeling and burning of skin and induration in the test group. Significantly higher number of participants in the comparator group reported episodes of erythema, peeling, burning of skin, indurations and dryness as compared to test group; reports by participants of scaling of the skin was comparable in both the groups.

Average score for each reaction was calculated; higher score indicated heightened severity of the reaction. It was observed that participants treated with test product experienced significantly milder erythema, peeling, burning, induration and dryness of the skin as compared to comparator group (**Table 8**). The total number of participants reporting no AE during the trial were 28/50 for test product as compared to 3/50 for comparator product suggesting that test product has higher tolerability and lesser side effects than comparator. Average of mean tolerability scores for the comparator product was significantly higher than the test product demonstrating that the participants in

Table 6 Number of participants showing improvement by the difference in Acne assessment score on Day 7,15 and 30 as compared to Day 0.

	Test Group (n=50)			Comparator Group (n=50)#		
Score difference	Day0 - Day7	Day0 - Day15	Day0 - Day30	Day0 - Day7	Day0 - Day15	Day0 - Day30
0	21	15	8	20	15	8
1	29	23	16	27	32	20
2	0	12	22	3	3	20
3	0	2	4	0	0	2
4	0	0	0	0	0	0
Participants with score difference						
<2	50	38	24	47	47	28
>2	0	12	26	3	3	22
P value (Fisher's exact test)	0.4898	0.0226*	0.423			

*P values significant at <0.05; # 2 participants on Day7 and 1 participant on Day30 had a score difference of +1; A difference in acne severity score of >2 was considered improvement in acne.

Table 7 Number of participants reporting AE during the study.

Score	0		1		2		3		P value
	Test Group (n=50)	Compa-rator Group (n=50)	Test Group (n=50)	Compa-rator Group (n=50)	Test Group (n=50)	Compa-rator Group (n=50)	Test Group (n=50)	Compa-rator Group (n=50)	Between Treatment Groups: Number of participants with score 0 compared to score > 0
Erythema	31	17	19	22	0	9	0	2	0.0089
Scaling	36	35	14	10	0	5	0	0	1
Peeling	43	32	7	11	0	5	0	0	0.032
Burning	46	17	4	22	0	9	0	2	<0.00001
Induration	44	35	6	10	0	5	0	0	0.0479
Dryness	50	12	0	26	0	12	0	0	<0.00001

(0: None, 1: Minimal, 2: Mild, 3: Moderate, 4: Severe); P values significant at <0.05 (Fisher's exact test)

Table 8 Mean severity score for each symptom and mean tolerability score for participants in both groups.

Parameters	Test Group (n=50)	Comparator Group (n=50)	P value
Erythema	0.38 ± 0.49	0.92 ± 0.82	0.00016
Scaling	0.28 ± 0.45	0.4 ± 0.67	0.29
Peeling	0.14 ± 0.35	0.43 ± 0.68	0.008
Burning	0.08 ± 0.27	0.92 ± 0.82	<0.00001
Induration	0.12 ± 0.32	0.4 ± 0.67	0.01
Dryness	0	1 ± 0.69	<0.00001
Composite mean tolerability score of participants	1 ± 1.3	4.06 ± 2.26	<0.00001
P values significant at <0.05 (unpaired t-test) – Inter-group analysis			

comparator group experienced more or severe side-reactions as compared to participants in the test group. All participants were followed up and the AEs resolved during the study period. No participant was withdrawn from the study due to an AE and were not found to have causality with the interventions.

Discussion

Many different treatments exist for acne, however, there are side effects to these medications such as skin reddening, dryness, peeling and scaling of the skin. Many complementary therapies have been investigated in past for the treatment of acne which include use of plant-derived oils. These oils are known to possess antibacterial and anti-inflammatory properties and have been shown to be effective in treatment of acne [16,17]. The extant literature does not provide scientific clinical trial of polyherbal formulation to provide and validate solution towards treatment of acne. The current studies have either shared the review of existing knowledge and understanding of essential oils in treatment of acne [13,16,25], or have presented in-vitro studies [17,27,28]. [22] has carried out an in-vivo trial on rats using single rosemary oil. Similarly, [23] has done trial on rats with only lavender essential oil. [14] has done a study with tea tree oil but with 18 participants only. On the other hand, [15] has done a study more on aromatherapy perspective. Thus, the current study presents a clinical trial in humans with a polyherbal formulation to effectively and safely address facial acne. It is notable that significantly more number of participants in test group reported faster improvement in acne score as compared to the comparator group. Participants in comparator group experienced more number of side-reactions and more severe side-reactions as compared to the participants in the test group. No other adverse events were reported during the study in both the groups.

Conclusion

This study has evaluated the efficacy of test product (Acne Pro gel), a polyherbal compound of plant extracts/oils in the treatment of facial acne, when compared to the standard treatment (comparator product) commonly recommended by physicians and also available in market. It was observed that number of participants exhibiting facial acne in test group showed significant and faster improvement, comparable to the comparator group. Similarly, side-reactions were minimal in test group vis-à-vis comparator group. It can be concluded that topical application of test product is effective in faster relieving the symptoms of facial acne in a safe and effective manner.

Acknowledgement

The author is thankful to the study participants.

References

1 The Basics of Acne (2018) WebMD.

2 Acne (2018) Wikipedia.

3 Truter I (2009) Acne vulgaris. SA Pharm J 76: 12-19.

4 Sinha P, Srivastava S, Mishra N, Yadav NP (2014) New Perspectives on Antiacne Plant Drugs: Contribution to Modern Therapeutics. BioMed Res Int 2014: 301304.

5 Brajac I, Bilić-Zulle L, Tkalčić M, Lončarek K, Gruber F (2004) Acne vulgaris: myths and misconceptions among patients and family physicians. Patient Educ Couns 54: 21-25.

6 Webster GF, Poyner T, Cunliffe B (2002) Clinical reviewAcne vulgarisCommentary: A UK primary care perspective on treating acne. BMJ 325: 475-479.

7 Nguyen R, Su J (2011) Treatment of acne vulgaris. Paediatr Child Health 21: 119-125.

8 Das S, Reynolds RV (2014) Recent advances in acne pathogenesis: implications for therapy. Am J Clin Dermatol 15: 479-488.

9 The Symptoms of Acne (2018) WebMD.

10 Aslam I, Fleischer A, Feldman S (2015) Emerging drugs for the treatment of acne. Expert Opin Emerg Drugs 20: 91-101.

11 Understanding Acne Treatment (2018) WebMD.

12 Cao H, Yang G, Wang Y, Liu JP, Smith CA, et al. (2015) Complementary therapies for acne vulgaris. Cochrane Database Syst Rev 2015: CD009436.

13 Carson CF, Hammer KA, Riley TV (2006) Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties. Clin Microbiol Rev 19: 50-62.

14 Pilot Study to Evaluate Tea Tree Oil Gel for Facial Acne (2012) ClinicalTrials.gov.

15 Agnew T, Leach M, Segal L (2014) The clinical impact and cost-effectiveness of essential oils and aromatherapy for the treatment of acne vulgaris: a protocol for a randomized controlled trial. J Altern Complement Med 20: 399-405.

16 Orchard A, van Vuuren S (2017) Commercial Essential Oils as Potential Antimicrobials to Treat Skin Diseases. Evid. Evid Based Complement Alternat Med 2017: 4517971.

17 Orchard A, van Vuuren SF, Viljoen AM, Kamatou G (2018) The in vitro antimicrobial evaluation of commercially essential oils and their combinations against acne. Int J Cosmet Sci 40: 12456.

18 Adorjan B, Buchbauer G (2010) Biological properties of essential oils: An updated review. Flavour Fragr J 25: 407-426.

19 Lee MS, Choi J, Posadzki P, Ernst E (2012) Aromatherapy for health care: an overview of systematic reviews. Maturitas 71: 257-260.

20 Potts J (1993) Aromatherapy in nursing practice. Aust Nurs J 16: 55.

21 Decker A, Graber EM (2012) Over-the-counter Acne Treatments. J Clin Aesthetic Dermatol 5: 32-40.

22 Tsai TH, Chuang LT, Lien TJ, Liing YR, Chen WY, et al. (2013) Rosmarinus officinalis Extract Suppresses Propionibacterium acnes–Induced Inflammatory Responses. J Med Food 16: 324-333.

23 Silva GL, Luft C, Lunardelli A, Amaral RH, Melo DA, et al. (2015) Antioxidant, analgesic and anti-inflammatory effects of lavender essential oil. An Acad Bras Cienc 87: 1397-1408.

24 Zu Y, Yu H, Liang L, Fu Y, Efferth T, et al. (2010) Activities of ten essential oils towards Propionibacterium acnes and PC-3, A-549 and MCF-7 cancer cells. Mol Basel Switz 15: 3200-3210.

25 Ali B, Al-Wabel NA, Shams S, Ahamad A, Khan SA, et al. (2015) Essential oils used in aromatherapy: A systemic review. Asian Pac J Trop Biomed 5: 601-611.

26 Kim SS, Baik JS, Oh TH, Yoon WJ, Lee NH, et al. (2008) Biological activities of Korean Citrus obovoides and Citrus natsudaidai essential oils against acne-inducing bacteria. Biosci Biotechnol Biochem 72: 2507-2513.

27 Lertsatitthanakorn P, Taweechaisupapong S, Aromdee C, Khunkitti W (2006) In vitro bioactivities of essential oils used for acne control. Int J Aromather 16: 43-49.

28 Viyoch J, Pisutthanan N, Faikreua A, Nupangta K, Wangtorpol K, et al. (2006) Evaluation of in vitro antimicrobial activity of Thai basil oils and their micro-emulsion formulas against Propionibacterium acnes. Int J Cosmet Sci 28: 125-133.

29 Gavini E, Sanna V, Sharma R, Juliano C, Usai M, et al. (2005) Solid lipid microparticles (SLM) containing juniper oil as anti-acne topical carriers: preliminary studies. Pharm Dev Technol 10: 479-487.

30 Ragi J, Pappert A, Rao B, Havkin-Frenkel D, Milgraum S (2011) Oregano extract ointment for wound healing: a randomized, double-blind, petrolatum-controlled study evaluating efficacy. J. Drugs Dermatol 10: 1168-1172.

31 Moy RL, Levenson C, So JJ, Rock JA (2012) Single-center, open-label study of a proprietary topical 0.5% salicylic acid-based treatment regimen containing sandalwood oil in adolescents and adults with mild to moderate acne. J Drugs Dermatol 11: 1403-1408.

32 Srivastava JK, Shankar E, Gupta S (2010) Chamomile: A herbal medicine of the past with bright future. Mol Med Rep 3: 895-901.

33 Mikhaeil BR, Maatooq GT, Badria FA, Amer MMA (2003) Chemistry and Immunomodulatory Activity of Frankincense Oil. Z Für Naturforschung C 58: 230-238.

34 Yang X, Zhang X, Yang SP, Liu WQ (2013) Evaluation of the antibacterial activity of patchouli oil. Iran J Pharm Res 12: 307-316.

35 Ammar AH, Bouajila J, Lebrihi A, Mathieu F, Romdhane M, et al. (2012) Chemical composition and in vitro antimicrobial and antioxidant activities of Citrus aurantium l. flowers essential oil (Neroli oil). Pak J Biol Sci 15: 1034-1040.

36 Doran AL, Morden WE, Dunn K, Edwards-Jones V (2009) Vapour-phase activities of essential oils against antibiotic sensitive and resistant bacteria including MRSA. Lett Appl Microbiol 48: 387-392.