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Formulation and evaluation of a topical gel containing *Rosemary* oil for the treatment of acne vulgaris

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Abstract
Acne vulgaris is a common skin condition that affects individuals of all ages. Conventional treatments for acne can have various side effects and may not be effective for all individuals. This study aimed to investigate the effect of *rosemary* extract in the treatment of acne vulgaris. The study was conducted on a group of individuals with acne vulgaris who were treated with *rosemary* essential oil in a gel product twice daily for a period of four weeks. The efficacy and safety of *rosemary* oil were evaluated by measuring the reduction in acne lesions and improvement in overall skin condition. The results of the study showed that *rosemary* oil was effective in reducing acne lesions and improving overall skin condition in individuals with acne vulgaris. The study also found that *rosemary* oil was well-tolerated and had minimal side effects. These findings suggest that *rosemary* extract could be a safe and effective natural alternative for managing acne vulgaris.

Keywords: Acne vulgaris, conventional treatments, *rosemary* essential oil (reo), *rosemary* extract, well tolerated, side effects, safe, effective, managing

1. Introduction
Acne vulgaris has been identified as the single largest contributor to skin disease burden worldwide [1], affecting almost 9.4% of the global population [2]. It affects adolescents and young adults aged 12 to 24 years, although it can persist or develop in adulthood as well. Acne vulgaris presents with a diverse range of clinical manifestations ranging from mild to severe, with primary lesions that include comedones, papules, pustules, nodules, cysts, and chronic inflammation that can lead to subsequent scarring, hyperpigmentation, or erythema [3-4]. The distribution of acne lesions can also vary, with the face being the most commonly affected area; however, lesions can occur on the chest, back, neck, shoulders, and other areas of the body [4]. The impact of acne extends to negatively affect quality of life, body satisfaction, self-esteem, and has been associated with increased rates of anxiety, depression, and even suicidal ideation [5]. Acne vulgaris is an inflammatory disorder involving the pilosebaceous unit (PSU), with pathogenesis that involves the following interrelated mechanisms: hyperseborrhea, hyperkeratinization of the follicular infundibulum, colonization by *Cutibacterium acnes* or *C. acnes* (formerly *Propionibacterium acnes*), and inflammation in pilosebaceous units [6]. Oxidative stress has also been shown to contribute to the disruption of the skin microbiota and the involved inflammatory response [7].
Treatment of acne aims to control and clear existing acne lesions, prevent permanent scarring as much as possible, limit the duration of the disorder and minimize morbidity [8]. Topical therapy is preferred in the treatment of acne because of the increased exposure of pilosebaceous units to treatment and decreased systemic absorption [8]. Topical treatments can be broadly classified into retinoids and antibiotics. Retinoids, or vitamin A derivatives are a principal element in the treatment and maintenance of acne vulgaris [9–11]. Retinoids generally exert comedolytic and anti-inflammatory actions by affecting the expression of genes involved in cellular proliferation, differentiation, and inflammation in the skin [12, 13]. Benzoyl peroxide (BPO) is another topical treatment for acne due to various mechanisms; BPO is an oxidizing agent with bactericidal activity against *C. acnes* [14]. Topical antibiotics are widely employed in the treatment of acne vulgaris, most commonly available are clindamycin and erythromycin. Topical antibiotics exhibit the highest efficacy in treating inflammatory lesions, but exhibit limited effectiveness against non-inflamed lesions; moreover, the usage of topical antibiotics can potentially cause the development of bacterial resistance, with the efficacy of erythromycin in particular declining due to antibiotic resistance [15].

The use of topical treatments in acne is greatly impeded by the incidence of side effects. Treatment discontinuation due to tolerability issues is considered a major hindrance to acne treatment. Retinoids, BPO, and topical antibiotics are strongly associated with erythema, desquamation, itching, burning, and skin sensitivity [16].

Systemic therapy is often necessary in moderate-to-severe acne as well as in acne that is refractory to topical therapies [17]. The prevention of social embarrassment and psychological impairment in acne patients is also considered as an indication for systemic therapy [8]. Isotretinoin, antimicrobials, and hormonal drugs are commonly used therapeutic agents. Isotretinoin, a systemic retinoid, is reserved for severe nodular or inflammatory acne [18]. The most serious risk of isotretinoin is its dose-independent teratogenic potential, especially in the first trimester of pregnancy. Major fetal malformations, premature birth, or spontaneous abortion are highly likely to occur when systemic retinoids are administered during pregnancy [19, 20]. Oral antibiotics are effective treatments for moderate-to-severe inflammatory acne cases where previous topical treatments have been ineffective or when acne has spread extensively over the body's surface area. The most common antibiotics in acne treatment are tetracyclines, macrolides, and trimethoprim/sulfamethoxazole (co-trimoxazole) [21]. Systemic antibiotics work by targeting the bacteria that cause acne, specifically *Cutibacterium acnes*. Oral antibiotics used in the treatment of acne are associated with side effects ranging from skin reactions to systemic events. Frequently reported side effects to include gastrointestinal disturbances such as nausea, vomiting, diarrhea, vaginal candidiasis, rash, pruritus, photosensitivity, and hepatitis [16, 21]. Antimicrobial resistance is a huge concern with the use of antibiotics [22-24]; in addition to the development of resistant *C. acnes* strains, prolonged treatment using antibiotics can disrupt the microbiome leading to a higher risk of respiratory tract infections, and antibiotic-resistant commensal flora at other body sites [22-24]. Hormonal therapy is another treatment option for women with acne and a good alternative to isotretinoin in some cases; it is used to control the effect of androgens on the sebaceous glands [25]. Hormonal agents may be categorized into androgen receptor blockers, adrenal androgen production blockers, and ovarian androgen production blockers; androgen receptor blockers consist of spironolactone, cyproterone acetate, chlormadinone, and flutamide, while adrenal androgen production blockers include glucocorticoids, and ovarian production blockers include gonadotropin-releasing hormone (GnRH) agonists and oral contraceptives [26]. Oral contraceptive pills are the most common form of hormonal therapy used to treat acne in women and are associated with menstrual irregularities, breast tenderness, and gastrointestinal disturbances such as nausea and vomiting [16]. Spironolactone, an androgen receptor blocker that inhibits 5α-reductase, is often used in combination with oral contraceptives; spironolactone is especially effective in cases of inflammatory acne [8]. However, spironolactone is associated with hyperkalemia, hypotension, menstrual irregularities, and breast tenderness [16, 26].

One potential solution to address the limitations of conventional acne treatments is to explore alternative treatment strategies for acne vulgaris with novel therapeutic approaches, such as phytotherapy, which has shown promising results in managing acne without relying on antibiotics. Phytotherapy may offer effective and safer treatment options, particularly in cases where antibiotic resistance is a concern [27, 28]. *Rosemary* or *Salvia rosmarinus* (commonly also known as *Rosmarinus officinalis*) is a perennial herbaceous plant belonging to the *Lamiaceae* family [29]. *Rosemary* is an evergreen shrub that can grow up to 1-2 meters in height with dark green, needle-like leaves that are about 2-4 cm in length and a distinct, woody aroma; the flowers of *rosemary* are small, blue, and appear in clusters at the tips of the branches [30]. *Rosemary* contains a variety of biologically active compounds, including terpenes, essential oils, and phenolic compounds. The proportions of the active compounds may differ depending on the plant's growth stage and bioclimatic conditions [31, 32].

The proposed mechanisms of action of *S. rosmarinus* extract in treating acne include its anti-inflammatory, antioxidant, and antimicrobial properties [31, 33, 34]. As mentioned earlier, inflammation plays a key role in the development of acne, and *rosemary* contains compounds that have been shown to have anti-inflammatory effects. In particular, rosmarinic acid, carnosol, and carnosic acid have been shown to inhibit the production of inflammatory cytokines and reduce inflammation [35-37]. REO demonstrates significant anti-inflammatory activity and was found to reduce TNF-α, IL-1, and IL-6 [38]. The anti-inflammatory activity of *rosemary* essential oil can be mainly attributed to 1, 8-cineole, camphor, and α-pinene [33]. Several DPPH assays indicate that REO is a potent free radical scavenger with significant antioxidant activity, which can be attributed to chavibetol, camphor, verbenone, borneol, and 1, 8-cineole [38, 39]. REO was found to prevent lipid peroxidation, which could potentially decrease oxidative stress from the oxidation of sebum [39]. *Rosemary* displays antimicrobial activity against a broad spectrum of bacteria, including bacteria commonly associated with acne, such as *C. acnes*, *S. aureus*, and *S. epidermidis*, and against multidrug-resistant bacteria [40-42]. REO is rich in 1, 8-cineole, camphor, camphene, and α-pinene can disrupt the cell wall of *C. acnes* and lead to a discharge of cell contents, with minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) comparable to erythromycin [43].

Topical dosage forms are preferred in acne treatment to selectively deliver drugs to the site of acne lesions and to minimize adverse effects of conventional dosage forms [44]. Topical dosage forms used in the treatment of acne include creams, gels, lotions, foams, and solutions [18]. Gels are common in the treatment of acne; the high-water content (70-99%) makes gels less likely to leave a residue or greasy feeling on the skin, which can be a problem with creams and ointments [45]. A benefit of formulating essential oils as a gel is the penetration-enhancing effect, allowing active phytochemicals to penetrate the skin more effectively [46]. *Rosemary* extract has been found to promote percutaneous absorption in topical gels [47]. The porous structure of hydrogels also provides a matrix for drug loading and protects the volatile oils from degradation at the same time [48]. Essential oils can be irritating to the skin if applied directly, so formulation as gel allows for controlled drug delivery, thereby reducing the risk of irritation [45]. Lastly, gels are easier to formulate in comparison with other semi-solid dosage forms [44].

The purpose of this study is to prepare a dermal product containing *Salvia rosmarinus* essential oil extract for acne treatment and apply the product on a sample of volunteers suffering from varying acne severities and determine its efficacy through treatment evaluation.

2. Materials and Methods

2.1 Materials

Carbopol 940 was purchased from Sigma-Aldrich, Germany. Triethanolamine, Ethanol, and other excipients were purchased from Merck, Germany. All other chemicals and reagents were of analytical grade and used as received.

2.2 Extraction of Essential Oil

Fresh *rosemary* leaves were procured from a reliable source and identified at the herbarium of Damascus University Faculty of Agriculture. The leaves were collected and dried in a well-ventilated area to remove moisture. They were made sure to be clean, dry, and free from any contaminants. The leaves were weighed and divided into batches to be extracted through hydro distillation using a Clevenger-type system, as recommended in British Pharmacopoeia 2008. In this method, steam is passed through the plant material, causing the essential oils to vaporize and carry over with the steam. The steam and essential oil vapors are then condensed, collected in a receiver, and separated. The oil was then filled in dark glass bottles and stored in a refrigerator with a temperature 8 ˚C until use.

2.3 Analysis of Essential Oil

Following extraction, analysis of the *rosemary* essential oil was conducted using gas chromatography-mass spectrometry (GC-MS) technique. An Agilent MS-GC instrument model 5937 was used to identify the main components of the oil and determine the concentrations of the major compounds in the essential oil. The results of the analysis will be included in the results and discussion section.

2.4 Preparation of the Gel

The gels were prepared using the jellifying agent Carbopol 940 in aqueous medium. The gel has been fixed with suitable materials to give it a creamy texture and appropriate excipients have been added to stabilize the efficacy of the product. *Rosemary* essential oil was then added to yield 3% w/w formulation. The chosen formulation of the gel was determined through experiment to ensure acceptable pH, homogenous appearance, stability, patient acceptance, and ease of application.

2.5 Participants, Sampling, and Interventions

Participants suffering acne vulgaris were recruited by publishing notices for inclusion into the study online. Volunteers approached the researchers and were enrolled as study participants if they met the inclusion/exclusion parameters following a careful interview by the researchers. A total of 52 subjects were assessed for eligibility, of which 15 were eligible for participation in the experiment.

Inclusion criteria

- Age between 18 to 30 years old.
- Diagnosis of acne vulgaris.
- Willingness to participate in the study and follow the instructions.
- Not taking any topical or systemic acne medications for the past month.

Exclusion criteria

- Pregnancy or lactation.
- Known allergy to *rosemary* or any of its components.
- Any history of chronic dermatological disorders, including autoimmune diseases.
- Current use of antibiotics, hormonal therapy, or any other acne treatment.

Furthermore, the Comprehensive Acne Severity Scale (CASS) was employed to determine the severity of acne vulgaris in patients. On this scale, mild acne is characterized by involving less than half of the area with numerous comedones, papules, and pustules; in moderate acne, more than half of the region is involved with the abovementioned lesions; in severe acne, the entire area is affected by the abovementioned lesions [49]. The experiment was set for four weeks with weekly arranged follow-up meetings for case evaluation and data collection. Participants were supplied with a freshly prepared 3% *rosemary* oil gel and were instructed to apply the gel twice daily for four weeks, and were advised not to utilize prescribed or over-the-counter anti-acne medicines during the study period and minimize their sun exposure time. The method of administration was to rinse their faces, dry gently with a soft towel, and apply a thin gel's film to the affected area via a cotton swab and leave it on. Each swab was used only once and then discarded according to medical waste management guidelines. Participants were also guided on the proper storage of the gel.

3. Results and Discussion

In this study, the use of *rosemary* essential oil was investigated as a potential treatment for acne vulgaris. Prior to using within formulation, components of the essential oil were analyzed, and the results are summarized in Table 1.

Table 1: Composition of *rosemary* essential oil

Primary Constituents	%
Camphor	37.74
Borneol	12.6
1, 8-cineole	9.61
Bornyl acetate	5.96
Limonene	3.24
A-pinene	2.46
Camphene	2.32
A-terpinene	1.87
B-myrcene	1.78
3-carene	1.43
Linalool	1.43
B-pinene	1.12
Total	81.56

A total of 15 participants of both sexes aged 17-25 with evident acne lesions were enrolled in the study. Assessed through CASS, five subjects (33.33%) were found to have mild acne, eight subjects (53.33%) had moderate acne, and two subjects (13.33%) had severe acne. The participants in this study applied the gel twice daily for a period of 4 weeks (30 days) with no concomitant acne treatment and underwent an assessment every week. Table 2 summarizes all the observations noted. Observations on the acne lesions were made based on changes from baseline condition in inflammation on the lesions, change in number and size of comedones, pustules, and papules. A decrease in any of the aforementioned parameters was considered case improvement. Treatment was stopped when signs of inflammation, comedones, pustules, and papules were no longer visible.

All 15 participants who completed the study, showed improvement in their acne condition within 4 weeks of treatment (Table.2).

Table 2: Results of the experiment

No. Subj.	Sex	Age	Place of Infection	Severity	Response to treatment (% improvement)	Final Evaluation	Estimation after Week 1	Estimation after Week 2	Estimation after Week 3	Estimation after Week 4	Before treatment	After treatment
1	F	23	Right cheek	Moderate	100%	Very Good	Less inflammation on lesions. No change in the no. of papules, and comedones decrease.	Decreased comedones and papules, improvement in overall skin.	Clear of acne. Treatment stopped.	-	Moderate	Complete disappearance
2	F	21	Chin	Mild	100%	Excellent	Improvement after 4 days with a decrease in papule size and inflammation.	Clear of papules and comedones and inflammation. Acne scars remain. Treatment stopped.	-	-	Mild	Complete disappearance
3	F	22	Right cheek, forehead	Mild	80%	Very Good	Little improvement.	Decrease in no. of comedones and papules, improvement of inflammation.	Decreased no. of comedones and papules, inflammation disappears.	Clear of acne on forehea. Right cheek has 3-4 papules.	Mild	Very Mild
4	F	21	Left cheek	Moderate	70%	Good	A general decrease in papule size. Acne lesion still shows signs of inflammation.	Improvement with less inflammation and no. of papules still the same.	Papule size and inflammation decreased, no change in papules.	No improvement	Moderate	Mild
5	F	19	Forehead	Moderate	50%	Good	Less inflammation on lesions. Only comedones decrease.	Decrease in inflammation and number of comedones.	No improvement.	No improvement	Moderate	Mild to Moderate
6	M	20	Cheeks	Severe	80%	Very Good	Less inflammation (redness) on lesions. Only comedones decrease.	Decrease in inflammation and number of comedones.	Decrease in inflammation, comedones and papules.	A greater decrease in inflammation, less comedones and papules	Severe	Mild
7	F	21	Left cheek	Mild	100%	Excellent	Acne cleared after 7 days of treatment. Treatment stopped.	-	-	-	Mild	Complete disappearance
8	F	22	Forehead, chin, right cheek	Moderate	70%	Very Good	Slightly less inflammation (redness) on lesions. No change in the no. of papules, comedones decrease.	Decrease in inflammation and redness, papules getting smaller. No visible pustules.	Notable improvement on forehead and chin lesions. Slightly less on right cheek.	No visible signs of inflammation in general. Right cheek has 5-6 small papules	Moderate	Very Mild
9	M	17	Cheeks	Severe	70%	Very Good	Less inflammation (redness) on acne lesions. Sizes of papules, pustules, and comedones are smaller.	Decrease in inflammation and redness, papules getting smaller.	Noticeable overall improvement with no visible pustules.	Greater improvement	Severe	Mild
10	F	25	Forehead, right and left cheeks	Moderate	70%	Very Good	Less inflammation (redness) on acne lesions. Sizes of papules, pustules, and comedones smaller.	Decrease in inflammation and redness, papules getting smaller.	Decrease in inflammation and no. and size of comedones and papules.	Almost complete clearance. Few papules and comedones are remain but smaller	Moderate	Mild
11	F	20	Forehead	Moderate	80%	Very Good	Less inflammation (redness) on acne lesions. Sizes of papules, pustules, and comedones smaller.	Decrease in inflammation and redness, papules and pustules getting smaller.	No Improvement	No Improvement	Moderate	Mild
12	M	17	Right and left cheeks	Moderate	70%	Very Good	Decreased inflammation, smaller papules and pustules.	Decreased inflammation, papules even smaller. Pustules cleared.	Decreased inflammation, papules getting smaller.	More improvement on acne lesion healing -- 70%	Moderate	Mild
13	M	23	Forehead	Mild	100%	Excellent	Clear of acne after 7 days of	-	-	-	Mild	Complete

							treatment. Treatment stopped.						disappearance
14	M	20	Right cheek, forehead	Mild	90%	Very Good	Decrease in inflammation and redness, papules and pustules getting smaller.	Lesser inflammation and redness, smaller papules. Pustules clear.	Lesser inflammation and redness, papules get smaller.	No improvement	Mild	Very Mild
15	F	20	Right and left cheeks	Moderate	90%	Very Good	Less inflammation (redness) on acne lesions. Only comedones seem to decrease.	Decrease in inflammation and number of papules, pustules, and comedones.	Clearing of pustules. Decrease in papule size, and comedones decreased greatly.	Disappearance of most papules and inflammation. Acne can be considered mild	Moderate	Mild

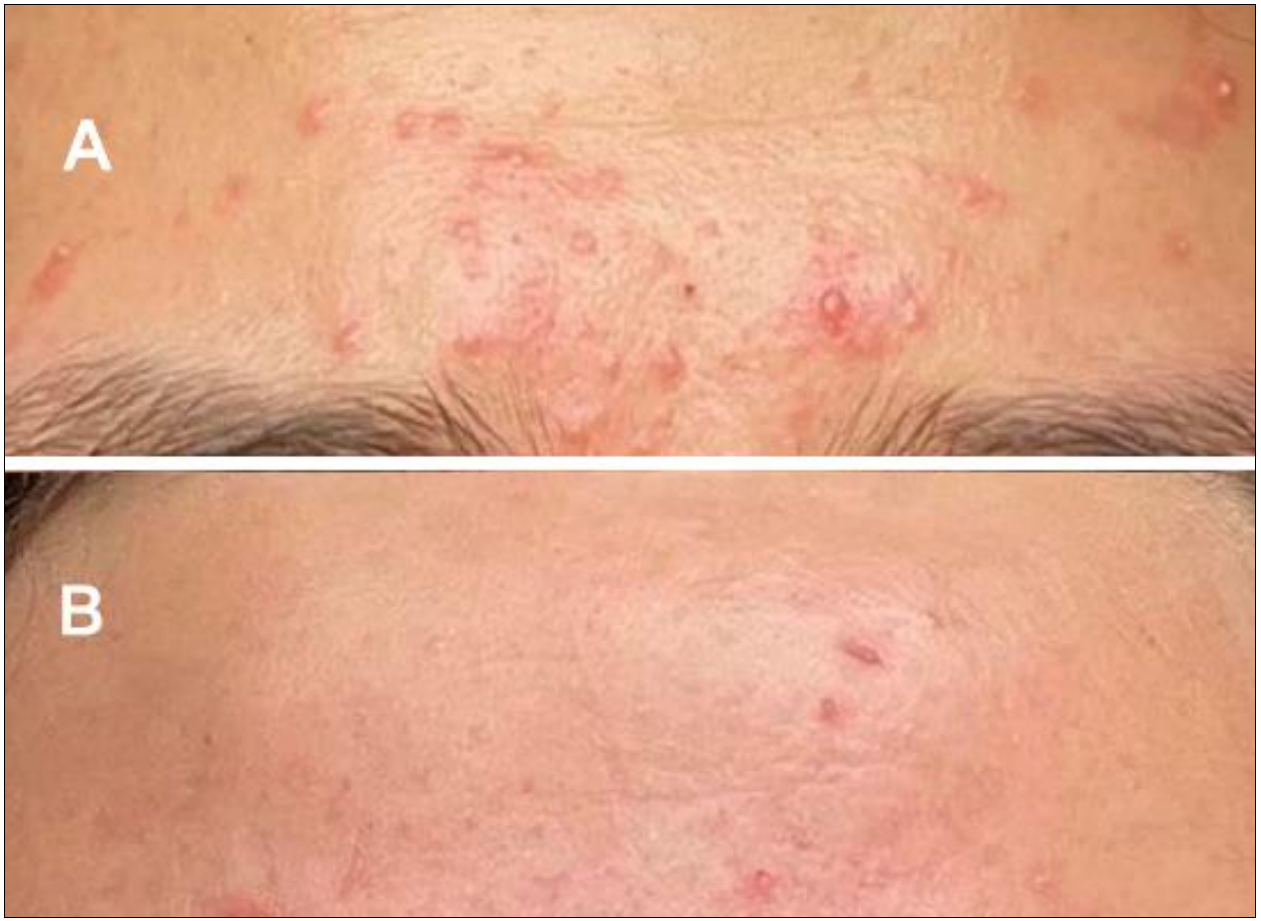

Fig 1: Subject 11 decrease in inflammation and redness, papules and pustules getting smaller. (A) Baseline (B) After Week 2 of treatment

An estimated maintained improvement of 50-100% in moderate acne cases was observed after 4 weeks, with one subject clear of acne after 21 days (3 weeks) of treatment and seven subjects showing improvement and reduced acne condition and noted decrease in papule size and inflammation after 30 days of treatment. Both of the two subjects with severe acne improved significantly after 30 days of treatment, showing reduced inflammation and number and size of papules and pustules after treatment. For the observed clarity of effect in the cases for subjects (6, 9, and 11), detailed accounts of patient history will be included.

Notably, rapid improvement was more pronounced in participants with mild to moderate acne, as compared to severe acne cases. In general, the observed change in acne lesions in the first week was primarily decrease of inflammation; redness surrounding papules and pustules decreased. Results suggest that mild cases can be clear of acne within 7-10 days. Consistent application for period greater than 7 days in moderate, severe, and mild cases that persist resulted in an observed decrease in a number of comedones, but more distinct were the decrease in inflammation, and decrease in numbers and sizes of papules and papules on acne lesions. It is highly likely that the compounds present in the *rosemary* essential oil were responsible for anti-inflammatory, and possibly anti-oxidant and antimicrobial action on the acne lesions. Analysis of the *rosemary* essential oil used in this research confirms the presence of camphor, borneol, 1, 8-cineole, camphene, and α-pinene. Research on the biological and chemical screening of these compounds reviewed earlier reports anti-inflammatory, anti-oxidant, and antimicrobial properties.

The most common adverse effects reported by the participants were mild skin irritation and dryness, which were consistent with previous studies on topical herbal extracts. No serious adverse events were reported during the study period, indicating that *rosemary* essential oil was generally well-tolerated by the participants. The results of the study demonstrated promising outcomes in the use of *rosemary* essential oil gel for acne vulgaris.

Some significant cases (Subjects) are presented in Detail. (Figures 1-3).

Subject 11- Moderate Acne

A 20-year-old female patient of oily skin type was suffering from moderate acne concentrated on the forehead area. She had not responded to systemic and topical erythromycin and doxycycline treatments at the age of 16. Prior to treatment with *rosemary* essential oil gel, patient was using topical tretinoin 0.1% and BPO 5% creams as prescribed by physician. The improvement was little and only during the use of the prescribed drugs. This patient was convinced to stop this prescription and use only our prepared gel containing *rosemary* essential oil extract. Figure 1 shows the case number 11 before and after the treatment.

Subject 9- Severe Acne

A 17-year-old male patient of oily skin type was suffering from severe acne concentrated on the cheeks. He had started topical treatments tretinoin 0.1% cream, BPO 5% cream, and erythromycin 0.4% solution a year before with limited effect. One month prior to treatment with *rosemary* oil gel, patient was prescribed systemic drug isotretinoin 20 mg; however, patient acne improved but complained suffering side effects of this treatment skin-mouth-eyes-lips drying, depression, and muscular fatigue. This patient was convinced to stop this prescription and use only our prepared gel containing *rosemary* essential oil extract. The patient did not report any adverse effects to *rosemary* gel. Figure 2 shows the case number 9 before and after the treatment.

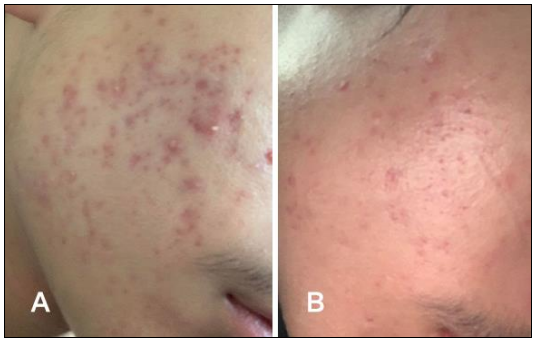

Fig 2: Subject 9 demonstrated noticeable overall improvement with no visible pustules. (A) Baseline (B) After Week 4 of treatment

Subject 6- Severe Acne

A 20-year-old male patient of mixed skin type was suffering from severe acne concentrated on the cheeks. He had been applying topical treatments of tretinoin 0.05% cream and clindamycin solution for two years with little improvement. He was prescribed doxycycline 100 mg capsules to be added to the treatment plan. The patient reported improvement for only some time approximated around 3 months, after which acne treatment progress stopped, despite maintaining the prescribed treatment plan. This patient was convinced to stop this prescription for a month and use only our prepared gel containing *rosemary* essential oil extract. The patient did not report any adverse effects of *rosemary* gel. Figure 3 shows case number 6 before and after the treatment.

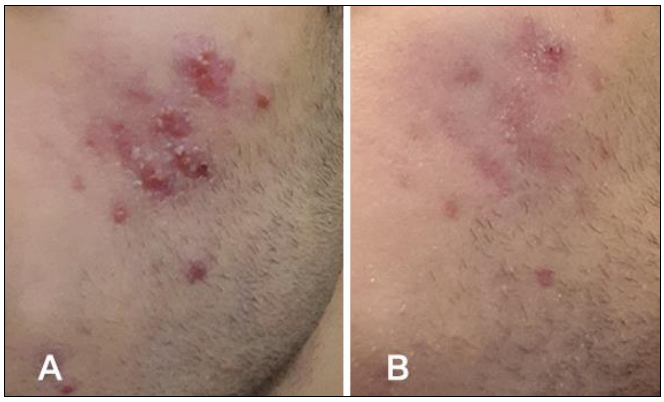

Fig 3: Subject 6 demonstrated decrease in inflammation and number of comedones and papules. (A) Baseline (B) After Week 4 of treatment

4. Conclusion

The results of this study demonstrate the effect of *rosemary* essential oil in treating severe acne vulgaris as well, with improvement in such cases observed through reduction in acne lesion count and in inflammation during the treatment period.

Also in this study, and in a manner consistent with previous scientific literature, the anti-inflammatory, antimicrobial, and antioxidant properties of *rosemary* essential oil chemical constituents such as 1, 8-cineole, camphor, camphene, and α-pinene may have contributed to its beneficial effects in the treatment of acne vulgaris. Results in this study suggest *rosemary* essential oil gel as a candidate pharmaceutical dosage form for monotherapy or as an adjunct or part of

combination therapy for acne vulgaris, thus also qualifying *rosemary* essential oil gel as subject for future research through conduction of larger randomized controlled trials with longer follow-up periods for long-term safety and efficacy.

Undoubtedly, herbal treatments are a source of unique biologically and chemically active compounds comparable in effect to conventional drug treatments, cause significantly lesser side effects, and are widely preferred. Finally, and from an economic aspect, there is a generally positive gain to be achieved from the exploitation of *rosemary* in Syria and the entire Mediterranean region, especially during the best harvest periods, in order to maximize the yields of active phytochemicals. This could yield to the production and marketing of more effective formulations containing *rosemary* essential oil. Such products can be produced locally and could act as substitutes for ineffective or unavailable conventional treatments.

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