

# Safety and Clinical Efficacy of Kūlaris™, an Herbal Supplement for Mild to Severe Acne Vulgaris – A 12-Week Randomized, Double Blind, Placebo-Controlled Study

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**Purpose:** There is a growing interest in nutraceutical supplements for ameliorating skin disorders owing to their multifaceted role and tolerability. In this study, we investigated the safety and efficacy of a unique herbal formulation (Kūlaris™) containing *Commiphora wightii* (guggul) and *Amorphophallus konjac* tuber extracts for the treatment of mild-to-severe acne.

**Patients and Methods:** In a randomized, placebo-controlled, parallel-group study design, 100 male and female subjects (18–40 years) with mild to severe acne were allocated (1:1 ratio) to receive 450 mg capsules of either Kūlaris or placebo once daily for 12 weeks.

**Results:** Kūlaris treatment markedly reduced acne severity, with the majority of subjects achieving success in the Investigator Global Assessment (IGA) score (odds ratio = 7.88,  $p < 0.0001$ ) compared with placebo. Kūlaris administration significantly reduced the inflammatory and non-inflammatory acne lesion counts ( $p < 0.0001$  vs placebo). The Cardiff Acne Disability Index (CADI) score was reduced significantly in the Kūlaris group after 6 ( $p < 0.0001$ ) and 12 weeks ( $p < 0.001$ ) from baseline, indicating an improvement in quality of life. However, the subjective assessment showed no significant changes in general skin health measures, such as skin quality, color, wrinkle reduction, and skin hydration, in either group. Kūlaris was well tolerated among study participants, with no reported adverse effects or observable clinical signs throughout the intervention period.

**Conclusion:** This study provides compelling evidence to support the potential use of Kūlaris as a therapeutic supplement or an adjunctive therapy to treatment of acne vulgaris.

**Keywords:** acne vulgaris, inflammation, guggulsterones, ceramide, quality of life

## Introduction

Acne vulgaris a persistent skin disorder of the pilosebaceous gland characterized by the retained hyperkeratosis, hyperplasia of the sebaceous glands, increased sebum production, follicle colonization by *Cutibacterium acnes*, and inflammation around the follicles.<sup>1</sup> Based on its severity acne may vary from mild, moderate, severe and very severe.<sup>2</sup> Acne is associated with psychological effects leading to low self-esteem, social isolation, anxiety and depression.<sup>3</sup>

Acne treatments involve topical, oral medications, and procedural therapies depending on the severity of the condition.<sup>4</sup> In general, synthetic medications like benzoyl peroxide, retinoids and antibiotics often deliver faster clinical improvements and hence considered as first-line treatment for acne.<sup>5</sup> On the contrary, natural care using herbal supplements offer holistic benefits contributing to broader dermatological and systemic health with fewer adverse effects.<sup>6,7</sup>

*Commiphora wightii* (Arn). (Fam. Burseraceae) is an ancient medicinal herb that produces an oleo-gum resin (guggul) with potential pharmacological benefits documented in traditional systems of medicine, such as Ayurveda, Yunani and Traditional Chinese medicine.<sup>8</sup> The ethnomedicinal uses of the plant include treatment of liver dysfunction, tumors, edema, inflammation, gynecological diseases, obesity, cardiovascular health, urinary disorders, vitiligo, and skin diseases.<sup>9,10</sup>

*Amorphophallus konjac* (Koch). is a popular food source for Japan, China, and Southeast Asia. Glucomannan, the purified konjac flour is used extensively as food additive and dietary supplement.<sup>11</sup> In addition to glucomannan, konjac is a rich source of glucosylceramides (GlcCer) that has proven efficacy in reducing the trans-epidermal water loss.<sup>12</sup> Previously, we have clinically demonstrated the skin health benefits of a standardized konjac extract (Skin-cera™).<sup>13</sup>

Considering the potential of *C. wightii* and *A. konjac*, we conceptualized a combination of the ingredients to study acne reduction alongside general skin health benefits in human subjects.

## Materials and Methods

### Study Design

This prospective, multi-centered, randomized, parallel group, placebo – controlled clinical trial was conducted at two study sites: Skin Xperts and Rajalakshmi Hospital and Research Center in Bangalore, Karnataka, India. This study was conducted according to the approved protocol and ethical principles of the Declaration of Helsinki, in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and New Drugs and Clinical Trials 2019. The Lifeline Ethics Committee of Basaveshwara Nagar, Bangalore approved the study protocol. The trial was prospectively registered in the Clinical Trial Registry of India (CTRI/2021/10/037244, dated October 11, 2021). The study outcomes were presented according to the CONSORT guidelines.<sup>14</sup>

### Subjects

A total of 100 male and female subjects aged 18–40 years with an Investigator’s Global Assessment (IGA) score of 2–4 (mild to severe acne) and willingness to provide informed consent were enrolled in the study. The sample size was calculated using R statistical software ([Supplementary file 1](#)).

The following criteria were used to exclude the participants during the enrolment: (1) Known medical conditions that may interfere with the evaluation of acne vulgaris – rosacea, seborrheic dermatitis, perioral dermatitis, corticosteroid-induced acne or folliculitis, carcinoid syndrome, squamous cell carcinoma, mastocytosis, acneiform eruptions caused by make-up or medication, bacterial folliculitis, facial psoriasis, and facial eczema; (2) allergic to herbal products or any component of the investigational product; (3) subjects receiving topical or oral corticosteroids within 14 days prior to the participation; (4) History of uncontrolled disease or immune deficient disorder; (5) Any feature in the test areas (face) that according to the investigator may influence the results, for example, but not limited to moles, tattoos, scars, irritated skin, scratches, cuts and excess hair; (6) known HIV or Hepatitis B positive or any other immuno-compromised state; (7) female subjects who are pregnant, nursing or planning to become pregnant during the study participation; (8) participating or having participated in another clinical trial during the last 3 months prior to the beginning of this study; (9) any additional condition(s) that in the Investigators opinion would warrant exclusion from the study or prevent the subject from completing the study.

### Interventions

Active treatment in capsule form contained 300 mg Kūlaris, a proprietary blend of *A. konjac* and *C. wightii* (guggul) extracts. The individual plant materials were authenticated at Ms. Rashmi Shetty, Department of Quality Control, Vidya Herbs Pvt Ltd., and the voucher specimen stored in the facility (*C. wightii*: VH/CW/19/21; *A. konjac*: VH/AK/20/21). The capsules contained dibasic calcium phosphate (50 mg) and microcrystalline cellulose powder (100 mg) as the excipients. Kūlaris is a standardized formulation containing  $\geq 4\%$  guggulsterone and  $\geq 0.5\%$  glucosylceramides. The placebo capsules (450 mg) contained only dibasic calcium phosphate (150 mg) and microcrystalline cellulose powder (300 mg) and were identical in size and appearance to Kūlaris capsules.

### Randomization and Blinding

The enrolled subjects were randomly assigned to treatment groups using block randomization. Randomization codes were generated by a biostatistician, based on which the subjects were randomized to the two treatment arms. The subjects, investigator, and other study personnel were blinded to the intervention by masking their identities using IP codes and identical capsule appearances.

## Study Procedure

One hundred subjects were randomized in a 1:1 ratio to receive either Kūlaris or placebo for 12 weeks. The subjects self-administered one capsule per day with water 30 minutes after dinner. The subjects visited the study site at baseline (visit 1), week 6 (visit 2), and week 12 (visit 3). At the baseline visit, each subject underwent physical examination of vital signs (diastolic blood pressure, systolic blood pressure, pulse rate, respiration rate, and body temperature). A subject diary was given to record capsule ingestion details, adverse events, and concomitant medications during the entire study period. The participants were given sufficient intervention to last up to the next visit. No standard care or acne-related medication was provided to subjects during the intervention period. However, the subjects were informed to use cleansers and moisturizers based on their skin conditions.

## Study Outcome

The primary efficacy measures included the proportion of subjects achieving “success” at week 12 on the Investigator’s Global Assessment (IGA) scale. Furthermore, the total acne, inflammatory, and non-inflammatory counts were included in the primary endpoint analysis.

The secondary outcome measures included the Cardiff Acne Disability Index (CADI) and dermatological subjective assessments to examine general skin health.<sup>15</sup> The skin quality was assessed using the Allergan Fine Lines Scale and Allergan Skin Roughness Scale.<sup>16,17</sup> Skin color and wrinkle were assessed using the Felix Von Lushan skin color chart and Modified Fitzpatrick Wrinkle Scale, respectively.<sup>18,19</sup> The Patient Satisfaction Questionnaire, which consists of a 5-point scale, was used to assess the subject perception of the intervention.

## Safety Assessment

Safety assessments were conducted at two timepoints: baseline (Day 0) and the final visit (week 12) of the intervention period, to evaluate the clinical safety profile of the study intervention.

Clinical examination was performed by the investigator and comprised a general health evaluation and physical assessment. The vital signs such as heart rate, blood pressure, body temperature and respiratory rate were measured using calibrated instruments. The serum biomarkers of liver and renal function such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine were evaluated using automated clinical chemistry analyzer. Complete blood count including hemoglobin, red blood cell (RBC) count, total and differential white blood cell (WBC) count, platelet count, hematocrit, Mean Corpuscular Volume (MCV) were measured using the hematology analyzer. All adverse events (AEs) and serious adverse events (SAEs) were actively monitored and documented throughout the study duration.

## Statistical Analysis

All categorical variables were summarized as frequency and percentage, and continuous variables were presented as mean ± standard deviation (SD). Data were analyzed with the MMRM model using R statistical software version 4.0.3. Safety data were analyzed using paired t tests. Statistical significance was set at  $p < 0.05$ .

## Results

A total of 100 human volunteers were screened for the inclusion and exclusion criteria. All 100 subjects were enrolled in the study (December 07, 2021, to April 23, 2022) and randomized to the Kūlaris or placebo groups ( $n = 50$  in each group). Nineteen of the 100 subjects lost to follow-up, and 81 completed the study (30 male and 51 female subjects). The flowchart of the participants is shown in [Figure 1](#). Per-protocol (PP) analysis was used to analyze the data. Baseline characteristics such as age, sex, race, and skin phenotype showed no differences between the groups ([Table 1](#)).

## Primary Efficacy Evaluation

The primary efficacy endpoint was the assessment of acne severity from baseline to the end of the study. Logistic regression analysis showed that the percentage of subjects having “success” in the IGA score was significantly higher in the Kūlaris group compared to placebo. The subjects administered with Kūlaris were 7.88 times more likely to have “success” in IGA than those administered with the placebo ([Table 2](#)).

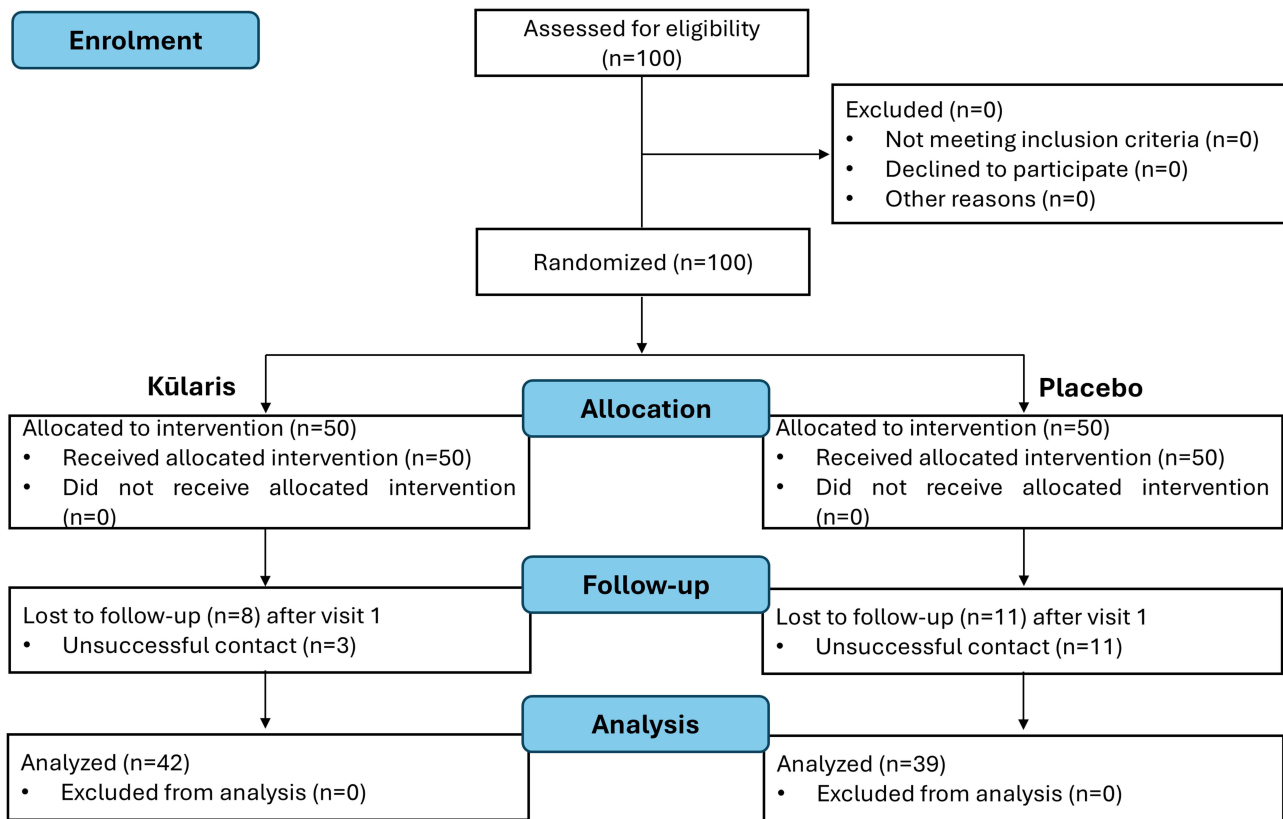


Figure 1 Participant flowchart.

Table 3 summarizes the changes in acne lesion count from baseline to week 12. The Kūlaris group showed a marked reduction in both inflammatory and noninflammatory acne counts after 12 weeks. The inflammatory acne counts in the Kūlaris group were reduced by 71.18% from baseline to week 12 (22.31±15.18 to 6.43±6.64), while it was reduced by 33.58% in the placebo group (20.31±11.54 to 13.49±10.62). Furthermore, the Kūlaris group showed a 68% reduction in the non-inflammatory

Table 1 Subject Demographic Data at Baseline

Characteristics	Kūlaris (N=50)	Placebo (N=50)
Age		
Mean	26.5	29.0
SD	5.49	6.61
Median	25.0	30.0
Min; Max	20.0, 40.0	18.0, 39.0
Sex, n (%)		
Female	26 (52)	25 (50)
Male	24 (49)	25 (50)
Race, n (%)		
Asian	50 (100)	50 (100)

(Continued)

**Table 1** (Continued).

Characteristics	Kūlaris (N=50)	Placebo (N=50)
Skin phenotype, n (%)		
Type II-White, burns easily, tans minimally with difficulty	12 (24)	12 (24)
Type III-White, burns moderately, tans moderately	11 (22)	13 (26)
Type IV-Beige or olive, burns minimally, tans moderately and easily	17 (34)	19 (38)
Type V- Moderately brown, rarely burns, tans profusely	10 (20)	6 (12)

**Note:** Categorical variables were summarized as frequencies and percentages, and continuous variables as mean  $\pm$  standard deviation (SD).

**Abbreviation:** N, Number of subjects.

**Table 2** Odds Ratio from Logistic Regression Analysis of Investigator's Global Assessment (IGA) Score

Characteristic	Odds Ratio	95% CI		#p-value
		Lower	Upper	
Treatment (Kūlaris vs placebo)	7.88	2.87	21.60	<0.0001
Gender	1.12	0.40	3.14	0.832
Age	0.98	0.90	1.06	0.656

**Note:** #Fischer's Exact test.

**Table 3** Change in the Inflammatory, Non-Inflammatory and Total Acne Lesion Counts from Baseline to Week 12

	Baseline	Week 6	Week 12	Change (Week 12 -Baseline)
Inflammatory				
Kūlaris (N=42)	22.31 $\pm$ 15.18	15.21 $\pm$ 12.72	6.43 $\pm$ 6.64	-15.90 $\pm$ 11.54****
Placebo (N=39)	20.31 $\pm$ 11.54	17.62 $\pm$ 11.48	13.49 $\pm$ 10.62	-6.82 $\pm$ 7.37
Non-inflammatory				
Kūlaris (N=42)	28.86 $\pm$ 22.99	20.74 $\pm$ 22.02	9.24 $\pm$ 15.14	-19.60 $\pm$ 12.98****
Placebo (N=39)	33.15 $\pm$ 19.68	29.10 $\pm$ 19.93	25.08 $\pm$ 21.67	-8.08 $\pm$ 13.03
Total lesion count				
Kūlaris (N=42)	49.31 $\pm$ 25.05	34.02 $\pm$ 25.22	15.67 $\pm$ 18.20	33.60 $\pm$ 22.68****
Placebo (N=39)	53.00 $\pm$ 28.45	46.62 $\pm$ 29.28	38.36 $\pm$ 30.91	14.60 $\pm$ 18.62

**Note:** Values are presented as the mean $\pm$ SD. Data were analyzed using the MMRM model, with the baseline lesion count considered as a covariate. \*\*\*\*p<0.0001 vs placebo.

**Abbreviation:** N, Number of subjects.

acne count from baseline to week 12 (28.86 $\pm$ 22.99 to 9.24 $\pm$ 15.14). However, the placebo group showed a reduction of 24.34% (from 33.15 $\pm$ 19.68 to 25.08 $\pm$ 21.67) after 12 weeks. The changes in inflammatory and noninflammatory lesion counts from baseline to the end of the study were significant between the groups ( $p$ <0.0001). A similar trend was observed for the total acne count. The change in the total count was significantly higher in the Kūlaris group than in the placebo ( $p$ <0.0001).

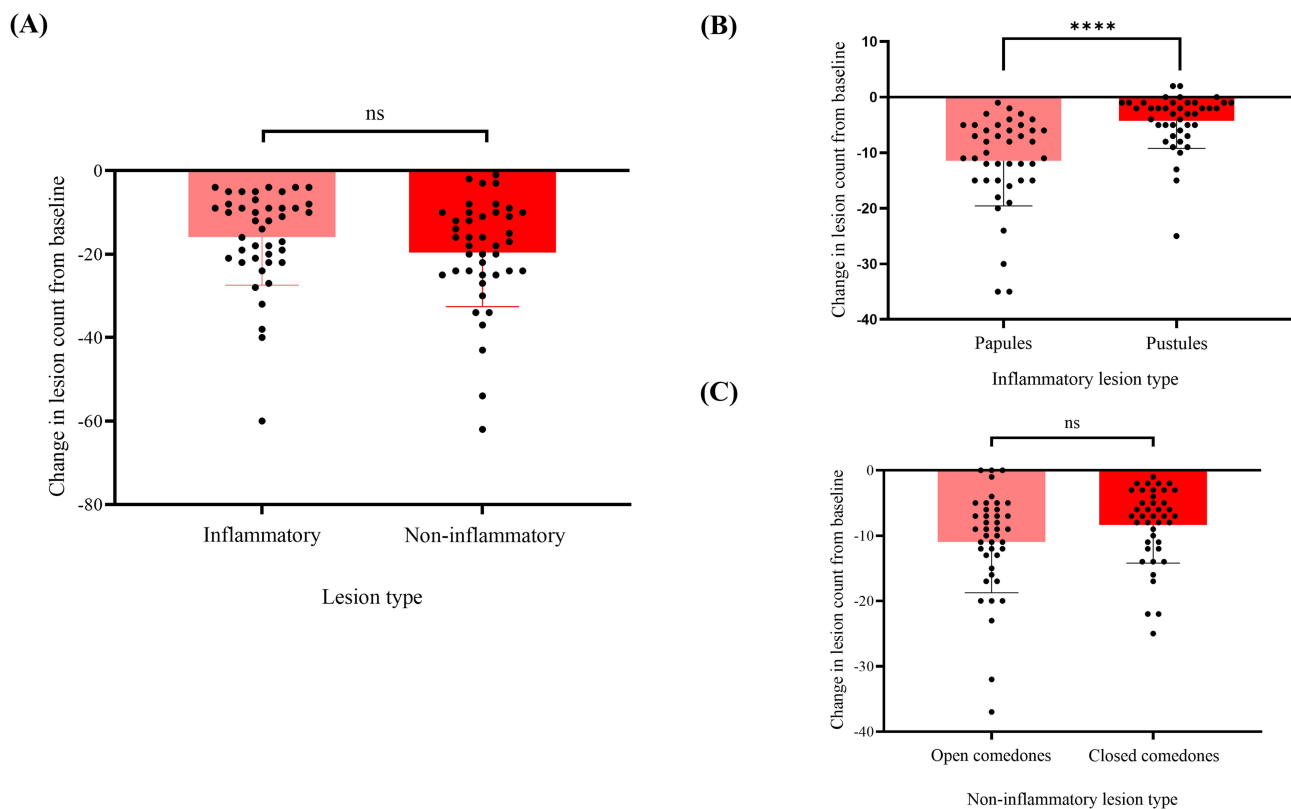
Further analysis of within-group lesion count comparisons in the Kūlaris-treated cohort revealed detailed treatment effects. As depicted in Figure 2A, no statistically significant change was observed between inflammatory and non-inflammatory lesions count. However, a comparative analysis within the inflammatory lesion types demonstrated that the treatment elicited a significant reduction in papules, while its effect on pustular lesions remained non-significant (Figure 2B). Additionally, as shown in Figure 2C, there was no significant difference between the changes in open and closed comedones over the treatment period.

Multiple linear regression was employed to examine the influence of baseline lesion count, age, and gender on total lesion count, inflammatory and non-inflammatory lesion counts in Kūlaris treatment group (Figure 3). For total acne count, the model was statistically significant overall ( $F = 4.20, p < 0.05$ ), with an adjusted  $R^2$  of 0.249, indicating that a substantial proportion of variance in the total lesion count was explained by the included predictors. Baseline lesion count emerged as a significant predictor ( $\beta = 0.363, SE = 0.105, p < 0.01$ ). The age ( $\beta = -0.229, p = 0.468$ ) and gender ( $\beta = 3.072, p = 5.33$ ) did not demonstrate statistically significant associations with total lesion count at the end of study. The predicted vs actual plot showed a strong alignment along the identity line, indicating a high degree of model accuracy (Figure 3A).

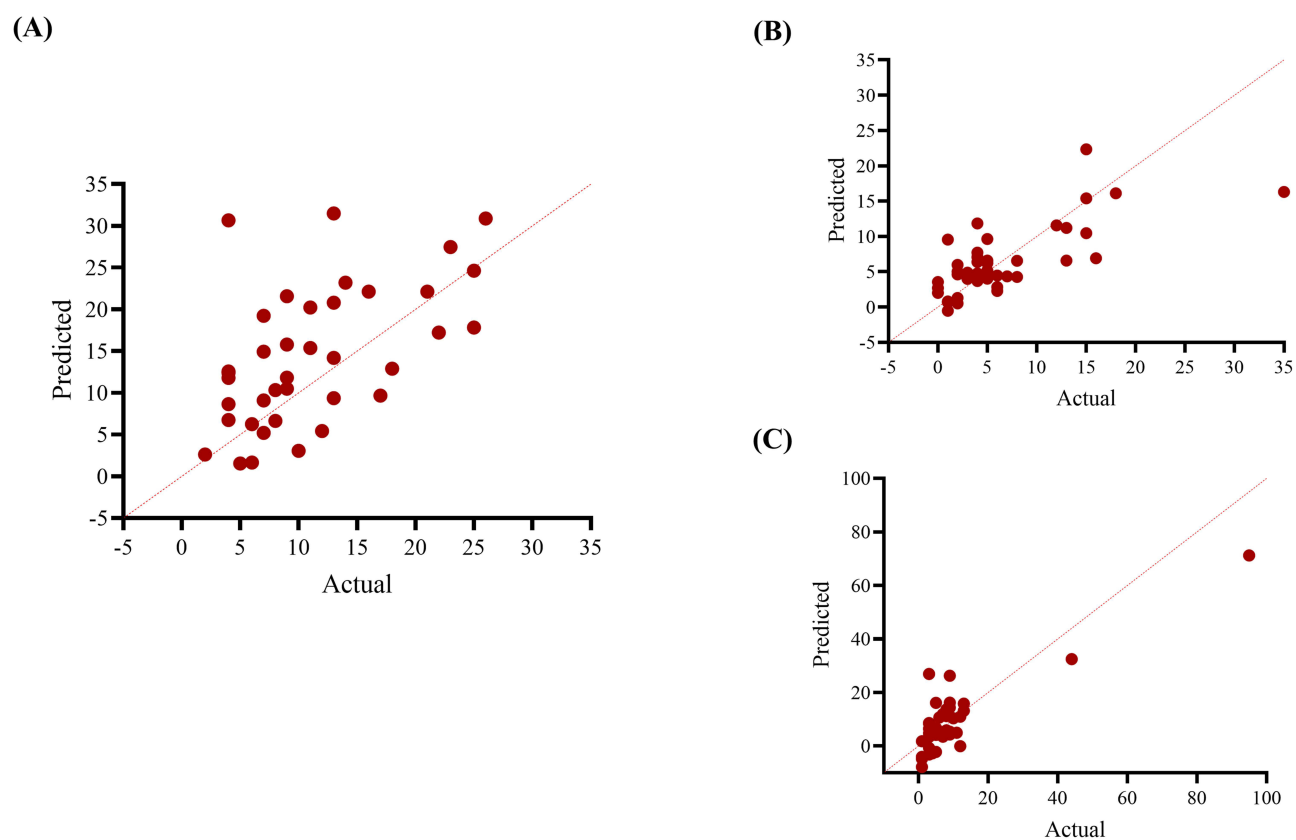
Figure 3B and C shows the scatter plots of the inflammatory and non-inflammatory acne lesion counts respectively. The final counts were significantly changed from baseline (Inflammatory lesion count:  $\beta = 0.308, SE = 0.051, p < 0.0001$ ; non-inflammatory lesion count:  $\beta = 0.551, SE = 0.056, p < 0.0001$ ). However, no significant associations were observed for age or gender.

## Secondary Efficacy Evaluation

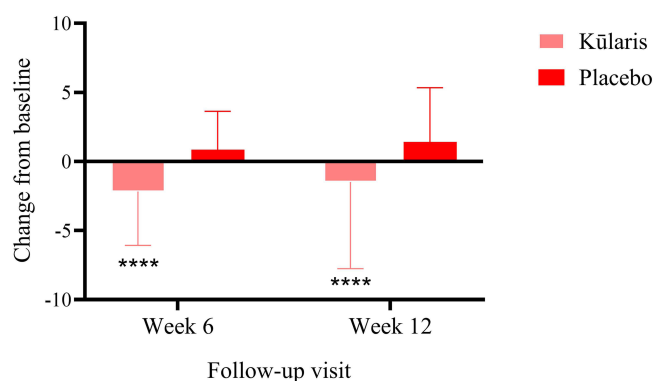
In the Kūlaris group, the CADI score progressively decreased from baseline to follow-up visits. However, the score marginally increased from baseline to subsequent visits in the placebo group. The change in the acne score from baseline to weeks 6 and 12 was significant in the Kūlaris group ( $p < 0.0001$ ) compared with the placebo at the respective visits (Figure 4).



**Figure 2** Comparison of changes in the final lesion count from baseline after 12-week administration of Kūlaris. (A) Change in lesion count (inflammatory vs non-inflammatory). (B) Change in inflammatory lesion types (Papules vs pustules). (C) Change in the non-inflammatory lesion types (Open and closed comedones). \*\*\*\* $p < 0.0001$ . ns: not significant.



**Figure 3** Multiple linear regression analysis evaluating predictors of acne lesion count. (A–C) Predicted vs actual lesion count scatter plots generated using baseline lesion count, age, and gender as covariates. (A) Total acne lesion count, (B) inflammatory acne lesion count and (C) non-inflammatory acne lesion count.



**Figure 4** Change in the Cardiff Acne Disability Index (CADI) score from baseline to follow-up visits. The data were analyzed by MMRM model considering the baseline lesion count as a covariate. \*\*\*\* $p < 0.0001$  vs placebo.

The effect of Kūlaris administration on skin quality was assessed using the validated scales (Table 4). Interestingly, the Allergan fine-line scale and Allergan skin roughness scale assessments showed a decreasing trend from baseline to follow-up visits in both groups. However, these differences were not statistically significant. Furthermore, the subjective assessment of skin color, wrinkles, and skin hydration showed no significant differences between the groups from baseline to the end of the study (Tables 5–7). There was no significant change in self-assessment scores from baseline to subsequent visits between the treatment groups (Table 8).

**Table 4** Effect of Kūlaris Treatment on the Change in Skin Quality from Baseline to Week 12

	Baseline	Week 6	Week 12	Change (Week 12 -Baseline)	†p-value
Allergan Fine Lines Scale					
Kūlaris (N=42)	1.40±0.70	1.36±0.62	1.12±0.63	-0.29±0.74	0.072
Placebo (N=39)	1.46±0.68	1.13±0.66	0.90±0.64	-0.56±0.79	
Allergan Skin Roughness Scale					
Kūlaris (N=42)	1.43±0.55	1.24±0.53	1.10±0.53	-0.33±0.65	0.091
Placebo (N=39)	1.54±0.60	1.18±0.51	0.92±0.58	-0.62±0.75	

**Notes:** Values are presented as the mean±SD. Data were analyzed using the MMRM model with the baseline score as a covariate. †Statistical significance between groups ( $p<0.05$ ) was considered significant.

**Abbreviation:** N, Number of subjects.

**Table 5** Change in Felix Von Lushan Skin Color Chart Score from Baseline to Week 12

	Baseline	Week 6	Week 12	Change (Week 12 -Baseline)	†p-value
Kūlaris (N=42)	24.07±2.52	23.45±2.54	22.67±4.52	-1.40±3.66	0.869
Placebo (N=39)	23.95±3.51	22.90±3.20	22.46±3.32	-1.49±2.32	

**Notes:** Values are presented as the mean±SD. Data were analyzed using the MMRM model with the baseline score as a covariate. †Statistical significance between groups ( $p<0.05$ ) was considered significant.

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**Table 6** Change in Modified Fitzpatrick Wrinkle Scale Score from Baseline to Week 12

	Baseline	Week 6	Week 12	Change (Week 12 -Baseline)	†p-value
Kūlaris (N=42)	0.76±0.66	0.98±0.68	1.26±2.72	0.50±2.86	0.179
Placebo (N=39)	0.97±0.63	0.90±0.68	0.74±0.68	-0.23±0.67	

**Notes:** Values are presented as the mean±SD. Data were analyzed using the MMRM model with the baseline score as a covariate. †Statistical significance between groups ( $p<0.05$ ) was considered significant.

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**Table 7** Change in Skin Hydration Scale Score from Baseline to Week 12

	Baseline	Week 6	Week 12	Mean Difference Week 12 -Baseline	†p-value
Kūlaris (N=42)	1.48±0.67	1.19±0.59	0.83±0.66	-0.64±0.82	0.509
Placebo (N=39)	1.49±0.60	1.03±0.58	0.74±0.64	-0.74±0.75	

**Notes:** Values are presented as the mean±SD. Data were analyzed using the MMRM model with the baseline score as a covariate. †Statistical significance between groups ( $p<0.05$ ) was considered significant.

**Abbreviation:** N, Number of subjects.

## Safety Evaluation

Assessment of laboratory parameters, such as AST, ALT, and creatinine, showed no significant changes from baseline to the end of the study in either group (Table 9). Furthermore, the hematological parameters varied marginally in the Kūlaris group from baseline to week 12. Similarly, the placebo group showed an insignificant change from the baseline, except

**Table 8** Summary of Patient Satisfaction Questionnaire

	Baseline	Week 6	Week 12	Mean Difference Week 12 -Baseline	†p-value
Kūlaris (N=42)	8.26±1.21	8.21±2.51	7.38±3.68	-0.88±4.17	0.365
Placebo (N=39)	8.69±0.95	8.31±2.79	8.05±3.69	-0.64±3.87	

**Notes:** Values are presented as the mean±SD. N: Number of subjects. Data were analyzed using the MMRM model with the baseline score as a covariate. †Statistical significance between groups ( $p < 0.05$ ) was considered significant.

**Abbreviation:** N, Number of subjects.

**Table 9** Summary of Serum Biochemical Analysis (Safety Assessment)

Parameter	Kūlaris (N=42)	Placebo (N=39)
<b>Aspartate aminotransferase (U/L)</b>		
Baseline	26.19±5.03	25.16±3.17
Week 12	25.64±5.48	26.95±6.42
Change	0.55±6.80	1.80±7.40
p-value (Baseline vs week 12)	0.604#	0.138#
<b>Alanine aminotransferase (U/L)</b>		
Baseline	26.21±8.92	25.02±6.76
Week 12	26.53±10.56	28.37±8.66
Change	0.32±9.69	3.35±8.26
p-value (Baseline vs week 12)	0.832#	0.016#
<b>Serum creatinine (mg/dL)</b>		
Baseline	0.80±0.16	0.85±0.18
Week 12	0.82±0.17	0.81±0.14
Change	0.02±0.17	0.03±0.17
p-value (Baseline vs week 12)	0.412#	0.257#

**Notes:** The values are mean±SD. Change = Baseline – Week 12. #Paired t-test,  $p < 0.05$  were considered statistically significant.

**Abbreviation:** N, Number of subjects.

for a significant reduction in eosinophils ( $p < 0.01$ ) and an increase in neutrophil % ( $p < 0.05$ ). However, these values were within the normal range and the changes were not clinically significant (Table 10). The vital signs were normal, and no AE or SAEs occurred during the study period.

## Discussion

The occurrence and progression of acne is associated with multiple factors including the hormonal changes, increase in sebum production, excessive colonization of *C. acne* and the subsequent inflammatory effects.<sup>20–22</sup> Plant metabolites can control acne majorly by their anti-inflammatory and antimicrobial activities.<sup>23</sup> In the present study, we have demonstrated the acne reducing effect of Kūlaris, a blended formulation of *C. wightii* and konjac ceramides. A 12-week oral ingestion of Kūlaris (300 mg/day equivalent to  $\geq 12$  mg guggulsterones) markedly subsided the inflammatory and non-inflammatory acne in the subjects compared to placebo. In a previous study guggulsterone administration at 50 mg/day for 3 months effectively reduced the inflammatory acne lesions comparable to tetracycline treatment.<sup>24</sup>

**Table 10** Summary of Haematological Analysis (Safety Assessment)

Parameter	Kularis (N=42)	Placebo (N=39)
<b>Hemoglobin (g/dL)</b>		
Baseline	12.53±1.20	12.54±1.26
Week 12	12.57±1.87	12.61±1.27
Change	-0.04±1.77	-0.07±1.04
p-value (Baseline vs Week 12)	0.869#	0.657#
<b>PCV (%)</b>		
Baseline	37.55±3.43	37.51±3.60
Week 12	38.16±3.99	37.49±3.06
Change	-0.61±3.46	0.02±2.17
p-value (Baseline vs Week 12)	0.257#	0.959#
<b>Platelet count (Lakhs/cumm)</b>		
Baseline	2.45±0.63	2.41±0.56
Week 12	2.66±0.57	2.55±0.66
Change	-0.21±0.77	-0.14±0.84
p-value (Baseline vs Week 12)	0.087#	0.308#
<b>RBC (10<sup>6</sup>/μL)</b>		
Baseline	4.26±0.49	4.22±0.45
Week 12	4.34±0.51	4.19±0.47
Change	-0.07±0.42	0.03±0.30
p-value (Baseline vs Week 12)	0.267#	0.518#
<b>WBC (cells/cmm)</b>		
Baseline	8736±8659	9324±12373
Week 12	6890±1764	6815±1784
Change	1845±8847	2509±12324
p-value (Baseline vs Week 12)	0.184#	0.211#
<b>Lymphocytes (%)</b>		
Baseline	36.37±5.26	35.10±5.99
Week 12	35.03±7.46	33.30±4.59
Change	1.34±10.71	1.80±7.21
p-value (Baseline vs Week 12)	0.422#	0.127#

(Continued)

**Table 10** (Continued).

Parameter	Kūlaris (N=42)	Placebo (N=39)
<b>Monocytes (%)</b>		
Baseline	4.68±0.94	4.74±0.93
Week 12	4.71±1.02	4.40±1.12
Change	-0.04±1.16	0.33±1.54
p-value (Baseline vs Week 12)	0.841#	0.185#
<b>Basophils (%)</b>		
Baseline	0.06±0.13	0.15±0.72
Week 12	0.03±0.08	0.03±0.07
Change	0.03±0.13	0.12±0.71
p-value (Baseline vs Week 12)	0.151#	0.294#
<b>Eosinophils (%)</b>		
Baseline	3.69±1.51	3.72±1.51
Week 12	3.14±1.38	3.04±1.21
Change	0.55±1.78	0.68±1.46
p-value (Baseline vs Week 12)	0.052#	0.006#**
<b>Neutrophils (%)</b>		
Baseline	55.33±4.98	56.41±6.35
Week 12	56.84±7.70	59.29±4.69
Change	-1.51±10.73	-2.89±7.09
p-value (Baseline vs Week 12)	0.367#	0.015#*

**Notes:** The values are mean±SD. Change = Baseline – Week 12. #Paired t-test. \*p<0.05; \*\*p<0.01.

**Abbreviation:** N, Number of subjects.

Comparative data analysis within the active treatment group revealed that Kūlaris treatment was slightly more effective in reducing the non-inflammatory lesions compared to the inflammatory acne lesions. Further, Kūlaris showed more pronounced efficacy in reducing the papules than pustular lesion. Previously, guggul extract was reported to have antimicrobial and anti-inflammatory activities.<sup>25,26</sup> Experimental studies have demonstrated that guggulsterone significantly reduces NO release, Cox-2 expression, prostaglandin E2 (PGE-2) production, and transcriptional activation of NF-κB in the cells.<sup>27–29</sup> Thus, it can be speculated that these biological attributes contribute to the observed acne-reducing effects of Kūlaris against acne vulgaris.

In the present study, we established the correlation of the final acne lesion count in Kūlaris treated subjects with the baseline severity, age and gender. A strong correlation was found between the baseline lesion counts and the post-treatment outcome. This aligns with existing dermatological evidence suggesting that the initial lesion burden is a strong determinant of therapeutic trajectory, regardless of lesion phenotype.<sup>30</sup>

The gender and age-related factors are widely acknowledged in acne pathophysiology.<sup>31</sup> However, it is interesting to note that there was a lack of significant associations of acne lesion count in active treatment group with age and gender. The minimal predictive influence of these factors in this study suggests that short-term lesion outcomes are more closely

governed by baseline severity and treatment effect than by demographic variation. This strengthens the argument for outcome monitoring anchored in individualized baseline profiles, rather than broad stratification by age or gender.

Reduced ceramide levels resulting in compromised skin barrier function are another important factor associated with inflammatory acne and other skin disorders.<sup>32</sup> It has been clinically demonstrated that subjects with low skin ceramide content are more prone to acne due to seasonal changes.<sup>32,33</sup> Considering these observations from earlier studies, we can rationalize the use of konjac ceramides in Kūlaris. Supplementation of ceramides with guggulsterones synergistically alleviated acne.

IGA is the US FDA approved tool used to clinically evaluate acne severity.<sup>34,35</sup> In the present study, concurrent with acne count reduction, the majority of subjects in the Kūlaris group achieved IGA success compared to the placebo. Furthermore, there was an improvement in the CADI score from baseline to the end of the study in the Kūlaris group compared with that in the placebo group. This suggests that active treatment can positively impact acne-related QoL.<sup>36</sup>

In the present study, we further investigated the overall impact of Kūlaris on general skin health properties, including skin quality, color, texture, and hydration level, using validated scales. Interestingly, no significant change was observed in these parameters following Kūlaris treatment compared with placebo. The mean subject self-assessment scores were similar in the Kūlaris and placebo groups, indicating that there was no dramatic improvement in the overall skin health of the subjects during the study period.

Given the absence of standard acne medications during the intervention period, the observed outcomes suggest that Kūlaris may serve as an effective stand-alone option for the management of acne vulgaris. Moreover, its profile as a functional supplement indicates potential complementary use alongside conventional acne therapies, offering an integrative approach to treatment.

While this study highlights the systemic efficacy of Kūlaris in ameliorating acne vulgaris, certain limitations must be acknowledged. Notably, the study did not incorporate instrumental dermatological assessments specific to acne, such as lesion count imaging, sebum level quantification, or skin surface analysis to objectively monitor clinical improvements. Additionally, the trial faced a significant dropout rate, which may have affected the statistical robustness and generalizability of the findings. Furthermore, hormonal profiling, a key confounding factor in acne pathophysiology was not included in the study protocol.

## Conclusion

In this clinical trial, we evaluated Kūlaris, a novel formulation combining *C. wightii* extract and konjac ceramides, for its efficacy in managing acne vulgaris. Following a 12-week oral supplementation at 300 mg/day dosage, subjects exhibited a statistically significant reduction in acne severity, underscoring the therapeutic potential of Kūlaris. The data convincingly support Kūlaris as a clinically effective and well-tolerated supplement for individuals with acne-prone skin. Its targeted bioactivity, coupled with the tolerability, positions Kūlaris as a promising adjunct or stand-alone intervention in acne management strategies.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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## Disclosure

The investigational product Kūlaris <sup>TM</sup> used in this study was a proprietary extract from Vidya Herbs Pvt. Ltd. The authors Heggar Venkataramana Sudeep and Kodimule Shyamprasad are employees of Vidya Herbs Pvt. Ltd. Divya Chandradhara is an employee of Bioagile Therapeutics Ltd., Bangalore, India. The authors declare that they have no other conflicts of interest.

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