Evaluation of the Efficacy and Tolerance of a Topical Gel With 4% Quassia Extract in the Treatment of Rosacea

Alicia Ferrari and Christian Diehl

J Clin Pharmacol 2012 52: 84 originally published online 22 February 2011
DOI: 10.1177/0091270010391533

Evaluation of the Efficacy and Tolerance of a Topical Gel With 4% Quassia Extract in the Treatment of Rosacea

Alicia Ferrari, MD, and Christian Diehl, MD

Background: *There are various treatment options available for rosacea, depending on the subtype, but treatment is still generally unsatisfactory. Some studies have reported antiparasitic and anti-inflammatory properties of Quassia amara.* ***Aim:*** *To check the efficacy and safety of a topical gel with 4% Quassia amara extract in the treatment of various grades of rosacea.* ***Methods:*** *A group of 30 patients with various grades of rosacea (I-IV) were investigated in a single-center, open-label study. They were treated with a topical gel with 4% Quassia amara extract for 6 weeks. Response was evaluated by the flushing, erythema, telangiectasia, papules, and pustules scores. At the end of therapy, overall improvement, safety, and tolerability were assessed.* ***Results:*** *Twenty-seven of 30 patients (90%) completed the study. The treatment resulted to be very effective, and the results achieved were in line with those published with topical metronidazole and azelaic acid. Safety and tolerability were excellent.* ***Conclusion:*** *Topical quassia extract could be a new, efficient, and safe weapon in the armamentarium for the management of rosacea.)*

Keywords: *Clinical trial; erythema; flushing; papules; pustules; quassia; rosacea; telangiectasia*

Journal of Clinical Pharmacology, 2012;52:84-88

Rosacea is a common chronic skin disorder observed primarily among patients with Fitzpatrick I & II skin types. In general, clinical observation is sufficient to diagnose conditions when the patient presents on the face, neck, chest, or ears with flushing, persistent erythema, telangiectasias, eruption of inflamed papules, pustules, and hypertrophy with fibrosis[1] of the sebaceous glands of the nose.

The exact cause of rosacea remains unknown, with no known cure available. Extrinsic and intrinsic factors can exacerbate conditions and consist of a series of vascular disorders with structural alterations of cutaneous vasculature,[2] compromised vascular integrity and increased angiogenesis,[3] and expression of angiogenesis factors (in particular vascular endothelial growth factor).[4] *Demodex folliculorum*, a species of face mite found in the hair follicle, may also play a key role in the onset and maintenance of the disorder. Recent focus has been given to the important mechanisms of matrix degradation[5] and abnormal generation of reactive oxygen species, provoking inflammation and vascular abnormalities.[6]

From Universidad Nacional de Córdoba, Argentina. Submitted for publication August 16, 2010; revised version accepted October 31, 2010 Address for correspondence: Christian Diehl, MD, Domingo Uriarte 192, B Lomas de San Martin, Cordoba 5008, Argentina; e-mail: chdiehl@hotmail.com. DOI:10.1177/0091270010391533

The standard course of treatment remains the topical prescription agents metronidazole and azelaic acid, which may be combined with adjunctive therapies, including oral antibiotics. *Quassia amara* is a tropical plant species widely used in folk medicine for a variety of indications, such as parasitic and digestive diseases. Its topical use is also frequently mentioned among popular indications.

Quassia amara features a shrub or small tree originating in South America. It contains high levels of active phytochemicals, including the triterpenoid quassinoids. Various biological activities are described in the literature, including antiparasitic activities against pediculosis[7,8] and anti-inflammatory properties.[9,10] Because of these previously disclosed properties, we have successfully used a hydroglycolic extract of quassia on patients with rosacea. Initial patient satisfaction prompted the decision to conduct a preliminary clinical trial with this topical preparation.

MATERIALS AND METHODS

Study Design

The study comprised 30 patients receiving a 4% quassia topical gel. The activity of the test gel was evaluated

Table I Assessment of Overall Erythema Severity

Numerical Score	Rating	Description
0	None	Either no visible erythema or minimal residual erythema
1	Mild	Slight erythema, either centrofacial or generalized to whole face
2	Moderate	Pronounced erythema, either centrofacial or generalized to whole face
3	Severe	Severe erythema with a red to purple hue, either centrofacial or generalized to whole face

by comparing each patient's condition at baseline with his or her condition at the end of the study. All patients provided informed consent before the beginning of the trial and were free to terminate their participation at any time. The Declaration of Helsinki and its revisions were followed.

Study Population

Male and female (not pregnant or nursing) patients enrolled for the study had grade I to IV rosacea (standard classification of rosacea[1]) and were at least 18 years of age. Exclusion criteria included known allergies to any component of the formula, previous history of skin cancer (melanoma or nonmelanoma) in affected areas, patient participation in other clinical studies within 3 months before this study, or patients whose mental condition did not permit good compliance.

Study Protocol

To avoid any carryover effects from preceding therapy, there was a washout period of 4 weeks after topical and/or systemic treatment of rosacea. Patients treated with any systemic, topical, or cosmetic treatment that could influence the parameters of evaluation of the study were rejected.

Patients were directed to apply the study gel to affected areas in the morning and evening for 45 days, in quantities of approximately 0.05 mL/cm^2. This product was delivered in the form of an aqueous gel containing 4% of a hydroglycolic extract of *Quassia amara* at 250% (wt/vol) standardized at 0.40% (wt/vol) of quassin. This gel also contained carbomer (0.8%) and xanthan gum (0.2%), along with a preservative system consisting of phenoxyethanol (0.12%) and benzyl alcohol (0.1%). Its viscosity was 50 000 Cps, and the pH was 5. No specific toxicological trial was performed on the standardized extract, given that *Quassia amara* possesses the status of "generally recognized as safe" by the US Food and Drug Administration.

At baseline, general patient data including sex, age, phototype (Fitzpatrick classification), grade of rosacea, time of onset and history, localization, and previous treatments were recorded. During the treatment phase, the therapeutic progress was assessed at 15-day intervals (after 15, 30, and 45 days). All evaluable patients who completed the study were considered in a global evaluation of the results achieved at the end of therapy.

Treatment efficacy was assessed by counting the number of inflammatory papules and pustules rated as 0, no papule/pustule; 1, number of papules/pustules < 5; 2, number of papules/pustules > 5 and < 20; and 3, >20 and rating the flushing (0, no flush; 1, intermittent flushing; 2, permanent flushing; 3, intense flushing), erythema (0, no erythema; 1, mild erythema; 2, moderate erythema; 3, severe erythema) (Table I), and telangiectasia (0, no; 1, mild; 2, moderate; 3, severe). Each visit included an evaluation of local tolerance and local and systemic adverse events as determined by both patients and physician. At each visit, 2 photographs were taken in daylight.

At the end of therapy, overall improvement was determined as complete remission, marked improvement (at least 3 parameters improved), moderate improvement (at least 2 parameters improved), no improvement, or deterioration. For evaluation, the latter 2 overall ratings were combined as "poor."

RESULTS

Patient Characteristics

Study enrollment occurred from June 2009 to August 2009. Thirty patients were enrolled in the study. The patient baseline characteristics are presented in Table II. The male/female ratio of enrolled patients was 20%/80%, their mean age was 50.3 years (range, 21-82 years), and the mean previous duration of rosacea was 4.73 years (range, 0.5-15 years). Approximately 33% of patients had received previous treatment for rosacea. The disposition of patients is summarized in Figure 1.

Overall, 90% of patients completed the study, and the remaining 10% (3 patients) were lost to follow

Table II Patient Characteristics

Characteristic	No.
Male/female patients	6/24 (20%/80%)
Mean age, y	50.3 (range, 21-82)
Phototype	
II	2 (6.6%)
III	24 (80%)
IV	4 (13.3%)
Grade (standard classification of rosacea, US National Rosacea Society)	
I	5 (16.7%)
II	15 (50%)
III	5 (16.7%)
IV	5 (16.7%)
Mean previous duration of rosacea, y	4.73 (range, 0.5-15)
Localization	
Chin	21 (70%)
Cheeks	30 (100%)
Forehead	15 (50%)
Nose	23 (76.7%)
Rhinophyma	2 (6.7%)
Ocular	5 (16.7%)
Patients with previous rosacea therapy	10 (33.3%)

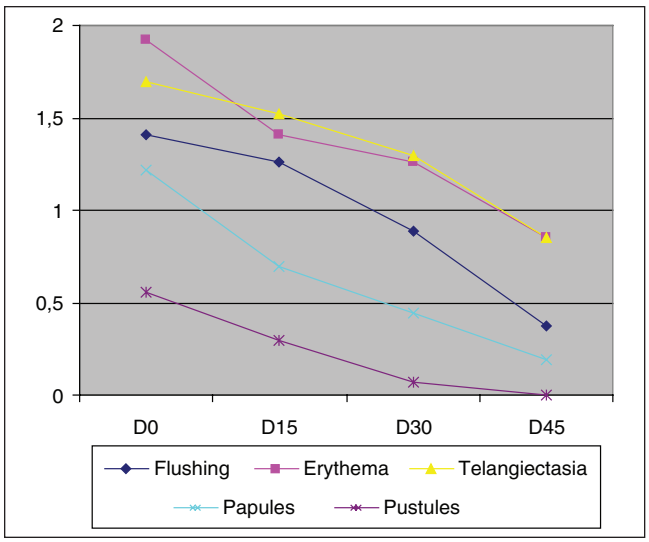

Figure 1. Evolution of mean scores of various parameters along the study.

up, mainly due to the fact that the study took place during an epidemic of influenza. No patient was discontinued due to occurrence of adverse effects.

Flushing

Patients experienced a continuous decline in mean flushing score throughout 6 weeks of treatment, from a mean of 1.41 ± 0.75 at baseline to a mean of 0.37 ± 0.49 at day 45, that is, a decrease in flushing score of 74% ($P < .001$) (Figure 1 and Table III).

Erythema

The mean erythema score exhibited a continuous decline during this study, from a mean of 1.92 ± 1.00 at baseline to a mean of 0.85 ± 0.77 at day 45, a decrease in erythema score of 56% ($P < .001$) (Figure 1 and Table III).

Telangiectasia

The mean telangiectasia score showed a continuous decline throughout 6 weeks of treatment, from a mean of 1.70 ± 0.82 at baseline to a mean of 0.85 ± 0.77 at day 45, a decrease in telangiectasia score of 50% ($P < .001$) (Figure 1 and Table III).

Papules

Patients experienced a continuous decline in the mean papules score during this study, from a mean of 1.22 ± 1.15 at baseline to a mean of 0.19 ± 0.40 at day 45, a decrease in papules score of 84% ($P < .001$) (Figure 1 and Table III).

Pustules

The mean pustules score experienced a dramatic and continuous decline throughout 6 weeks of treatment, from a mean of 0.56 ± 0.70 at baseline to a mean of 0.00 at day 45, as shown in Figure 1 and Table III. This shows a decrease in pustules score of 100% ($P < .001$) during the study.

Overall Improvement

An overall improvement occurred over time in this study. More than 37% of patients experienced excellent improvement or complete remission; 22% felt a marked improvement, nearly 30% a moderate improvement, and only 11% had no improvement throughout 6 weeks of treatment (Table IV and Figure 2).

Comparatively, greater results were obtained in patients with severe grades of rosacea (all patients,

Table III Mean ± SD Score of Various Parameters Along the Study

Parameter	Day 0	Day 15	Day 30	Day 45
Flushing	1.41 ± 0.75	1.26 ± 0.59[a]	0.89 ± 0.42	0.37 ± 0.49[a]
Erythema	1.92 ± 1.00	1.41 ± 0.80[a]	1.26 ± 0.66[a]	0.85 ± 0.77[a]
Telangiectasia	1.70 ± 0.82	1.52 ± 0.75[a]	1.30 ± 0.95[a]	0.85 ± 0.77[a]
Papules	1.22 ± 1.15	0.70 ± 0.82[a]	0.44 ± 0.58[a]	0.19 ± 0.40[a]
Pustules	0.56 ± 0.70	0.30 ± 0.54[a]	0.07 ± 0.27[a]	0.00

[a]$P < .001$.

Table IV Overall Improvement at the End of the Therapy

	No. of Patients	%
No. of parameters improved		
1	3	11.1
2	8	29.6
3	6	22.2
4	6	22.2
5	4	14.8
Improvement		
No improvement	3	11.1
Moderate improvement	8	29.6
Marked improvement	6	22.2
Complete remission (4 or 5 parameters improved)	10	37.1

except 1, with grades III or IV showed marked improvement or complete remission).

Adverse Effects and Tolerance

No adverse effects such as itching, edema, burning, and stinging were reported during this study. The tolerance was excellent in all patients who completed the treatment.

DISCUSSION

To the best of our knowledge, this is the first clinical trial of topical quassia extract for the treatment of various grades of rosacea. This preliminary study demonstrates the safety and efficacy of 4% quassia extract gel for the treatment of all grades of rosacea. Patients experienced significant reductions in flushing, erythema, papules, pustules, and telangiectasia after 6 weeks of treatment. Improvements in global assessment of disease severity determined by the investigators also showed excellent results at the end of this study, and the patients experienced continuous improvements throughout the duration of the study.

The real efficacy of quassia extract may be explained not only by its antiparasitic action on *Demodex folliculorum* but also its strong anti-inflammatory and antioxidant effects. Verma et al[11] have reported the potent inhibitory activity of an alcoholic extract of *Quassia amara* on production of LPS-stimulated pro-inflammatory mediators in J774 murine macrophages. Interestingly, the concentration of quassia extract used in their work was the same (10% wt/vol) as the concentration used in this study.

Among the pro-inflammatory mediators screened in this study, quassia extract displayed a potent inhibitory activity (3.98-fold, $P < .01$) on TNF-ά, on IL-1ß (2.25-fold, $P < .01$), and most interestingly on nitric oxide production (5.10-fold, $P < .01$), the increased production of which is known to increase vasodilation.[12]

In another study, natural triterpenoids (the major active constituents of *Quassia amara* extract) were recently shown to alleviate skin inflammation in a mouse model of psoriasis.[13] No comparison was made between current rosacea treatment and quassia extract. This may be the subject of future investigations.

In conclusion, it appears that topical quassia extract may represent a new, safe, and effective weapon in our armamentarium for the management of rosacea. Based on this encouraging evaluation, additional clinical trials involving larger groups of patients and employing double-blind, placebo protocols may be warranted.

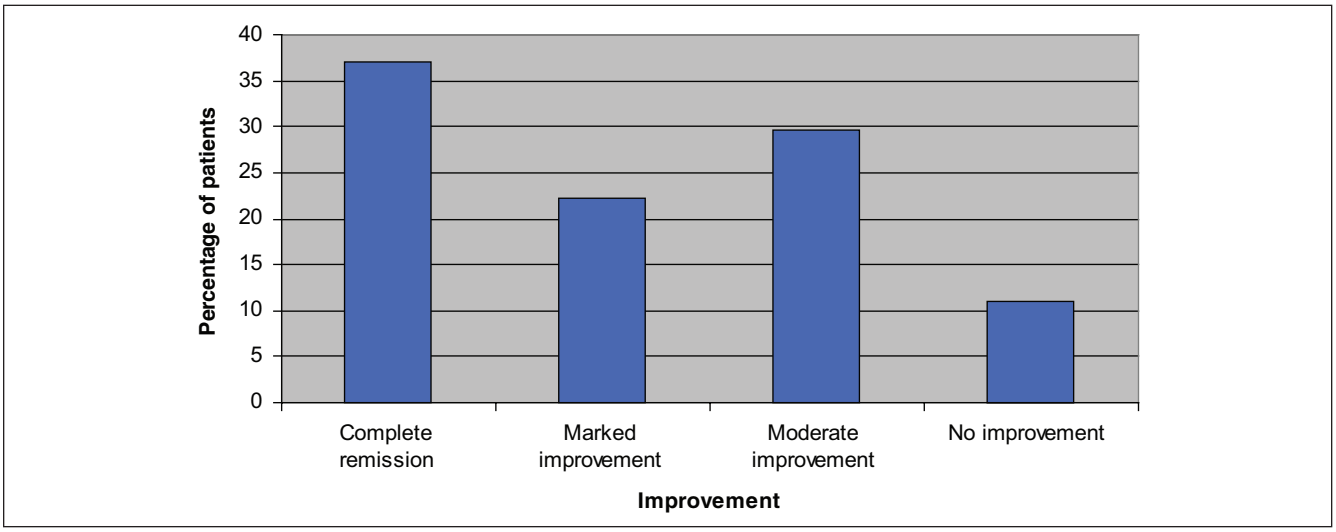

Figure 2. Overall improvement at the end of therapy.

Financial disclosure: None declared.

REFERENCES

1. Wilkin JK, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2002;46:584-587.

2. Dahl MV. Pathogenesis of rosacea. *Adv Dermatol*. 2001;17:29-45.

3. Crawford GH, Pelle MT, James WD. Rosacea, 1: etiology, pathogenesis and subtype classification. *J Am Acad Dermatol*. 2004;51: 327-341.

4. Gomaa AH, Yaar M, Eyada MM, Bhawan J. Lymphangiogenesis and angiogenesis in nonphymatous rosacea. *J Cutan Pathol*. 2007; 34(10):748-753.

5. Bonamigo RR, Bakos L, Edelweiss M, Cartell A. Could matrizmetalloproteinase-9 be a link between Demodex folliculorum and rosacea? *J Eur Acad Dermatol Venereol*. 2005;19(5):646-647.

6. Jones D. Reactive oxygen species and rosacea. *Cutis*. 2004; 74(3 suppl):17-20, 32-34.

7. Jensen O, Nielsen AO, Bjerregaard P. Pediculosis capitis treated with Quassia tincture. *Acta Derm Venereol*. 1978;58(6):557-559.

8. Ninci ME. Prophylaxis and treatment of pediculosis with Quassia amarga. *Rev Fac Cien Med Univ Nac Cordoba*. 1991;49(2): 27-31.

9. Toma W, Gracioso JS, Hiruma-Lima CA, Andrade FDP, Vilegas W, Souza Brito ARM. Evaluation of the analgesic and antiedematogenic activities of Quassia amara bark extract. *J Ethnopharmacol*. 2003;85:19-23.

10. Hall H, Lee KH, Imakura Y, Okano M. Anti-inflammatory agents III: structure-activity relationships of brusatol and related quassinoids. *J Pharm Sci*. 1983;72(11):1282-1284.

11. Verma N, Tripathi SK, Sahu D, Das HR, Das RH. Evaluation of inhibitory activities of plant extracts on production of LPS-stimulated pro-inflammatory mediators in J774 murine macrophages. *Mol Cell Biochem*. 2010;336(1-2):127-135.

12. Amin AR, Attur MG, Thakker GD. A novel mechanism of action of tetracyclines: effects on nitric oxide synthases. *Proc Natl Acad Sci U S A*. 1996;93:14014-14019.

13. Wang H, Syrovets T, Kess D, et al. Targeting NF-kB with a natural triterpenoid alleviates skin inflammation in a mouse model of psoriasis. *J Immunol*. 2009;183:4755-4763.