EVALUATION OF THE EFFICACY AND TOLERANCE OF A TOPICAL GEL WITH 4% QUASSIA EXTRACT IN THE TREATMENT OF ROSACEA

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INTRODUCTION

Rosacea is a common condition, in particular among skin types I-II patients. Although not being a life-threatening condition, it can have a deep impact on the patient's self-esteem and quality of life, and hence justifies a high number of consultations by the dermatologists.

The clinical pattern is well-known, consisting of facial flushing, appearance of telangiectasias and persistent redness of the face, eruption of inflammatory papules and pustules, hypertrophy of the sebaceous glands of the nose with fibrosis. Recent classification schemes resulted to be helpful in the management of patients with rosacea.[(1)]

The etiology of rosacea remains unknown, and multiple intrinsic and extrinsic factors have been related with the etiopathogenesis of rosacea, suggesting a multifactorial condition.

Besides obvious extrinsic factors as climatic exposure, chemicals or ingested foods, intrinsic factors are focusing on a series of vascular disorders with structural alterations of cutaneous vasculature,[(2)] less of vascular integrity and increased angiogenesis[(3)] and expression of angiogenesis factors (in particular VEGF)[(4)].

Demodex folliculorum has certainly a key role, not certainly as a causative factor of rosacea, but more probably in the worsening of the conditions of the patients and maintenance of the disease, and its mechanism of action in much better understood than it was in the past.

Recently, focus was given on the great importance on the mechanisms of matrix degradation, especially the high levels of matrix metalloproteinases (MMPs) constantly observed in the tissues of patients with rosacea.[(5)]

The current trend is to consider that the main causative factor of rosacea could be an antioxidant system defect in these patients, leading to the abnormal generation of reactive oxygen species (ROS) provoking inflammation and vascular abnormalities.[(6)]

The treatment of rosacea is mainly based upon topical therapies:

Metronidazole and azelaic acid are the major players, acting more as anti-inflammatory agents than as antibiotics or antiparasitic, but also more and more topical antioxidants are used in rosacea.

Second-line therapies are oral antibiotics (tetracyclines and metronidazole) at anti-inflammatory and antioxidant doses.

Quassia amara is a tropical species widely used in folk medicine in lots of indications. It contains a great number of active ingredients and phytochemicals, among them quassinoids (triterpenoid compounds) seem to be the most active ones. Various biological activities were described in the literature, among them antiparasitic properties on pediculosis[7,8] and anti-inflammatory properties[9,10].
Due to these previously disclosed properties, we have successfully used an hydroglycolic extract of Quassia in patients with rosacea, and hence decided to conduct a clinical trial in rosacea patients with this topical active ingredient.

MATERIALS & METHODS

Study design

The study was a monocentre, controlled, intra-individual study with direct individual benefit, including 30 patients receiving a 4% Quassia topical gel. All patients gave inform consent prior to the beginning of the trial and were free to terminate their participation at any time. The declaration of Helsinki and its revisions was followed.

Study population

Male and female (not pregnant or nursing) patients enrolled for the study had grade I to IV rosacea (Mills and Kligman classification) and were at least 18 years of age.
Exclusion criteria comprised known allergy to any component of the formula, previous history of skin cancer, patients having be part of another clinical study in the course of 3 months preceding the study, or patients whose mental condition did not permit them a good compliance to the study.

Study protocol

In order to avoid any carry-over effects from preceding therapy, there was a wash-out period of 4 weeks following topical and / or systemic treatment of rosacea, and the patients treated with any systemic, topical or cosmetic treatment susceptible of interference with the parameters of evaluation of the study were rejected.
Patients were informed to the product under study to the affected areas in the morning and evening for 45 days. This product was delivered under the form of an aqueous gel containing 4% Quassia extract, the latest containing 0.40g % p/v of Quassin.
At baseline, general patient data including sex, age, phototype (Fitzpatrick classification), grade of rosacea, time of evolution and history, localization and previous treatments were recorded.
During the treatment phase, the therapeutic progress was assessed at 15 days intervals (after 15, 30 and 45 days).
All evaluable patients 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 1**) 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, two photographs were taken in daylight.
At the end of therapy, overall improvement was determined as either complete remission, marked improvement (at least three parameters improved), moderate important (at least two parameters improved), no improvement or deterioration. For evaluation the latter two overall ratings were combined as “poor”.

Table 1- 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.

RESULTS

Patients Characteristics

Study enrollment occurred from June, 2009 to August, 2009.
30 patients were enrolled in the study.
The patient baseline characteristics are presented in **Table 2**.
The male / female ratio of enrolled patients was 20/80, their mean age was 50.3 (21-82), the mean previous duration of rosacea was 4.73 years (0.5-15). 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-up, mainly due to the fact that the study took place during an epidemic of flue.
No patient was discontinued due to occurrence of adverse effects.

Figure 1- Patient disposition

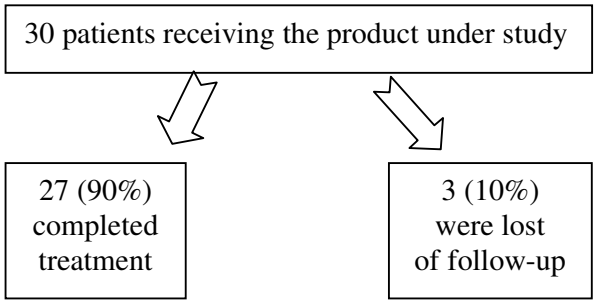


Table 2- Patient characteristics

Male/female patients	6/24 (20% / 80%)
Mean age (years)	50,3 (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 (years)	4.73 (0,5 – 15)
Localization	Chin 21 (70%) Cheeks 30 (100%) Forehead 15 (50%) Nose 23 (76.7%) Rhynophyma 2 (6.7%) Ocular 5 (16.7%)
Patients with previous Rosacea therapy	10 (33.3%)
Mean baseline flushing score Mean baseline erythema score Mean baseline telangiectasia score Mean baseline papules score Mean baseline pustules score	1.41 (± 0.75) 1.92 (± 1.00) 2.15 (± 0.45) 1.22 (± 1.15) 0.56 (± 0.70)

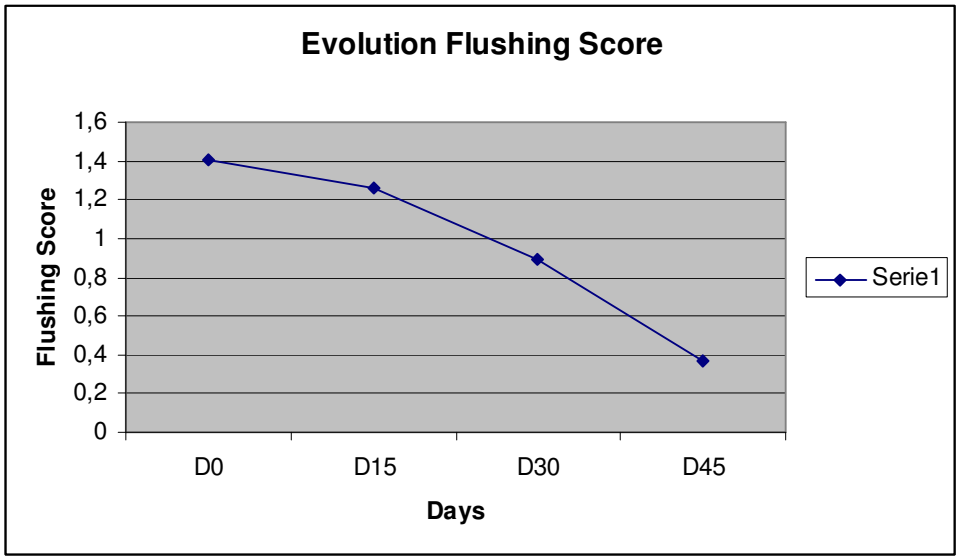
Flushing

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 D45, i.e. a decrease in flushing score of 74% ($p<0.001$) (**Figure 2**)
Table 3 is summarizing these results.
At the end of the study, only 37% of the patients having completed the study were complaining intermittent flushing, whilst 100% were complaining some grade of flushing at baseline.

Table 3. Flushing score along the study

Score	DO	D15	D30	D45
0	0	0	4	17
1	21	22	22	10
2	3	3	1	0
3	3	2	0	0
mean	1.41 (±0.75)	1.26 (±0.59)	0.89 (±0.42)	0.37 (±0.49)

Figure 2- Reduction in flushing score along the study



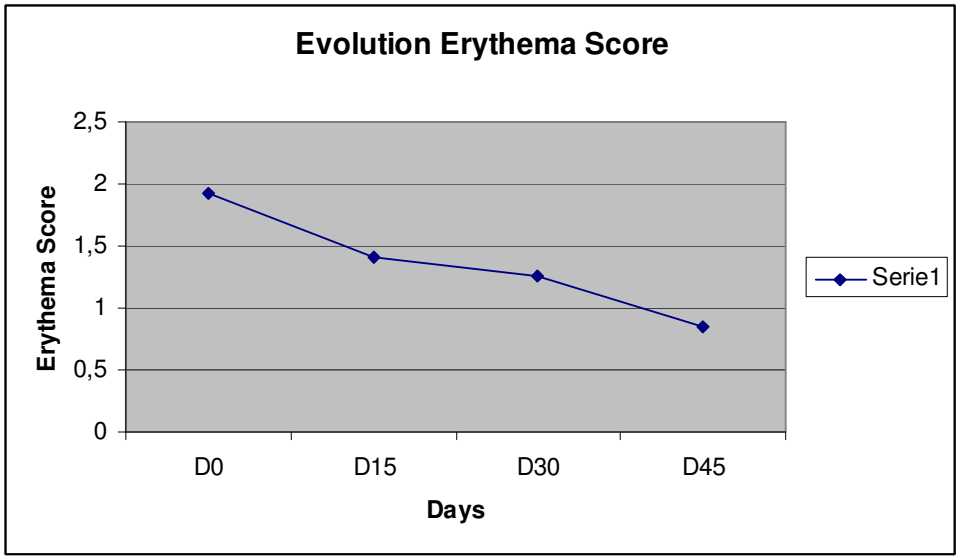
Erythema

The mean erythema score experienced a continuous decline along this study, from a mean of 1.92 (± 1.00) at baseline to a mean of 0.85 (± 0.77) at D45 (**Figure 3**) i.e. a decrease in erythema score of 56% ($p<0.001$)
The values of erythema at each visit are recorded in **Table 4**.
At the end of study, 33% of patients were rid of erythema, whilst all of them were displaying same grade of erythema at baseline.

Table 4- Erythema score along the study

Score	DO	D15	D30	D45
0	0	0	2	9
1	14	22	21	15
2	1	1	2	2
3	12	4	2	1
mean	1.92 (±1.00)	1.41 (±0.80)	1.26 (±0.66)	0.85 (±0.77)

Figure 3- reduction in erythema score along the study



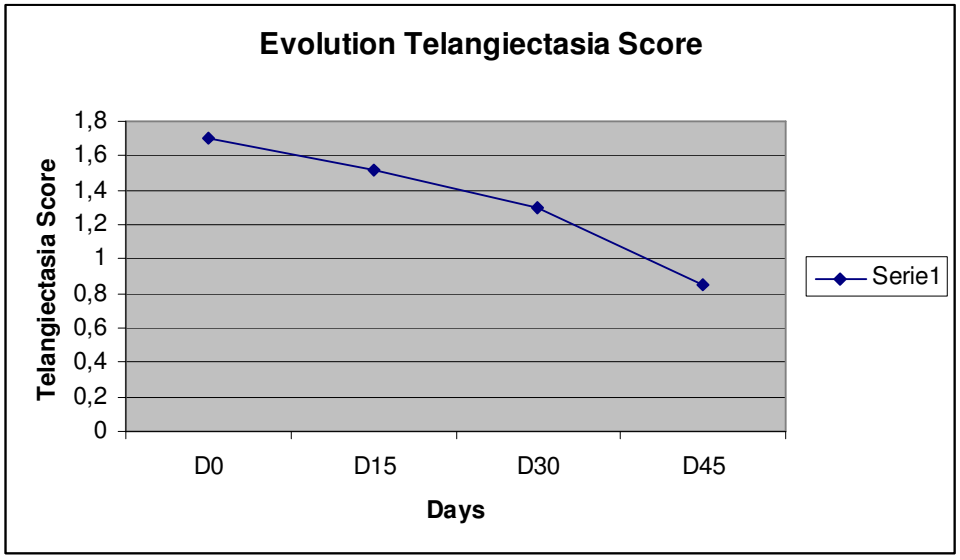
Telangiectasia

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 D45 (**Figure 4**) i.e. a decrease in telangiectasia score of 50% ($p<0.001$).
In **Table 5** detailed results are recorded.
At the end of the study, 37% of the patients having completed the study were rid of telangiectasia, whilst only one patient was not displaying telangiectasia at baseline.

Table 5- Telangiectasia score along the study

Score	DO	D15	D30	D45
0	1	2	6	10
1	11	11	10	11
2	10	12	8	6
3	5	2	3	0
mean	1.70 (±0.82)	1.52 (±0.75)	1.30 (±0.95)	0.85 (±0.77)

Figure 4- Reduction in telangiectasia along the study



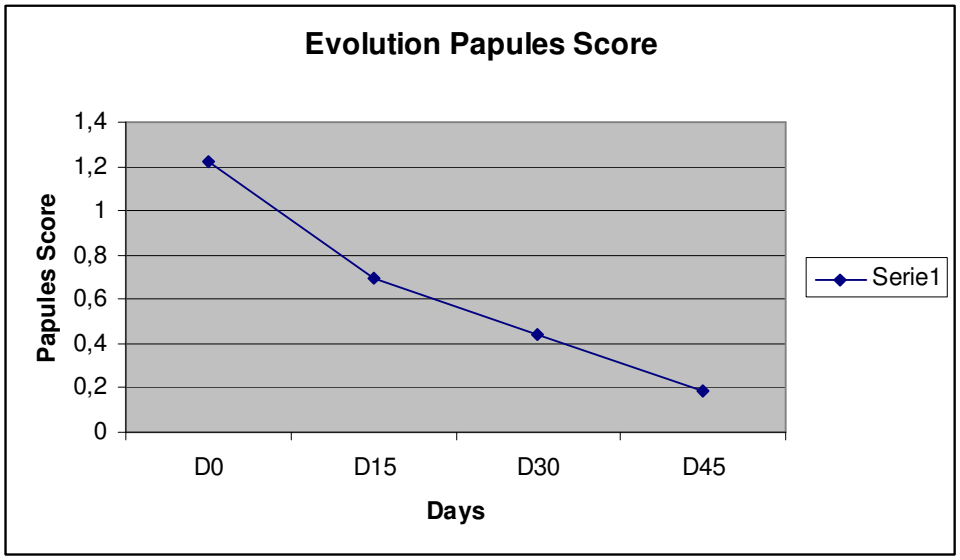
Papules

Patients experienced a continuous decline in the mean papules score along this study, from a mean of 1.22 (± 1.15) at baseline to a mean of 0.19 (± 0.40) at D45 (**Figure 5**) i.e. a decrease in papules score of 84% ($p<0.001$)
Detailed results are reported in **Table 6**.
At the end of the study, 81% of patients having completed the study were rid of papules, when they were only 33% at the beginning of the score.

Table 6. Papules score along the study

Score	DO	D15	D30	D45
0	9	13	16	22
1	9	10	10	5
2	3	3	1	0
3	6	1	0	0
mean	1.22 (± 1.15)	0.70 (± 0.82)	0.44 (± 0.58)	0.19 (± 0.40)

Figure 5- Reduction in papules score along the study



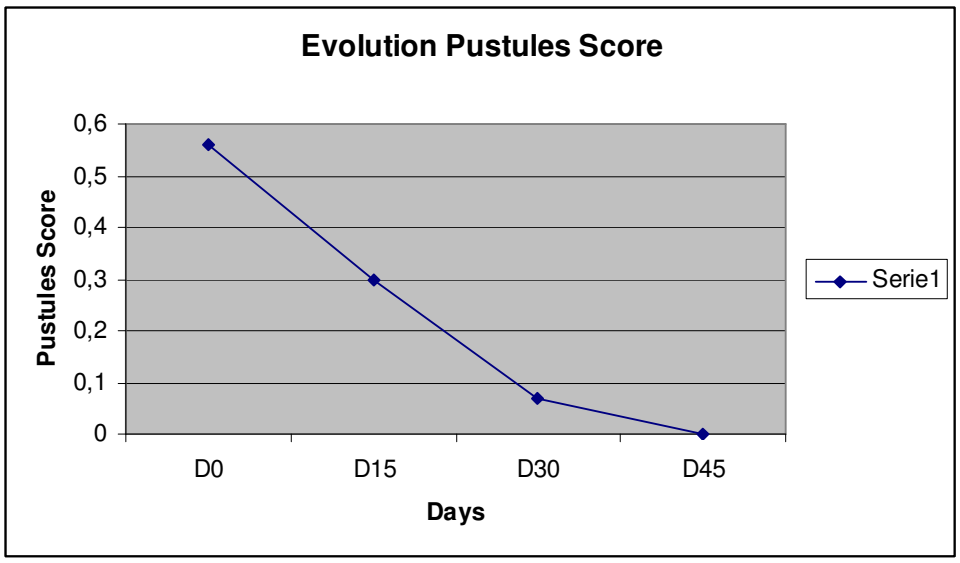
Pustules

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 D45, as shown in **Figure 5**. This means a decrease in pustules score of 100% ($p<0.001$) along the study.
Detailed results are recorded in **Table 7**.
At the end of the study, name of the patients was showing pustules, whilst 44% of them had same grade when starting the treatment.

Table 7- Papules score along the study

Score	DO	D15	D30	D45
0	15	20	25	27
1	9	6	2	0
2	3	1	0	0
3	0	0	0	0
mean	0.56 (±0.70)	0.30 (±0.54)	0.07 (±0.27)	0.00

Figure 6- Reduction in pustules score along the study



Overall improvement

An overall improvement occurred over time along this study.
More than 37% of patients experienced excellent improvement or complete remission; 22% of them felt a marked improvement, nearly 30% a moderate and only 11% had no important throughout 6 weeks of treatment. (**Table 8 and Figure 7**)

Figure 7- Overall improvement at the end of therapy

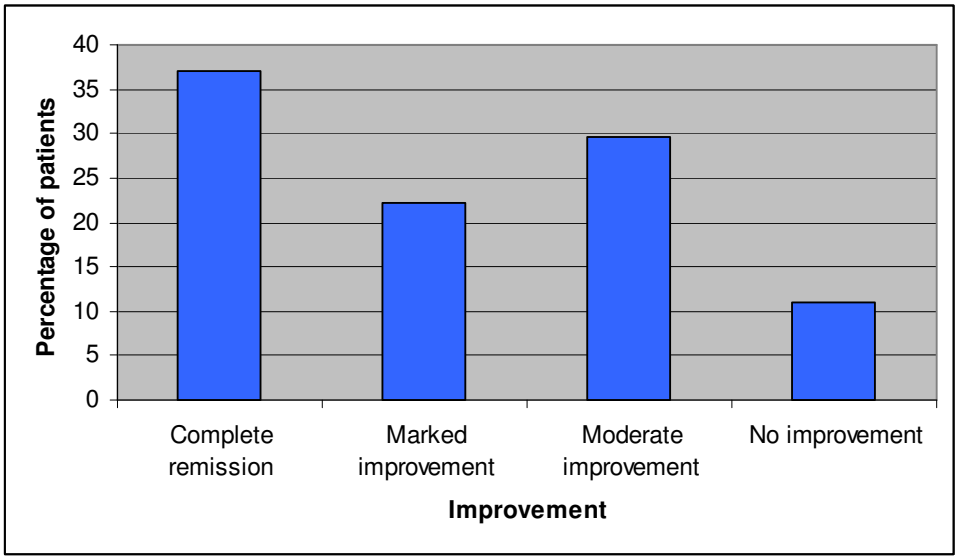


Table 8- Overall improvement at the end of the therapy

Number of parameters Improved	**Number Of patients (%)**	**Improvement**	**Number of Patients (%)**
1	3 (11,1%)	No improvement	3 (11.1)
2	8 (29,6%)	Moderate improvement	8 (29,6)
3	6 (22,2%)	Marked improvement	6 (22.2)
4	6 (22,2%)	Complete remission	10 (37.0)
5	4 (14,8%)		

Adverse effects-Tolerance

No adverse effect such as itching, edema, burning and stinging was reported along this study.

The tolerance was excellent in all the patients having completed the treatment.

DISCUSSION

To the best of our knowledge, this is the first time that a clinical trial is conducted using topical Quassia extract in the treatment of various grades of rosacea.

This study demonstrated the effectiveness and complete safety of 4% Quassia extract gel in the treatment of all grades of rosacea.

This therapy showed major improvements in flushing, erythema, papules and pustules, and very significant improvement, significant although less important, in telangiectasia after 6-weeks treatment.
Improvements in global assessment of disease severity determined by the investigator also showed excellent results at the end of this study and the patients improved continuous improvements throughout the duration of the study.

This real efficacy of Quassia extract may be explained by its antiparasitic action on Demodex folliculorum, but also its strong anti inflammatory properties and probably also its antioxidant effect.

As there is no previous study published using this active ingredient, no comparison is possible. Nevertheless, we have tried to compare them with previously published results obtained following topical treatment of rosacea with metronidazole and azelaic acid, both widely accepted and used in this pathology.
In a recent systematic review of rosacea treatments [(11)], topical metronidazole was shown to be more effective than placebo (odds ratio 5,96; 95% confidence interval 2,95-12.06).
Our personal review of papers describing the results of use of topical Metronidazole (either 0.75% or 1% gel or cream) in rosacea[(10,11,12,13,14,15,16,17,18)] showed that taken altogether, these studies are featuring an average duration of treatment of 10,89 weeks vs. our 6-weeks treatment.
Regarding the percentage of reduction in lesion count, the mean value is 60.75% ($\pm$ 6.18) vs. 25.2% ($\pm$ 14.0) ($p<0.001$), compared to our result of 84% in papules and 100% in pustules.

In the review of clinical trials conducted with azelaic acid[(20)] either 15% or 20% gel or cream, the mean value of the duration of treatment was also 10,80 weeks compared to our 6-weeks treatment.
The mean number of lesions was 19,86 ($\pm$ 6.80) at baseline and 7.60 ($\pm$ 4.93) at the end of treatment, meaning a decrease in the number of lesions of 61.7% ($p=0.001$) compared to our result of 84% in papules and 100% in pustules.
The mean reduction in erythema score was 40,0% ($-$ 18.9) ($p<0.01$) compared to our result of 56.0% ($\pm$ 12.4) ($p<0.001$).
The mean reduction in telangiectasia score was 19.4% ($\pm$ 12.3) ($p=0.6$) vs. our results of 50% ($p<0.001$).

In summary, it appears that topical Quassia extract is significantly more efficient than topical metronidazole (0.75% or 1%, gel or cream) and than Azelaic acid (15% or 20%, gel or cream) in the treatment of the following symptoms of rosacea: papules, pustules and erythema. Activity of topical Quassia extract is significantly higher than those of MZ or AZA on the reduction of telangiectasia.

Further, a total absence of side effects was observed throughout this study, whilst some side effects were sometimes described with MZ or AZA.

In conclusion, it appears that topical Quassia extract could be a new, efficient and safe weapon in our armamentarium for the management of rosacea in topical way. However, since in this previous encouraging report had only been studied small number of patients, further clinical trials involving double-blind protocol, comparative studies with current therapies and a larger number of patients are warranted to assess the precise efficacy of topical Quassia extract in rosacea.

Product	Author	Study Design	Frequency and duration	Number of patients	Percent reduction in lesion count vs. placebo	Significant reduction in erythema	Adverse effects	Onset of efficacy (weeks)
0,75 %gel	Aronson [12]	R, SF, DB	Twice daily 9 weeks	47	51% vs 4%	Yes	None	3 w
0,75% gel	Bleicher [13]	R, SF, DB	Twice daily 9 weeks	40	65% vs 15%	Yes	None	3 weeks
1% gel	Beutner [14]	R, PG, SB	Once daily 10 weeks	>1200	67% (1% gel) Vs 58% (1% cream) Vs 46% (vehicle)		3% (1%gel) 4% (1%cream) 4% (vehicle)	
0,75% cream	Drake [15]	R, PG, DB	Twice daily 12 weeks	143	62,5% vs 43%			
1% cream	Breneman [16]	R, PG, DB	Once daily 10 weeks	89	53% vs 17%	Yes	2%	2-4
1% cream	Jorizzo [17]	R, PG, DB	Twice daily 12 weeks	61	65% vs 25%	Yes	Mild reactions	4
1% cream + sunscreen	Tan [18]	R, PG, DB	Twice daily 12 weeks	61	65% vs 25%	Yes		4
0,75% lotion	Breneman [19]	R, PG, DB	Twice daily 12 weeks	65	57% vs 27%			
0,75% gel	Wolf [20]	Open MC	Twice daily 12 weeks	582	53%	Yes		4

Table 9: Summary of clinical data reviewed regarding the efficacy of topical metronidazole in rosacea.

Authors year	Type of study	Nº of patients	Product used	Control	Posology	Duration of treatment	Results
Bjerke [21] 1999	R, DB,	114	20% AZA cream	Vehicle	2x daily	3 months	Nº of inflammatory lesions Before/after AZA 30.8/8.3 Before/after vehicle 31.7/15.3 Reduction in erythema score 47.9 % vs 37.9 % Reduction in telangiectasia score 22.3% vs 23.5%
Carmichael [22] 1993	R,DB	33	20% AZA cream	Vehicle	2x daily	9 weeks	Nº of inflammatory lesions Before/after AZA 14.2/2.5 Before/after vehicle 15.0/6.6 Reduction in erythema score 7.2 % vs 2.8% Reduction in telangiectasia score - 2.3% vs + 2.2%
Thiboutot study I [23] 2003	R,DB	329	15% AZA Gel	Vehicle	2x daily	12 weeks	Nº of inflammatory lesions Before/after AZA 17.5/6.8 Before/after vehicle 17.6/10.5 Reduction in erythema score 44% vs 29% Telangiectasia Unchanged in 77% vs 80%
Thiboutot study II [24] 2003	R,DB	335	15% AZA Gel	Vehicle	2x daily	12 weeks	Nº of inflammatory lesions Before/after AZA 17.8/8.9 Before/after vehicle 18.5/12.1 Reduction of erythema score 45% vs 28% Telangiectasia Unhanged in 73% vs 78%
Bamford [25] 1999	R,DB	53	20% AZA Cream	Vehicle		9 weeks	Nº of inflammatory lesions Before/after AZA 18.1/4.5 Before/after vehicle 19.4/7.6 Reduction of erythema score 56% vs 42% Telangiectasia Unchanged in 73% vs 76%

Table 10: Systematic analysis of clinical assessing the efficacy of topical azelaic acid in rosacea. [20]

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