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# A Report on Three Recent Clinical Trials Using *Mahonia aquifolium* 10% Topical Cream and a Review of the Worldwide Clinical Experience With *Mahonia aquifolium* for the Treatment of Plaque Psoriasis

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This monograph summarizes 3 recent clinical trials and the worldwide clinical experience with *Mahonia aquifolium* in patients with psoriasis. Study 1 was an open-label study to evaluate the safety of *Mahonia aquifolium* in 39 patients treated for 12 weeks. Assessments made were modified PASI, global assessment, psoriasis history questionnaire, Dermatology Life Quality Index, and Psoriasis Disability Index. The results indicate statistically significant improvement in PASI score and Dermatology Life Quality Index after 4 weeks of treatment. This response continued 1 month after the end of treatment. Study 2 was a clinical trial of 32 patients with mild to moderate bilateral psoriasis treated up to 6 months. One side of the body received *Mahonia* and the other standard psoriatic treatment (eg, Dovonex cream). The primary outcomes were patient ratings of the *Mahonia*-treated side alone and the comparison between treatments received on each side of their body. Eighty-four percent of patients rated the *Mahonia*-treated psoriasis as good to excellent response. When compared with standard treatment, 63% of patients rated *Mahonia aquifolium* equal to or better than the standard psoriatic treatment. Study 3 was an observational study of 33 patients with mild to moderate bilateral psoriasis treated for 1 month. The results indicate improvement in psoriasis after 1 week of treatment. The side treated with *Mahonia* did as well or better than the side treated with the vehicle cream. Results from these 3 open-label clinical trials are in agreement with published data that include placebo-controlled studies. Taken together, these clinical studies conducted by several investigators in several countries indicate that *Mahonia aquifolium* is a safe and effective treatment of patients with mild to moderate psoriasis.

*Keywords:* psoriasis, *Mahonia aquifolium*, natural products

## INTRODUCTION

Psoriasis is characterized by changes in the skin that include hyperkeratosis, parakeratosis, and akantosis.[1] They are attributed to an increased mitosis rate in the basal region of the epidermis, as well as disorders of maturing and differentiating keratinocytes. These changes in the dermis and epidermis cause the typical desquamation of the stratum corneum observed in psoriasis. The psoriatic lesions indicate an inflammatory reaction caused by the secretion of pro-inflammatory cytokines[2] from macrophages, lymphocytes, and neutrophils.[3] These cytokines may stimulate the inflammatory response via the lipoxygenase and the cyclooxygenase (COX) pathways.

The red, scaling psoriatic plaques often itch and burn. People with psoriasis may suffer discomfort, including pain and itching and emotional distress.[4]

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Psoriasis affects 1% to 2% of the population of the United States or about 5.5 million people.[4]

The symptoms of psoriasis often require treatment. Treatment can be difficult because the severity and distribution of psoriatic plaques varies greatly. Psoriasis most often occurs on the elbows, knees, scalp, lower back face, palms, and soles of the feet, but it can occur anywhere on the skin.[4] Localized psoriasis often responds to topical medications, of which steroid creams, vitamin D analogue creams, anthralin, coal tar, and ultraviolet light treatments are the most common remedies. More generalized involvement of the skin may require systemic treatments with retinoids, immunosuppressives, PUVA, or biologic medications. The effectiveness, cost, and side effect profiles of these medications indicate the need for additional treatment options.

One alternative treatment with minimal side effects is *Mahonia aquifolium*. *Mahonia aquifolium* (Barberry, Oregon grape, Berberis) belongs to the Berberidaceae family and grows wild in Europe and North and South America (Fig. 1). The root and wood of *Mahonia aquifolium* contain many isoquinoline alkaloids, including berberine, palmatine, berbamine, oxyacanthine, jatrorrhizine, bervulcine, magnoflorine, and columbamine. Of these, berberine is the best characterized.[5]*Mahonia aquifolium* has been used as a medication for inflammatory skin diseases such as psoriasis.[6,7] More recently, clinical trials have been conducted comparing *Mahonia aquifolium* with other treatments. This report describes 3 recent trials and review the clinical data currently available on the use of *Mahonia aquifolium* for the treatment of psoriasis.

**FIGURE 1**. The Mahonia aquifolium plant.

## STUDY 1: SAFETY STUDY

Investigator: Wayne P. Gulliver, MD, FRCPC Chairman of Dermatology at Memorial University and NewLab Clinical Research Inc. St John's, Newfoundland.

### Materials and methods

#### *Study design*

An open-label study was conducted to evaluate the safety of *Mahonia aquifolium* in 39 patients with chronic plaque psoriasis. Patient eligibility was evaluated during a screening visit before entry into the study. Qualified participants had mild to moderate psoriasis, with a PASI <12. Eligible participants discontinued all psoriasis therapies for 2 weeks prior to baseline assessment. Each patient was instructed to apply *Mahonia* cream twice a day for 3 months. Patients were evaluated at regular intervals throughout 12 weeks of therapy. Follow-up was conducted 1 month after completion of therapy.

#### *Study treatments*

*Mahonia aquifolium* (Prime Pharmaceutical Corporation, Toronto, Canada) cream was standardized to contain 0.1% berberine. The *Mahonia aquifolium* used was purified from *Berberis aquifolium Pursh* (Oregon hollygrape) and manufactured under current good manufacturing practices.[8]

#### *Study protocol*

The study protocol required 9 patient visits, including the screening visit. Study participants who met the enrollment criteria returned after the baseline assessment for treatment. Participants then returned for regular visits throughout the 3-month treatment period. Evaluation was conducted at each patient visit.

#### *Study participants*

Male and female patients with mild to moderate chronic psoriasis were enrolled in the study. Exclusion criteria included patients who were receiving systemic medications or had any other comorbid conditions. Patients were said to be noncompliant when they missed any patient visit.

#### *Participant enrollment*

Patient eligibility was determined during a screening visit before entry into the study. The eligibility of the

patient was assessed by a board-certified dermatologist and a complete medical history, physical examination, and laboratory tests including a complete blood count, electrolytes, and kidney function tests were performed. At baseline assessment, each patient was scored on a modified PASI scale, and each patient completed a psoriasis history questionnaire, the Dermatology Life Quality Index (DLQI), psoriasis disability index. Photographic evaluation of lesions was conducted.

*Participant monitoring*

Study participants were assessed after 1, 2, 3, 4, 6, 8, and 12 weeks of therapy. A follow-up visit was conducted 1 month after the end of therapy, at week 16.

*Efficacy measurements*

Vital signs were monitored at weeks 4 and 12. Modified PASI scoring was conducted at each visit. Global assessment was conducted each month (baseline, weeks 1, 4, 8, 12). A psoriasis history questionnaire, DLQI, and a psoriasis disability index were completed at baseline and weeks 4, 12, and 16.

*Safety assessment*

The safety of treatment was determined from patient reports of adverse events.

*Statistics*

Paired $t$ tests were performed on the data. Statistical significance was indicated by $P < 0.05$.

**Results**

*Patient demographics and baseline disease characteristics*

A total of 39 patients began this study. Of these, 35 patients completed 4-week assessments, 27 patients completed 8 weeks of treatment. Twenty-four patients completed 12 weeks of treatment and 19 patients completed all 12 weeks of treatment and 1-month follow-up visit. The demographic and baseline characteristics of the participants were similar, with a mean age of 45.5 years (Table 1). Eleven patients had moderate psoriasis (PASI between 6 and 12) with the remainder having mild psoriasis (PASI between 0 and 6).

*Discontinuation of treatment*

Nineteen patients completed this study. No patient discontinued treatment due to any adverse event or worsening of symptoms. The main reason for withdrawing from this study was lack of efficacy.

*Treated population*

At each visit, each patient was scored on a modified PASI scale. The results of the PASI scores demonstrate a statistically significant improvement in PASI at each evaluation (Table 2). This improvement continued 1 month after the end of therapy.

Patients reported a significant improvement in the DLQI (Table 3). This improvement was significant at week 4 and continued to week 12. This improvement was remained 1 month after discontinuation of therapy, at week 16.

Photographic evaluation (Fig. 2) of patients showed significant improvement from baseline to week 4. This improvement continued at week 12.

*Safety profile of* Mahonia *cream*

All patients were included in the safety analysis. There were no drug-related adverse events, no significant changes in vital signs or laboratory evaluations.

# STUDY 2: PATIENT RESPONSE STUDY

Investigator: Howard J. Donsky, MD, FRCPC. University of Rochester Medical School, Rochester, NY.

**Materials and Methods**

*Study design*

A clinical trial of 32 people with mild to moderate psoriasis was conducted with *Mahonia aquifolium*. Patient eligibility was evaluated during a screening visit before entry into the study. Qualified participants had bilateral psoriasis on joints such as elbows and knees. Each patient served as their own control. Each patient was instructed to apply *Mahonia* cream to one side of their body and the treatment cream to the equivalent bilateral site for an extended period of time

**Table 1**. Patient demographics and baseline disease characteristics at baseline.

| Parameter | No. (%) |
|---|---|
| No. of patients | 39 |
| Mean age, y | 45.5 |
| Gender | |
| Male | 28 (54.8) |
| Female | 11 (45.2) |
| Mean PASI score | 5.6 |

**Table 2.** Treatment outcomes: PASI scores.

| | Baseline | Wk 4 | Wk 8 | Wk 12 | Wk 16 |
|---|---|---|---|---|---|
| No. | 39 | 35 | 27 | 23 | 19 |
| Mean ± SD | 5.6 | 2.3 ± 2.3* | 2.1 ± 2.1* | 2.2 ± 2.4* | 1.4 ± 3.2* |
| *P* | | <0.001 | <0.001 | <0.001 | <0.001 |

*Indicates significant difference from baseline. $P < 0.05$.

(1, 3, 6 months). Patients were evaluated at their next visit.

*Study treatments*

*Mahonia aquifolium* (Prime Pharmaceutical Corporation) cream was standardized to contain 0.1% berberine. The *Mahonia aquifolium* used was purified from *Berberis aquifolium Pursh* (Oregon hollygrape) and manufactured under current good manufacturing practices.[8] Standard topical treatments for psoriasis were used as the comparison treatment. These treatments included Calcipotriol (Dovonex) and fluticasone propionate (Cutivate).

*Study protocol*

The study protocol required 2 patient visits, including the screening visit. Study participants who met the enrollment criteria were given treatment creams at the initial screening visit. Participants then returned for one additional visit at weeks 4, 12, or 6 months. Evaluation was conducted at the next patient visit.

*Study participants*

Male and female patients with mild to moderate psoriasis were enrolled in the study. All patients had bilateral psoriasis on equivalent parts of their body. Exclusion criteria included patients who were receiving systemic medications or had any other comorbid conditions.

Patients were said to be noncompliant when they missed any patient visit. Two patients were dropped from the study because they did not return for follow-up visits.

**Table 3.** Treatment outcomes: Dermatology Life Quality Index.

| | Baseline | Wk 4 | Wk 12 | Wk 16 |
|---|---|---|---|---|
| No. | 39 | 35 | 23 | 19 |
| Mean ± SD | 5.5 | 3.9 ± 2.8* | 3.2 ± 2.8* | 2.2 ± 3.6* |
| *P* | | <0.002 | <0.001 | <0.003 |

*Indicates significant difference from baseline. *P* value <0.05.

*Participant enrollment*

Patient eligibility was determined during a screening visit before entry into the study. The eligibility of the patient was assessed by a board-certified dermatologist and a medical history and physical examination were performed.

*Participant monitoring*

Study participants were asked to rate their response to both medications at the second visit. In addition, study participants were asked to compare the response of the *Mahonia*-treated side of their body with the side receiving standard medication.

*Efficacy measurements*

The results of treatment were assessed at the second patient visit. The primary outcomes were the patient ratings of the *Mahonia*-treated side alone and the comparison between treatments received on each side of their body. The scales used for these outcomes are shown in Tables 4 and 5.

*Safety assessment*

The safety of treatment was determined from patient reports of adverse events.

## Results

*Patient demographics and baseline disease characteristics*

Thirty-two patients began this study. Of these, 30 patients completed both visits. The demographic and baseline characteristics of the participants were randomly chosen and consisted of adult men and women. The only medical condition these participants were receiving was treatment of psoriasis. All patients had mild to moderate bilateral psoriasis, as diagnosed by the same board-certified dermatologist.

*Discontinuation of treatment*

Thirty patients completed this study. No patient discontinued treatment due to any adverse event or worsening of symptoms. Two patients were lost to follow-up at the second visit.

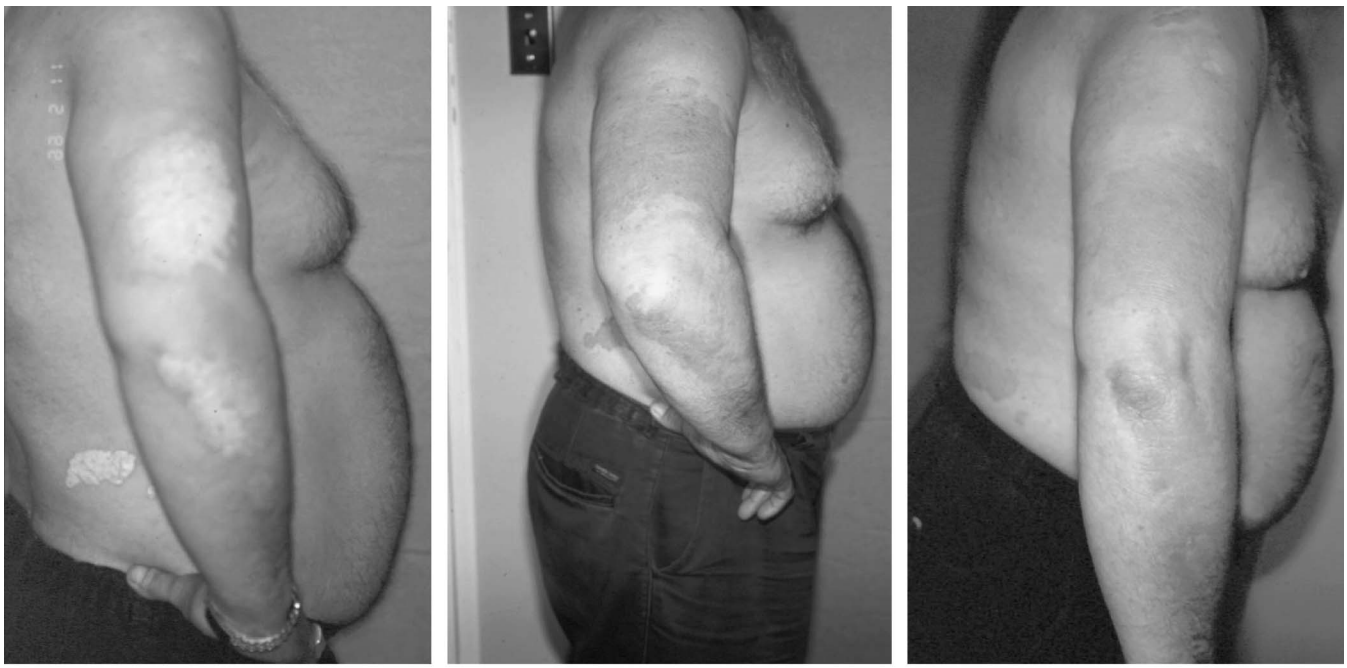


**FIGURE 2**. Psoriasis in a typical patient before treatment (a) and after 4 (b) and 12 (c) weeks of treatment with *Mahonia aquifolium*.

*Treated population*

Patients were asked to rate the amount of improvement of the *Mahonia*-treated psoriasis. The responses obtained are shown in Table 4. Twenty-five patients (84%) rated the *Mahonia*-treated psoriasis as good to excellent response. Two patients received minimal response. The psoriasis of 3 patients did not respond to the *Mahonia* cream.

When compared with the standard treatment used on the equivalent bilateral side of the patient's body, 19 patients (63.3%) of patients rated the *Mahonia* cream as equal to or better than the standard treatment they were receiving (Table 5). Eleven patients (37%) rated the *Mahonia* cream inferior to the standard psoriasis treatment.

*Safety profile of* Mahonia *cream*

All patients were included in the safety analysis. No patient reported any adverse events such as burning or itching of either treatment (*Mahonia* cream or standard topical cream for psoriasis).

## STUDY 3: OBSERVATIONAL STUDY

Investigator: Kevin C. Smith, MD, FRCPC (Diplomate, American Board of Dermatology) Niagara Falls,

**Table 4**. Patient response form.*

| Patient response | Rating | Patient response (total = 30) No. (%) |
|---|---|---|
| None | 0–1 | 3 (10.0) |
| Minimal | 2–4 | 2 (6.7) |
| Good | 5–7 | 17 (56.7) |
| Excellent | 8–10 | 8 (26.7) |

*Each patient was asked to rate their experience with the *Mahonia aquifolium* cream using the criteria below.

**Table 5**. Comparative treatment form.*

| Comparison of *Mahonia* cream with standard treatment | Patient response (total = 30) No. (%) |
|---|---|
| Worse than | 11 (36.7) |
| Equal to | 11 (36.7) |
| Better than | 8 (26.7) |

*Each patient was asked to compare their experience with the *Mahonia aquifolium* cream to the standard treatment cream for psoriasis.

Ontario, Canada (Dr. Smith presented his study at the Canadian Dermatology Association Annual Conference June 2000).

## Materials and methods

### *Study design*

A clinical trial of 33 patients with mild to moderate psoriasis was conducted with *Mahonia aquifolium*. Patient eligibility was evaluated during a screening visit before entry into the study. Qualified participants had bilateral psoriasis on joints such as elbows and knees. As patients entered the study they were randomly assigned to 1 of 2 groups: *Mahonia*-treated group or the standard-treated group. Each patient was instructed to apply the treatment cream to one side of their body and the vehicle used to deliver the cream to the equivalent bilateral site for a period of time (1, 2, and 4 weeks). The psoriatic plaques of each patient were photographed and scored 0 to 3 for scaling, thickness, and redness prior to treatment and at each patient visit.

### *Study treatments*

*Mahonia aquifolium* (Prime Pharmaceutical Corporation) cream was standardized to contain 0.1% berberine. The *Mahonia aquifolium* used was purified from *Berberis aquifolium Pursh* (Oregon hollygrape) and manufactured under current good manufacturing practices.[8] Standard topical treatments for psoriasis were used as the comparison treatment. These treatments included Calcipotriol (Dovonex) and Tazorac gel.

### *Study protocol*

The study protocol required 4 patient visits, including the screening visit. Study participants who met the enrollment criteria were given treatment creams at the initial screening visit. Participants then returned for 3 additional visits at weeks 1, 2, and 4. Photographic assessment and scoring of each psoriatic plaque for scaling, thickness, and redness was conducted at each patient visit.

### *Study participants*

Male and female patients with mild to moderate psoriasis were enrolled in the study. All patients had bilateral psoriasis on equivalent parts of their body. Some patients were receiving methotrexate and/or UV light treatment during the study. Exclusion criteria consisted of treatment of other comorbid conditions.

Patients were said to be noncompliant when they missed any patient visit. All patients completed this study.

### *Participant enrollment*

Patient eligibility was determined during a screening visit before entry into the study. The eligibility of the patient was assessed by a board-certified dermatologist and a medical history and physical examination were performed.

### *Participant monitoring*

Photographs of all psoriatic plaques were taken at each patient visit. At each visit, each psoriatic plaque was scored for scaling, thickness, and redness on a scale of 0 to 3, with zero the minimum and 3 was the maximum score each plaque could receive.

### *Efficacy measurements*

The results of treatment were assessed prior to treatment and at each patient visit. The primary outcomes were the photographs and physician ratings of scaling, thickness, and redness for each psoriatic plaque.

### *Safety assessment*

The safety of treatment was determined from patient reports of adverse events.

### *Statistics*

This was an observational study, not designed to produce data for statistical analysis.

## Results

### *Patient demographics and baseline disease characteristics*

Thirty-three patients completed this study. The demographic and baseline characteristics of the participants were randomly chosen and consisted of adult men and women. All patients had mild to moderate bilateral psoriasis, as diagnosed by the same board-certified dermatologist.

### *Discontinuation of treatment*

All patients completed this study. No patient discontinued treatment due to any adverse event or worsening of symptoms.

### *Treated population*

In *Mahonia*-treated patients, the first symptom to improve was scaling. In some cases, improvement was observed after the first week of *Mahonia* treatment. The thickness of *Mahonia*-treated plaques declined over a period of 2 to 4 weeks, and redness improved gradually.

*Mahonia* treatment was accepted by all patients, and adherence to the protocol was excellent. In all patients,

the side treated with *Mahonia* cream did as well or better than the side treated with vehicle cream. In no case were the results of the *Mahonia* cream inferior to the vehicle cream.

*Safety profile of* Mahonia *cream*

All patients were included in the safety analysis. There were no dropouts from the treatment protocol. Two patients stopped *Mahonia* cream due to bilateral exacerbations of psoriasis. The cause of the exacerbation was not clear but did not seem to be related to the application of *Mahonia* cream to one side of the body.

# DISCUSSION

The Safety Study demonstrates *Mahonia aquifolium* is a safe and effective treatment of psoriasis. The Patient Response Study indicates that *Mahonia aquifolium* cream is as effective as standard psoriatic treatment (for example, Dovonex cream). This was confirmed visually in the open-label study presented here. This safe and effective cream could greatly benefit patients with psoriasis.

### Mechanism of action of *Mahonia aquifolium* in psoriasis

The pathogenesis of psoriatic lesions is not well understood. What is known is that the increased rate of cell proliferation contributes to psoriasis. Laboratory studies[9] have shown that berberine, the primary alkaloid isolated from *Mahonia aquifolium*,[10] inhibits keratinocyte growth in vitro. Cell proliferation can be also be altered by inhibiting DNA and protein synthesis.[11] Schmeller et al[11] demonstrated that berberine inhibits DNA synthesis by intercalating into DNA and blocking the action of reverse transcriptase. Further studies by Augustin[12] used immunohistochemistry to show that the topical application of *Mahonia aquifolium* reduced the inflammatory and keratinocyte hyperproliferation markers typically seen in psoriasis.

The antipsoriatic effects of *Mahonia aquifolium* have been attributed to the primary alkaloid extracted from this plant, berberine. The anti-inflammatory effects of berberine have been linked to the inhibition of lipoxygenase and lipid peroxidation[5,13,14] and the cyclooxygenase pathway through the reduction of prostaglandin $E_2$.[15] More recent evidence indicates berberine may inhibit the ability of cytokines to promote the inflammatory response.[16,17] All these pathways are believed to contribute to the inflammation of psoriasis.

### Comparison with previous clinical studies

Previous placebo-controlled and open clinical trials[1,6,7,18] have reported the clinical effectiveness of *Mahonia aquifolium* in the treatment of psoriasis. The first clinical studies were conducted by Weisenauer.[6] These authors reported a multicenter, randomized, double-blinded study of 93 patients with mild to moderately severe psoriasis and compared topical *Mahonia aquifolium* with the oral formulation of this treatment. At the end of this study, more than 70% of patients in both treatment groups experienced significant improvement.

Gieler et al[7] conducted an open, prospective, multicenter trial on a large number of patients (N = 433) with subacute and chronic psoriasis at 89 sites in Germany. These patients were treated with *Mahonia aquifolium* ointment (Rubisan) and evaluated using a modified psoriasis activity and severity index (PASI) score. At the start of the study, 30.1% of patients had significant or severe symptoms of psoriasis. Twelve weeks later, between 70% and 81.1% of patients experienced improvement. At the end of the study, only 5.6% of patients reported remaining symptoms of psoriasis. Adverse events upon application of *Mahonia aquifolium* ointment included burning and itching sensations. However, the tolerability of *Mahonia aquifolium* ointment was described as very good by 82.4% of patients. The authors concluded that *Mahonia aquifolium* was a well-tolerated preparation that should be used as an alternative treatment to conventional psoriasis treatment.

To determine the efficacy and safety of *Mahonia aquifolium* in the treatment of psoriasis, Weismauer and Ludtke[1] conducted a randomized, placebo-controlled clinical trial with 82 psoriasis patients of all severity ratings. Patients were instructed to apply one type of ointment (either *Mahonia aquifolium* or placebo) to the left side of their body and the other ointment to the right side of their body. After 4 weeks of treatment, patients and physicians rated the therapy's success on a 3-point rating scale. Statistically significant differences were observed in the patients' assessments. Adverse events such as itching and burning sensations and allergic reactions were reported in 4 patients. The authors concluded *Mahonia aquifolium* was a potent and safe therapy for moderately severe cases of psoriasis.

Augustin[12] compared the effectiveness and healing of *Mahonia aquifolium* with the conventional treatment, dithranol (anthralin) ointment in 80 patients. Treatment effectiveness was measured using the PASI index and immunohistochemistry of the treated sites.

**Table 6**. Clinical trials with *Mahonia aquifolium*: efficacy and safety.

| Author | Description | No. of patients | Efficacy | Adverse reactions |
|---|---|---|---|---|
| Weisenauer (1992) | Multicenter, randomized, double-blind study with topical and oral *Mahonia aquifolium* | 93 | Significant improvement in >70% of patients in both groups | |
| Gieler et al (1995) | Open, prospective, multicenter trial with topical *Mahonia aquifolium* ointment | 433 | Modified PASI score decreased from 5.5 ± 4.0 to 2.3 ± 2.6; overall symptoms improved in 81.1% by physician assessment and 79.7% by patient assessment | Burning, itching, and redness; overall tolerability rated as good or very good by 82.4% of patients |
| Weisenauer and Ludtke (1996) | Randomized, placebo-controlled study with topical *Mahonia aquifolium* ointment | 82 | Statistically significant ($\alpha$ = 5%) difference in patient's assessment but not for physician assessment | Self-reported ''allergic reaction,'' itching, or burning in 4 patients |
| Augustin (1999) | | 80 | | |

Subjects were treated on one skin site with *Mahonia aquifolium* ointment 3 times a day and treated with dithranol on a different site in rising concentrations once a day. Biopsies at the test sites were performed in 49 patients before treatment and 4 weeks after initiation of treatment. Monoclonal antibodies to ICAM-1, CD3, HLA-DR, keratin 6, keratin 16, and Ki-67 were used to detect changes in cellular immune activity and keratinocyte proliferation.

Marked reduction in cellular immune activity and keratinocyte proliferation was detected by immunohistochemical staining in both *Mahonia aquifolium* and dithranol-treated sites; although greater reductions were seen in dithranol-treated sites.

### Overall Conclusion

To summarize, several open-label and placebo-controlled clinical trials have been performed to assess the efficacy and safety of *Mahonia aquifolium* (Table 6). Wiesenauer[6] demonstrated in a double-blind study that topical *Mahonia aquifolium* produced a statistically significant difference ($P < 0.05$) in the patient's assessment of disease severity. Gieler et al[7] and Augustin[12] demonstrated high rates of disease improvement and a low side effect profile.

Results from these 3 open-label clinical trials are in agreement with published data that includes placebo-controlled studies.

Taken together, these clinical studies conducted by several investigators in several countries indicate that *Mahonia aquifolium* is a safe and effective treatment of patients with mild to moderate psoriasis.

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