

# *Petasites hybridus* (Butterbur root) Extract in the Treatment of Asthma – An Open Trial

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## Abstract

The efficacy and tolerability of a butterbur root extract (Petadolex®) for the treatment of asthma was analyzed in a prospective, non-randomized, open trial. Subjects included 64 adults and 16 children/adolescents treated for two months with the extract, followed by two months during which the intake of the extract was optional. Concomitant asthma medication was permitted. The number, duration, and severity of asthma attacks decreased, while peak flow, forced expiratory volume (FEV1), and all measured symptoms improved during therapy. In addition, more than 40 percent of patients using asthma medications at baseline reduced intake of these medications by the end of the study. This study suggests the *Petasites hybridus* extract Petadolex is an effective and safe therapy for the treatment of asthma. (*Altern Med Rev* 2004;9(1)54-62)

## Introduction

Asthma is a chronic inflammatory disorder of the airways.<sup>1,2</sup> In the past, the predominant pathophysiology of acute asthma was considered to be bronchospasm occurring in response to a variety of specific and nonspecific stimuli such as allergens and irritants. However, the main pathophysiology of the attack is now understood to be an inflammatory response, with inflammation leading to bronchospasm.<sup>3</sup> The initial trigger in asthma may be the release of inflammatory mediators from bronchial mast cells, macrophages, T-lymphocytes, and epithelial cells. These mediators direct the migration and activation of other inflammatory cells, such as

eosinophils and neutrophils, to the airways where they cause alterations in epithelial integrity, abnormalities in autonomic neural control of airway smooth vascular tone, increased vascular permeability, mucus hypersecretion, change in mucociliary function, increase in airway smooth muscle responsiveness, and structural changes in airway architecture.

Increased appreciation of the role of inflammation in the pathophysiology of asthma has led to new treatment strategies. Studies have shown improvements in asthma symptoms caused by high doses of inhaled corticosteroids are associated with improvement in markers of airway inflammation.<sup>4,5</sup> These observations confirm the strong link between airway inflammation, bronchial hyperresponsiveness, and asthma symptoms and severity.

Allopathic asthma treatment commonly consists of long-term therapy (control medication) and quick-relief therapy (relief medication). Current management guidelines stress the importance of first-line therapy with inhaled corticosteroids (e.g., beclomethasone, budesonide, fluticasone, triamcinolone) to suppress the inflammatory process.<sup>2</sup> The main concern with inhaled corticosteroid treatment is the potential for dose-related systemic effects, including adrenal suppression, osteoporosis, growth inhibition, skin bruising, cataracts, and ocular hypertension.<sup>6</sup>

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Cromolyn and nedocromil sodium have similar anti-inflammatory properties, but are less effective in treating asthma than inhaled corticosteroids.

The cysteinyl leukotrienes C4, D4, and E4 cause smooth muscle constriction and proliferation and are important mediators in the pathophysiology of the inflammatory process. Based on this knowledge, a new class of anti-inflammatory agents – the leukotriene antagonists – were developed.<sup>7</sup> Leukotriene antagonists possess both anti-inflammatory and bronchodilation activity. Two types can be distinguished based on mechanism of action: leukotriene-receptor-antagonists (zafirlukast and montelukast) and leukotriene-synthesis-inhibitors (zileuton). These medications appear to improve lung function and reduce the use of inhaled and oral corticosteroids; however, they have the potential for side effects. Zileuton requires liver function monitoring and systemic vasculitis has been associated with zafirlukast and montelukast.

Beta-agonist medications are used both for acute and long-term asthma management, often in conjunction with oral corticosteroids and/or leukotriene antagonists. Long-acting beta-agonists like salmeterol and formoterol act as bronchodilators by relaxing the smooth muscle cells of the airways. In contrast, short-acting beta-agonists like salbutamol, fenoterol, terbutaline, albuterol, pirbuterol, and reproterol are used for quick relief on demand rather than as control medication.

The Petasites extract used in this study – Petadolex<sup>®</sup>, softgel capsules (manufactured by Weber & Weber International GmbH & Co. KG, Germany) contain 50 mg of a standardized lipophilic extract of the rhizome of *Petasites hybridus*, the butterbur plant. The extract is obtained by high pressure, liquid carbon dioxide extraction in a standardized and patented procedure, and contains a minimum of 15 percent petasins. Petasins are a group of sesquiterpene compounds mainly thought to be responsible for the pharmacological actions of the butterbur extract.<sup>8,9,10</sup> The manufacturing process removes pyrrolizidine alkaloids that are potentially hepatotoxic and carcinogenic.<sup>11</sup> The finished product has been available in Germany

since 1972 and licensed as a pharmaceutical under German regulations. This same extract has been available in the United States since 1997 as a dietary supplement.

Historically, Petasites has been used therapeutically for its analgesic effects and to reduce spasms in the gastrointestinal tract and in asthma. Recently, a multicenter, randomized, double-blind, placebo-controlled clinical trial for migraine prophylaxis was conducted on 229 evaluable patients with and without aura. The study found Petasites extract safe and effective in reducing the frequency of migraine attacks, the number of migraine days per month, and headache intensity.<sup>12</sup> The first clinical experiences with Petadolex in patients with asthma were published by Gruia.<sup>13</sup> *In vitro* examinations with smooth muscle cells of various origins<sup>14</sup> and in guinea pig tracheal rings<sup>15</sup> confirmed the spasmolytic activity of Petasites. In addition to spasmolytic action, Petasites exhibits anti-inflammatory activity. In mouse macrophages<sup>16</sup> and porcine leukocytes<sup>17</sup> Petasites extract was shown to inhibit inflammatory leukotriene synthesis.

A clinical trial of Petasites root powder in patients with chronic asthma and chronic bronchitis demonstrated improved lung function in all groups treated with Petasites powder.<sup>18</sup> The benefit was probably at least in part due to the inhibition of leukotrienes. Trials using synthetic leukotriene antagonists have shown superiority compared to placebo in respect to various lung function parameters, such as FEV1, peak expiratory flow, use of relief medication, and number of asthma symptoms.<sup>19</sup>

Rhinitis and asthma frequently coexist, and rhinitis is recognized as a risk factor for subsequent asthma. A Petasites leaf extract (CO<sub>2</sub>-extract Ze339 – not identical to Petadolex) was shown to be equally effective as cetirizine in the treatment of seasonal allergic rhinitis in a randomized controlled trial.<sup>20</sup> In another trial, levels of inflammatory mediators (including histamine and leukotrienes) in the nasal fluid of individuals with allergic rhinitis were significantly reduced after taking a Petasites extract for five days.<sup>21</sup> In another randomized, controlled trial with 20 patients with seasonal allergic rhinitis, CO<sub>2</sub>-extract Ze339

*Table 1. Demographic and Baseline Characteristics*

Age, years, mean (range)	35.3 (6-85)
Age distribution, percent of patients	
6-17 years	20.0
≥ 18 years	80.0
Gender, percent of patients	
male	45.0
female	55.0
Weight in kg, mean (range)	69.0 (25-155)
Concomitant disease, percent of patients	41.3
Asthma diagnosis, percent of patients	
mild	77.5
moderate	22.5
Asthma duration in years, mean (range)	7.9 (0-75)
Asthma medication, percent of patients	
Inhaled corticosteroids	27.5
Short-acting beta-agonists	52.5
Additional asthma medication, percent of patients	68.8

**Methods**

**Subjects**

Eighty patients with either mild or moderate asthma were included in this open study from November 2000 to March 2002; 77.5 percent had mild asthma, 22.5 percent had moderate asthma.<sup>2</sup> Patients ranged in age from 6-85 years and were required to have a stable course of the disease. In addition to Petadolex, all other available asthma medications were allowed. For detailed demographic and baseline data see Table 1.

**Study Design**

This open trial consisted of a two-week run-in phase and a treatment phase lasting 2-4 months. During the run-in phase, patients

protected against AMP-induced nasal responsiveness. This observation is in keeping with an inhibition of leukotriene synthesis by Petasites, since leukotriene receptor antagonists also attenuate AMP responses.<sup>22</sup>

The following study was conducted to examine the efficacy and safety of an extract of *Petasites hybridus* in the treatment of asthma.

recorded asthma symptoms, dosage of asthma medication, and number, duration, and severity of asthma attacks. Patients then received the trial medication and a diary. Adults took 50 mg Petadolex three times daily, while children were given 50-150 mg daily, depending on age. Patients were examined by their physician four and eight weeks after issue of trial medication. FEV1 was measured each time. After two months of treatment, patients were free to continue with the trial medication for another two months; hence the maximum duration of treatment was four months, the minimum two months.

### *Efficacy Measurements*

The efficacy of the therapy was measured by the following parameters: number, duration, and severity of asthma attacks; asthma symptoms (coughing, difficulty breathing, chest tightness, difficulty exhaling, wheezing, expectorations) using a four-point scale; FEV1; peak flow; asthma medication usage; and evaluation by patient and physician.

### *Statistical Analysis*

Analysis was conducted using descriptive statistics (mean, standard deviation, median, minimum, maximum, and quartiles). Changes in asthma medication, FEV1, and peak flow were calculated intra-individually and expressed as percentage change from baseline.

## **Results**

### *Asthma Attacks*

Seventeen of the study's 80 subjects reported an asthma attack during the study (21.3%), eight of whom had attacks during the retrospective (baseline) period. The number of asthma attacks was calculated per week and per patient. Asthma attacks decreased by 48.1 percent from baseline to week 8 of the treatment period. In the first four weeks of the follow-up phase, during which intake of Petadolex was optional, asthma attacks decreased further (by a total of 70.4%) but increased during the last four weeks, mainly due to one child who had an exceptionally high number of asthma attacks (n=34) while attending school camp during hay fever season (Table 2).

Duration of asthma attacks was calculated per week, per attack, and per patient. The duration of asthma attacks was documented for 74 of 103 attacks. The mean duration of asthma attacks during weeks 1-4 was strongly affected by one patient who reported an attack that lasted nine hours, leading to an increase in the mean duration. Apart from that period (i.e., weeks 1-4) the duration of asthma attacks was reduced by 90.5 percent (Table 2).

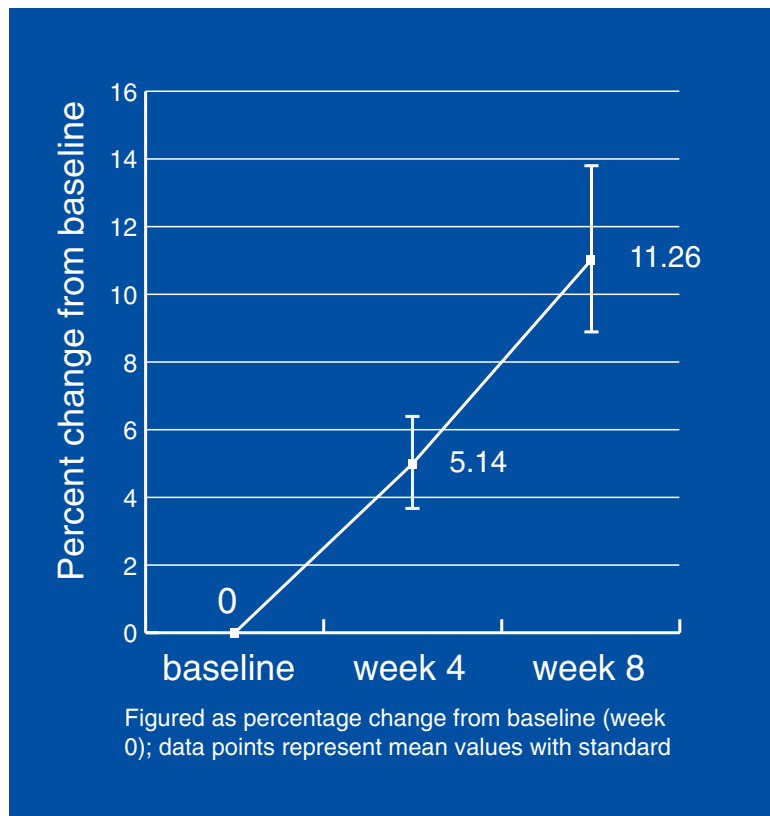
Asthma severity was scored using a four-point scale (0=no attack, 1=mild, 2=moderate, 3=severe). Severity was calculated per week, per attack,

*Table 2. Asthma Attacks: Mean Changes in Various Parameters during Treatment with Petadolex (number of valid cases in brackets)*

Asthma attacks	baseline	weeks 1-4	weeks 5-8	weeks 9-12	weeks 13-16
Number	0.54 (13)	0.35 (17)	0.28 (17)	0.16 (16)	0.56 (16)
Duration (min)	14.17 (12)	19.45 (16)	3.53 (14)	2.86 (14)	1.35 (14)
Severity (4-point score)	0.54 (13)	0.31 (17)	0.17 (17)	0.12 (16)	0.09 (16)

and per patient. Severity decreased continuously during treatment up to week 8 (by 68.5%) and during the follow-up phase during which intake of Petasites extract was optional (total decrease versus baseline by 83.3%) (Table 2).

*Figure 1. Lung Function: Change in FEV1 during Treatment with Petadolex (n=65)*



**Pulmonary Function**

For the efficacy evaluation, patients were only included if they had lung function (FEV1, peak flow) measured at each of the three visits (baseline, after four weeks, and after eight weeks). Not every patient had lung function measured and documented in this trial, thus resulting in variable valid cases. Since lung function is dependent on age, sex, weight, and the type of test instrument used, the percentage change from baseline was calculated intra-individually. The mean improvement for FEV1 (Figure 1) was 11.3 percent (n=65), for peak flow 28.5 percent (n=50). Comparing baseline with the treatment effect after eight weeks, 70.6 percent of the evaluable patients (n=68) had an improved FEV1 and 83.9 percent of patients (n=56) had an improved peak flow.

**Asthma Symptoms**

Various asthma symptoms (coughing, difficulty breathing, chest tightness, difficulty exhaling, wheezing, expectoration) were recorded in each patient’s diary using a four-point verbal scale over the duration of the study. After eight weeks of treatment with Petadolex, the documented symptoms improved between 47-65 percent (n=70-75) depending on the type of symptom. Following the initial treatment phase slightly more than half of the patients (n=39) continued on the extract, while the remainder (n=31) discontinued treatment; both groups were followed for eight weeks. With increasing time, patients discontinued the voluntary phase, with 64 percent of subjects being evaluable at 14 weeks and 32 percent being evaluable at 16 weeks. All symptoms increased in severity at the end of the observation period (week 16) compared to week 8 in the group that had discontinued Petadolex. In contrast, most symptoms improved further (weeks 8-16) in the group on Petadolex. Figures 2a and 2b illustrate the course of asthma symptoms during the study, using the symptom “wheezing” as an example.

**Asthma Medication**

Twenty-two patients (27.5%) were being treated with inhaled corticosteroids at the beginning of the study. At the end of the study (weeks 9-16) 42.9 percent of the evaluable patients (n=14) had reduced the amount of inhaled steroids during therapy with Petadolex; and one patient increased dosage. The reduction in the amount of inhaled steroids was calculated intra-individually as percentage change from baseline, which corrects for the different brands and potencies of inhaled medications. Values for all four treatment phases must have been available for inclusion in the analysis. After 9-16 weeks (n=14) there was a 16.1-percent reduction in the amount of inhaled steroids used (Figure 3).

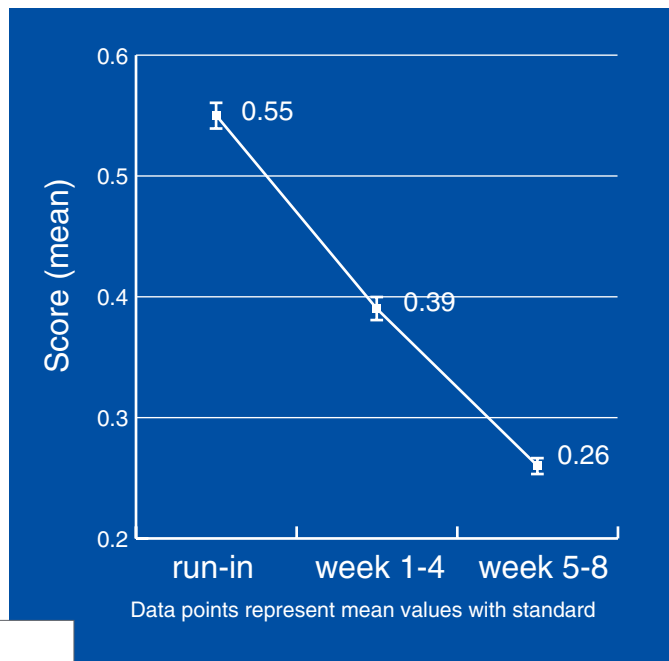
Forty-two patients (52.5%) took short-acting beta-agonists; 48.3 percent of these patients reduced the amount of short-acting beta-agonists during weeks 9-16. The daily dosage was reduced by a mean of 13.4 percent, calculated as percentage change from baseline (n=29).

Except for four patients, all subjects with evaluable corticosteroid or short-acting beta-agonists data had taken the Petasites extract during the follow-up phase.

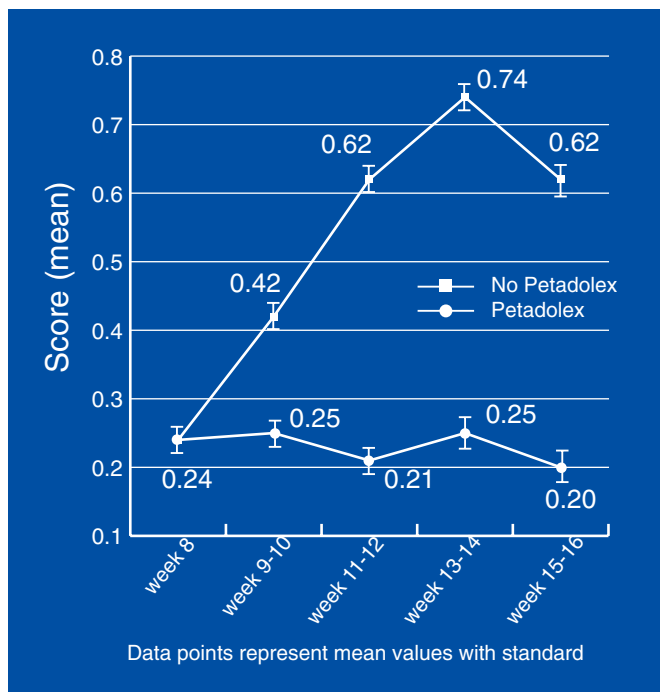
### Evaluation of Efficacy by Patient and Physician

Seventy-six patients were asked by the investigator at the week 8 visit to offer an assessment of the efficacy of their treatment. Improvements were rated as very good, good, moderate, or poor. Ninety-five percent (n=72) reported

*Figure 2a. Wheezing: Change of the Mean Score during Treatment with Petadolex (n=70-75)*



*Figure 2b. Wheezing: Change of the Mean Score Starting at Week 8 in Patients Treated with (n=39) or without (n=31) Petadolex*

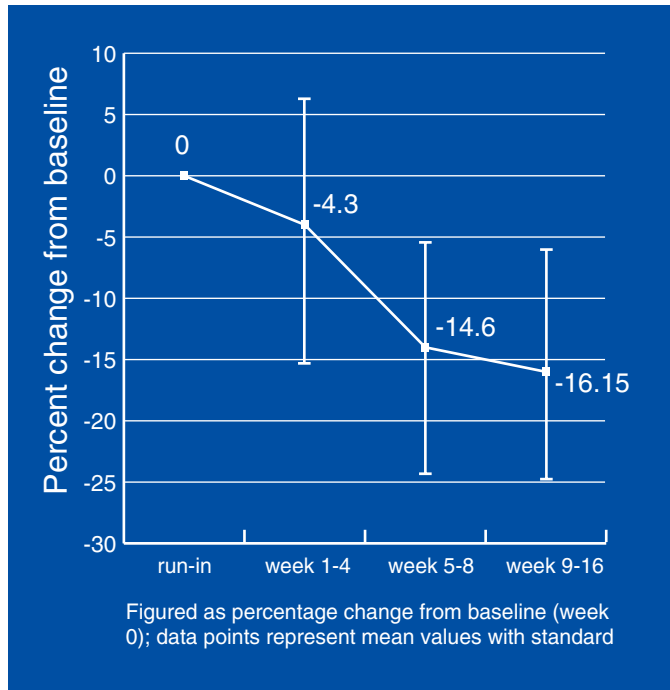


Petadolex was effective in treating their asthma, with 83 percent (n=63) rating their improvement as very good or good (Figure 4). The physician evaluation was comparable, with an efficacy rating of very good or good for 68 of 76 patients (89.5%).

### Safety and Tolerability

Tolerability was rated as good or very good by 67 of 76 patients (88.2%). None of the 76 patients or physicians rated the tolerability as “poor.” During the study, 11 adverse events were reported by seven subjects. Adverse events reported by children were abdominal pain/flatulence, sneezing, allergic conjunctivitis, allergic rhinitis, and halitosis. Adults reported hair loss, coughing, dyspnea, difficulty exhaling, and severe depression. Two patients required treatment of adverse events. One patient was treated for allergic rhinitis and the other patient was hospitalized and treated for coughing, dyspnea, difficulty exhaling, and severe

**Figure 3. Asthma Medication: Change in Inhaled Corticosteroid Usage during Treatment with Petadolex (n=14)**



depression. The adverse events were not rated by the treating physician to be causally related to the intake of Petadolex and did not lead to withdrawal of the subjects from the study.

**Discussion**

The objective of this multicenter, open study was to analyze the efficacy and tolerability of Petadolex capsules in patients with mild-to-moderate asthma. Eighty patients completed the study – none was excluded from the analysis. However, due to missing data, not all variables could be analyzed for the complete patient population.

This study suggests 150 mg of an extract from *Petasites hybridus* taken for 8-16 weeks may be effective in reducing the severity of various asthma-related parameters.

In the course of the study, 21.3 percent of the study population reported asthma attacks. After two months of treatment the mean number of

daily asthma attacks was reduced by nearly half. Attacks decreased further in the follow-up phase, only to increase at the very end due to the aforementioned patient with an extraordinary number of attacks. Asthma duration and severity decreased even more effectively – by 80-90 percent – at the end of the follow-up phase. In this subgroup of patients with asthma attacks, 66.7 percent had an improved FEV1 and 91.7 percent had improved peak flow.

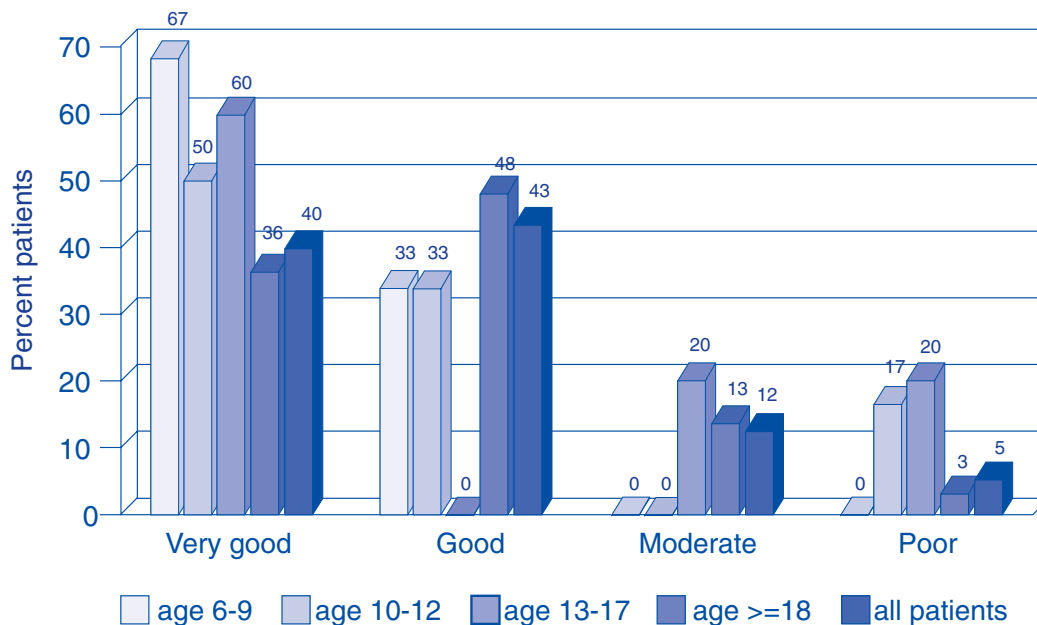
Lung function tests are performed to assess and monitor airflow obstruction. Increased FEV1 and peak flow are indicative of an improved airflow. More than a 10-percent increase in FEV1 in this study should be considered clinically relevant. With 70.6 percent of the patients having an increased FEV1 and 83.9 percent having increased peak flow, it can not be concluded the mean improvement in lung function was due to dramatic changes in only a few patients.

In the one-third of the study’s patients who treated asthma only with Petadolex capsules, no impairment of lung function was observed at the end of the study, and 80 percent of those patients had an improved FEV1 or peak flow. This suggests Petadolex may be effective in the treatment of asthma not only in combination with additional asthma medication but also as a stand-alone medication.

Subjects who took Petadolex capsules also noted a mean 50-percent, self-reported improvement in documented asthma symptoms after two months of treatment. Although in the final two months the use of Petasites extract capsules was optional, one-half of the patients continued taking the extract. Compared to week 8, the severity of symptoms decreased further in the group remaining on Petadolex, whereas symptoms increased in severity in the group that discontinued Petadolex. Coughing was an exception, probably influenced by two acute cases of bronchitis. The results of the follow-up phase support the observation suggesting improvement was due to treatment with Petadolex.

*In vitro*, the same extract used in this study has demonstrated spasmolytic as well as anti-inflammatory activities. Beta-agonists and corticosteroids are standard therapies for asthma, which,

**Figure 4. Assessment of Efficacy by the Patient (n=76)**



Very good=very good improvement, good=good improvement, moderate=moderate improvement, poor=unchanged or worse condition

as noted, is characterized by bronchoconstriction and inflammation of airway cells. In this study, treatment with Petadolex led to a reduction in the use of beta-agonists and corticosteroids by a mean of 15 percent. In the follow-up phase, the usage of corticosteroids was further reduced, with 43- and 48-percent of evaluable patients able to reduce corticosteroids and beta-agonists, respectively. The circumstance of patients reducing the amount of asthma medication of their own accord and without being instructed to do so by the investigator is noteworthy.

The reduction in the usage of asthma medications at the end of the study suggests the improvements in lung function were due to therapy with Petadolex and not to increased asthma co-medication. Of evaluable patients with an improved FEV1, 87.5 percent had also reduced the amount of corticosteroids. Only one patient increased steroid usage. A similar result was ob-

tained with beta-agonists.

Compliance was extremely good with no dropouts due to adverse events. The low number of adverse events and the conclusion that the adverse events were not rated to be causally related to intake of the extract demonstrates Petadolex was safe and well tolerated in this trial.

The study results suggest the *Petasites hybridus* extract Petadolex is an efficacious and well-tolerated therapy for the treatment of asthma in children and adults.

### Disclosure

The open study described in this article was funded by Weber&Weber, Inning, Germany, manufacturer of Petadolex.



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