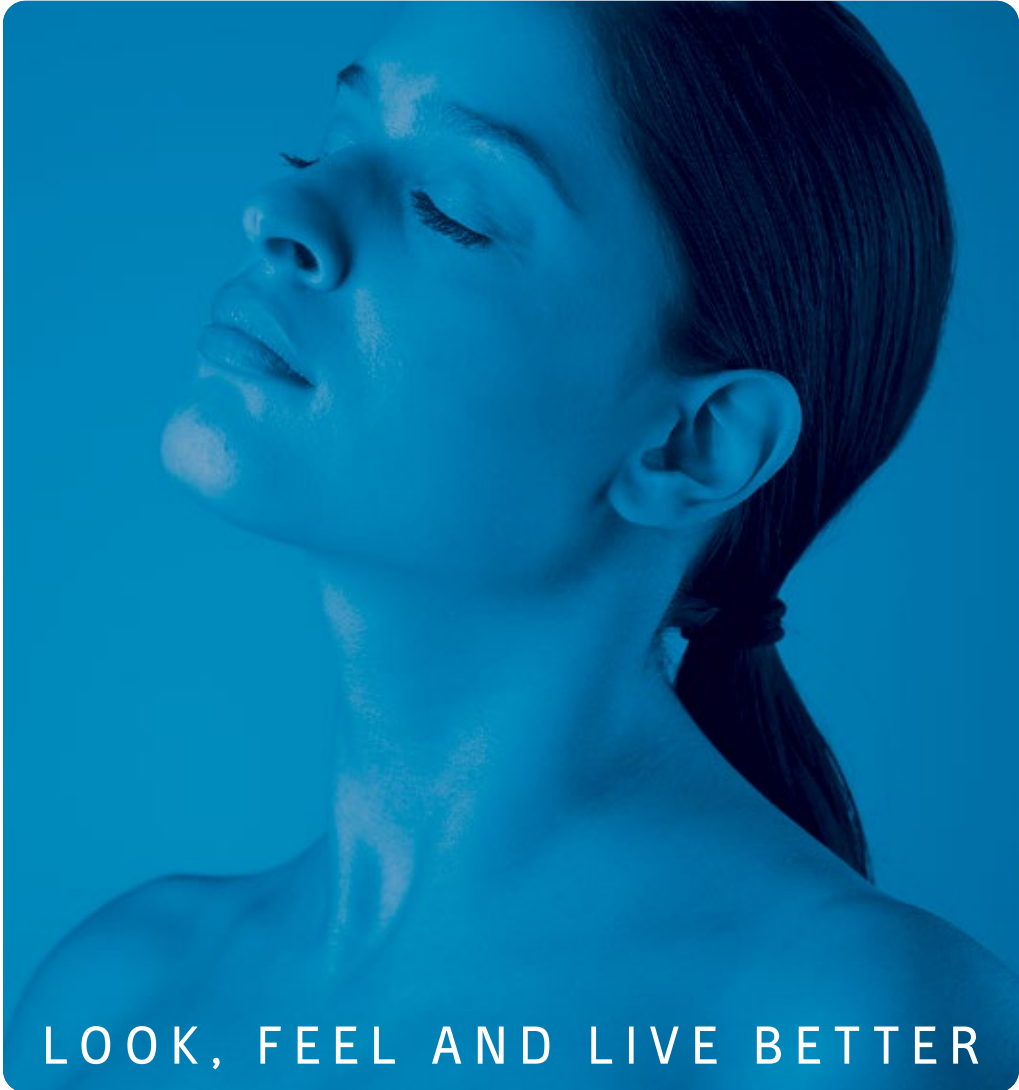


PYCNOGENOL®

Respiratory Health



LOOK, FEEL AND LIVE BETTER



Respiratory health: hay fever and asthma

Airway obstruction and symptoms in asthma and hay fever alike are the result of inappropriate responses of the body's immune system towards instances which are mistakenly perceived as harmful. Allergens causing these reactions to the respiratory system are most commonly pollen, dust, and animal hair. When an allergic person comes into contact with an allergen, a particular subset of the immune system, the mast cells, release the tissue-hormone histamine. During this immediate reaction histamine triggers the spectrum of symptoms so common to allergies: sneezing, nasal congestion, coughing, wheezing, itching, and bronchial swellings. Essentially the same mechanisms prevail in allergic asthma which causes episodes of wheezy breathlessness. However, asthmatic attacks may also be triggered by chemical irritants such as tobacco smoke or car exhaust, certain medications, cold air and even exercise or psychic influences.

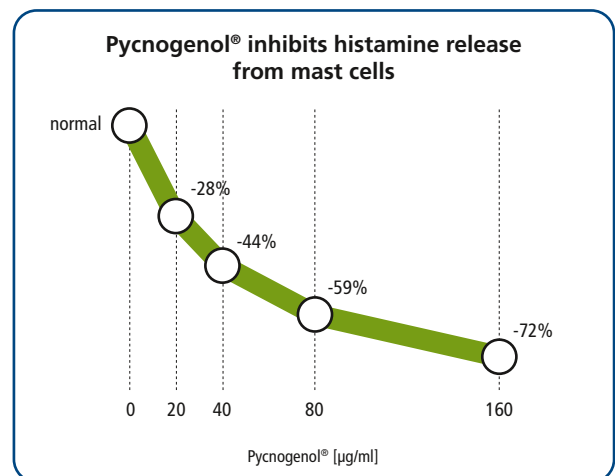
Pycnogenol® normalizes immune response

In human studies Pycnogenol® has shown diverse anti-inflammatory activity [Grimm et al., 2006]. Blood from human Pycnogenol® consumers was found to inhibit the inflammatory "main switch" NF-kB by in average 15%. The expression of a majority of pro-inflammatory genes is governed by NF-kB, such as leukotrienes, cytokines and adhesion molecules. Some of these molecules are known to play a role in the onset of asthma. The partial inhibition of NF-kB lowers the sensitivity level for triggering an immune response, which will help prevent an asthmatic attack. Following consumption of Pycnogenol® activated immune cells from human volunteers secreted significantly less connective tissue degrading enzymes matrix metalloproteinases (MMP-9) [Grimm et al., 2006]. These enzymes greatly affect pulmonary function of asthmatic patients. For detailed information please refer to PYCNOGENOL® AS ANTI-INFLAMMATORY.

Pycnogenol® has antihistaminic potency

Pycnogenol® was found to dose-dependently inhibit the release of histamine from mast cells challenged with an irritant [Sharma et al., 2002]. Pycnogenol® will thus help prevent an immediate immune reaction towards challenge with an antigen as it occurs in hay fever. Interestingly, in these experiments with mast cells Pycnogenol® was found to be at least as

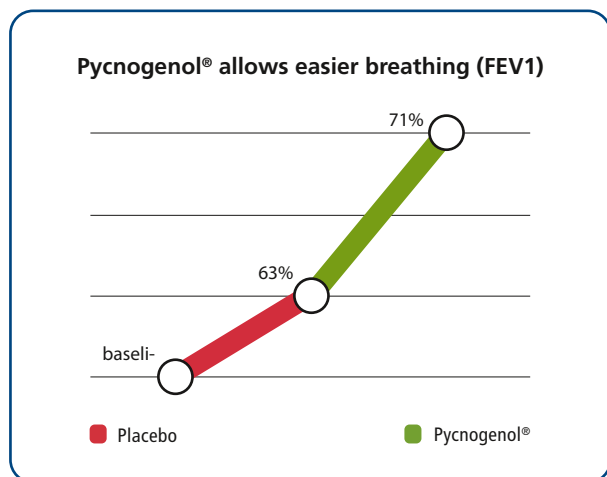
effective for blocking histamine release as a widely used pharmaceutical anti-histaminic remedy: sodium chromoglycate.



Pycnogenol® for management of asthma

A double-blind, placebo-controlled, cross-over study has investigated the effect of Pycnogenol® in 22 patients (18- 50 year of age), suffering from asthma since 1 and up to 16 years [Hosseini et al., 2001]. Patients were randomly assigned to either the Pycnogenol® group, receiving 1 mg/lb/day (without exceeding 200 mg/day), or to the group receiving placebo for 4 weeks. Thereafter, subjects were crossed over to the alternate regimen.

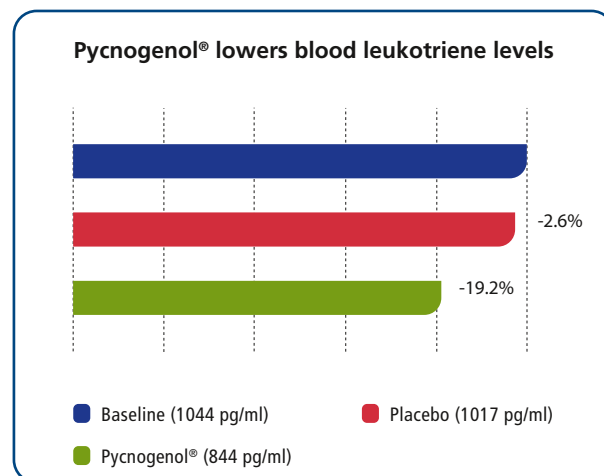
The patients' airway function was assessed by the "forced expiration volume in 1 second" (FEV1), by means of a spirometer. The subject fills his lungs and the air volume exhaled fast within 1 second is measured. The exhaled volume is expressed relative to the total lung volume, so the FEV1 value represents the percentage of a patient's lung volume he can exhale in a second. Naturally, the percentage is lower in asthmatics as their airways are constricted, and breathing is aggravated. After 4 weeks treatment with Pycnogenol® the patients could exhale 71% of their lung volume as compared to 59% at trial start and 63% in response to placebo, respectively.



The severity of asthma symptoms was rated on a 4 point scale, ranging from symptom free (0) in several steps to mild intermittent (1), to a moderate intermittent form (2) up to a severe persistent form (3). Symptom scores were in average 2.23 before treatment and 2.79 while receiving placebos, which are considered as being a "severe persistent" form. In response to treatment with Pycnogenol® the average symptom severity score was significantly lowered to 1.75, a "moderate persistent" form.

The improvement of airway function was paralleled by a reduction of leukotrienes, pro-inflammatory mediators, in the blood. Leukotrienes attract immune cells to the bronchi and activate them. This causes

bronchial constriction and airway obstruction in asthma. Pycnogenol® significantly reduced the leukotriene values in the blood of patients, as compared to both baseline values as well as placebo medication. As expected, placebo had no significant influence on leukotriene levels in the blood.



Pycnogenol® was well tolerated, only one patient experienced gastrointestinal discomfort, however, this occurred only during the first 3-4 days. The patients generally noted an improvement of their breathing ability when they received Pycnogenol®.

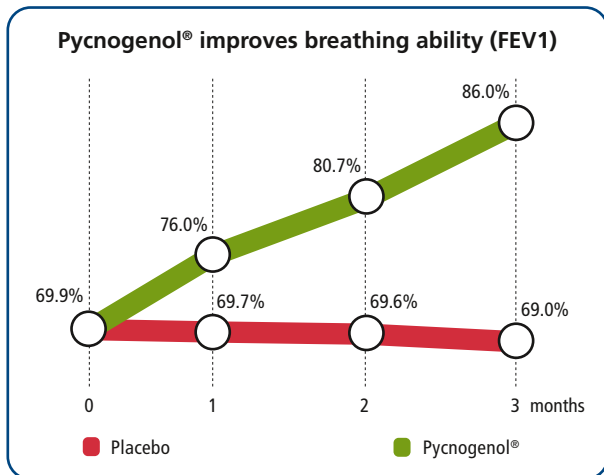
Pycnogenol® for management of childhood asthma

The vast majority of asthmatics have developed the disease already during childhood, most of them before they reached the age of five years. In many cases children develop hay fever which thereafter progresses to asthma. Asthma medication with children is a sensitive issue, representing a challenge for everybody involved: the treating physician, the parents and the child patients itself. This results from the high symptom variability in children, further complicated by the dynamics of the development and growth of the child organism. Parents on their side feel uncomfortable with having their child permanently take prescribed medications.



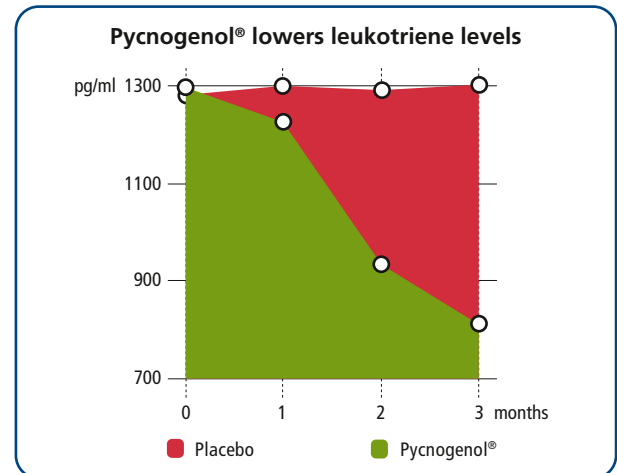
A double-blind, placebo-controlled study has investigated 60 children with mild to moderate asthma, aged 6 to 18 years, over a period of 3 months [Lau et al., 2004]. A minority of 9 patients took oral medication with Accolate® (Zafirlukast). All patients were depending on rescue inhalers (with albuterol) to control occurring asthma attacks. Thirty children were assigned to treatment with Pycnogenol® (1mg/lb/day) and another 30 children to the control group receiving placebo for 3 months. One month prior to treatment was taken as run-in period to establish baseline conditions.

contrast, the placebo-treated group had symptoms only marginally improved which remained above 2 until completion of the trial.



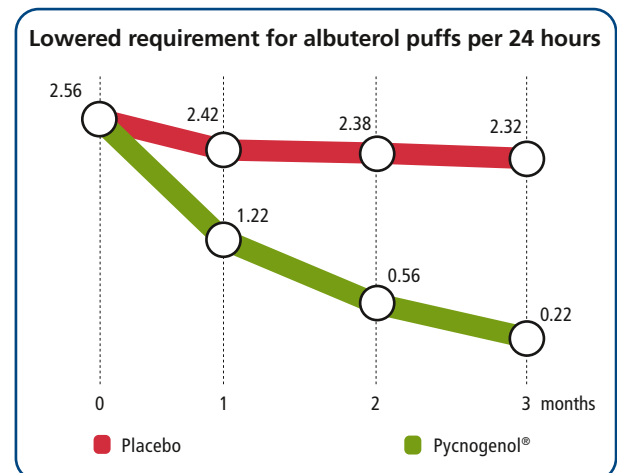
The study showed that easiness of breathing improved significantly already after 1 month treatment with Pycnogenol®, as measured using the FEV1 method. Breathing was expressed as percentage of total lung volume which can be exhaled in a second. Breathing ability was further improving after two months and three months treatment, whereas placebo had no effect at any time.

The severity of asthma symptoms was rated on a 4 point scale. At baseline, mean symptom score was 2.3 which is between 2 = moderate (“somewhat disturbing”) and 3 = severe (“interfering with daily activities”). Symptoms gradually decreased during Pycnogenol® treatment and reached 0.2 at trial end with patients thus being almost symptom free. In



The improvement of airway function was paralleled by a reduction of inflammatory mediators (leukotrienes), tested from the urine of the patients. The leukotrienes cause the inflammatory condition and bronchial constriction. Pycnogenol® significantly reduced leukotriene values already after 1 month and further decreased them throughout the trial period. As expected, treatment with placebo had no influence on leukotriene levels.

The most compelling outcome of the study is the dramatically reduced necessity of using rescue inhalers



as severe asthma attacks appeared much less frequently. After 1 month 8 out of 30 children taking Pycnogenol® didn't require rescue inhalers at all anymore, and the number of children completely off the inhaler increased to 12 and 18 after 2 and 3 months treatment, respectively.

The author of the study concluded that Pycnogenol® is an effective and safe nutritional approach for children to manage mild to moderate asthma.

Pycnogenol® offers help for the management of hay fever and asthma:

- Demonstrated immune modulation in humans
- Controlled clinical trial with asthmatic patients
- Controlled clinical trial demonstrating efficacy in childhood asthma

References

- Grimm T et al.* Inhibition of NF-kB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol®). *J Inflamm* 3: 1-15, 2006.
- Hosseini S et al.* Pycnogenol® in the management of asthma. *Journal of Medicinal Food*, 4: 201-209, 2001.
- Lau BHS et al.* Pycnogenol® as an adjunct in the management of childhood asthma. *J Asthma* 41: 825-832, 2004.
- Rohdewald P.* A review of the French maritime pine bark extract (Pycnogenol®), an herbal medication with a diverse pharmacology. *Int J Clin Pharmacol Ther* 40(4): 158-168, 2002.
- Sharma SC et al.* Pycnogenol® inhibits the release of histamine from mast cells. *Phytother. Res.* 17: 66-69, 2003.

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