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# Improvement of common cold with Pycnogenol®: a Winter registry study

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***Aim.*** **This registry study aimed to evaluate the use of Pycnogenol® (pine bark extract), an anti-inflammatory, anti-oxidant and anti-edema natural compound, on symptoms of common cold. Main targets were the evaluation in otherwise healthy subjects of signs/symptoms, the reduction in days of disease, and the prevention of complications.**

***Methods.*** **All subjects used the "best management" for colds and one group added Pycnogenol® capsules (50 mg, bid/die) from day zero. The resulting registry groups were comparable. A total of 70 subjects used Pycnogenol® and 76 acted as controls.**

***Results.*** **The number of days with a perceived cold affecting the patients was reduced in the supplement group (3.1;0.4 days) in comparison with controls (4.2;0.2). Lost working days were significantly decreased in the supplement group (0.55;0.3 *versus* 0.67;0.3 in controls). The need to use any other compound (on demand basis; OTC products) to manage symptoms and the occurrence of any clinically significant complications were significantly lower in the Pycnogenol® group. The most frequent complications were the extension of the cold to a period longer than 4 days, a tracheal extension and a bronchial involvement. Pycnogenol® was significantly effective in reducing the number of complications. The daily evolution of the "pillar cold signs" indicates a significantly faster resolution in the supplement group. With supplementation the decrease in symptom scores appears to be significantly more important. Pycnogenol® supplementation appears to make regression faster for all symptoms in comparison with controls.**

***Conclusion.*** **In this pilot registry, Pycnogenol® appears to decrease symptoms of cold and shorten its course also preventing some complications.**

**KEY WORDS:** Cold - Rhinovirus - Dietary supplements - Pinus pinaster.

The common cold is generally considered the most common human disease, affecting people in all countries and social contexts. Adults may have two to five infections every year, particularly in crowded communities; children in contact with other children may have six to ten cold episodes every year, with up to twelve colds/year for kindergarten or school children.[1-10] However, some episodes may be minimally symptomatic. The common cold is a viral disease localized in the upper respiratory tract.[1-6]

Cold episodes may be associated with symptoms such as nasopharyngitis, rhinopharyngitis, increase in temperature, ear and throat complications and respiratory problems. Common symptoms include cough (usually a few days after the onset), sore throat, runny nose and fever. Symptoms disappear in five to ten days. In some cases, particularly in older, higher-risk subjects, residual symptoms may last up to three weeks.

The frequency of common cold episodes tends to increase in older subjects and in patients at risk mainly due to a deterioration of the immune system. Over 200 viruses may cause the common cold. Rhinoviruses are considered the most frequent. In industrialized countries, particularly in crowded communities, 30% of the population may be affected every winter. The costs due to lost working hours, medications, complications and altered social interactions are significant.

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An effective vaccine is not available as many different viruses (which also change over time) are involved. Hand cleaning and washing may reduce the exchange of viruses. Supplements, particularly vitamin C and zinc, may be effective in decreasing the rate of colds and the length of each episode.[4-8] Treatments such as aspirin, analgesics and antipyretics may alleviate specific symptoms.[9-16] Nose drops, sprays and aerosols may be effective in controlling nasal block and congestion. Decongestants (*i.e.*, pseudoephedrine, ipratropium and other nasal spray) may reduce the symptoms of a runny nose. Symptoms associated with a runny nose may be controlled by antihistamines (first generation), but these products cause significant adverse effects such as drowsiness, impaired attention and driving performance, etc. Increased fluid intake may improve symptoms or reduce respiratory problems, and warm, humidified air and eucalyptus extracts may give some symptomatic relief on nocturnal symptoms (cough, congestion, sleep difficulty) without side effects. However, most of these common remedies have not been properly tested. Cough medications are used only for symptom relief.[14-21] Cough and cold medications in children (<6 years) generally are not advised as they may cause significant complications and provide unproven benefits. Second-generation antihistamines are not effective on colds.[17-25]

Troxerutin has also been used with the rationale that controlling edema and swelling, particularly at the nasal mucosa, may reduce the length of cold episodes and symptoms.[26] The mild anti-inflammatory action of troxerutin and the general control of inflammation may be effective in controlling a cold.[27]

Antibiotics have very limited indications. When a bacterial infection is also present or develops as a consequence of a cold, antibiotics may have a role.[20-24, 28] About 30% of older patients may develop some complications (upper respiratory tract infection, bronchitis, pneumonia). In high risk subjects (severe risk conditions, heavy smokers, diabetics, handicapped subjects, patients with previous, chronic cardiovascular or pulmonary problems), complications may be severe and cause hospital admission with increasing social/human costs.[28] At the moment no specific treatment or prevention for colds is available.[28]

The aim of this supplement registry study [29, 30] was to evaluate the effects of the use of standardized French maritime pine bark extract from Pinus pinaster (Pycnogenol®, Horphag Research), an anti-inflammatory, anti-oxidant and anti-edema natural compound, on signs and symptoms of the common cold. Main targets were the evaluation of the reduction of signs/symptoms, the reduction of days of disease, the reduction in use of other symptomatic treatments, and the control of cold-related potential complications. Pycnogenol® has been used in several other studies including inflammatory chronic conditions (osteoarthrosis, asthma) chronic venous disease, microcirculatory, sport and vascular studies etc., and anecdotally appeared to have decreased the incidence and gravity of colds. A larger previous study evaluating several supplementation plans indicated a significant effect on the common cold with Pycnogenol®.[31]

## Materials and methods

Subjects with colds were followed up; otherwise healthy volunteers – without any other clinical problems, risk conditions or in treatment with drugs or other supplements - were studied to evaluate cold evolution. No other treatment was used. After an awareness briefing, the subjects defined Day 0 (zero) as the day with detectable, initial signs/symptoms starting Pycnogenol® treatment. On the following day, defined as Day 1, the follow-up was initiated with a target observational period for the cold lasting from Day 1 to 4.

### *Dosages and groups*

Oral Pycnogenol® capsules were used at a dosage of 50 mg, bid/die from Day 0. Controls were evaluated from the same population, in the same period and season. All these healthy subjects had no nose/throat or ear clinical conditions. Only subjects with BMI<26 were included in the registry follow-up. Included subjects did not have cold or flu (no flu vaccination) within the 3 months before inclusion, and they had used no drugs, except for occasional situations (*i.e.*, painkillers) not lasting more than 2 days. The registry was made in winter. Subjects between 25 and 65 years were included. Subjects with previous sinusitis, ear and throat infections (including tonsils) and nasal septum deviations or obvious malformations had been excluded in the preselection.

Subjects willing to participate were briefed at the

TABLE I.—*The "pillars" of cold (Merck Manual 2011) + headache: 1 to 5 are almost always present while 6 to 8 are not common but may be present in some 15-20% of patients. The signs/symptoms were scored by patients on a 10 cm horizontal analogue scale line (Cyril Maxwell, Clinical Research for all. Cambridge medical publications, Cambridge, 1973).*

| |
|---|
| 1. "Scatchy" sore throat. |
| 2. Sneezing. |
| 3. Rhinorrhea |
| 4. Nasal obstruction. |
| 5. Malaise. |
| 6. Cough. |
| 7. Temperature. |
| 8. Headache. |
| Note: only subjects with at least 6 of these "pillar signs" were included. |

beginning of the winter season and asked to contact one of the monitors on the first day of a probable cold (Day 0). When the cold and its relative pillar signs/symptoms were clearly identified, the follow up started (Day 1). Symptoms were self-monitored for 4 days. On the basis of the model studies,[26, 31] these days were considered the most important and most affected by supplementation.

The signs/symptoms were self-evaluated using a visual analogue scale line (VASL, 0-10). The most frequent symptoms were evaluated. The "pillars" of cold (Table I) as used in our registry are defined according to the Merck Manual:[28, 26-31] symptoms 1 to 5 are almost always present while 6-8 are less common but may be present in some 15-20% of patients. The symptoms were scored on a 10 cm horizontal analogue scale line according to Maxwell.[33] Only subjects with at least 6 of these "pillar signs" were included.

### *Best management*

Currently there is no best management for the common cold. Antipyretics and analgesics are used, but their efficacy is unproven. Nasal obstruction is relieved by topical nasal decongestant, but rebound congestion may be an important side effect. No vaccines are available. Good hygiene, including hand washing, may reduce the spread of colds but does not act on individual patients.

### *Supplement studies*

Supplement studies [29, 30] aim to define the field of activity of supplements and possible preventive, preferably non-clinical applications. The best fields of application for supplements are preclinical, borderline applications or the supplementary management of risk conditions. Supplements -unless there are specific claims- are not generally used for treatment of signs/symptoms or clinical conditions. The aim of supplement studies is to produce supplementary data to be compared to "background" historical data (*i.e.*, based on the best available management for comparable subjects) or to other management plans. In this study supplements were used according to the following rules:

1. the use of supplements was suggested to the evaluation subjects; they were not formally prescribed but suggested as an option to possibly improve the management of the risk condition;

2. supplements were only used in addition to what was considered at the time the available "standard or best-management/care" for that condition according to relative international guidelines;

3. the use of supplements should not interfere with any other treatment or preventive measure;

4. the periods of follow-up were considered variable, according to the needs and availability of the patients or study subjects. The observation period may therefore be variable, not fixed. Ideally, the supplement administration is used as long as needed to see results or changes;

5. the type of evaluation is always a registry;

6. the supplement is available in the market and voluntarily acquired by the study subjects. A quantity of product is made freely available for underprivileged subjects.

The evaluation of compliance concerning the use of a supplement is a significant indicator of how many subjects are actually willing to use the product. Accessory information in this type of evaluation are:

1. * How many subjects are willing to initiate treatment after briefing;

2. ** How many subjects would follow the management method with supplements as they observed potential benefits or good tolerability;

3. *** How many subjects would be willing to continue the supplement administration or use it again in a comparable situation.

There was no defined group allocation, no randomization organized by the investigators. Subjects decided on the basis of the awareness briefing of the supplement group they joined. No placebo was used.

*Open label*

Patients were informed about any supplement or treatment and knew what the treatment was. A possible placebo effect was also carefully explained and considered. Data were analyzed after the observation period, ideally when sufficient evidence had been collected or when fund limitations would eventually stop the collection of the observations. The time needed to see differences among groups was also considered an evaluation target.

Pycnogenol® (French pine bark standardized extract from Pinus Pinaster) has been used for years for its anti-inflammatory, anti-edema, anti-oxidant qualities and for its action on microcirculation and in several clinical and risk conditions.[35-37] The product is safe, and anecdoctal reports indicated that the common cold appeared to be attenuated in patients using Pycnogenol® for venous problems.

This study was basically a small-scale, independent, pilot, registry study; the products (supplements) were not prescribed. All products were available over-the-counter in the market. All results and data were evaluated by an external reviewing panel not in contact with patients. Commercial sponsorship from the producers of the tested supplement was not available for specific evaluations.

*Adverse events*

Possible adverse events due to the supplementation were monitored in a diary and evaluated in a daily diary for 10 days after the symptomatic phase (day 0-4).

*Statistical analysis*

The plan for this supplement evaluation was to have data collected and registered from at least 30 subjects completing the study in each group. All VASL-derived data were considered as non-parametric. The evaluation was made using the ANOVA (with Bonferroni's correction), the Mann-Whitney U-Test and the Wilkoxon Rank test (to define, giving treatments a rank order, the best treatment).[33, 34]

## Results

A total of 76 volunteers used Pycnogenol®, 70 completed the study. There were 82 controls, of whom 76 completed the follow-up (Table II). The 12 drop-outs (6 in each group) occurred for non-medical reasons. The supplement and control groups were comparable at the end of the follow up period for their age and sex distribution and for their clinical presentation.

1. Affected days: Table II shows the number of days with perceived cold and a runny nose significantly affecting the patient's normal life. The best result was obtained in the supplement group (3.1;0.4 days; P<0.05) in comparison with controls (4.2;0.2).

2. Lost working days were significantly lower in the supplement group (0.55;0.3; *versus* 0.67;0.3 in controls; P<0.05).

3. The need to use any other compound (on demand basis; OTC products) to manage signs and

TABLE II.—*Main clinical results.*

| | A. PYCNO | B. CONTROLS | P |
|---|---|---|---|
| Registry patients | 76 | 82 | |
| Completed registry | 70 (38F) | 76 (43F) ns | |
| Age | 32.2; 3.2 | 33.1; 3.2 | ns |
| Drop-outs | 6 | 6 | <0.05 |
| 1. Affected days average; SD | 3.1; 0.4 | 4.2; 0.4 | <0.05 |
| 2. Lost working days | 0.55; 0.3 | 1.67; 0.3 | <0.05 |
| 3. Use of any other otc product** and treatments (on demand basis) % | 22/70 | 49/76 | <0.05 |
| nasal drops % | 23/70 | 43/76 | <0.05 |
| Aspirin +Vit C % | 12/70 | 22/76 | <0.05 |
| antihistamines % | 6/70 | 9/76 | <0.05 |
| aerosols % | 14/70 | 22/76 | <0.05 |
| 4. Complications after 4 days (total): | 5/70 | 18/76 | <0.02 |
| A. Disease 'extension' to >4 days % | 3/70 | 11/76 | <0.02 |
| B. Tracheal extension % | 2/70 | 12/76 | <0.013 |
| C. Bronchial extension % | 1/70 | 5/76 | <0.02 |

symptoms and the occurrence of any clinically significant complications were significantly lower in the Pycnogenol® groups (P<0.05). Nasal drops, Aspirin+vitamin C, antihistamines (first generation) and aerosols were the products used.

4**.** Complications after 4 days. The most frequent complications were the extension of the cold to a period longer than 4 days, a tracheal extension and a bronchial involvement. Pycnogenol® was significantly effective in reducing the most frequent complications (P<0.05).

5. The Pillar symptoms of cold (Table III). The daily evolution of the 'pillar signs' are indicated. In general, signs and symptoms appear to slowly and progressively regress in days. With supplementation the regression appears to be significantly faster (P<0.05). Pycnogenol® supplementation appears to make regression faster for all symptoms (P<0.05) in comparison with controls. The average value of the scores was significantly different for all 4 days of follow-up.

Compliance was good; >95% of the supplement doses were correctly used.

Adverse events. There were no adverse events during the registry period and in the following 10 days.

TABLE III.—*Daily variations of the "pillar" symptoms (+headache). *: P<0.05.*

| Pycnogenol® | | Day | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|
| 1. "Scatchy", sore throat | Average | | 8.1 | 7.2 | 6.3 | 6 | 4.4 |
| | SD | | 0.7 | 0.4 | 0.7 | 0.6 | 0.2 |
| 2. Sneezing | | | 7.6 | 5.6 | 4.4 | 3.3 | 3 |
| | | | 0.3 | 0.4 | 0.3 | 0.4 | 0.3 |
| 3. Rhinorrhea | | | 7.7 | 6 | 5.4 | 4.4 | 3.2 |
| | | | 0.4 | 0.6 | 1 | 0.7 | 0.4 |
| 4. Nasal obstruction | | | 7.7 | 5.5 | 5.1 | 4.1 | 3.3 |
| | | | 1.1 | 0.5 | 0.6 | 0.4 | 0.3 |
| 5. Malaise | | | 8.4 | 7.1 | 5.1 | 4 | 2.7 |
| | | | 0.4 | 0.6 | 0.6 | 0.5 | 0.2 |
| 6. Cough | | | 3.6 | 4.3 | 4.9 | 5.2 | 4.1 |
| | | | 3.2 | 0.4 | 0.4 | 0.3 | 0.3 |
| 7 Temperature | | | 7.5 | 6.5 | 5.5 | 3.1 | 2.2 |
| | | | 0.4 | 0.3 | 0.3 | 0.5 | 0.6 |
| 8. Headache | | | 6.5 | 5.6 | 3.3 | 2.1 | 1.2 |
| | | | 0.3 | 0.4 | 0.3 | 0.5 | 0.2 |
| Total | | | 57.1 | 47.8 | 40 | 32.2 | 24.1 |
| Average | | | 7.13 ns | 5.9* | 5* | 4.02* | 3.01* |
| Controls | | Day | 0 | 1 | 2 | 3 | 4 |
| 1. "Scatchy", sore throat | Average | | 8.3 | 8.3 | 8.1 | 7.2 | 6.1 |
| | SD | | 0.5 | 0.3 | 0.3 | 0.4 | 0.4 |
| 2. Sneezing | | | 7.7 | 7.3 | 6.6 | 5.3 | 4.3 |
| | | | 0.3 | 0.4 | 0.4 | 0.3 | 0.3 |
| 3. Rhinorrhea | | | 7.5 | 8.3 | 7.3 | 7 | 5.4 |
| | | | 0.3 | 0.3 | 0.4 | 0.3 | 0.2 |
| 4. Nasal obstruction | | | 7.8 | 7.6 | 7.6 | 6.5 | 6.3 |
| | | | 0.4 | 0.4 | 0.3 | 0.4 | 0.3 |
| 5. Malaise | | | 8.4 | 8.4 | 7.5 | 7.2 | 6.4 |
| | | | 0.4 | 0.3 | 0.4 | 0.5 | 0.3 |
| 6. Cough | | | 4.1 | 5.6 | 5.4 | 6 | 4.4 |
| | | | 0.3 | 0.3 | 0.4 | 0.4 | 0.3 |
| 7. Temperature | | | 7.6 | 7.1 | 6.5 | 4.1 | 3.2 |
| | | | 0.4 | 0.4 | 0.3 | 0.4 | 0.5 |
| 8. Headache | | | 6.3 | 6 | 5.2 | 3.1 | 2.2 |
| | | | 0.2 | 0.4 | 0.2 | 0.2 | 0.1 |
| Total | | | 57.7 | 58.6 | 54.2 | 46.6 | 38.3 |
| Average | | | 7.2 | 7.3 | 6.7 | 5.8 | 4.85 |

## Discussion

The economic impact of the common cold is not well known or understood.[7-13] Some episodes are undetected, not reported to health care providers, or have a course with minor intensity and do not cause significant problems. Complications may be common and can be expensive.[34, 38]

In the USA, the common cold leads to 75-100 million physician visits every year, and it is possible to estimate that an equivalent number of patients do not go to physicians for a simple cold. A presumptive estimate is that some $ 8-9 billion per year are lost for common cold episodes. USA customers spend about $ 3 billion on over-the-counter drugs and another $ 400 million on prescription medicines for symptomatic relief. It is possible that one-third of the patients that visit doctors may receive an antibiotic prescription. However, the patients tend to go to a physician only in cases of severe signs and symptoms and in cases of complications or when complications (i.e in higher risk subjects) are feared.[39-41] A large number of subjects possibly self medicate themselves or simply cope with their cold without any significant treatment.[30-32, 35-38] Some 22-189 million school days are missed annually for cold episodes, and parents may miss some 130 million workdays to be at home to care for their children. Some 200 million workdays may be missed by employees suffering from a cold. The total social burden and economic impact of cold-related work loss exceeds $ 20 billion per year. [4-12; 37-41] This accounts for some 40% of time lost from work in the United States. The reliabililty of the available data is questionable as most cold episodes are not recorded.

Most cold "patients" are completely unknown. More and larger research in different populations is needed. Although the common cold is possibly the most common disease, its real meaning and many of its aspects are still obscure.

The costs related to colds are very important. Even shortening the course of a cold by one or two days could have a significant impact on health management by decreasing millions of days of disease and lost working hours. Preventive measures are very generic and their efficacy may be questionable.[41] The epidemiology of colds is different in very dense urban populations interacting daily in crowded environments (*i.e.*, underground, schools).

As a comparison with Pycnogenol®, the use of troxerutin, including several flavonoids, to shorten the length and decrease severity of colds (in the model study) seems to have some effect on colds, but there are only limited results.[26]

Our pilot experience – in this registry and in the previous study with multiple supplement combinations [31] - indicates that there could be an important role for Pycnogenol® in decreasing the length and intensity of cold episodes, both when used alone in comparison with controls and when used in association with other supplements.[31] In comparison with results obtained in controls Pycnogenol® may offer a significant solution to make the course of colds shorter and decrease symptoms.[42] In more complex subjects, such as chronic diseases or infections, sinusitis,[43] or other nasal alterations (*i.e.*, septum deviations and anatomic abnormalities), and in older subjects with chronic bronchitis, respiratory problems or metabolic conditions, a cold may act as a clinical detonator towards severe complications. Considering that millions of patients are affected by colds, even some deaths may occur as a consequence of complications.[44-46]

The positive effects of Pycnogenol® may be more important in high-risk patients. The alterations in nasal mucosal flow seen in colds [31] with edema (using laser Doppler) are comparable to an acute mucosal inflammation leading to progressive restriction of airflow.[47, 48] Flu prevention studies suggest [49, 50] that flu shots have no action on the occurrence of colds while colostrum appears to reduce cold episodes. At the moment the possible important action of "natural", phytotherapic products in colds is under evaluation.[31, 52]

## Conclusions

Supplementation with Pycnogenol® affects symptoms of the common cold, improving clinical conditions and allowing a faster regression of in the worst days of follow up. Pycnogenol® controls excess inflammation and swelling in the nasal mucosa. In several studies, Pycnogenol® decreases abnormal capillary filtration that causes edema and swelling in a sequence comparable to the effects seen in this study on rhinorrhea. More studies on colds and specific- prospective, randomized trials are needed in this specific field.

Even an improvement in symptoms for a day when achieved for millions of people may produce a sig-

nificant reduction in cost. Pycnogenol®, alone or in combination,[31] may be an important option in these patients, considering its safety. It is possible that better effects of supplementation in higher-risk subjects could be observed if the supplement were used for more than a week.

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