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# Supplementary Management with Pycnogenol®-Centellicum® may Slow Down the Progression of Pulmonary Fibrosis and Improve Post-COVID-19 Lung Healing

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**Keywords:** Pulmonary Fibrosis; Antifibrotic Drugs; Epithelial Cells; Interstitial Pneumonia; Embolism

**Abbreviations:** IPF: Idiopathic Pulmonary Fibrosis; IIP: Idiopathic Interstitial Pneumonia; HRCT: High-Resolution Computer Tomography; PCL: Post-COVID-19 Lung Disease

ABSTRACT

The aim of this study was the evaluation of the supplementary activity of the combination of Pycnogenol® (150 mg/day) and Centella asiatica (Centellicum® 3 x 225 mg/day) (PY-CE) for 8 months in subjects with Idiopathic Interstitial Pneumonia (IIP). Recently the post-COVID-19 lung disease has emerged with large numbers of patients left with chronic lung conditions as a result of COVID-19. Considering the antifibrotic activity of the combination PY-CE, we also tested this supplementary management in post-COVID-19 patients.

**Results:** 19 subjects with Idiopathic Interstitial Pneumonia (IIP) were included in the study. High Resolution by CT scans at inclusion confirmed the presence of lung fibrosis. 10 were treated with the Pycnogenol® Centellicum® combination and 9 served as controls. Oxidative stress that was very high in all subjects at inclusion, decreased significantly in the supplement group ($p<0.05$). The Karnofsky performance scale index significantly improved in the supplement group in comparison with controls ($p<0.05$). The symptoms, fatigue and muscular pain were significantly lower after 8 months in supplemented patients ($p<0.05$) as compared with controls. At the end of the study, the small cystic lesions (honeycombing) and traction bronchiectasis were considered stable or in partial regression in 4 subjects in the supplemented group (vs none in the control group) with a significant improvement in tissue edema in the supplemented subjects. **Ultrasound Lung Sampling:** The white fibrotic component at inclusion was 18.5±2.2% of the image in controls vs 19.4±2.7% in the supplement group. At the end of the study, there was no improvement in controls (18.9±2.5%) vs a significant improvement in supplemented subjects (16.2±2.1%; $p<0.05$).

In addition, 18 subjects with post-COVID-19 lung disease were included in the study. 10 were treated with the Pycnogenol® Centellicum® combination and evaluated after 2 weeks, 8 patients served as controls. Preliminary results show that symptoms associated with post-COVID-19 Lung disease after 2 weeks were significantly improved with the supplement combination ($p<0.05$). Oxidative stress and the Karnofsky performance scale index was significantly improved in the supplements group as compared with controls ($p<0.05$).

**Conclusion:** According to these observations, Pycnogenol® controls and decreases edema in several conditions and Centellicum® - modulating the apposition of collagen – modulates the development of irregular cicatrization, keloidal scarring and fibrosis. More time is needed to evaluate this effect in a larger number of post-COVID-19 lung disease patients. This disease has affected almost 5 million subjects worldwide, leaving

severe consequences. Pycnogenol® and Centellicum® may improve the residual clinical picture in post-COVID-19 lung disease (PCL) patients and may reduce the number of subjects evolving into lung fibrosis. The evolution from edema to fibrosis seems to be slower or attenuated with this supplement combination both in Idiopathic pulmonary fibrosis (IPF) and in PCL patients.

## Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common issue of Idiopathic Interstitial Pneumonia (IIP) and causes progressive pulmonary fibrosis. Symptoms (exertional dyspnea, non-productive cough, and 'Velcro' lung crackles) tend to increase progressively. The diagnosis of IPF is based on the clinical picture and High-Resolution CT Scans (HRCT) or lung biopsy, when needed. Currently, treatment with antifibrotic drugs and oxygen therapy may help relieving symptoms but it is not clear if the progression can be changed. Most patients show a progressive degeneration of the lungs with a median survival (possibly, based on initial conditions, management, and age) from 3 to 5 years [1-5]. Histology shows interstitial pneumonia in most cases. Environmental, genetic, and unknown factors contribute to alveolar epithelial cells dysfunction or reprogramming leading to the abnormal fibroproliferation in the lungs. The key histological findings (subpleural fibrosis with fibroblast foci, sites of dense proliferation and intense scarring), alternating with areas of apparently normal tissue are visible with a diffuse heterogeneity of the tissues. Scattered areas of interstitial inflammation (with lymphocytes and plasma cells) tend to increase in time. Accessory symptoms (low-grade fever or myalgias) are uncommon. Clubbing can be seen in some 50% of the cases.

A classic sign is the presence of fine dry inspiratory crackles (Velcro) at both bases of the lungs. Most blood tests tend to be normal. More severe signs (pulmonary hypertension and right ventricular dysfunction) may develop [1-7]. IPF is often overlooked or confused with bronchitis, asthma, or heart failure. Diagnosis is made with High-Resolution Computer Tomography (HRCT). Chest x-ray shows diffuse reticular opacities in the lower-peripheral zones, small cystic lesions (caused by honeycombing), and some dilated airway (traction bronchiectasis). HRCT shows diffuse, patchy, subpleural, reticular opacities in the lower and peripheral lung zones. Ground-glass opacities (in more than 30% of the lungs) tend to suggest a different diagnosis. Lab tests are basically within normal values in most patients. Lung's health of most subjects tends to deteriorate in a relatively short period of time. The worst prognosis is related to older age, male sex, lower forced vital capacity and lower diffusing capacity of the lung for carbon monoxide or CO ($D_{LCO}$ also known as $T_{LCO}$). $D_{LCO}$ is the extent to which oxygen passes from the air sacs of the lungs into the bloodstream. This refers to the test commonly used to evaluate this parameter.

Acute problems (infections, embolism, pneumothorax, and heart failure) may cause acute lung deterioration. This condition has a high mortality and morbidity: lung cancer is more frequent in these patients for concomitant risks, but the causes of death are associated with respiratory failure [6,7]. The aim of this study was the evaluation of the supplementary activity of the combination of Pycnogenol® and Centella asiatica (as Centellicum®) (PY-CE) in subjects with IIP progression. During the recent period, a significant problem (the post-COVID-19 lung disease) has emerged with very large numbers. Considering the antifibrotic characteristics of the combination PY-CE (effective in blocking the passage from edema to fibrosis, in different tissues), we also tested this supplementary management in post-COVID-19 patients [8].

## Methods

### Part I Idiopathic Interstitial Pneumonia

Patients included: subjects with Idiopathic Interstitial Pneumonia (IIP) were included. The subjects had a Karnofsky performance scale index from 80 to 60 (Table 1). Only males aged <65 were included. No other disease was present. No drugs were used excluding specific management for IFP, i.e. pirfenidone. No metabolic conditions were present, and the participants' BMI was under 26. The subjects with IIP were in management for fast growing atherosclerotic carotid plaques with no surgical indications, using Pycnogenol® and Centellicum® according to our previous studies. In these subjects, fibrosis of the lung was a 'secondary' problem and the effects on the lungs were studied as a corollary evaluation to the initial management of atherosclerosis. The main target was the evaluation of changes in the Karnofsky performance scale. Cardiac Ultrasound showed no signs of significant pulmonary hypertension. There was a good left ventricular function. There were no valvular abnormalities.

**Table 1:** Karnofsky Performance Status Scale Definitions Rating (%) Criteria.

| | | |
|---|---|---|
| Able to carry on normal activity and to work; no special care needed. | 100 | Normal, no complaints; no evidence of disease. |
| | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| | 80 | Normal activity with effort; some signs or symptoms of disease. |

| | | |
|---|---|---|
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. | 70 | Cares for self; unable to carry on normal activity or to do active work. |
| | 60 | Requires occasional assistance but is able to care for most of his personal needs. |
| | 50 | Requires considerable assistance and frequent medical care. |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. | 40 | Disabled; requires special care and assistance. |
| | 30 | Severely disabled; hospital admission is indicated although death not imminent. |
| | 20 | Very sick; hospital admission necessary; active supportive treatment necessary. |
| | 10 | Moribund; fatal processes progressing rapidly. |
| | 0 | Dead |

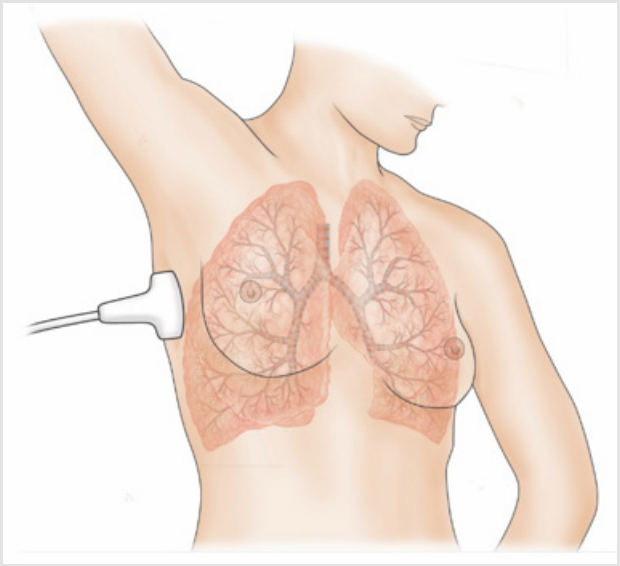

**Figure 1:** Position of the probe for transaxillary lung ultrasound 'biopsy'.

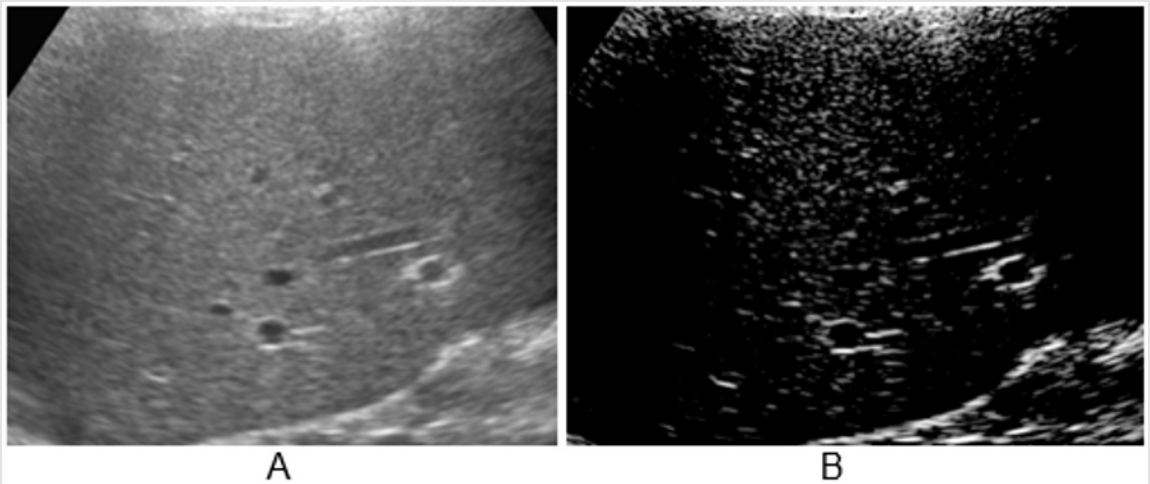


**Figure 2:** A: Aspect of HR scan, lung 'slice' (Preirus, Hitachi).
B: High-density white components in normal lung (<8% of the total image).

Lung Ultrasound: a section of lung is imaged (Figure 1) in a vertical scan. The image is elaborated (Adobe Premiere) for white components (speckles), corresponding to the most fibrotic components and areas of fibrosis in a normalized grey scale. The grey scale median is an expression of the white components (fibrotic, associated with collagen) in the ultrasound section. The section is obtained with a vertical, trans axillary scan (arm elevated). The 'slices' [4] are scanned for fibrotic components and for vascularization. The content of white 'speckles' corresponds to the presence of fibrotic elements. In a normal lung section of this

type, the white components are about 8% of the section or less. Figure 2 shows an elaboration of a 'slice' of lung tissue with its 'white' components corresponding to high collagen level (full black is the density of blood). The same software is used to image the arterial plaques to define their content in fibrotic (white) components or i.e., thrombotic (black on ultrasound scans, same density of blood). Supplement study: This study (and the subsequent post-COVID-19 lung study) were conducted as supplement registry studies [8,9]. The role of the combination Pycnogenol®-Centellicum® to control fibrosis has been previously defined in several clinical models [10]. 150 mg/day of Pycnogenol® was administered in 3 doses and Centellicum® (centella asiatica) was given at the doses of 225 mg 3 times per day. Both supplements are produced by Horphag Research.

Statistics [11-13]. A number of at least 15 subjects for each group (SM and SM + supplementation) was considered necessary to evaluate differences in target parameters over 4 weeks. All results and data were considered as non-parametric; the Mann-Whitney U-test and the ANOVA were used for symptoms/complaints. A predictive analysis [14] was performed at the end of the study based on the observed data and results.

### Part II: Post-COVID-19 Lung Disease

In an additional evaluation, subjects with Post-COVID-19 Lungs Disease (PCL), a second group of subjects (the study is in progress) were included in a registry; these were previously symptomatic patients, briefly admitted into hospitals (no ICU) and then sent home with some signs/symptoms (under control) with a standard management, based on the controls of the most common symptoms. A number of these subjects (all males) had also used as a supplementary management the combination of Pycnogenol® (150 mg/day in 3 doses) and Centellicum® (Centella asiatica, at the doses of 225 mg 3 times/daily). They were all using the supplementation before being diagnosed with COVID-19 and hospital admission, to slow down the progression of atherosclerotic, carotid plaques. Standard management was based on anti-inflammatory drugs; aerosols (no routine corticosteroids); antibiotics if indicated; vitamins, electrolytes, mild respiratory exercise (Triflo); appropriate diet (including proteins). Other drugs, like corticosteroids or cough meds, were used as needed. Table 3 shows the most common symptoms and the Karnofksy performance scale index in 2 weeks of observation or supplementation.

## Results

### Part I. Idiopathic Interstitial Pneumonia

19 subjects with Idiopathic Interstitial Pneumonia were included in the study. 10 were treated with the Pycnogenol® Centellicum® combination and 9 served as controls. No side effects were seen for the supplementation. A good tolerability was observed. Table 2 shows the two main groups of subjects. They were comparable at inclusion. Oxidative stress was very high in all subjects at inclusion and decreased significantly after 8-month treatment in the supplement group ($p<0.05$). The Karnofsky scale significantly improved in the supplement group in comparison with controls ($p<0.05$). The symptoms, fatigue and muscular pain were significantly lower at the end of the study in all supplemented patients ($p<0.05$). As inclusion criteria, HRCT had been indicative of fibrosis. Chest x-ray had shown diffuse reticular opacities at inclusion (mainly at the lower-peripheral zones). Diffuse, small cystic lesions (defined as honeycombing) had been observed. Some dilated airways (traction bronchiectasis) had been detected. CT had also shown diffuse, patchy, subpleural, reticular opacities (at the lower and peripheral lung zones). At the end of the study, the small cystic lesions (characteristic of honeycombing) and the traction bronchiectasis were stable or in partial regression in 4 subjects in the supplemented group (vs none in the control group) with a significant improvement in tissue edema in supplemented subjects (in 8 out of 10 patients) compared to the control group (1 out of 9 patients). Ultrasound Lung Sampling: The white fibrotic component at inclusion was 18.5±2.2% of the image in controls vs 19.4±2.7% in the supplement group (ns). At the end of the study, there was no improvement in controls (18.9±2.5%) vs a significant improvement (decrease) in the supplemented subjects (16.2±2.1%; $p<0.05$). Rescue medication (including corticosteroids) were used significantly less ($p<0.05$) in the supplement group.

**Table 2:** Summary Table of the idiopathic interstitial pneumonia (IIP) subjects.

| | Group A | Group B |
|---|---|---|
| **Management** | **Standard m (pirfenidone)** | **Sm + pycno-cent** |
| Number completing | 9 | 10 |
| Age; SD | 62.3;1.4 | 62;1.6 |
| Follow up Days; SD | 244;12 | 243;8.3 |
| Oxstress inclus | 409;13 | 412;22 |
| (Carr units; sd) End Study | 389;22 | 319;12* |
| Symptoms inclus | 7.3;0.4 | 7.22;0.7 |
| Score 0-10; SD End study | 7.1;0.3 | 5.84;0.32* |
| Karnofsky inclus | 71.3;2.2 | 70;2.4 |
| (In %);SD End study | 73.2;1.8 | 78.3;2.2* |
| Fatigue score inclus | 7.5;0.5 | 7.64;0.4 |
| (0-10);SD End study | 7.6;0.4 | 6.8;0.3* |
| **Ultrasound White fibr. Component %; SD** | | |
| Inclus | 18.5;2.2% | 19.4;2.7% |
| End study | 18.9;2.5% | 16.2;2.1%* |
| Side effects | Minimal | None |
| Drop outs (non-medical causes) | 2 | 1 |
| Rescue medications (corticosteroid cough meds) | 9/9 | 4/10 |

VARIATION OF THE MOST IMPORTANT ITEMS. *=$p<0.05$ vs controls

## Comments

IPF is the most common of IIPs. Symptoms are often misleading and may suggest other diseases [15].Therapy is complex and difficult: Pirfenidone and nintedanib are available for treatment in selected patients. These drugs tend to slow the progression of fibrosis and control symptoms down. However, they often cause side effects and costs are still high. Pirfenidone reduces lung fibrosis through downregulation of the production of growth factors and procollagens I and II. The recommended dose of pirfenidone in patients with idiopathic pulmonary fibrosis (as in the subjects in this registry) is 801 mg, 3 times a day (total daily dose of 2,403 mg). Supportive measures (oxygen and physical therapy) also help to control the symptoms as well as nutrition and weight and stress control. The use of prostaglandin E1 is supportive as it improves the pulmonary microcirculation, relieving vasospasm and increases the exchange rate of $O_2$ and $CO_2$ at bronchiolar levels with a more dynamic perfusional circulation, within the same limited, reduced exchange surface.

The evaluation of the pulmonary circulation is an important issue as a better gas exchange can be obtained with a better perfusion even in subjects suffering from severe fibrosis. The role of oxygen in promoting fibrosis must be evaluated. Cardiac ultrasound is especially important. Alterations (including dilatation) in the right ventricle volume indicate severe pulmonary conditions and a possible fast deterioration. When the right ventricle becomes larger, pulmonary hypertension is involved and a negative, fast evolution is possible. Most of these patients benefit from PGE1 infusions as they are also vascular subjects. The use of prostaglandin – off label – in these patients, to increase pulmonary circulation, does not produce side effects and it is well tolerated.

### Part II. The Post-Covid-19 Lung (PCL) Experience

Preliminary results (Table 3) 18 subjects with post-COVID-19 lung disease were included in the study. 10 were treated with the Pycnogenol® Centellicum® combination and 8 served as controls. Supplementation did not cause side effects and was well tolerated. The preliminary results on symptoms associated with post-COVID-19 Lung disease after 2 weeks were significantly improved with the supplement combination as compared with baseline. Oxidative stress and the Karnofsky performance scale were significantly improved in the supplements group as compared with controls ($p<0.05$). Morphological CT or ultrasound scans will show (the study is in progress) the evolution of the tissue scarring, but over a longer period of time.

**Table 3:** Subjects evaluated 2 weeks after hospital exit (with manageable, not life-threatening symptoms).

| Post-COVID-19 lung 2 weeks follow up | SM+PY-CE | | Standard Management (SM) | |
|---|---|---|---|---|
| | inclusion | 2 weeks | inclusion | 2 weeks |
| Number (age;SD) | 8 (55.4;3) | | 10 (58.8;2.3) | |
| 1.Pulm edema x-ray | 10/10 | 3/10* | 8/8 | 4/8 |
| 2.Upper respir. symptoms | 10/10 | 3/10* | 8/8 | 4/8 |
| 3.Cough | 10/10 | 2/10* | 8/8 | 3/8 |
| 4.Throat pain | 6/10 | 1/10* | 5/8 | 2/8 |
| 5.Salivary glands enlargement | 7/10 | 0* | 4/8 | 1/8 |
| 6.Fatigue | 10/10 | 2/10* | 8/8 | 3/8 |
| 7.Muscular pain | 10/10 | 2/10* | 8/8 | 3/8 |
| 8.Shortness of breath | 10/10 | 3/10* | 8/8 | 4/8 |
| 9.Ox-stress (CARR UNITS) | 432;22 | 341;24* | 437;25 | 394;22 |
| 10-Effort dyspnea | 8/10 | 3/10* | 7/8 | 4/8 |
| Karnofsly(%;SD) | 77;2.2 | 89.8;3* | 76.3;3.2 | 83.2.5* |
| Side effects | | 0 | | 0 |

*=$p<0.05$

## Conclusion

According to these observations, Pycnogenol® helps to control and decrease edema in several conditions and Centellicum® (Centella asiatica)- modulating the apposition of collagen in the affected tissues–possibly, slows down or modulates the development of irregular cicatrization, keloidal scarring and fibrosis [9-10,15]. More time and specific evaluation methods [16] are needed to evaluate this effect and a larger number of PCL patients may be considered for a disease that has affected almost 5 million subjects worldwide so far, leaving severe consequences. Pycnogenol® and Centellicum® may improve the residual clinical picture in PCL and, in the long-term reduce the number of subjects progressing to lung fibrosis [8,16]. The key passage and evolution from edema to fibrosis seems to be slower or attenuated with this safe supplement combination both in IPF and in PCL.

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