Melasma (or chloasma) is a common disorder of cutaneous hyperpigmentation predominantly affecting sun-exposed areas in women. The pathogenesis of melasma is not fully understood and treatments are frequently disappointing and often associated with side effects.

Pycnogenol® is a standardized extract of the bark of the French maritime pine (*Pinus pinaster*), a well-known, potent antioxidant. Studies *in vitro* show that Pycnogenol® is several times more powerful than vitamin E and vitamin C. In addition, it recycles vitamin C, regenerates vitamin E and increases the endogenous antioxidant enzyme system. Pycnogenol® protects against ultraviolet (UV) radiation. Therefore its efficacy in the treatment of melasma was investigated.

Thirty women with melasma completed a 30-day clinical trial in which they took one 25 mg tablet of Pycnogenol® with meals three times daily, i.e. 75 mg Pycnogenol® per day. These patients were evaluated clinically by parameters such as the melasma area index, pigmentation intensity index and by routine blood and urine tests.

After a 30-day treatment, the average melasma area of the patients decreased by 25.86 ± 20.39 mm² (*p* < 0.001) and the average pigmented intensity decreased by 0.47 ± 0.51 unit (*p* < 0.001). The general effective rate was 80%. No side effect was observed. The results of the blood and urine test parameters at baseline and at day 30 were within the normal range. Moreover, several other associated symptoms such as fatigue, constipation, pains in the body and anxiety were also improved.

To conclude, Pycnogenol® was shown to be therapeutically effective and safe in patients suffering from melasma. Copyright © 2002 John Wiley & Sons, Ltd.

*Keywords:* Pycnogenol®; melasma; chloasma; hyperpigmentation; dietary supplement; plant extract.

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**INTRODUCTION**

Melasma (or chloasma) is a common disorder of macular hyperpigmentation, which involves mostly the sun-exposed areas of the face and neck (Grimes, 1995; Kauh and Zachian, 1999). Although melasma is seen in both sexes and all races, women are most commonly affected (Muzaffar *et al.*, 1998; Goh and Dlova, 1999). The pathogenesis of melasma is not fully understood. Aetiological factors in the pathogenesis of melasma include genetic factors, exposure to UV radiation, pregnancy, oral contraceptives, cosmetics, photo-toxic drugs and anti-seizure medications (Pathak *et al.*, 1986; Grimes, 1995). Three clinical patterns of hyperpigmentation are recognized in patients with melasma. These include a centrofacial, a malar and a mandibular pattern. Histologically, increased pigment may be situated epidermally, dermally or on both sites (Sanchez *et al.*, 1981; Pathak *et al.*, 1986).

Ultraviolet radiation is known to generate reactive oxygen species (Cunningham *et al.*, 1985) and thus lead to oxidative stress. Oxidative stress plays a major role in the biological effects produced by UV radiation (Hruza and Pentland, 1993). Accordingly, UVR exposure of the skin causes oxidative damage to the skin and its components (Hattori *et al.*, 1996).

Current treatments can be divided into two categories, i.e. local treatment (or external therapy) and general treatment (internal therapy). The former includes external application (Griffiths *et al.*, 1993) of hypopigmenting agents (tretinoin/hydroquinones), chemical peels and laser therapy; the latter includes the oral administration of vitamin C or/and vitamin E, intravenous injection of vitamin C or/and glutathione (Grimes, 1995). Although these treatments are effective, their efficacy is not fully established and often they are associated with side effects.

In the choice of therapies for melasma, the treating physician has to establish a risk–benefit ratio for each therapeutic modality. There is a need to develop a more effective product with no or fewer side effects for better management of melasma.

Pycnogenol® is a French maritime pine (*Pinus pinaster*) bark extract produced by a standardized and validated extraction process. It contains monomeric phenolic compounds (catechin, epicatechin and taxifolin) and condensed flavonoids (procyanidins). In addition, it contains phenolic acids: *p*-hydroxy benzoic, protocatechuic, gallic, vanillic, *p*-coumaric, caffeic and ferulic acids (Rohdewald, 1998).

There is ample experimental evidence to support the antioxidant (Noda *et al.*, 1997; Packer *et al.*, 1999) and antiinflammatory (Blazsó *et al.*, 1994; 1997) activities of Pycnogenol®. Considering the strong antioxidant and antiinflammatory profile of Pycnogenol®, this study was conducted to assess the efficacy of Pycnogenol® in
melasma, at the Xiyuan Hospital of China, Academy of Traditional Chinese Medicine appointed by the Institute of Food Safety Control and Inspection, Ministry of Public Health of China (MPHC), according to the standard method proposed and approved by the MPHC.

PATIENTS AND METHODS

Patients. Thirty non-pregnant, non-nursing women suffering from abnormal pigmentation of melasma were enrolled in this 30-day open design study. They were aged between 29 and 59 years (mean age, 41 years) and their mean course of disease was 8 years. None of the patients took health foods, medication or used cosmetics that could relieve melasma.

The patients were instructed to take one 25 mg tablet of Pycnogenol® with meals three times a day, i.e. a total daily dose 75 mg.

Clinical evaluation. Clinical evaluation of the therapeutic effects was made at the first visit (before treatment, day 0) and then at the end of the 30-day treatment (day 30). The evaluation of subjective symptoms (fatigue, pain, constipation and feelings of impatience) was made on day 0, day 15 and day 30.

At the first visit, the history of melasma, its duration, relationship to pregnancy, hormonal therapy, sun exposure and cosmetic use was taken. Patients were asked about their previous use of hydroquinones and family history of melasma.

Efficacy. At each visit, the melasma area was determined planimetrically, and the pigmentary intensity of melasma was rated colorimetrically. For the melasma area, the diameter of the melasma area was measured by a ruler at three different places and the mean values were determined. The pigmentary intensity was rated using the national standard colour chart. On day 30, the overall response was scored with a 3-point semi-quantitative scale: 2 represents markedly improved; 1 represents effective and 0 ineffective.

The therapeutic effects were assessed at the end of the treatment. When a patient achieved a reduction of pigmentary intensity of melasma by two units or a reduction of the initial melasma area by >1/3 and no new melasma appeared, the case was considered to be ‘markedly improved’ and the overall response was scored as 2. When the reduction of the pigmentary intensity was one unit and the reduction of the initial size was <1/3, and no new melasma appeared, the treatment was considered ‘effective’ and the overall response was scored as 1. When no change occurred in the skin lesions or the pigmentary intensity, the treatment was considered ineffective and scored as 0.

Other associated subjective symptoms of the patients such as fatigue, pains, state of anxiety and constipation were also observed and recorded. These symptoms were graded according to their degree of seriousness on a 3-point semi-quantitative scale: 3 represents major symptoms; 2 moderate; and 1 minor. These were integrated on day 0, day 15 and day 30. The improvement of the symptoms was graded on a scale where 2 represents markedly improved; 1 represents effective and 0 ineffective for each symptom. The scores of the improvements were calculated on day 15 and at the end of the treatment.

Safety. The patients were examined on day 0 and on day 30 for routine blood and urine examinations. These included red blood cell (RBC) count, haemoglobin (Hb) and white blood cell (WBC) count. Biochemical parameters included serum albumin (ALB), total protein (TP), alanine-aminotransferase (ALT), AST, UREA, creatinine (CRA), plasma glucose (GLU), plasma lipids (total cholesterol; triglycerides (TG); high-density lipoprotein-cholesterol (HDL) and urinalysis.

The patients were also examined by abdominal B-ultrasonography, electrocardiography (ECG) and thoracic fluoroscopy.

Statistics. A descriptive analysis of data was performed using SDAS software on an IBM personal computer. The statistical analysis included analysis of variance (ANOVA) and Students’s t-test for for parametric data. Non-parametric data were analysed by means of Mann-Whitney and Wilcoxon tests. The values in the text and tables are expressed as mean ± SEM.

RESULTS

All 30 patients completed the 30 day treatment period. The results are shown in Table 1. The overall efficacy rate was 80%. These are further depicted in Fig. 1.

The average pigmentary intensity of the 30 women decreased significantly (p < 0.001, Table 2) on day 30, representing an improvement of 0.47 unit. The average melasma area was also significantly decreased (p < 0.001, Table 2), showing a reduction of 25.8 mm2.

The results of the improvement of other associated symptoms in individual cases are shown in Table 3. It is interesting to note that Pycnogenol® produced relief from fatigue, pain, constipation and feelings of impatience in those patients showing these symptoms. The overall symptom-index was reduced from 3.93 ± 3.11 to 2.73 ± 2.42 (p < 0.001) after 15 days and to 2.00 ± 1.95 (p < 0.001) after 30 days of treatment with Pycnogenol®. The efficacy rate varied between 57% and 70% (Table 3).

The tolerability of Pycnogenol® was considered very good and no side effects relating to Pycnogenol® were reported during the study. Pycnogenol® was considered systemically safe based on the evaluation of biochemical

Table 1. Incidence of effectiveness and overall efficacy rate in 30 evaluated patients after 30 days treatment with Pycnogenol®

<table>
<thead>
<tr>
<th>Incidence of effectiveness</th>
<th>Markedly improved</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy rate (%)</td>
<td>23.33</td>
<td>56.67</td>
<td>20.00</td>
<td>80.00</td>
</tr>
</tbody>
</table>

Table 2. The reduction of pigmentary intensity and melasma area, after 30 days of treatment with Pycnogenol®

<table>
<thead>
<tr>
<th>Item</th>
<th>Cases</th>
<th>Day 0</th>
<th>Day 30</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmentary intensity (unit)</td>
<td>30</td>
<td>2.10 ± 0.71</td>
<td>1.63 ± 0.61</td>
<td>0.47 ± 0.51</td>
</tr>
<tr>
<td>Melasma area (mm²)</td>
<td>30</td>
<td>68.65 ± 44.06</td>
<td>42.79 ± 35.59</td>
<td>25.8 ± 20.39a</td>
</tr>
</tbody>
</table>

* p < 0.001.

Table 3. Improvement of other symptoms after 30 days of treatment with Pycnogenol®

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of cases</th>
<th>Markedly improved</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Efficacy rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>69.23</td>
</tr>
<tr>
<td>Thoracic/costal pain</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>70.00</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>61.54</td>
</tr>
<tr>
<td>Impatience</td>
<td>16</td>
<td>2</td>
<td>7</td>
<td>7</td>
<td>56.52</td>
</tr>
</tbody>
</table>

DISCUSSION

The pathogenesis of melasma is not fully understood. Aetiological factors in the pathogenesis of melasma include genetic influences, exposure to UV radiation, pregnancy, oral contraceptives, cosmetics, phototoxic drugs and anti-seizure medications (Pathak et al., 1986; Grimes, 1995). Familial history, pregnancy, hormonal therapies, use of cosmetics and other medications were among the exclusion criteria.

As the outermost organ of the body, the human skin is frequently and directly exposed to sun and thus to UV radiation. UV radiation is known to generate reactive oxygen species (Cunningham et al., 1985) and thus leads to oxidative stress. Environmental factors such as exposure to the sun and oxidative stress causing erythema and inflammatory actions may be considered the main factors affecting the pathogenesis of melasma in patients selected in the present study.

Current treatments of melasma can be divided into two categories, i.e. local treatment (or external therapy) and general treatment (or internal therapy), the former includes external application of hypopigmenting agents, chemical peels and laser therapy; the latter includes the oral administration of antioxidants such as vitamin C or/and vitamin E, intravenous injection of vitamin C or and glutathione. Local treatment often brings side effects such as irritant and allergic dermatitis, ochronosis and atrophy.

Topical treatment with tretinoin (retinoic acid 0.1%) showed significant effectiveness using objective measures (colorimetric and histological), however, moderate cutaneous side effects of erythema and desquamation occurred in 88% of tretinoin-treated patients compared with 29% of vehicle-treated patients (Griffiths et al., 1993).

The use of hydroquinones is not advised, because of the risk of depigmentation, allergic contact dermatitis, nail discoloration and ochronosis (a chronic disfiguring condition). Use of topical corticosteroids may produce side effects such as skin atrophy and telangiectasia.

Laser therapy represents a novel approach. Although studies have demonstrated some success with laser therapy in the treatment of diseases of hyperpigmenta-
Wireless communication relies on various technologies to facilitate the transmission of information between devices. These technologies include Bluetooth, Wi-Fi, and cellular networks, each with its own set of advantages and limitations. Bluetooth operates in the 2.4 GHz frequency band, allowing for short-range, low-power communication. Wi-Fi, on the other hand, operates in both the 2.4 GHz and 5 GHz bands, offering faster speeds and greater range. Cellular networks use a range of frequencies, with LTE and 5G offering high-speed data transfer.

The choice of technology depends on factors such as the required bandwidth, range, and cost. For example, Bluetooth is often used for connecting devices within close proximity, such as earphones and smartphones. Wi-Fi is commonly used for home and office networking, as well as for mobile internet access. Cellular networks are primarily used for mobile phone communication and data transfer on the go.

The future of wireless communication is likely to involve a combination of these technologies, with the emergence of new standards such as 6G, which promises even faster speeds and more advanced features. As technology advances, we can expect to see continued improvements in wireless communication, enabling new applications and services that were not possible before.
REFERENCES


