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Review Article

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Relief from Menopausal Symptoms by Non-hormonal Treatment with Pycnogenol® (French Maritime Pine Bark Extract)

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Abstract

Declining estrogen levels are connected to endothelial dysfunction and weakening of antioxidative defense. Endothelial dysfunction is linked to vasomotoric and sexual problems. Reduced synthesis of antioxidants as consequence of fading estrogen supply results in oxidative stress and promotes painful menstrual problems. In addition, psychosomatic symptoms as insomnia, depression and deficits in cognitive function are frequent. Compensation for loss of estrogen by hormone replacement therapy is problematic for some women because of adverse effects so that there is a need for a non-hormonal option for relief from menopausal symptoms.

The ability of French maritime pine bark extract (Pycnogenol®) to alleviate climacteric symptoms was tested in clinical trials with perimenopausal women. The Woman's Health Questionnaire was used in Taiwan and Japan in randomized, placebo-controlled, double-blind studies with 155 and 156 women respectively. An Italian study compared symptoms by Menopause Symptoms Questionnaire in a Pycnogenol® group of 38 women with 32 controls.

Climacteric symptoms decreased dependent on the length of treatment. The highest dose, 200 mg/day Pycnogenol® improved all symptoms relative to placebo, lower doses improved only some symptoms, suggesting a dose-dependent effect.

Vasomotoric problems were ameliorated in all 3 studies, insomnia decreased with 200 mg and 60 mg Pycnogenol® daily. In addition, in the most informative study from Taiwan, a consistent improvement of psychosomatic symptoms was reported.

A rationale for the attenuation of vasomotoric and sexual problems is proposed based on enhanced availability of nitric oxide (NO) via interaction of Pycnogenol® with endothelial nitric oxide synthase. Enhanced availability of NO is potentially also involved in the improvement of sleep, memory and psychic symptoms following Pycnogenol® intake. The relief from menstrual problems is connected with the anti-inflammatory properties of Pycnogenol®.

By improving endothelial function and antioxidative status Pycnogenol® offers a versatile non-hormonal option for relief of climacteric symptoms.

Keywords

Menopause; Pycnogenol®; Endothelial dysfunction; Oxidative stress

Introduction

The major hormonal change in menopause, the fading production of estradiol, is associated with several menopausal symptoms such as hot flushes, night sweats, disturbed sleep, mood swings, deficits in memory and concentration and problems with the urogenital tract.

In addition, menopause affects also lipid metabolism, cholesterol and triglyceride levels are elevated [1-5]. Furthermore, the lack of estradiol's antioxidative effects evokes oxidative stress [6]. The combination of oxidative stress with high cholesterol, especially LDL, is prone to produce peroxidized lipids. Peroxidized lipids within the cardiovascular system may lead to hypertension, atherosclerosis, embolism and cardiovascular events [7-9].

Thus, menopausal problems are not confined to more or less temporary symptoms; the decrease of estradiol may cause serious cardiovascular consequences. The endothelial dysfunction has a key role in producing these unwanted effects and events.

With progressing stages of menopause the endothelium-dependent vasodilation declines independently from aging [10]. The endothelium regulates vascular homeostasis by releasing vasodilators as nitric oxide (NO), prostacyclin and bradykinin as well as the vasoconstrictors endothelin and angiotensin II [11]. Endothelial NO, the most potent vasodilator, has in addition antithrombotic, antiproliferative and anti-inflammatory properties [6,12,13].

A decline of NO production or an inactivation of NO by oxygen radical's results in endothelial dysfunction.The function of the endothelium can be controlled by monitoring of the arterial diameter under increased blood flow as flow-mediated dilation (FMD). FMD stimulates the endothelial NO production.

The endothelial NO synthase (e-NOS) is activated by the endothelial estrogen receptor ERα. The estrogen deficiency in menopause reduces the expression of ERα [14] so that NO release declines with the consequence of endothelial dysfunction.

Endothelial dysfunction is highly associated with the risk of cardiovascular events [10,11]. The menopausal hormone therapy (MHT) was initiated to substitute the loss of oestrogens by diverse hormonal products. The benefits of MHT have been specified in the Revised Global Consensus Statement on MHT in 2016 [15]. However, also this revised consensus repeated the warnings of the consensus statement from 2012 for age-dependent risks for thromboembolism and breast cancer.

The publication of these statements stimulated the desire for non-hormonal options for relief from menopausal symptoms [16]. The extract from the bark of the French maritime pine (Pycnogenol®) offers a safe natural way to relieve menopausal symptoms.

Mechanisms of Action of Pycnogenol®

Direct improvement of endothelial function and NO availability by Pycnogenol®

A significant ($p<0.05$) augmentation of forearm blood flow was found in a double-blind, randomized, placebo- and active substance controlled study following intake of Pycnogenol®, placebo had no

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effect [17]. The administration of an NO-synthase inhibitor abolished the effect completely, suggesting that Pycnogenol® increased blood flow by enhancing NO production.

This study confirmed results of an ex-vivo study on aortic rings [18]. Pycnogenol® exerted an endothelium dependent relaxing effect on the contracted aortic tissue. Relaxation could be counteracted by an inhibitor of e-NOS, but restored by L-arginine, thus demonstrating the enhanced availability of NO following exposure to Pycnogenol® [18].

Another double-blind, randomized and placebo-controlled study with cardiovascular patients could demonstrate an improved flow mediated vasodilation under Pycnogenol®, but not with placebo [19].

These 3 studies point to an improvement of endothelial function via enhanced availability of NO under the influence of Pycnogenol®.

Improvement of endothelial function with Pycnogenol® by interaction with vasoactive substances

In addition to enhancement of NO availability, Pycnogenol® interacts with a second vasodilator. In diabetic patients, the blood levels of the vasodilator prostaglandin F1a increased significantly after supplementation with Pycnogenol® [20]. On the other side of the vascular homeostasis, Pycnogenol® reduced blood levels of vasoconstrictors as angiotensin II [21], thromboxane A2 and endothelin-1 [22,23].

These findings demonstrate that Pycnogenol® is able to balance the equilibrium between vasodilation and vasoconstriction thus normalizing endothelial function, which is of outmost importance for maintenance of normal circulation.

Reduction of oxidative stress by Pycnogenol®

Before menopause, women are protected against free radicals by estradiol which provides antioxidative enzymes via estrogen receptor ERα [24]. The down-regulation of genes coding for antioxidative enzymes exposes the female organism to oxidative stress. The surplus of free radicals inactivates NO and produces lipid peroxides, starting the process of athero-sclerosis and cardiovascular diseases.

The gap in antioxidative defense may be filled in by supplementation with antioxidants like Pycnogenol®. In numerous clinical studies, Pycnogenol® has shown its potential as a very potent scavenger of free radicals. It increased the total antioxidant status of plasma in menopausal women, in patients with erectile dysfunction [25] and normal healthy volunteers [26] and decreased plasma free radicals in smokers [27], menopausal women [28] and subjects with borderline hypertension [29], with high oxidative stress [30], diabetic retinopathy [31], healthy professionals [32] and patients with psoriasis [33] and athletes [34].

Experiments with arterial endothelial cells showed a 100% higher activity of superoxide dismutase and catalase and higher glutathione in presence of Pycnogenol® [35]. As Pycnogenol® itself is an excellent scavenger of free radicals [36] and reinforces the enzymatic antioxidative defense, supplementation with Pycnogenol® seems to be an appropriate method for reducing oxidative stress in menopause.

Clinical Studies with Menopausal Women

Relieve of menopausal symptoms

In a first clinical study with peri-menopausal women, 200 women were enrolled in a randomized, double-blind, placebo controlled trial at the Department of Obstetrics and Gynecology in Taipei [37]. Patients were included into the study according to their hormone levels: serum levels of FSH> 30 IU/ml and estrogen E2 levels <20 pg/l. Patients received twice daily 100 mg Pycnogenol® capsules or placebo capsules over a period of 6 months. Compliance was controlled by phone every 2 weeks. Climacteric symptoms were evaluated by a Chinese version of the Women's Health Questionnaire (WHQ), designed by Hunter 1992 [38]. Patients were matched in respect to frequency of climacteric symptoms, age and BMI. The drop-out rate was 22.5%, mainly because of non-compliance, 155 women completed all questionnaires. Questionnaires were collected at visits after 1, 3 and 6 months. Patients had to score symptoms from heavy discomfort 1 to no discomfort 4. The WHQ contains 36 questions relating 9 symptoms.

At inclusion, complaints in both groups were between little discomfort [3] and clear discomfort [2] (Table 1). During treatment, majority of scores in the placebo group remained unchanged, most items improved relative to start, but none was superior to Pycnogenol® treatment. In the Pycnogenol® group, every symptom improved significantly ($p<0.001$) after 6 months, with a continuous increase to better values over the period of investigation (Table 1).

Remarkably, the Taiwanese women in both groups had nearly no problems with vasomotoric symptoms at enrollment, scores indicated little discomfort, values raised to 3.75, indicating nearly no discomfort after 6 months with Pycnogenol®. Clear discomfort was found for memory / concentration and attractiveness in both groups, with improvement to little discomfort under Pycnogenol®, but not with placebo. Patients did not report unwanted effects, estradiol levels remained unchanged.

Interestingly, blood pressure decreased slightly, but significantly during treatment (Table 2). LDL was lowered $p<0.001$ compared to placebo, HDL increased relative to baseline. Total anti-oxidative status (TAS) increased $p<0.01$ after 6 months, no changes were observed under placebo at 6 months. No unwanted effects were reported.

In an Italian study, 38 menopausal women received 100mg Pycnogenol® daily, the control group of 32 women remained without supplementation [28]. All participants of the study were consulted to perform a life style program to limit menopausal symptoms by exercise and a limited consumption of salt, sugar, caffeine and alcohol.

The participants had to score after inclusion and 8 weeks later 33 symptoms listed in the Menopause Symptoms Questionnaire (www.34-menopause-symptoms.com). Scores ranging from 0 – absence of symptoms – to 4 – very severe symptoms. Whereas no significant change of symptoms was reported in the control group (data not shown), most of the scores in the Pycnogenol® group were improved significantly *vs.* baseline (Table 3). The items hot flushes, irregular heartbeat, electric shocks, digestive problems and bloating showed significantly better scores compared to control. No significant changes could be observed for items with very light symptoms-severity at inclusion (not shown in Table 2). Plasma free radicals dropped from 423 Carr units to 310 under Pycnogenol®, whereas values increased from 434 to 441 in the placebo group.

In contrast to the Taiwanese study, hot flushes prominent at inclusion could be reduced to tolerable scores. Even in this comparably short treatment period, most scores could be reduced by one point into the direction of mild symptoms. No unwanted effects were reported, compliance was excellent.

Table 1: Mean change of the climacteric symptoms evaluated by the WHQ scale.

Pycnogenol® group (n= 80)				
	Enrollment	**1 month**	**3 months**	**6 months**
Somatic problems	2.61 (0.97)	3.05** (0.69)	3.14** (0.50)	3.21** (0.41)
Depressed	2.89 (0.91)	3.16** (0.74)	3.21** (0.54)	3.29** (0.46)
Vasomotoric problems	3.28 (0-96)	3.57* (0.59)	3.64** (0.50)	3.76tt** (0.43)
Memory/concentration	2.39 (0.92)	2.85** (0.77)	3.03** (0.51)	3.06** (0.25)
Attractiveness	2.26 (0.92)	2.77 (0.82)	2.98** (0.56)	3.09** (0.28)
Anxiety	2.85 (0.91)	3.22** (0.58)	3.27** (0.50)	3.27** (0.44)
Sexual behavior	2.67 (0.90)	3.04* (0.72)	3.18** (0.57)	3.23** (0.42)
Sleep	2.55 (0.88)	2.98** (0.63)	3.22** (0.50)	3.31** (0.47)
Menstrual problems	2.89 (0.93)	3.15** (0.68)	3.21* (0.53)	3.25** (0.44)
Placebo group (n= 75)				
	Enrollment	**1 month**	**3 months**	**6 months**
Somatic problems	2.57 (1.00)	2.69ttt (0.89)	2.75tt (0.87)	2.69 (0.87)
Depressed	2.91 (0.89)	2.99t (0.88)	2.91 (0.87)	2.89 (0.80)
Vasomotoric problems	3.27 (0.91)	3.25 (0.86)	3.28 (0.76)	3.34 (0.71)
Memory/concentration	2.39 (0.90)	2.54t (0.85)	2.64t (0.82)	2.67 (0.82)
Attractiveness	2.41 (0.85)	2.58 (0.80)	2.63 (0.80)	2.59 (0.80)
Anxiety	2.91 (0.88)	2.86 (0.85)	2.84 (0.87)	2.92 (0.88)
Sexual behavior	2.71 (0.81)	2.76 (0.77)	2.81 (0.84)	2.79 (0.83)
Sleep	2.51 (0.919	2.67tt (0.85)	2.64 (0.86)	2.56 (0.90)
Menstrual problems	2.80 (0.95)	2.81 (0.87)	2.96tt (0.97)	2.92 (0.85)

Note: All means of symptoms were stat. sign. different to enrollment for the Pycnogenol® group (p>0.001), not indicated by asterisk.

Significant differences to enrollment for the placebo group are indicated as tp<0.05,

ttp<0.01, tttp<0.001.

Significant differences to placebo are indicated by *p<0.01, **p<0.001.

Table 2: Means and standard deviations of blood pressure, lipid profile and antioxidant status (TAS) before and during intake of Pycnogenol®.

	Pycnogenol®		
	Enrollment	**3 months**	**6 months**
Systolic blood pressure	116.37	110.27*** (12.75)	111.86** (14.09)
Diastolic blood pressure	72.14	69.37* (8.30)	69.58* (9.61)
HDL	44.70	45.31**(7.31)	46.75* (8.08)
LDL	111.44	105.27t (25.16)	100.41*tt (24.24)
Triglycerides	90.37	99.32 (55.04)	94.46 (55.04)
TAS	1.42	1.49** (0.14)	1.55***t (0.55)

Note: Mean difference to start is significant at the level 0.05*, 0.01**, 0.001***. Mean difference to placebo is significant at the level 0.01t, 0.001tt. (Independent samples t-test.)

Values obtained during treatment with data from enrollment have been compared using the t-test for independent samples significant differences at *p>0.05, **p>0.01, ***p>0.001.

A third randomized, double-blind, placebo-controlled study was performed at the Department of Obstetrics and Gynecology at the Keiju Medical Center in Nanao City, Japan. 156 peri-menopausal women received either 30 mg Pycnogenol® or placebo twice daily for a period of 12 weeks [39], compliance was controlled by counting number of remaining capsules at 4 and 12 weeks. Study was unblinded following statistical evaluation of the data. Patients were contacted in weekly intervals to ensure compliance and asked for unwanted effects. The participants were investigated at 4 and 12 weeks for blood pressure, blood lipid profile and serum levels for FSH, estradiol E2, insulin-like growth factor (IGF), IDF binding protein 3 (IGF BP-3) and dehydroepiandrosterone (DEA).

Menopausal symptoms were evaluated by the WHQ, in addition to the WHQ the Kupperman index was used in the modified form of Abe et al. [40]. Comprising 17 items: hot flushes; perspiration; local sensation of cold; shortness of breath; numbness; hypesthesia; difficulty in falling asleep; fitful sleep; irritability; nervousness; melancholy; vertigo; nausea; weakness (fatigue); stiff shoulder, pain in joints, muscular pain; headache; palpitation; tingling sensation.

The investigation demonstrated that hormone levels varied profoundly between women, but were neither increased nor reduced by Pycnogenol® relative to placebo. The climacteric symptoms according to WHQ were reduced relative to baseline in every item except formication and abnormal perception by Pycnogenol® and placebo. Significant changes vs placebo were observed for vasomotoric items (p<0.0359), sleeping problems (p<0.0025), feeling tired (0.048). The Kupperman index (Figure 1) indicated a significant (p<0.05) improvement of menopausal symptoms relative to placebo. No women complained from unwanted effects.

Discussion

The common outcome of the three controlled trials with different ethnics is the gradual improvement of menopausal symptoms following the intake of Pycnogenol®. The symptom relief is time-

Table 3: Scores from the Pycnogenol® group from Menopause Symptom Questionnaire.

Score 0-4	Inclusion	8 weeks	Statistics
Common symptoms			
1. Hot flushes	3.1; 0.3	1.1; 0.5	**
2. Night sweats	3.1; 0.3	2.1; 0.8	*
3. Irregular periods	3.7; 0.1	2.1; 1.1	*
4. Loss of libido	2.1; 1.1	1.1; 0.6	*
5. Vaginal dryness	2.2; 1.1	1.2; 0.3	*
6. Mood swings	1.9; 0.9	1.1; 0.4	*
Changes			
7. Fatigue	3.3; 0.4	2.4; 1.2	*
8. Hair Loss	2.12; 1.1	1.2; 0.4	*
9. Sleep disorders	1.3; 1.2	1.1; 0.4	*
10. Difficult concentrating	2.1; 0.9	1.1; 0.4	*
11. Memory lapses	2.5; 0.4	1.3; 0.6	*
12. Dizziness	2.8; 0.3	2.1; 1.1	*
13. Weight gain	2.4; 0.9	2.1; 0.5	*
14. Incontinence	1.7; 0.9	1.2; 0.3	NS
15. Bloating	3.2; 0.5	1.2; 0.3	**
16. Allergies	1.1: 0.8	0.9; 0.4	NS
17. Brittle nails	2.5; 0.2	0.9; 1.1	*
18.Changes in odor	1.2; 0.5	1; 0.4	NS
19. Irregular heartbeat	3.1; 0.4	2.3; 0.3	**
20. Depression	1.9; 0.3	1.1; 0.4	*
21. Anxiety	2.9; 0.2	1.1; 0.3	*
22. Irritability	3.1; 0.7	1.4; 0.6	*
23. Panic disorder	2.2; 1.2	1.1; 0.3	*
Pain			
24. Breast pain	2.6; 1.2	1.3; 0.3	*
25. Headaches	3.2; 0.3	2.2; 0.3	*
26. Joint pain	2.7; 0.6	0.9; 0.3	*
27. Burning tongue	1.1; 0.5	1; 0.2	NS
28. Electric shocks	2.5; 0.2	0.6; 0.2	**
29. Digestive problems	3.1; 0.3	1.1; 0.4	**
30. Gum problems	2.2; 0.55	1.2; 0.3	*
31. Muscle tension	2.8; 0.3	1.1; 0.3	*
32. Itchy skin	2.9; 0.3	1.2; 0.3	*
33. Tingling extremities	2.2; 0.8	1.1; 0.3	*

Note: *Significant *vs.* baseline, **significant *vs.* control

dependent, as could be demonstrated by the increase of scores obtained after 1, 3 and 6 months [37]. One may conclude that the improvement is also dose-dependent, even when the comparison of the three studies has its limits. However, the fact that the number of symptoms which are significantly different to placebo decreases with the applied dose: 200 mg/day for 1 month produced relief of 8 groups of symptoms [37], 100 mg/day for 8 weeks improved 5 symptoms out of 33 [28] and 60 mg/day for 12 weeks ameliorated 3 symptom domains out of 15 [39].

As could be expected from the vaso-regulating effect on the endothelium, in all three studies the vasomotoric problems were significantly improved vs placebo. The slight, but significant decrease of blood pressure [37] points also to a better vascular regulation under Pycnogenol®. Insomnia, together with feeling tired and worthless, was significantly ameliorated in the study of Kohama [39], sleep problems were significantly improved also in the study of Yang [37]. The Italian women had no sleep problems at enrollment or at the end of the study [28].

The ability of Pycnogenol® to enhance NO production could give the rationale also for the improvement of sleep problems. As shown in animal experiments. NO makes a key contribution to daily homeostasis of sleep [41]. NO synthase containing neurons overlap in different regions of the brain neurons contributing to sleep mechanisms. NO in neurons of the pontine tegmentum favors sleep [42,43]. The inhibition of NO synthase in turn suppresses sleep [43-45]. These results from mechanistic animal experiments highlight the role of NO for sleep-wake regulation. The improvement of sleep – or decrease of tiredness – could be related to an activation of NO by Pycnogenol®.

The improvement of another domain of the questionnaires, the psychosomatic symptoms, could be also related to the elevated production of NO under the influence of Pycnogenol®. In three clinical studies with students [46], professionals [32] and elderlies [30] the intake of Pycnogenol® evoked better scores for memory and learning and a positive mood.

"Loss of estrogen jeopardizes the integrity of brain in menopause", results in neuronal damage and apoptosis [47]. Furthermore, estrogen modulates the release of neurotransmitters acetylcholine, norepinephrine and dopamine [47]. NO, as another neurotransmitter, is involved in the process of memory and learning. Activity of n-NO synthase increases during learning, as has been shown in several animal experiments [48]; NO also modulates the levels of dopamine, norepinephrine and serotonin [49,50]. These NO-mediated mechanisms could provide the basis for the beneficial effects of Pycnogenol® on concentration and learning and on the psychosomatic symptoms as depression, anxiety and on the other side, attractiveness.

The domain Sexual Behavior is also closely linked to NO and endothelial health. The abundance of e-NOS in the endothelium of sinusoids and blood vessels of the erectile tissue of the vaginal anterior wall and clitoris tissue signalizes the importance of NO for female sexual activity [51]. An increased availability of NO will lead to better blood flow into the genital tract and to subsequent lubrication. Even when NO is only one part of the many factors stimulating female sexual activity, the relaxation of blood vessels mediated by e-NOS, as a central component for a successful sexual activity, is most probably the reason for Pycnogenol®'s positive effects on female sexual behavior.

The anti-inflammatory activities of Pycnogenol® have been shown to reduce menstrual pain [52], pain from dysmenorrhea [53], endometriosis [53] and pain in late pregnancy [54]. Pycnogenol®'s analgetic effects are caused by inhibition of anti-inflammatory mediators [55,56]. Therefore, a reduction of menstrual problems, as observed [52,53] in the trial of Yang et al. [37], was to expect.

Conclusion

3 clinical studies demonstrated that menopausal symptoms were improved, yet not completely removed with Pycnogenol®, improvements were time- and dose-dependent.

The relief from menopausal symptoms reported in the 3 clinical studies is most probably based on the improvement of endothelial function and the reduction of oxidative stress by Pycnogenol®. The positive effects on blood pressure, vaso-motoric problems and on sexual behavior could be related to the vasodilation caused by NO via stimulation of e-NOS by Pycnogenol®. The improvement of sleep, memory and concentration of the menopausal women could be related to an enhanced availability of NO in the brain under the

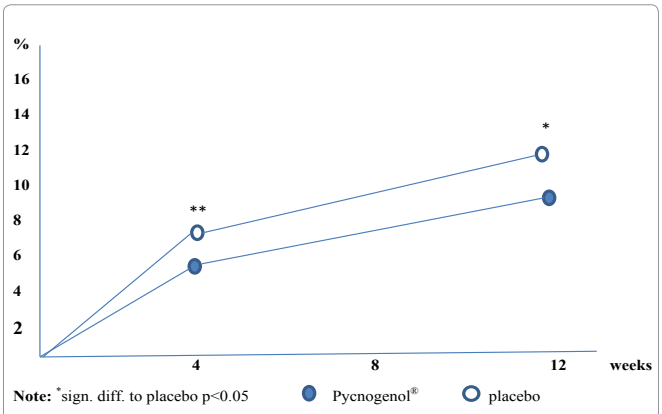

Figure 1: Relative change to baseline of total Kupperman index [42].

influence of Pycnogenol®. Better sleep and mental fitness will lead to a better quality of life, thus reducing negative feelings like anxiety of depression.

As none of the participants in the studies complained about unwanted effects, and Pycnogenol® has shown in clinical studies with 12.000 subjects only mild side effects in the same range as placebo, Pycnogenol® provides a safe non-hormonal option for relief from menopausal symptoms.

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