# UPDATE ON THE CLINICAL PHARMACOLOGY OF PYCNOGENOL®

*P. Rohdewald*

Westfälische-Wilhelms-Universität Münster, Twenteweg 15; D-48161 Münster, Germany; Tel: +49 251 8714405; Fax: +49 251 8714403; email: rohdewa@uni-muenster.d

Abstract—Pycnogenol® (PYC), obtained as a dry extract from the bark of the French maritime pine, has attracted the interest of researchers worldwide; more than 300 publications in Medline reflect this scientific interest. This review summarizes clinical studies published in scientific journals between 2010 and 2015.

Knowledge of the metabolism of PYC was expanded during the last years. Its active metabolite M1, a valerolactone, is accumulated via active transport in blood cells and undergoes further intra-cellular metabolism. PYC exerts 4 basic functions: Inhibition of α-glucosidase, stimulation of synthesis of hyaluronic acid and collagen, stimulation of nitric oxide production and inhibition of inflammatory mediators. The effects of PYC in inhibiting inflammatory processes and stimulating endothelial function have been corroborated by new clinical studies. Further insight into the effects of PYC in chronic venous insufficiency and hemorrhoids resulted from ex-vivo experiments and clinical studies. The improvement of local microcirculation terminated tinnitus and Meniere's disease in 87% of the patients vs 35% in controls. Inhibition of aromatase and growth factors by PYC was correlated with substantial amelioration of endometriosis, 90% of patients became pain free. The spectrum of contributions of PYC to women's health has been broadened by new positive effects on sexual function, evaluated by the Female Sexual Function Index. Erectile function of infertile men, evaluated by the Int. Index of Erectile Function was improved from moderate to normal values. Concentration of sperms increased by 79% to normal levels by administration of combinations of PYC with aminoacids and roburin. Furthermore, the administration of PYC exerted a significant positive influence on cognitive functions as memory, learning and daily capabilities.

Hence the administration of PYC offers a multitude of health benefits. The improvements seen in vascular health need to be confirmed in further studies. New results regarding benefits in cognitive function may lead to new topics of research with PYC.

*Keywords—Pine bark extract, Pycnogenol, endothelium. Circulation., anti-inflammatory*

*Introduction*

Pycnogenol® (PYC), a proprietary extract of Horphag Research, produced from the bark of the French maritime pine *(Pinus pinaster*, subsp. *atlantica*) meets the requirements of the monograph: Maritime Pine Extract of the US Pharmacopoeia 37, Dietary Supplements. PYC is used world-wide as a dietary supplement, herbal drug, in cosmetics and for dental care. Since the first comprehensive review in 2002 [26] 9 reviews appeared covering publications about PYC until 2014. The present review refers to 33 clinical studies appearing between 2010 until 2015.

*1. Source and composition*

The bark, the raw material for production of PYC, is tested according to the monograph Maritime Pine of the USP 37, Dietary Supplements. The bark contains predominantly procyanidins (Fig 1). The extract, as described in the USP 37, is standardized to contain not less than 75% procyanidins. The procyanidins are biopolymers, composed from catechin and epicatechin subunits. Phenolic acids, as ferulic acid, caffeic acid, protocatechuic acid (Fig. 2) and catechin and taxifolin (Fig. 3) are contained as glucosides as well as in free form as minor constituents. More details about the composition had been given in a previous review [26]. All components of PYC exert antioxidative and antiinflammatory properties and contribute to the manifold health benefits of the extract.

**Fig. 1 Example for a procyanidin molecule, procyanidin trimer**

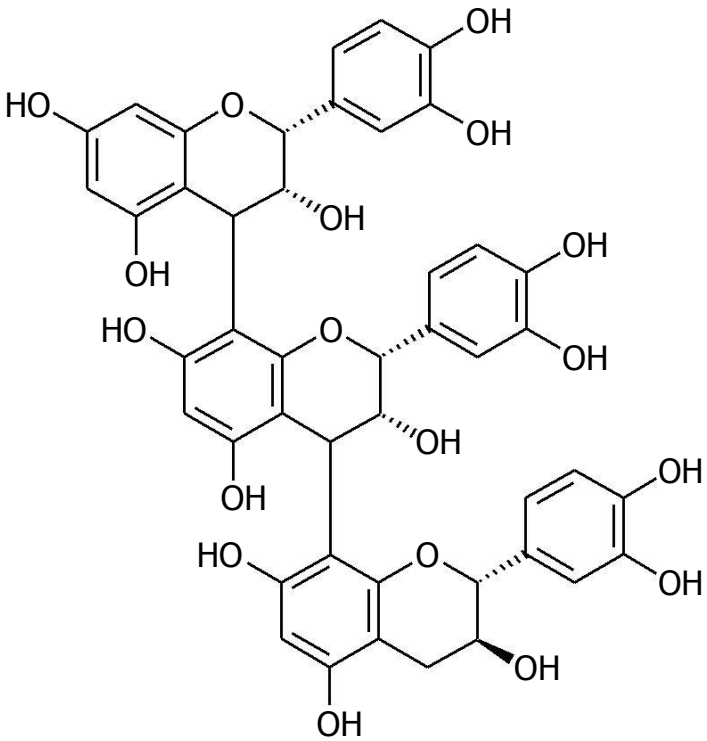
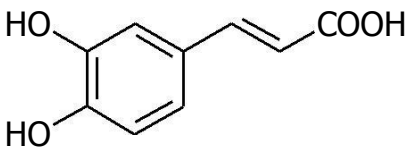
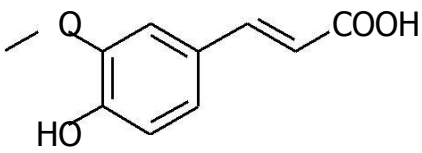


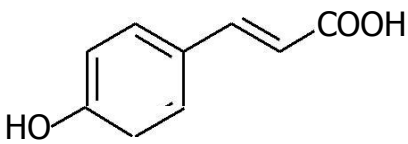
**Fig. 2 Phenolic acid species in PYC**



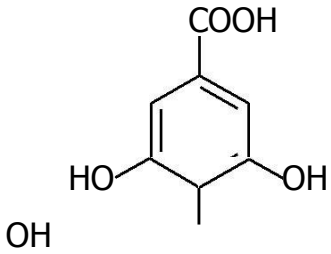

**caffeic acid**



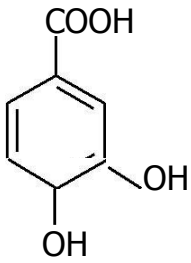

**ferulic acid**



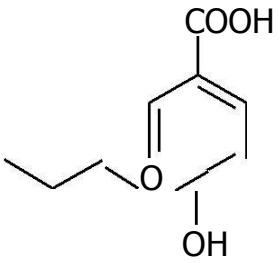

**coumaric acid**




**gallic acid**



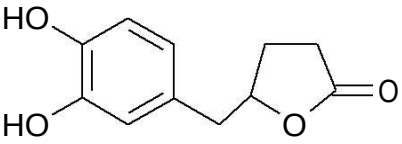

**protocatechuic acid**



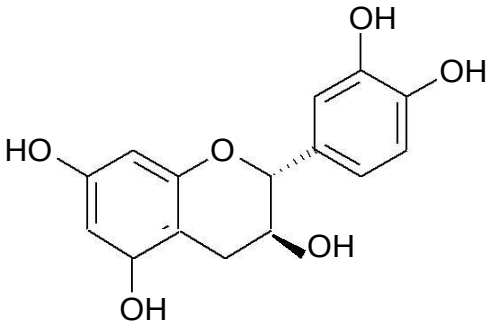

**vanillic acid**

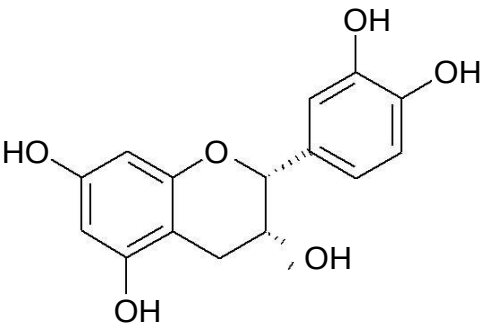
**Fig. 3 M1, catechins, taxifolin**



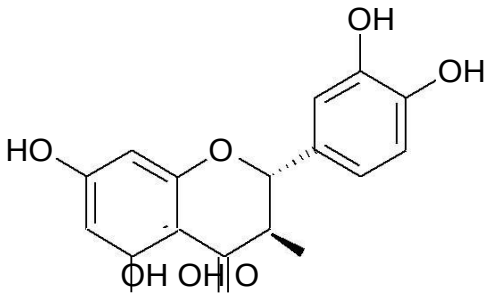

**M1**




**(+)-Catechin**




**(-)-Epicatechin**




**(+)-Taxifolin**

*2. Safety*

PYC has been currently tested in 131 clinical trials comprising 11.305 participants. In these studies 3500 volunteers received placebo, 7362 participants PYC. The rate of reported unwanted effects was 2% in the placebo group and 1.9% in the PYC group. No serious adverse effects were reported after oral intake of doses between 60-300mg PYC, unwanted effects were mild as headache, dizziness, nausea and sleepiness and skin irritation. One case of each heart pain, mouth ulcer, supraventricular tachycardia, eczema and diarrhea had been spontaneously reported as well as three cases of urticaria. Gastric troubles have been occasionally observed, intake of PYC after meals removed these symptoms.

*3. Absorption and metabolism*

The main constituents of PYC, the procyanidins, are metabolized inside the GIT. Procyanidins are cleaved to catechin units undergoing ring fission to form valerolactones [26]. It is reported for the first time that the most active metabolite M1, the **ð** (3,4 dihydroxy-phenyl gamma)-valerolactone (Fig. 3) accumulates in blood cells and endothelial cells via facilitated transport, most probably by the GLUT-1 transporter [31]. Erythrocytes concentrate the M1 30 fold versus plasma, thus representing a substantial compartment for M1. Within the erythrocytes M1 forms a glutathione conjugate [16]. The clinical relevance of

these new findings is currently under investigation.

*4. Anti-inflammatory activity*

Series of cell culture, animal and clinical studies proofed the anti-inflammatory activity of PYC [22,24,26,27]. Important are *ex-vivo* experiments with human plasma following intake of 300mg PYC which revealed that plasma contains sufficient amounts of bioactive compounds to inhibit ($p<0.05$) inflammatory mediators: Gene expression of COX-2, activation of NFκB, activity of COX-1 and COX-2, phospholipase A2 and release of elastase [22]. Expression of inducible nitric oxide synthase (iNOS) was also inhibited [31]. The clinical relevance of these findings is reflected in the reduction of inflammatory symptoms in the following clinical studies.

*4.1 Improvement of inflammatory symptoms in patients*

*4.1.1 Asthma*

In a randomized, double-blind, placebo-controlled study with children PYC reduced ($p<0.001$) use of β-agonists, asthma symptom scores and leukotriene levels [22]. Added to inhaled glucocorticoids, 100mg PYC lowered asthma symptom scores in adults ($p<0.05$) compared to glucocorticoids alone, IGE titer decreased further by 15% [3].

*4.1.2 Osteoarthritis*

Three double-blind, placebo-controlled studies showed a significant decrease of pain scores and osteoarthritis symptoms following intake of 100-150mg PYC versus placebo ($p< 0.05$) [22], less non-steroidal drugs were needed.

These clinical studies suggest the use of PYC for relief of inflammatory symptoms in asthma as well as in osteoarthritis, at least as add-one supplementation.

*5. Results of supplementation with PYC in clinical studies*

*5.1 Effect of PYC on endothelium-dependent vasodilation*

An in-vitro study demonstrated that the extract stimulates endothelium-dependent nitric oxide production by enhancing activity of endothelial nitric oxide synthase (e NOS) [26]. The activation of e-NOS was confirmed *in vivo* in a randomized, double-blind, placebo and active drug (180mg PYC) controlled trial by the increase of flow mediated dilation (FMD) ($p<0.05$) in healthy volunteers [22]. FMD was also improved ($p<0.001$) in a randomized, double-blind, placebo-controlled, cross-over study with patients with stable coronary artery disease after oral application of 200mg/day PYC [12]. The stimulation of endothelial function and nitric oxide production is a prerequisite for PYC's role in enhancing and normalizing circulation.

The combination of 100mg PYC and 350mg coenzyme Q10, given as an adjunct to medical treatment, lowered blood pressure and increased heart ejection fraction versus placebo ($p>0.05$) in a study with 53 volunteers [1]. An improved cochlear flow after intake of 150mg daily PYC for 1 month resulted in significant relief from tinnitus and Meniere's disease [19] compared to controls ($p>0.05$). 87% of patients were symptom free after 6 months compared to 35% of patients serving as controls without treatment.

*5.2 Normalization of erectile function*

Erectile function (EF) is closely linked to endothelial health as nitric oxide is essential for penile erection.

Erectile function in men with moderate erectile dysfunction was improved by a combination of 80mg PYC with L-arginine and by another combination of

80mg PYC with aminoacids and roburins. The International Index of Erectile Function questionnaire indicated an enhancement to normal EF of 29 from a value of 17
(moderate erectile dysfunction) after intake of the combinations for one month, while placebo had no effect in these cross-over studies [22,30]. These combinations enhanced additionally fertility of men with oligoashtenoteratozoospermia.
Concentration of spermatozoa was enhanced from 134 to 240m (79%), endothelial NOS expression and motility of spermatozoa increased. No changes were observed under placebo [22,28].

Supplementation with L-arginine and PYC for six months enhanced significantly EF and testosterone levels versus placebo in volunteers with mild to moderate EF [17].

These findings underline the importance of the improvement of nitric oxide production by PYC for endothelial function influencing positively many aspects of vascular function.

*5.3 PYC for diabetes care*

As reviewed in [27] PYC lowers dose-dependently glucose levels in diabetic patients, most probably by inhibiting a-glucosidase, and ameliorates diabetic retinopathy and diabetic ulcers. Central macular thickness was significantly reduced ($p>0.001$) compared to placebo in patients with diabetic retinopathy by a combination of 50mg PYC with vitamins [11]. Recurrence of retinal vein thrombosis was significantly better prevented following intake of 100mg PYC in comparison to the intake of 100mg Aspirin® during a period of 9 months [ 25].

The combination of blood glucose lowering, anti-edema and antithrombotic activity of PYC provides the basis for the use of PYC in mild cases of diabetes type 2.

*5.4 Venous system*

*5.4.1 Enhanced elasticity of veins*

*Ex-vivo* tests demonstrated the strengthening of varicose venous walls following intake of PYC. Venous segments were taken from patients with varicose veins after surgery. One group of patients received 150mg PYC during 3 months before surgery, the other group remained untreated. Venous segments were mechanically dilated and stretched. Tonic recovery and elasticity was greater in segments of varicose veins from patients pre-treated with PYC [4].

*5.4.2 Treatment of chronic venous insufficiency (CVI)*

A randomized study compared 150 and 300mg PYC with a 1000mg of a mixture of hesperidine and diosmin (Daflon®) in treating CVI. Both doses of PYC were superior to Daflon ($p>0.05$) in relieving symptoms of CVI. [22].

Improvement of symptoms of CVI was tested on patients wearing stockings or receiving PYC orally or getting a combined treatment. 150mg PYC was more effective than stockings in relieving pain and swelling ($p<0.05$). Best results were obtained with the combination of stockings and PYC [9].

*5.4.3 Treatment of hemorrhoids*

Hemorrhoidal bleedings were treated within 48 hrs with 300mg PYC taken orally and with a combination of PYC tablets and an ointment containing 0,5% PYC. Hemorrhoidal symptoms were faster reduced with PYC versus an untreated control group ($p>0.05$), the combination of oral and topical PYC provided best symptom relief [2]. Women with post-partum hemorrhoids were earlier free of symptoms after 150mg PYC compared to the control group ($p>0.05$) [5].
The superior effectivity of PYC versus

stockings is in line with the series of foregoing clinical studies demonstrating the relief from symptoms of chronic venous insufficiency following the intake of PYC.

*5.5 Improvement of women's health*

*5.5.1 Menopause symptoms and Endometriosis*

Menopausal symptoms as hot flushes, night sweats, mood swing and sexual problems were ameliorated versus baseline and control group after eight weeks of intake of 100mg PYC [13]. In a randomized double-blind, placebo-controlled study peri-menopausal Japanese women recovered from menopausal symptoms after 60mg PYC [15].

Symptoms of endometriosis were better reduced by co-administration of 100mg PYC and oral contraceptives (OC) compared to the use of OC alone ($p>0.01$) [20]. In a Japanese study, pain resulting from endometriosis was reduced by combining OC with 60mg PYC [14]. The co-administration of PYC and OC blocked more effectively the expression of aromatase and vascular epithelium growth factor within the eutopic endometrium compared to OC ($p> 0.05$) [21].

*5.5.2 Female sexual function*

A combination of 20 mg PYC with L-arginine, L-citrulline and rose hip extract improved sexual function according to answers to the Female Sexual Function Index (FSFI). Treatment with 4 tablets per day of the combination enhanced the FSF score in a placebo-controlled study from 45 to 72, whereas placebo changed FSFI scores by less than 10% [8]. In another randomized, double-blind, placebo-controlled study, 4 tablets per day of this PYC-containing combination improved sexual function as desire, arousal, satisfaction and lubrication according to the FSFI by 73%. Kupperman's Index and Women's Health Questionnaire indicated better sexual function compared to placebo ($p< 0.05$) [29] The improvement of several aspects of quality of live of women advocates the use of PYC to ameliorate the symptoms of menopausal transition.

*5.6 Benefits for skin care*

The skin condition of postmenopausal women was studied by corneometry, cutometry, visioscan, ultrasound and biopsies. Oral application of 75mg PYC improved ($p< 0.05$) hydration and skin elasticity and stimulated expression of mRNA for hyaluronic acid and collagen de-novo synthesis ($p< 0.01$) [23].

Volunteers suffering from psoriasis benefited from 150mg PYC orally. Affected areas, erythema, desquamation and quantity of exfoliating cells decreased versus control group ($p< 0.05$). Skin moisture improved. In comparison to standard treatment, less drugs were used in the PYC group and treatment time was 30% shorter [6].

30mg PYC given in a combination product containing skin building blocks reduced significantly ($p>0.0001$) the extent of photo-aging compared to placebo [10].

The detection of the stimulation by PYC of mRNA directed to production of building blocks for the skin gives a new insight in PYC's importance for cosmetic application.

*5.7 Enhancement of cognitive function*

Nitric oxide has been shown in a number of studies to promote memory and learning [32]. The stimulation of the activity of nitric oxide synthase by PYC [22] provides a rationale for its positive effects on cognitive function. A randomized, double-blind, placebo-controlled study objectified positive reports on PYC's effect in ADHD [24].

Teachers rating of child attention problems showed a decrease of inattention and hyperactivity ($p>0.07$) after 1mg/kg/bw/day of PYC compared to placebo ($p>0.04$).

Intake of 100mg PYC improved scores of students for attention, memory and mood relative to control. Success rate in examinations was slightly, but significantly higher ($p>0.05$) [18]. Volunteers between 35-55 years scored better than controls ($p>0.05$) under 150mg PYC in tests for professional daily tasks and mood parameters [7].

The stimulation of attention and memory in children as well as in adults is most probably caused by the increase of nitric oxide production by the metabolites of PYC. Nitric oxide could allow a better blood flow in the brain by vasodilation and acts inside the brain as a neurotransmitter [32].

### *Conclusion*

Clinical trials confirmed on a broad basis previous findings with PYC regarding anti-inflammatory activity and beneficial effects for chronic venous insufficiency and sexual functions. The importance of the stimulation of nitric oxide production by PYC for endothelial and erectile function has been corroborated. The role of PYC for skin elasticity has been confirmed by m-RNA analysis. The reports about better mental performance following PYC intake suggest further investigations in extended clinical studies.

The basis for clinical safety has been considerably enlarged as PYC has been tested on more than 7000 participants in clinical studies with a low rate 2% of mild unwanted effects.

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