Grape Seed Extract

Antioxidant Supplementation and Vascular Disease Prevention
Introduction

_Euromed_ is a company specializing in botanical extracts and active ingredients to be used as phytomedicines. _Euromed_ deals with the development and production of these therapeutically active raw materials.

For this reason the botanical raw materials are subject to strict selection and inspection. The products are manufactured according to methods developed by the _Euromed_ company. These methods include inspections to guarantee a standard quality from both the analyticochemical and therapeutic points of view, and are the state of the art in many different fields such as research and development, analyses, processes and devices and therapeutic applications with a scientific basis.

_Euromed_ guarantees the quality of its products with a broad phytochemical know-how.
Table of Contents

1. Grape Seed Extract: General Information 3
   1.1 Description 3
   1.2 Indications 3
   1.3 Extract Specifications 4
   1.4 Dosage and Methods of Administration 4
   1.5 Contraindications and Interactions 4
   1.6 Side-effects 5

2. From Plant to Extract 6
   2.1 Botanical Data 6
   2.2 Historic Use 7
   2.3. Chemistry of Vitis vinifera 8
   2.4. Preparation of the Extract and Quality Control 11
   2.5 Standardization 12

3. Venous Disorders 15
   3.1 Varicose Veins 15
   3.2 Lymphedema 17
   3.3 Capillary Fragility 18

4. Pharmacology 19
   4.1 Pharmacodynamics 19
   4.2. Pharmacokinetics 22

5. Toxicology 23
   5.1 Acute Toxicity 23
   5.2 Chronic Toxicity 23
   5.3 Teratogenesis 23
   5.4 Mutagenesis 23

6. Clinical Pharmacology 25
   6.1 Free Radical Scavenging Activity 25
   6.2 Ophthalmology 27
   6.3 Vascular System 29
7. Efficacy
8. Therapeutic Safety
9. Bibliography
1. Grape Seed Extract:
   General Information

1.1 Description

The purified extract of *Vitis vinifera* is a standardized herbal extract from grape seeds.

Grape seed extract is a herbal preventive and therapeutic agent for vascular diseases, such as:
- varicose veins
- lymphedema
- capillary fragility

Edemas are inhibited and the capillary permeability is improved, the walls of the vessels are stabilized.

According to clinical data, symptoms can be expected to be reduced within the first 30 days of taking grape seed extract from euromed.

The extract of *Vitis vinifera* does not interact with other drugs.

1.2 Indications

Due to the high content of procyanidolic oligomers grape seed extract manufactured by euromed is usually used for the treatment of vascular diseases, such as varicose veins, lymphedema and capillary fragility.
1.3 Extract specifications

The *Vitis vinifera* extract available from EUROMED is a purified grape seed extract with a procyanidolic value of minimum 95.

1.4 Dosage and Methods of Administration

A daily oral dose between 150 and 300 mg grape seed extract is common practice.

**Tab. 1:** Internationally marketed preparations containing grape seed extract

<table>
<thead>
<tr>
<th>Preparation Name</th>
<th>Method of Extraction</th>
<th>Content of <em>V. vinifera</em> Extract</th>
<th>Total Extract/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grape Seed Plus</td>
<td></td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Defender</td>
<td></td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td>Endotelon</td>
<td></td>
<td>50 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>PROVINE</td>
<td>water soluble</td>
<td>20 mg</td>
<td></td>
</tr>
</tbody>
</table>

1.5 Contraindications and Interactions

There are no known contraindications to the use of grape seed extract. There are no known interactions with drugs usually prescribed.
1.6 Side-effects

Grape seed extract is generally well tolerated. There have been no side effects observed, when standardized *Vitis vinifera* seed extract was taken. No side effects known
2. From Plant to Extract

2.1 Botanical Data

Grapevine seeds

*Vitis vinifera* L. (Family: *Vitaceae*. English names: common grape vine, grapevine, European grape; German names: Weinrebe, Wildrebe, Edelrebe) is a perennial, woody vine, usually growing in tendrils. The vine is a 30 to 45 cm high climber with deep, heavily-branched roots and a woody trunk 1.5 cm in diameter with striped, loose bark. The alternate leaves are thin, circular to circular-ovate, 5 - 23 cm in diameter, with dentate or serrated margins, 5 - 7 lobed, glabrescent above and often grey-tomentose beneath. The fruits are soft, pulpy berries, 6 - 22 mm long, arranged in large, long clusters (Fig. 1). The seeds are 2 - 4 in number, sometimes absent, pyriform or ovoid, with a rather long beak.

The cultivated grapevine is divided into 3 groups, which differ relating to their morphology and geographic origin: *occidentalis* includes the grapes from Western Europe and the Nile Valley, *orientalis* are grapes from the Jordan Valley and *pontica* designates grapes from the region between these areas. Some American species and hybrids between *Vitis vinifera* and the American species have been introduced into Europe during the past hundred years. These species are reported to be more disease resistant [5, 16, 21].
2.2 Historic Use

Fossilized leaves and seeds from Miocene and Tertiary deposits of continental Europe, England, Iceland and North America are evidence of the ancient origin of *Vitis vinifera*. Grapes and wine production are mentioned in Egyptian hieroglyphics, dating from 2400 BC.

Grape harvest is also shown on wall paintings found in the tombs of ancient Thecae. The cultivation of *Vitis vinifera* is generally concentrated in the warm to temperate regions of the Northern Hemisphere, mainly in Europe and the southern regions of Central Asia. South Africa, USA (California), Argentina, Chile, Australia and New Zealand are further regions of cultivation.

Grapes were already used as remedies by the ancient Egyptians and the Hippocrates (5th - 4th century BC), Theophrastus (4th century BC), Dioscurides, Pliny (1st century AD) and Galen (2nd century AD) [10]. The astringent and hemostatic properties of the leaves were used in the treatment of diarrhea, hemorrhage, varicose veins and hemorrhoids.
The juice of grape leaves was used as eye wash, the juice of the unripe fruits against throat infections. The raisins are demulcent, cooling, laxative, stomachic and used against thirst, coughs, hoarseness and consumption. Leaves and grapes of *Vitis vinifera* were medically used for very different indications and with various preparations [5].

2.3. Chemistry of *Vitis vinifera*

Analytical studies and reports over the chemistry of *Vitis vinifera* do not make a clear distinction between the different parts of the plant. However, the spectrum of its constituents is well known (Table 2 and 3).

*Phenolic substances*

The standardized mixture of polyphenols obtained from grape seeds contains mainly procyanidol oligomers, dimers, trimers, tetramers and oligomers up to 7 units as well as small amounts of monomers (catechin and epicatechin) [5].

Oligomers and polymers of catechin and epicatechin are found in the skin and particularly in the seeds of grapes [35, 36].

These constituents are also named procyanidins, procyanidolic oligomers (PCO), leucoanthocyanins or condensed tannins. The procyanidins are constituted by a variable number of flavan units linked by B1 - B4, B5 - B8, C4 - C4 or C4 - C8 bonds. The structure of the main dimers are shown in Figure 2. In a sample of grape seeds the amino acid leucine was the largest component found (11.4 %) [33].
Lipids
Seeds of *Vitis vinifera* contain a semi-drying oil (6 – 20%) with fatty acids like palmitic, stearic, oleic (37%) and linoleic (55%) acids and also sitosterol, tocopherol and phospholipids, partly bound to lipoproteins [33].

Tab. 2: Characteristic compounds in *Vitis vinifera*

<table>
<thead>
<tr>
<th>Important components</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Phenolic Substances [5, 9, 17, 31, 33, 35, 36, 38]</td>
</tr>
<tr>
<td>♦ Organic acids [5]</td>
</tr>
<tr>
<td>♦ Vitamins and enzymes [33]</td>
</tr>
<tr>
<td>♦ Nitrogenous compounds [33]</td>
</tr>
<tr>
<td>♦ Terpenes and essential oils [15, 36]</td>
</tr>
<tr>
<td>♦ Waxes [14]</td>
</tr>
<tr>
<td>♦ Lipids [33]</td>
</tr>
<tr>
<td>♦ Other substances [33]</td>
</tr>
</tbody>
</table>

Procyanidin B₁  \( R¹=\text{OH}, R²=\text{H} \)  
Procyanidin B₂  \( R¹=\text{H}, R²=\text{OH} \)  
Procyanidin B₃  \( R¹=\text{OH}, R²=\text{H} \)  
Procyanidin B₄  \( R¹=\text{H}, R²=\text{OH} \)
**Fig. 2:** Structures of the main procyanidin dimers of *Vitis vinifera* [5].

<table>
<thead>
<tr>
<th>Procyanidin B₅</th>
<th>R¹=H, R²=OH</th>
<th>Procyanidin B₆</th>
<th>R¹=OH, R²=H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procyanidin B₇</td>
<td>R¹=OH, R²=H</td>
<td>Procyanidin B₈</td>
<td>R¹=H, R²=OH</td>
</tr>
</tbody>
</table>
2.4 Preparation of the Extract and Quality Control

*Vitis vinifera* originates from cultivated plants, growing in western Europe.

When the plant material arrives at EUROMED an exhaustive inspection of the raw material is carried out according to the current methods in order to guarantee the quality of the final product.

EUROMED regularly evaluates the possible contamination of the drug material. Microbiological purity and presence of heavy metals, aflatoxins and pesticide residues are routinely examined. In doing so the company assures that the limits fixed by international standards or literature are not exceeded.

Only high-quality raw plant material, selected according to the strictest criteria, is used.

EUROMED applies an unique extraction process to obtain the extract. This careful process provides a high yield of valuable constituents and a high-grade extract.
Due to the unique extraction processes, EUROMED produces a purified standardized extract from the seeds of *Vitis vinifera*:

- **GRAPE SEED EXTRACT**
  
  *EXTR. VITIS VINIFERAE E SEM.*

  Pink-beige powder, astringent taste with a light aromatic smell.

EUROMED grape seed extract meets the highest quality standards. Therefore, it is possible to satisfy the requirements for an effective and safe medication.

### 2.5 Standardization

The consistent quality of the EUROMED grape seed extract is guaranteed by the standardized production process. The EUROMED grape seed extract has a procyanidolic value of minimum 95. The HPLC profile is the main procedure for defining the identity and quality of the grape seed extract (Figure 3).
Fig. 3: HPLC Chromatogram of grape seed extract
**Analytical specification of EUROMED grape seed extract:**

- **Appearance**  
  Pink-beige powder, astringent taste with a light aromatic smell

- **Identification**  
  HPLC fingerprint

- **Loss on drying**  
  Max. 5.0 %

- **Procyanidolic value**  
  Min. 95.0

- **Assay**  
  Total polyphenols min. 85%  
  (Spectrophotometric method)  
  Polyphenol monomers max. 25%  
  (HPLC)

- **Microbiology**  
  Acc. Ph.Eur.3rd ed., 5.1.4, category 3B
3. Venous Disorders

3.1 Varicose Veins

Varicose veins are dilated, tortuous superficial veins with incompetent valves. The greater and lesser saphenous systems are most commonly involved, but it is not unusual for secondary branches of the superficial system of veins also to become dilated. They most often appear after the age of 20, but in women can develop in at puberty, during pregnancy, and with the commencement of menopause. In men there is a fairly even onset of symptoms up to age 70.

The etiology remains largely obscure, but varicose veins are known to be aggravated by hormonal factors in the female, increased intraabdominal pressure, and in rare instances, arteriovenous fistulas.

Primary varicose veins

Primary varicose veins occur in the absence of deep venous disease and generally have a benign course. They are brought to the attention of the patient first by cosmetic deformity and second by the symptoms which develop with prolonged standing. The patient complains of a feeling of heaviness in the leg, combined with fatigue, which gets progressively worse leading toward secondary symptoms unless there is a impressive improvement.
Secondary varicose veins which occur from obstruction and valvular incompetence of the deep venous system are much more serious. When the varicose veins are secondary due to deep venous obstruction, loss of valves, and incompetent perforating veins, the symptoms are more severe and accompanied by swelling.

The diagnosis of primary varicose veins is largely made by inspection of the legs in the upright position. The varicosities appear as dilated, often tortuous channels which are most commonly observed in the greater and lesser saphenous systems. When isolated clusters are observed in atypical locations, the possibility of an underlying incompetent perforating vein or arteriovenous fistula should be considered. To assess whether or not incompetent perforating veins are contributing factors, further test systems may be employed.

The classical treatment in venous disorders is compression therapy of the insufficient areas. Pathophysiological considerations on microcirculatory and capillary permeability difficulties, protein edemas, inflammatory reactions as well as the fact that compression therapy in most cases is not performed with necessary consequence, show that phytopharmaceutical treatment and prophylaxis with high quality, safe preparations and clinically proven efficacy is indicated.
3.2 Lymphedema

Lymphedema is an abnormal accumulation of lymph in the extremities and occurs from multiple causes. The most common one is caused by varicose veins.

Swelling starts in the feet

When the varicosis causes a chronic venous insufficiency, the liquid re-resorption of the venous part of the capillaries is disturbed. Following this, liquid collects in the tissue and develops an edema. Painless swelling of the involved extremity is the earliest and most common symptom. It usually starts in the foot and ankle and then progresses proximally. Initially the swelling tends to subside somewhat at night.

The location and nature of the edema readily separate lymphedema from edema due to other causes. In the legs, the dorsa of the toes and foot are nearly always involved; this is uncommon in other causes of swelling. The edema is often stable and pointed pressure creates an indentation which is slowly relieved.
3.3 Capillary Fragility

Phagocytes, stored at the vessel endothel, start two important mechanisms of pathogenesis. A) The acute generation of reactive oxygen species in active cells; B) Degranulation/release of lysosomale enzymes (e.g. collagenase, elastase, phospholipase). In the beginning, this process is physiologically known as basic resistance (micro- and macrophages from blood reach the inflammation area and start the reparative inflammation/wound healing). Activation of this process over time results in a malfunction. Pathogenic microvascular changes develop and excessively injure the capillary endothel. This leads to tissue edems and causes problems in the microcirculatory blood flow.

The above mentioned acute generation of reactive oxygen species are known as "respiratory burst". Highly reactive superoxide anion radicals develop, mainly effected by tissue hypoxis. Removal of hypoxis can lead to reperfusion damage and the development of reactive superoxide anion radicals. These radicals quickly reduce by substitution of electrons. Further processing of these radicals develops aggressive hypochloric acid and hydroxil radicals.
4. Pharmacology

4.1 Pharmacodynamics

The main active components of *Vitis vinifera* have not yet been completely defined. In this regard, the most interesting group of components are polyphenols like ellagic acid, phytoalexins (e.g. Resveratrol, viniferins, pterostilbenes) and also anthocyanins and procyanidins [5].

The particular mode of action of the extracts of grape seed has not been completely investigated, either. But some interesting facts have been discovered which explain the success of grape seed extracts in the treatment of vascular diseases.

**Free Radical Scavenging Abilities**

To study the free radical scavenging ability of grape seed extract an *in-vitro*-test was performed, using 5, 25, 50, 100, 200 mg of a grape seed proanthocyanidin extract. The generation of superoxid anion and hydroxyl radicals was inhibited between 78 and 81 %. This effect was more successful than the dose of 25 and 50 μmol Vitamin C or 50 – 141.3 μmol Vitamin E [1].

Procyanidins of *Vitis vinifera* (CAS 85594-37-2) were studied in phosphatidylcholine liposomes in two different models of free radical generation: 1. Iron-promoted and 2. ultrasound-induced lipid peroxidation. In the iron-promoted model procyanidins showed dose-dependent antilipoperoxidant activity (IC$_{50}$ = 2.5 μmol/L).
In the other model procyanidins were highly active in preventing conjugated diene formations in both the induction (IC$_{50}$ = 0.1 µmol/L) and propagation (IC$_{50}$ = 0.05 µmol/L) phases. Additionally procyanidins delayed the onset of the breakdown phase (48 h) and markedly reduced the signal intensity of the DMPO-OH radical spin adduct (40 µmol/L effects 100 % inhibition) depending on the dose.

Procyanidins inhibited the xanthine oxidase activity, the proteolytic enzymes collagenase and elastase, and the glucosidases hyaluronidase and β-glucuronidase. These findings could explain the capillary protective effect of procyanidins [24].

Proanthocyanidins (0.2 - 3000 µMol) extracted from grape seeds showed a dose-dependent hydroxyl radical scavenging effect in vitro (deoxyribose degradation system) [23]. A survey of possible mechanisms of action of procyanidins is shown in Fig. 4.

![Fig. 4: Site-specific mechanisms of the impact of vascular protective activity of procyanidins (from Lit. [24]).](image)

---

1 5,5-Dimethyl-1-pyrroline-N-oxide
Antiexudative and Antiedematous Effects

The antiexudative and antiedematous ability of procyanidins was examined in two further animal studies:

Procyanidins were given to rats p. o. in an amount of 6 mg/kg bodyweight/day for 6 days. The edema of the hind paw induced by carrageenin and dextran were inhibited. The capillary wall was stabilized and the increase of capillary permeability caused by local cutaneous application of xylene was prevented [40].

Procyanidins in the amount of 400 mg/kg bodyweight/day p. o. which were administered 7 days before a surgical interruption of the hindlimb lymphatic system decreased the volume of the hindlimb of rats by about 50 % [8].

Inhibition of Angiotensin I Converting Enzyme.

A fraction of procyanidolic oligomers of Vitis vinifera (5 mg/kg i. v.) inhibited the enzyme converting angiotensin I of a homogenate of rabbit lung in vitro (I₅₀ = 0.08 mg/mL). These findings show the possibility of a slight effect of procyanidolic oligomers on the moderation of arterial pressure [28].
4.2. Pharmacokinetics

70% of a single dose of 50 mg/kg p. o. of flavonolic oligomers are eliminated within 24 hours: 6% in expired air, 19% in urine and 45% in feces (rat). Major urinary metabolites are hippuric acid, ethylcatechol and m-hydroxyphenylpropionic acid. The major metabolite in the feces is ethylcatechol. Vanillic acid and m-hydroxyphenylpropionic acid are the major biliary metabolites [13]. Procyanidolic oligomers seem to have a specific affinity to tissues rich in glycosaminoglycans [19].

Studies with $^{14}$C-labelled procyanidins by oral route in mice and after intraduodenal application in rats revealed a rapid gastrointestinal absorption with $C_{\text{max}}$ at 45 min. and a calculated half-life of 5 h [19] (Fig. 5).

![Fig. 5: Blood radioactivity after oral administration of 14C-labelled procyanidins to mice. Each point represents the mean + SE of 5 mice [9].](image)
5. Toxicology

Low toxicity

According to studies with the main component of grape seed extract, procyanidins, the toxicity of extracts of grape seed is apparently very low.

5.1 Acute Toxicity

The calculated oral LD₅₀ of procyanidins in rat and mice is > 4000 mg/kg bodyweight [3].

5.2 Chronic Toxicity

No chronic toxic effects

Procyanidins in the amount of 60 mg/kg bodyweight p. o. daily during a period of 6 months in rats and 12 months in dogs were tolerated well and did not show any toxic effects.

5.3 Teratogenesis

Procyanidins are devoid of teratogenic and toxic effects on fertility and the peri- and post-natal phases [3].

5.4 Mutagenesis

Procyanidins in the amount of 60 mg/kg bodyweight p. o. daily during a span of 6 months in rats and 12 months in dogs were tolerated well and did not show any mutagenic effects [3].
Antimutagenic Effects

In vitro-studies revealed effects of procyanidins on spontaneous mitochondrial as well as nuclear mutability. Depending on the dose, procyanidins (0.25 resp. 0.5 mg/L) reduced the mitochondrial and nuclear mutability of *Saccharomyces cerevisiae* S 288 C between 50 and 92 % versus the control. The inhibition of the spontaneous mutation from canavanine sensibility to canavanine resistance has also been observed during the test of nuclear mutability [22].
6. Clinical Pharmacology

Preparations of procyanidins have documented effects in the treatment of capillary fragility, varicose veins, telangectases, microcirculatory disorders, diabetic microvascular diseases, acrocyanosis, lymphedema, alteration of blood rheology, increased platelet aggregation, macular degeneration, poor night vision and ocular photosensitivity [30].

Although some details about preparations and studies are missing, the following data give rise to the assumption that extracts of grape seed have positive effects on vascular diseases and other damages caused by free radicals.

6.1 Free Radical Scavenging Activity

Different concentrations of a grape seed proanthocyanidin extract were studied in an in-vitro-test in comparison to vitamin C and vitamin E succinate, superoxide dismutase, catalase and mannitol. The test was performed by using a chemiluminescence assay and cytochrome c reduction. A concentration dependent inhibition was demonstrated for the grape seed extract. At a 100 mg/l concentration the extract inhibited the generated superoxide anion and hydroxyl radicals by 78 and 81 %. Under same conditions vitamin C inhibited these two oxygen free radicals by approx. 12 - 19 %, while vitamin E succinate inhibited them by 36 - 44 %. The result for superoxide dismutase and catalase was an inhibition of 83 %, while manitol inhibited the radicals by 87 % [1].
The radical scavenging activity of procyanidins of *Vitis vinifera* (CAS 85594-37-2) were studied in phosphatidylcholine liposomes in two different models of free radical generation: 1. Iron-promoted and 2. ultrasound-induced lipid peroxidation. In the iron-promoted model procyanidins clearly showed a dose-dependent antilipoperoxidant activity (IC$_{50}$ = 2.5 µmol/L). In the other model procyanidins were highly active in preventing conjugated diene formations in both the induction (IC$_{50}$ = 0.1 µmol/L) and propagation (IC$_{50}$ = 0.05 µmol/L) phases. Additionally procyanidins clearly delayed the onset of the breakdown phase (48 h) and markedly reduced the signal intensity of the DMPO-OH$^2$ radical spin adduct (40 µmol/L effects 100 % inhibition) in dependency of the dose [24].

In the second part of this testing, procyanidins showed besides the radical scavenging activity an inhibition of the xanthine oxidase activity, the proteolytic enzymes collagenase and elastase, and the glucosidases hyaluronidase and β-glucuronidase. These results prove by molecular testing the capillary protective effect of procyanidins. It could be concluded that the capillary protective effects of procyanidins is effected by a pluristic mechanism which effects radical scavenging activity and inhibition of key enzymes [24].

Proanthocyanidins from grape seeds of *Vitis vinifera* in concentrations of 0.2 - 3000 µMol showed a dose-dependent hydroxyl radical scavenging effect *in vitro* using the desoxyribose degradation system. These results show that procyanidins are effective agents against oxidative stress [23].

---

2 5,5-Dimethyl-1-pyrroline-N-oxide
6.2 Ophthalmology

In a double-blind, placebo-controlled study 2 x 20 patients with visus between -4 D and -12 D were examined. They received either 3 x 50 mg/day procyanoside oligomers or placebo for 30 days. Pattern LED VEPs (visual evoked potentials) point out an increase in amplitude in 12 out of 14 patients (85.7%). ERG (electroretinogram) was improved in alpha point times in 8 patients (40%). The placebo-group did not show any significant changes according to these electrofunctional parameters [32].

91 myopic patients were treated with proanthocyanidins in the amount of 300 mg/day p.o. for 30 days. Pre-/post-observation showed a significant improvement of the adaptometric curve and of subjective parameters in this open study [29].

In an open, controlled study in 2 centers with a total of 100 volunteers the effect of procyanidins on light vision after glare was tested. 50 volunteers received procyanidins in the amount of 200 mg/day p.o. for 5 weeks, 50 served as control. Pre-/post-observation was done with Comberg’s nyctometer, Beyne’s lantern and ergovision. The results demonstrate that general visual abilities after glare were significantly improved in volunteers of the verum group, compared to the control group (Fig. 6) [4, 6].
Ocular contrast sensitivity improved

Fig. 6: Recovery of visual acuity (volunteers) after treatment with procyanidins 200 mg/day for 5 weeks [4, 6].

75 patients affected by ocular stress, caused by working at a display unit, were studied in a double blind, placebo controlled trial. The parameters under investigation were contrast sensitivity and a general assessment of the subjective symptomatology. A 60 day treatment of 300 mg/day proanthocyanidins significantly improved the contrast sensitivity and the subjective symptomatology in comparison with the control group (Fig. 7) [12].
6.3 Vascular System

The capillary resistance of hypertensive and diabetic patients was studied by percutaneous capilloydynamometry measured by the Lavollay technique. During an open trial with 28 patients the capillary resistance rose from $15.4 \pm 1.8$ mm Hg to $18.1 \pm 3.2$ mm Hg.

During a double blind placebo-controlled trial (6 in the verum group, 8 in the placebo group) the capillary resistance rose from $14.6 \pm 0.98$ mm Hg to $18 \pm 3.35$ mm Hg in the verum group, versus $15.5 \pm 1.30$ mm Hg to $14.7 \pm 1.3$ mm Hg in the placebo group [18].

Fig. 7: Contrast sensitivity after treatment with procyanidins 300 mg for 60 days [12].
7. Efficacy

In a double-blind reference-controlled study with 50 patients with symptoms of chronic venous insufficiency, 25 patients received procyanidins (150 mg/day), 25 patients received diosmin (8450 mg/day) per os for 1 month. Patients of the procyanidins-group showed a faster and longer lasting effect than those of the reference group [7].

A double-blind placebo controlled study was conducted with 92 patients. The patients were suffering from venous difficulties, either severe or moderate forms of paresthiasis. 300 mg Procyanidins daily p. o. during 28 days improved clinical parameters such as pain, paresthiasis, nocturnal cramps and edema by more than 50 %, compared to the initial value. Efficacy of verum therapy was confirmed in 75 % of the patients versus 41 % of the patients in the placebo group [37].

In another double-blind placebo-controlled study 2 x 16 patients received the daily amount of 300 mg procyanidolic oligomers (PCO) from grape seeds over 5 days preceding a face-lift operation, and from days 2 to 6 postoperatively. The preventive effect of procyanidolic oligomers on the development of edemas was proven. PCO had the effect of reducing edemas faster than the placebo. The average duration until the disappearance of edemas in the verum-group was 11.4 days, versus 15.8 days in the placebo-group (p = 0.01). Also the general assessment of the surgeon was statistically better in the verum-group (p = 0.04) [2].
8. Therapeutic Safety

**Good tolerance in clinical trials**
Grape seed extract has generally been well tolerated in clinical trials.

**Positive benefit/risk ratio**
Adverse effects are as of yet unknown.
Grape seed extract preparations in the above mentioned dosages clearly have a positive benefit/risk-ratio.
9. Bibliography


(9) Dupuy P, Puisais J: Comptes rendus 241 (1955), 48, quoted in Lit. 5


EUROMED HERBAL EXTRACTS . GRAPE SEED


(14) Hegnauer R: Chemotaxonomie der Pflanzen, Band 6, Birkhäuser Verlag Basel, Stuttgart (1990) 689 - 698

(15) Hegnauer R: Chemotaxonomie der Pflanzen, Band 9, Birkhäuser Verlag Basel, Stuttgart (1990) 754-762


(20) Laparra J, Michaud J, Masquelier J: Plantes médecine Phytothér 11 (1977) 133, quoted in Lit. 5


(22) Liviero L, Puglisi PP, Morazzoni P, Bombardelli E: Fitoterapia 65 (1994) 203


HERBAL EXTRACTS . GRAPE SEED


(38) Trousdale EK, Singleton VL: Astilbin and engeletin in grapes and wine. Phytochemistry 22 (1983) 619-620
