Horse Chestnut Dry Extract

For the Treatment of Chronic Venous Insufficiency

EUROMED

Introduction

EUROMED is a company specialized in making botanical extracts and active principles used as phytomedicines in pharmacy. EUROMED develops and produces therapeutically active raw materials.

The botanical raw materials are subject to strict selection and inspection, and products are manufactured according to methods developed by the EUROMED company. They include inspections to guarantee a standard quality from both analyticochemical and therapeutical points of view and take into consideration the state of art in different fields: research and development, analyses, processes and devices, therapeutic applications on a scientific basis.

EUROMED guarantees the quality of its products by a broad phytochemical know-how.

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1 Horse Chestnut Extract: General Information

1.1 Description

The horse chestnut dry extract is a standardized herbal extract of the seeds of *Aesculus hippocastanum* L. (Fam. *Hippocastanaceae*).

All natural

The extract of *Hippocastani semen* is a herbal preventive and therapeutic agent for chronic deep vein insufficiency. It offers

Herbal remedy for chronic venous insufficiency

- protection against: leg edema and venous ulcers
- relief of inflammatory and non-inflammatory edema as well as cramps of the legs.

Subjective symptoms such as pruritus, pain and feeling of heaviness in the legs are also improved.

The horse chestnut extract (as available from EUROMED) gives most patients some relief of symptoms within the first 15 days.

The extract of *Hippocastani semen* has not been reported to interact with other drugs.

1.2 Indications

The extract of horse chestnut (as available from EUROMED) are used in the treatment of chronic venous insufficiency (CVI) stage I and stage IIIa caused by various conditions (e.g. postthrombotic syndrome). It is also recommended for the treatment of inflammatory edema after minor injuries [6, 9].

1.3 Extract Specifications

Horse chestnut preparations usually contain about 200 mg *Hippocastani semen* extract (as available from EUROMED).

1.4 Dosage and Methods of Administration

An oral dose of 250-312.5 horse chestnut extract (corresponding to 100 mg aescin) given twice daily in a delayed release is recommended by the German Commission E Monograph [42]. Table 1 gives a survey of popular European *Hippocastani semen*-mono-preparations available on the market. Horse chestnut extract is in addition frequently used in combination with other plant extracts.

1.5 Contraindications and Interactions

Horse chestnut extract should be used with caution in edemas not due to CVI. There are no known contraindications to the long-term use of *Hippocastani semen* extract. There are no known interactions with drugs usually prescribed.

1.6 Side-effects

Well tolerated

Horse chestnut extract is generally well tolerated. Side effects are rare when the standardized extract is taken. In exceptional cases mild gastric symptoms may occur. In these cases, it is advisable to take the preparation with the meals [6].

Table 1: European mono-preparations containing horse chestnut dry extract

Preparation Name	**Content of Horse chestnut Extract [mg] (Aescin)**	**Total Extract/day [mg]**
Aescorin N	150 (30 – 38)	300 - 450
Aescusan 20 / retard 50	250 / 263 (50)	750 / 526
Aescuven forte	150 (30)	600
Essaven 50 mono	216 –2 62 (50)	432 - 524
Hoevenol	238 - 263 (50)	476 - 789
Logomed Venen Dragees	270	540 - 810
Noricaven novo	250 (50)	250 - 750
Perivar Rosskaven	263 (50)	526
Plissamur forte	250 (50)	250 - 750
Rexiluven	112 - 137 (25)	336 - 411
Somaven Venentabl.	263 (50)	526
Vasoforte N	250 (38 - 42)	500 - 750
Vasotonin	62.5 (16 %)	375
Venen-Dragees	108 (20)	648
Venen-Tabletten Stada	263 (50)	526
Venentabs retard ratiopharm	263 (50)	526
Veno-biomo Dragees	186 - 228 (50)	186 - 456
Venogal S	100 (16 %)	600
Venoplant retard	263.2 (50)	526
Venopyronum retard / Venopyronum N forte	167 - 250 (40) / 263 (50)	619 - 750 526
Venostasin retard/ Venostasin S	240 - 290 (50) 353 - 400 (75)	480 - 580 706 - 800
Venotrulon	124 - 165 (30)	124 - 825

2 From Plant to Extract

2.1 Horse Chestnut Seed (*Hippocastani semen*): Botanical Data

Hippocastani semen

The *Hippocastani semen* from *Aesculus hippocastanum* L. have been introduced from the Balkan Peninsula by Turkish soldiers during the siege of Vienna in 1529. The seeds used as horse feed were subsequently called horse chestnut. *Aesculus hippocastanum* L. is widely distributed throughout the temperate zones of Europe and Asia [28]. The horse chestnut tree grows in woody valleys or parks [16].

Horse chestnut should not be confused with the edible chestnut, which is of a different plant species. Common names of the horse chestnut are sow chestnut (*d. Saukastanie*), buckeye, bongay, fish poison, conkers, Marronier (*fr.*), Marronier d'Inde (*fr.*) [10].

The horse chestnut tree is a large tree that grows to a height of 25-30 m. It can be identified by its large hand-shaped leaves, erect white or red blossoms in spring and sticky leave-buds in autumn.

Round spinous capsular fruits contain two to three seeds (Fig. 1). The seed is spherical to oval, slightly flattened of 2 to 4 cm in size. The shiny dark-brown testa has a large round light-brown spot. The seed has a bitter taste, thus making it inedible for human beings [16].

HORSE CHESTNUT SEED EXTRACT

Fig. 1: Horse chestnut seed (*Hippocastani semen*)

2.2 Historic Use

Ancient medicinal plant

The horse chestnut was used as a medicinal plant since the 18th century. Leaves, blossoms and bark were recommended for the treatment of cough, rheumatism, gout, fever, uterine bleeding, intestinal catarrh and as an astringent but have lost their therapeutic importance.

Horse chestnut seeds have been used in folk medicine against wounds, intestinal diseases and hemorrhoids [16]. In 1835 FREMY was able to detect saponins in *Hippocastani semen.* Aescin, a triterpenglycoside, was subsequently identified to be responsible for most of the therapeutic qualities of horse chestnut seeds. ARTAULT DE VEVEY noted in 1908 the good efficacy of horse chestnut seeds in hemorrhoids, varicosis of the legs, which he attributed to the reduction of the size of the varicose nodes and the favorable influence on circulation [29, 31].

Horse chestnuts are said to have analgesic, antipyretic, astringent, expectorant, narcotic, tonic and vasoconstrictive properties. They have been used for backache, neuralgia, rheumatism, whooping cough, hemorrhoids and other rectal complaints [10].

Nowadays horse chestnut seeds are used for the treatment of phlebitis, thrombophlebitis, postthrombotic syndrome, edema, erythema of the legs, cellulitis and hypotension [6]. The use of *Hippocastani semen* has been well documented and recognized continuously up to the present day. This is reflected in the German monograph, which recommends the use of horse chestnut seeds to relieve symptoms of chronic venous insufficiency [42].

2.3 Chemistry of horse chestnut extract

The horse chestnut seed extract contains starch, proteins, triterpensaponins (8 – 28 %), fatty oil, cellulose and flavonolglycosides (0.2 - 0.3 %). Triterpene saponins of the diester of the β-amyrine-type form a complex mixture of β-aescin (Fig. 2), kryptoaescin, α-aescin (a mixture of β-aescin and kryptoaescin) and aescinoles. Furthermore, flavonolglycosides have been detected in the drug [49]. The main compounds of horse chestnut extract are listed in Table 2.

The most important active ingredients are the triterpene saponins. Particular attention should be paid to β-aescin as it is mediating the antiexsudative effect of *Hippocastani semen* extract [53].

Another compound of interest is proantho-cyanidin A_2 (Fig. 3), a dimeric procyanidine arising from the condensation of monomeric flavanols, which has been found to be a strong inhibitor of oxidative activity [1, 21].

Aescin is considered the main effective substance

Table 2 :Compounds of horse chestnut extract [55, 53]

Active agents
• Aescin (2 – 10 %) • Flavonolglycosides (0.2 - 0.3 %) • Proanthocyanidin A_2 (< 0.5 %)
Other compounds
• Starch (30 – 50 %) • Reducing glycosides (app. 6 %) • Fatty oil (2 – 7 %) • Proteins (7 – 11 %) • Minerals (3 – 4 %)

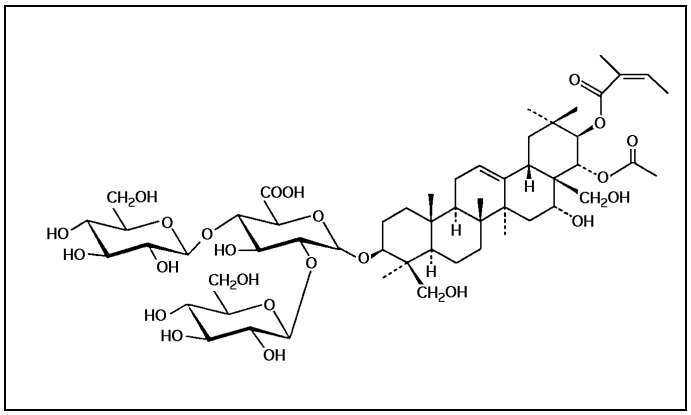

Fig. 2: Main component of β-Aescin [53]

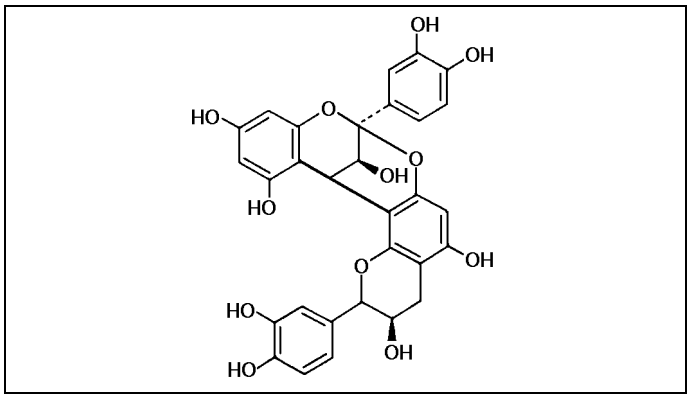

Fig. 3: Procyanidin A_2 [1]

2.4 Preparation of the Extract and Quality Control

Standard quality assured

Horse chestnut, the tree of *Hippocastani semen* originates from plants growing in central Europe. From these seeds, specially identified and with a standard quality EUROMED manufactures horse chestnut extract.

The quality of EUROMED horse chestnut extract is steadily improved. Permanent professional botanical inspections are part of the growth of the trees.

Adequate size and condition of the plants are of great importance to the quality of the extract of EUROMED *Hippocastani semen*. The seeds are exclusively collected manually.

Inspection of the drug upon its arrival at EUROMED

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.

Furthermore EUROMED evaluates the possible contamination of the drug. Only high-quality raw plant material selected according to the strictest criteria is used.

Strict quality control of the extracts

EUROMED applies an extraction process which provides a high yield of valuable constituents and a high-grade extract in a careful way.

According to the original processes EUROMED produces a dry extract from the seeds of *Hippocastani semen*:

An extract of the whole seed is used

- **EXTR. HIPPOCASTANI E SEM. SICCUM (HORSE CHESTNUT DRY EXTRACT)**
  Fine, light brown powder, hygroscopic.

EUROMED horse chestnut extract satisfies the highest quality standards. This way it is possible to meet the requirements for an effective and safe medication.

2.5 Standardization

The consistent batch to batch quality of the EUROMED horse chestnut extract is guaranteed by the standardized production process.

Consistent batch to batch quality

The analytical specifications of the EUROMED horse chestnut extract are:

* Aspect	Fine powder, light brown color, hygroscopic
* Identification	TLC
* Loss on drying	Max. 20.0 %
* Ash	Max. 8.0 %
* Assay	Triterpene derivatives as Aescin calculated as dried substance, Min. 20.0 % (DAB-10)
* Microbiology	Acc. Ph. Eur. 3rd ed., 5.1.4., category 3B

3 Chronic Venous Insufficiency

CVI is often underestimated

Chronic venous insufficiency (CVI) is an often-underestimated serious health problem, which can reduce quality of life and is expensive for society.

3.1 The Vein System

The veins are much more than a system of conduits collecting blood for the heart. The vein wall can contract or relax and the venous valves control the direction of blood flow. It provides the mechanism for pumping blood against gravity back to the heart.

The hydrostatic pressure in the veins of the feet rises to about 90 mm Hg when a person is standing. When a person is walking, the muscles contract and squeeze blood into the veins, propelling it further to the heart. When the muscles relax, the biscupid valves in the veins keep the blood from flowing backwards.

If a person is standing for a prolonged time, 15 – 20 % of the total blood volume can be sequestered and lost for the circulation [25].

3.2 Epidemiology

CVI, an extremely common disease

Chronic venous insufficiency is an extremely common disease in western countries, which can even affect young healthy adult persons.

86 % of the adult population suffer from venous problems

The "Tübinger Studie", a representative survey conducted in 1981 in Germany, evaluated the incidence of diseases of the veins in the general population. It was found that an overwhelming part of the population is suffering from venous diseases. One in 8 persons had advanced CVI, another 15 % had clinical signs of a CVI and additional 58 % show some changes of the venous system. Thus only 14 % of the studied persons were considered to be disease-free [24]. Women were more at risk and had more severe forms of CVI.

Genetic and environmental risk factors for CVI

Advanced age (Fig. 4), heredity, multiple pregnancy, obesity and low social status were proposed as risk factors for CVI. Genetic and environmental influences seem to be responsible for the world-wide variance of incidence.

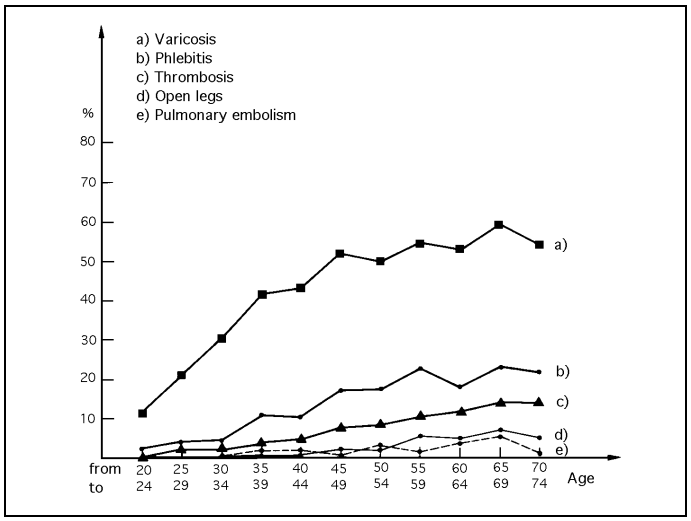

Fig. 4: Chronic venous diseases in relation to age in a representative population of 4026 men and women [24]

Impairment of professional life

Approximately 5 % of the participants of the study declared that the severity of the symptoms of CVI disturbed their professional life, resulting in temporary disablement (45 %), change of work, retraining or premature retirement (55 %) [24].

Pregnant women are particularly at stake for developing CVI. 30 % of all women during their first pregnancy and 55 % during subsequent pregnancies suffer from varicose veins [3].

3.3 Etiology

Numerous risk factors

The modern lifestyle of western civilization is thought to be at the origin of varicose veins. Factors, which interfere with the blood flow to the heart such as incorrect posture, lack of physical activity, unbalanced nutrition, unilateral strain, constipation and hereditary factors, contribute to the development of CVI. Hormones also play an important role [3, 8].

Primary varicosis is the result of a hereditary weakness of venous vascular walls or valves whereas secondary varices can develop after deep vein thrombosis. Varicosis or thrombosis reduce venous blood flow and induce venous stasis which entails the migration of protein molecules from the capillaries to the interstitium.

Capillary endothelial cells, injured by venous stasis express endothelial-leucocyte adhesion molecules and vasoactive compounds. Toxic oxygen radicals generated by leucocytes induce inflammation which leads to edema, trophic changes and ulcers in the skin [8].

The collagen content and elasticity of the venous walls are reduced in CVI [32]. The capillary wall is partly constituted of proteoglycans, which exert a “molecular sieving” function and are impaired in CVI. An increased activity of enzymes, which decompose proteoglycans has been observed in CVI (Fig. 5) [18, 33].

The impairment of microcirculation was observed in studies showing an increased plasma viscosity, erythrocyte aggregation and rigidity in CVI compared to controls [32].

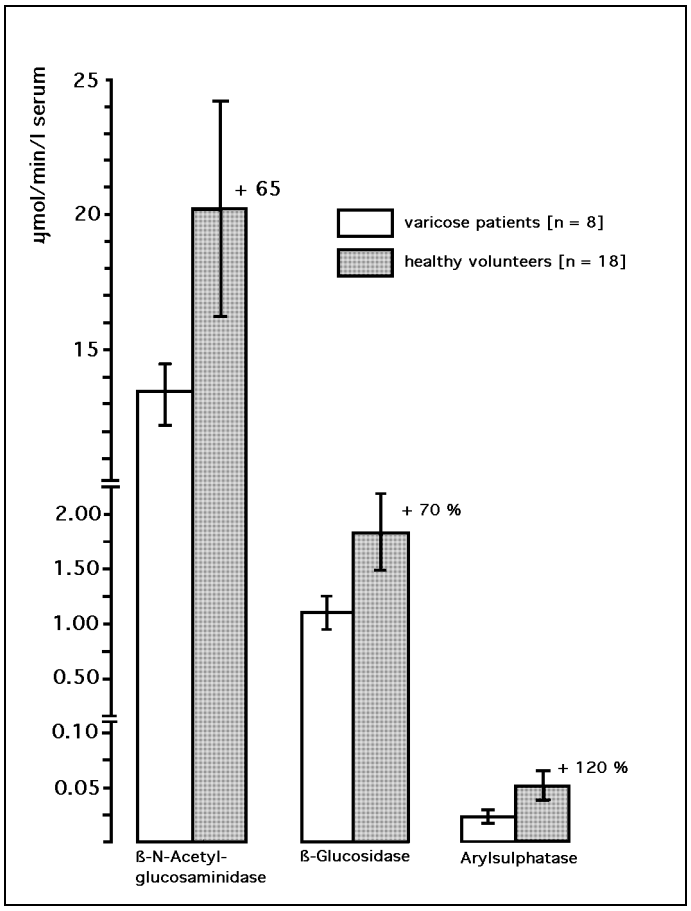

Fig. 5: Activity of three proteolytic enzymes in healthy persons (white columns) and patients with CVI (gray columns) [33]

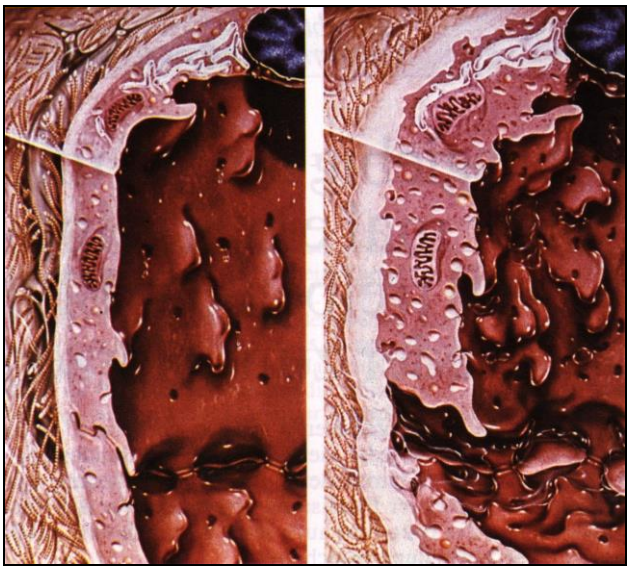

Fig. 6: Capillary wall in normal subjects (left) and in CVI (right). In venous stasis endothelial cells are swollen and become permeable to proteins [5]

3.4 Symptoms

Pain and edema are the main symptoms of CVI

Main symptoms of CVI are pain, edema, tense, heavy and restless legs as well as leg cramps. The frequency of the above-mentioned symptoms in a normal population is shown in Fig. 7 [24].

The symptoms are worse in the evening when the legs are swollen. Night-work worsens edema; these workers are particularly at risk for developing CVI [38]. Itchy skin and pigmentation are the first signs of trophic changes of the skin. The symptoms can considerably affect the physical condition as well as the quality of life of those affected by CVI [24].

Frequently it is pain or edema, which causes the patient to consult a physician.

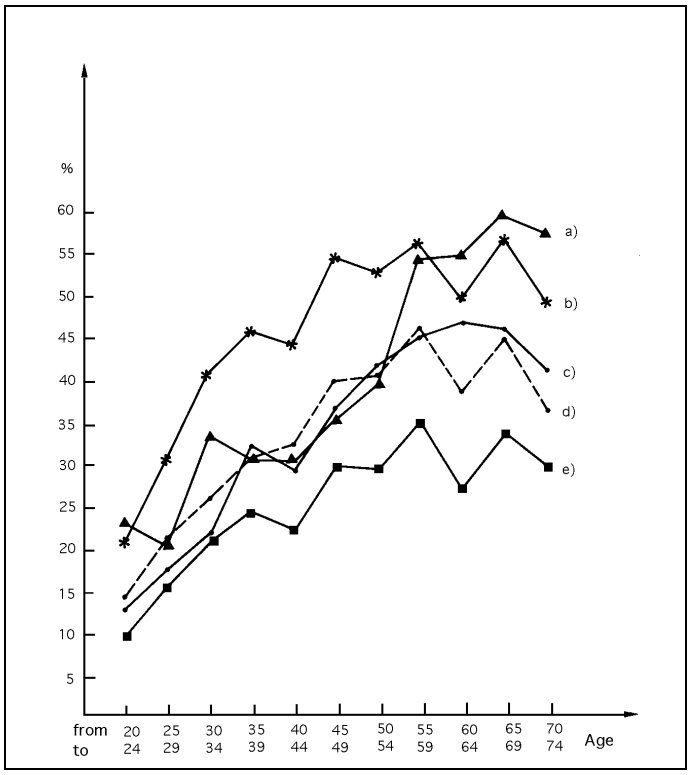

Fig. 7: CVI-related symptoms in a normal population in relation to age: a) nocturne leg cramps; b) tense or heavy legs; c) swollen legs; d) restless legs; e) painful legs [24]

3.5 Stages

The classification of CVI according to WIDMER comprises three clinical stages (Table 3).
Dilated veins around the ankle may be the first sign of CVI in stage I. Edema may be present at evening or after long journeys. Stage II is characterized by chronic edema and beginning trophic changes of the skin. In stage III florid or healed leg ulceration indicate serious impairment of the microcirculation [26, 38, 54].

Table 3: Stages of chronic venous insufficiency [54]

Stage I
• Dilated veins around the ankle (Corona phlebectatica paraplantaris) • Leg edema
Stage II Skin involvement
• Pigmentation of the skin • Thickening of the skin (Lipodermatosclerosis))
Stage III
a) Healed leg ulceration b) Florid leg ulceration

3.7 Therapy

Early treatment important in CVI

Patients with CVI require hospital or sanatorium treatment, including surgical intervention and often are forced into early retirement. Complications of CVI such as thrombophlebitis, leg ulceration and trophic damage of the skin are common. Therefore it is important to treat CVI in an early and therapeutically favourable stage in order to prevent time-consuming and expensive complications [13, 14].

Treatment of CVI should have an influence on the following factors:

- Improvement of microcirculation and venous tone
- Reduction of edema
- Reduction of vascular permeability [3].

Changes in lifestyle are also of great importance in the treatment of CVI. Physiotherapy, weight loss and physical activity should be prescribed to every patient. Legs should be kept in an elevated position during the night in order to reduce or prevent edema. In most of the cases the treatment must be completed by compression and medical treatment [2, 30, 48].

Two treatment approaches

Currently two treatment approaches are used, the standard mechanical compression including bandages and stockings, and venoactive substances. Although compression has been proved to be an effective treatment in CVI, the compression therapy is known to be inconvenient, uncomfortable for the patient and therefore subject to poor compliance [14]. In some patients compression therapy is contraindicated (e. g. congestive heart disease, arteriosclerosis), in others impossible (e.g. rheumatic diseases). About 50 % of the patients prematurely interrupt compression therapy [24].

Surgical treatment and sclerosis of varicose veins may be useful in difficult cases, but is risky and causes scars [35].

Herbal remedies for CVI have gained high importance

Phytopharmaceutical agents such as horse chestnut seed extract (as available from EUROMED) have been used successfully for a long period of time. As additional data elucidating the mechanism of action and clinical application of these agents have been published, the use of horse chestnut seeds has been widely accepted as the medical treatment of choice in phlebology [2].

Aescin, the active agent in horse chestnut extract, has an effect against edema by reducing the increased capillary permeability. Moreover, horse chestnut extract has been documented in experiments to have anti-inflammatory qualities [27].

Another advantage of horse chestnut extract is its low leveled side-effects. As a result of experimental studies and clinical tests conducted during the last 15 years *Hippocastani semen* preparations have taken a predominant role in drug therapy of CVI [2].

The favorable benefit/risk ratio combining therapeutic efficacy with safety in use, especially in combination with compression treatment, should be considered when treating patients with CVI [13].

4 Pharmacology

4.1 Pharmacodynamic

Many different mechanisms account for efficacy

The therapeutic benefit of horse chestnut extract (as available from EUROMED) in treating the symptoms of CVI is essentially based on reduction of capillary permeability, its venotonic activity and vascular protection. Furthermore it has been found by recent studies that horse chestnut extract (as available from EUROMED) has an anti-inflammatory and free radical scavenging effect.

Most of the pharmacological effects of horse chestnut extract are mediated by aescin. Aescin has been shown to inhibit the activity of proteolytic enzymes which destroy elastic fibres resulting in a loss of the elastic qualities of the vascular wall [18, 20, 33].

4.1.1 Anti-Edematous Effect

Anti-edematous effect by reducing capillary permeability

Dry extract from *Hippocastani semen* (as available from EUROMED) has an anti-edematous effect. The pathologically increased permeability of the vascular membranes is reduced to a normal level by horse chestnut seed extract [43]. It is assumed that aescin is able to reduce the number and/or diameter of small pores in the capillary wall [41].

The intravenous application of aescin has an anti-exsudative effect in animal studies. Experimentally induced edema can be reduced by the i. v. injection of 2 to 4 mg/kg aescin by 40 – 70 % (Fig. 8). Aescin has an equal effect on non-inflammatory edema, as it is encountered in CVI (Fig. 9) [18].

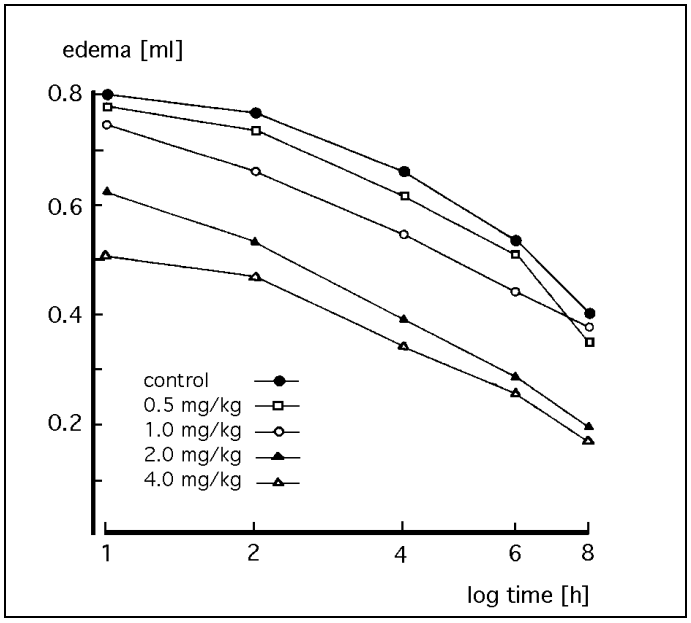

Fig. 8: Dose-dependant effect of aescin on rat paw edema [18]

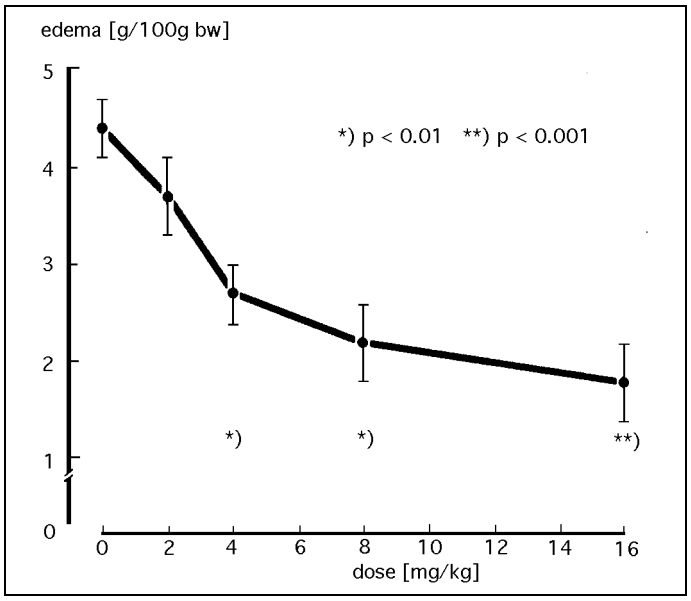

Fig. 9: Reduction of non-inflammatory edema in rats following oral aescin [18]

4.1.2 Anti-Inflammatory Effect

Anti-inflammatory effect of horse chestnut extract

GUILLAUME et al. could demonstrate that the administration of horse chestnut extract (200 - 400 mg/kg p. o.) can decrease the formation of inflammatory edema induced by carrageenin in rats (Fig. 10). The amount of plasma extravasation and leucocyte emigration into pleural exsudate in the carrageenin-induced pleurisy was also significantly decreased.

Daily treatment with *Hippocastani semen* extract decreased the weight of subcutaneous granulomas, a model for subchronic inflammation, indicating an effect on connective tissue formation [27].

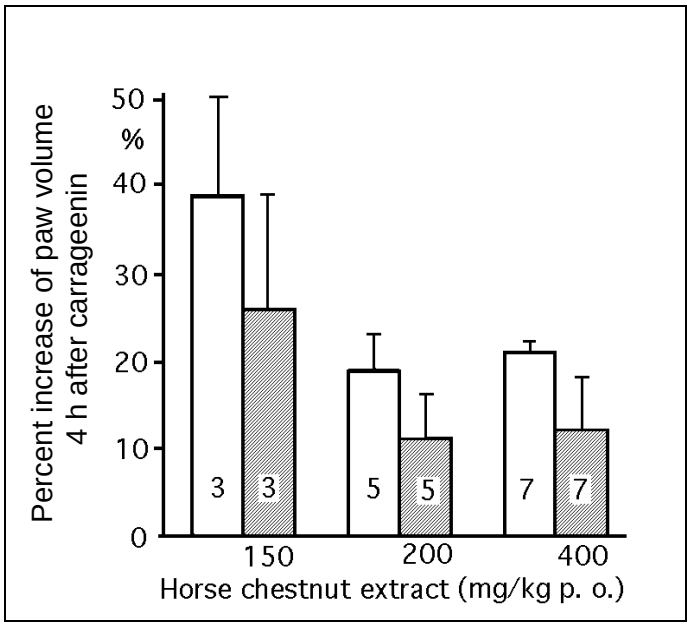

Fig. 10: Effect of horse chestnut extract on carrageenin induced edema in rats. White bars: Control; gray bars: Horse chestnut extract [27]

4.1.3 Venotonic Action

Venotonic effect

Hippocastani semen extract (as available from EUROMED) has a marked venotonic activity. Low concentrations of horse chestnut extract can increase the venous tone in isolated veins through the enhancement of the constrictive effect of noradrenaline. It has no effect on arterial vessels.

The venotonic activity of horse chestnut extract has been demonstrated in dogs, volunteers and patients with CVI by experiments using plethysmography and radioactive measurements of blood flow velocity. A contracting effect on valves was also observed. Thus horse chestnut extract is effective in orthostatic dysregulation [17, 27].

LONGIAVE et al. (1978) could demonstrate that aescin increases the venous tension by enhancing the generation of the prostaglandin $PGF_{2\alpha}$ in the veins. A dose-dependent increase of the tone of isolated human saphenous and rabbit portal veins was observed after the addition of 5 - 10 µg aescin. As shown in Fig. 11 the effect was abolished by indomethacin, which is known to inhibit $PGF_{2\alpha}$ [37].

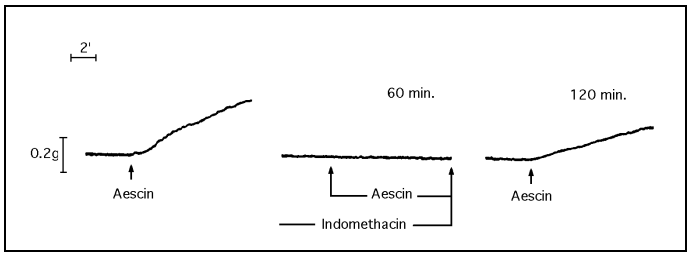

Fig. 11: Left: Effect of aescin 10 µg/ml on isolated human saphenous vein. Middle: Aescin loses its pharmacological activity after exposing the tissue to indomethacin (1 µg/ml) for 60 min. Right: Aescin recovers almost completely its ability to induce contraction 120 min later after having removed indomethacin [37]

4.1.4 Vasculotropic Action

A failure of the subcutaneous microcirculation can cause cellulitis. CRISTONI and coworkers were able to show a significant increase of the capillary density in the forearm of healthy persons after the dermal application of aescin preparation with the technique of videocapillaroscopy. This effect was also observed after 2 or 3 months of treatment [11].

Improvement of vascular resistance

Horse chestnut extract dose dependently diminishes the cutaneous capillary hyper-permeability induced by histamine or serotonin in the rat. Vascular resistance was significantly increased in the guinea pig as measured by the pressure needed to burst skin vessels [27].

4.1.5 Anti-Oxidative Effect

Scavenging of free radicals by Hippocastani semen extract

The anti-oxidative mechanism of horse chestnut extract has been demonstrated by GUILLAUME et al. [27]. Lipid peroxidation was inhibited *in vitro* (Fig. 12) and *in vivo* by horse chestnut extract. Furthermore, the deleterious action of free oxygenated radicals on cells and surrounding tissues was limited in 2 different models.

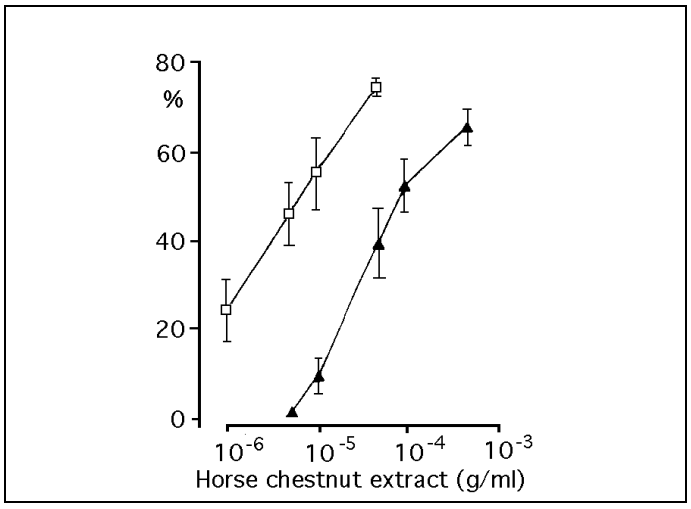

Fig. 12: Effect of horse chestnut extract on lipid peroxidation *in vitro*. Percent inhibition of oxidation by α-tocopherol (•) and horse chestnut extract (σ) [27]

In a recent study from FACINO et al. proanthocyanidin A_2, a compound isolated from *Aesculus hippocastanum*, has been found to be a strong scavenger of free radicals [21]. Proanthocyanidin A_2 prevented oxidation *in vitro* and inhibited proteolytic and hydrolytic enzymes. It was therefore concluded that horse chestnut extract (as available by EUROMED) can prevent oxidative damage and premature aging of the skin.

In another study, 65 types of plant extracts were studied for evidence of superoxide anion-scavenging effects. Amongst these plants, *Aesculus hippocastanum* L. was detected as the most potent inhibitor of oxidative activity and protector of proteolytic activity [39].

4.2 Pharmacokinetics

The extract of *Hippocastani semen* is a complex compound. Therefore pharmacokinetic experiments are difficult and only available for some of its constituents.

Uptake studies have been performed for aescin. About 10 – 15 % of oral aescin are absorbed in the intestinum. Plasma half-life varies from 10 – 19 hours. The anti-edematous effect of horse chestnut extract (as available from EUROMED) is present for 3 - 5 days. Oral aescin is more effective than injection, as plasma concentrations remain low and elimination is slower [22].

In a bioavailability study of β-aescin with sustained release, c_{max} (maximal concentration) and t_{max} (time of maximal concentration) were1.23 h and 13.3 ng/ml respectively ($AUC_{(0-24)}$ area under the curve 213.2 ng/ml h) [44].

The effect of horse chestnut extract in edema decreases after exceeding maximum doses. The mechanism of action probably consists of integration in the vascular wall, a process which lasts a long time [23].

5 Toxicology

Low toxicity

The toxicity of horse chestnut extract (as available from EUROMED) is generally low.

Acute Toxicity

The acute oral toxicity of horse chestnut extract has been studied in mice, guinea-pigs and rats. The LD_{50} of oral horse chestnut extract is 990 mg/kg body weight for mice, 1530 mg/kg for rabbits 2150 mg/kg for rats and 130 mg/kg for dogs [42, 31].

Chronic Toxicity

An oral dose of 80 mg horse chestnut extract/kg body weight in dogs and 400 mg/kg in rats given over 34 weeks did not induce any toxic changes. Similar results were obtained with rats [42, 31].

Reproduction Toxicology

A slight embryotoxic effect was observed in rabbits after 300 mg/kg horse chestnut extract (corresponding to 30 times the recommended dose for human beings) [31].

Genotoxicity/Carcinogenicity

There are no data available.

6 Clinical Pharmacology

6.1 Antiedematous Effect

Transcapillary filtration decreased by horse chestnut extract

The effect of horse chestnut extract (as available from EUROMED) on transcapillary filtration and intravasal volume in female patients with CVI was studied by PAUSCHINGER [45]. Using venous occlusion plethysmography, he observed that transcapillary filtration was decreased by 22 % after an single application of 600 mg horse chestnut seed extract. Intravasal volume was also reduced in comparison to placebo (Fig. 13).

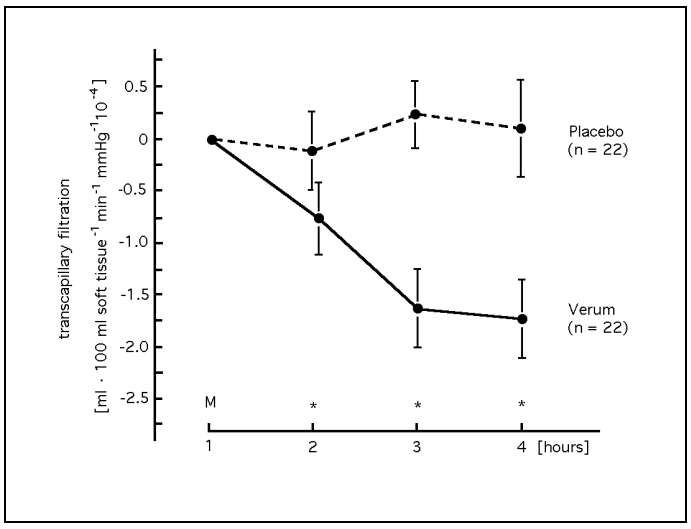

Fig. 13: Reduction of intravasal volume after intake of horse chestnut extract [45]

The effect of horse chestnut on transcapillary filtration was assessed in a randomized placebo-controlled crossover double-blind trial of 22 patients with proven CVI by measuring the capillary filtration coefficient and the intravascular volume of the legs by venous occlusion plethysmography [4]. The capillary filtration coefficient and the intravascular volume were significantly decreased three hours after 600 mg *Hippocastani semen* extract compared to placebo. The authors concluded that horse chestnut seed extract has an inhibitory effect on edema formation**.**

Proteolytic enzyme activity reduced

As shown in Fig. 14, continuous treatment of patients with CVI with 900 mg horse chestnut seed extract (as available from EUROMED) for a period of 12 days led to a significant reduction in the pathologically increased activity of three proteolytic enzymes ($p < 0.01$ vs. placebo) [33, 34].

As the reduction of the activity of the three enzymes was of the same order of magnitude, the authors proposed that the drug has a protective action towards the site of the enzyme release. Thus the capillary walls can be rendered less fragile and permeable for macromolecules.

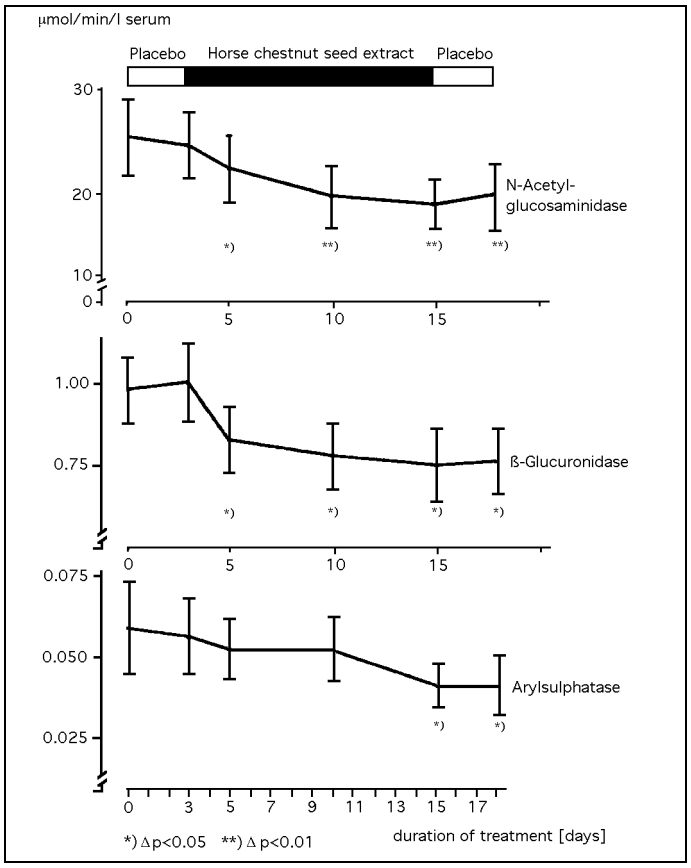

Fig. 14: Activity of lysosomal enzymes in CVI patients during treatment with placebo and horse chestnut extract (900 mg per day) [33]

6.2 Anti-Inflammatory Effect

Antiphlogistic action

Horse chestnut extract has antiphlogistic qualities. Two independent studies using local aescin were conducted in healthy volunteers [7, 9]. Hematoma was experimentally induced and subsequently treated with topical horse chestnut extract, placebo or diclofenac in a total of 211 probands. *Hippocastani semen* proved to be significantly superior to placebo ($p < 0.001$) and to diclofenac ($p < 0.0004$) for pain at pressure.

7 Proof of Clinical Efficacy

7.1 Clinical Trials with Placebos

Several controlled double-blind studies

Several controlled double-blind studies have demonstrated that the horse chestnut seed extract (as available from EUROMED) is effective in relieving all the major symptoms of CVI including painful legs, the most bothersome complaint.

The antiedematous effect and the influence on subjective parameters of a treatment with 600 mg horse chestnut extract daily was tested in a double-blind placebo controlled study involving 40 patients with confirmed chronic venous insufficiency [47]. During the 4 weeks of treatment the edema volume of the foot and the distant lower leg decreased significantly ($p < 0.001$) compared to placebo (Fig. 15). Pain, tiredness, feeling of tension and pruritus in the legs were also significantly improved.

Reduction of edema in pregnant women

The beneficial effect of horse chestnut extract was confirmed in a double-blind placebo controlled crossover study involving 20 pregnant women with CVI and edema. Leg volume as measured by water plethysmography was reduced by 128.6 and 114 ml, respectively, after 2 weeks. Complaints of heaviness, tickling and nocturne leg cramps were reduced by horse chestnut extract. No side effects were reported [50].

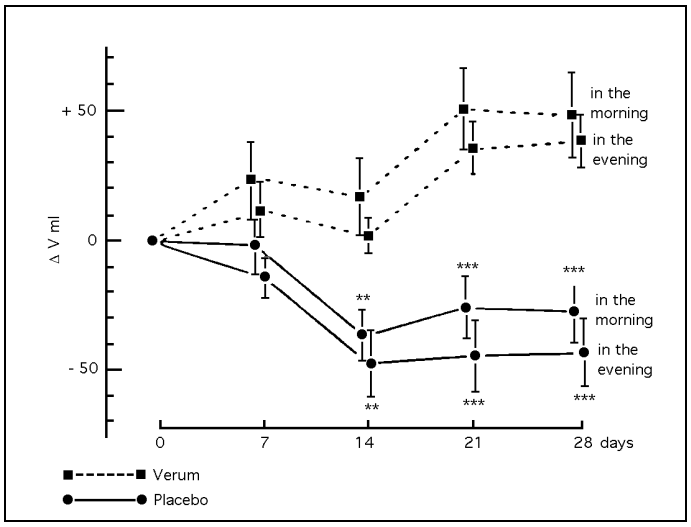

Fig. 15: Change of volume of the foot and lower leg as measured by venous occlusion plethysmography during the treatment with horse chestnut extract. **p < 0.01; ***p < 0.001 vs. Placebo [47]

Horse chestnut extract was investigated for its edema-curing and edema-protective action. In a randomized double-blind placebo controlled trial horse chestnut extract was given for 8 weeks to 80 patients. Edema was provoked and leg volume and circumference measured.

Horse chestnut extract protects from edema

The filtration of water into the extravasal region was reduced by horse chestnut extract and increased by placebo. The authors concluded that the progression of edematous disease can be inhibited by horse chestnut extract [36].

In a randomized placebo-controlled double blind study on 40 patients suffering from leg edema in CVI stage II, the edema-reducing effect of *Hippocastani semen* extract was investigated. Patients of both sexes aged between 25 and 65 received horse chestnut extract containing 150 mg aescin/day or placebo over a period of 6 weeks. Body weight and subjective complaints during and after the completion of the treatment were measured. Leg edema was measured before and after provocation by hydroplethysmography and venous occlusion plethysmography [15].

Edema was significantly ($p < 0.001$ vs. placebo) reduced in the verum group. After edema provocation, there was a significant difference in favor of verum ($p < 0.01$) (Fig. 16).

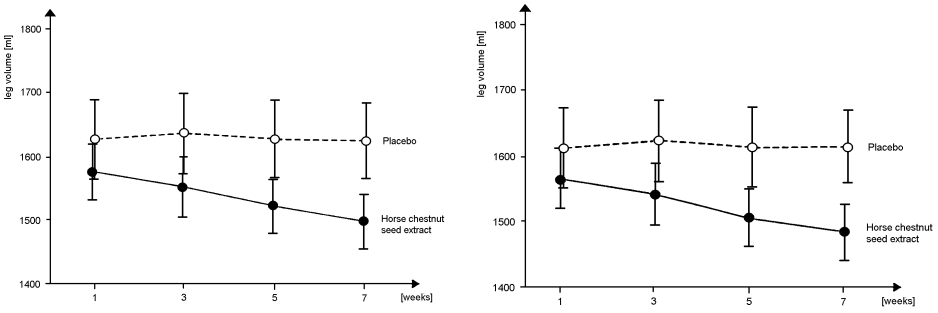

Fig. 16: Leg volume before (left) and after (right) edema provocation [15]

Improvement of subjective symptoms

Subjective symptoms were decreased in frequency and severity in the group treated by horse chestnut extract than in the placebo group. Treatment was well tolerated and no side effects have been reported [15].

7.2 Clinical Trials with Other Therapy

Efficacy of horse chestnut extract equal to compression therapy

In order to compare the efficacy of *Hippocastani semen* to compression therapy, a randomized, partially blinded, placebo-controlled study was carried out [14]. A total of 240 patients with CVI were studied. After a two-week run-in with placebo, patients were randomized either to compression, horse chestnut seed extract (50 mg aescin/day) or placebo. Patients allocated to compression treatment received a diuretic for 7 days to ensure the best stocking fit.

After 12 weeks the lower leg volume was found to be decreased by 43.8 ml with horse chestnut extract ($p < 0.005$ vs. placebo) and 46.7 ml with compression therapy ($p < 0.002$ vs. placebo), whereas it was increased by 9.8 ml with placebo. The two therapies were equivalent (Fig. 17).

Compliance with drug therapy was reported to be good and no serious treatment-related adverse effects occurred. The authors concluded that horse chestnut extract offers an alternative to compression for patients with edema resulting from CVI [14, 12].

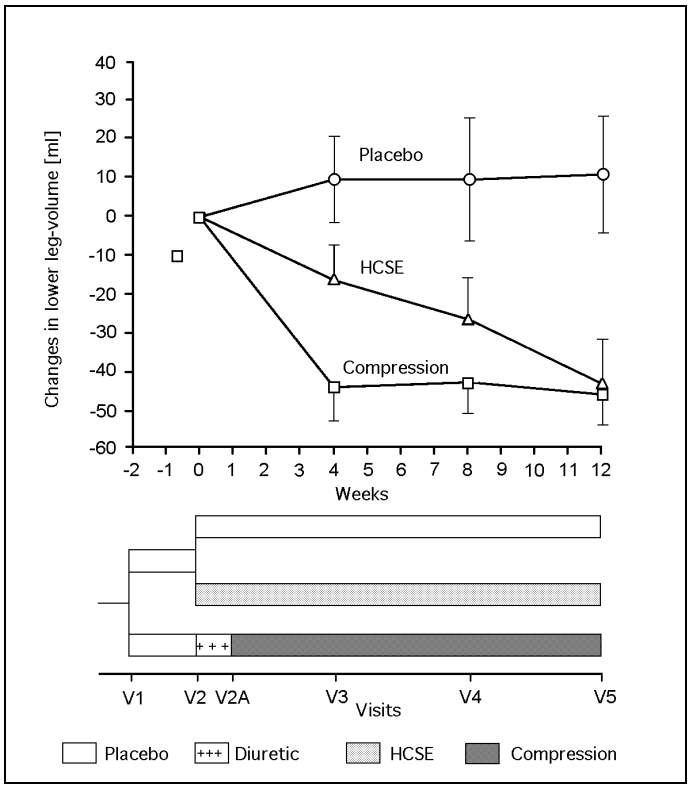

Fig. 17: Changes in lower leg-volume versus baseline. No differences between compression therapy and horse chestnut extract (HCSE) could be detected after 12 weeks of treatment [14]

Horse chestnut extract was compared to oxerutin in a double-blind, randomized, placebo controlled clinical trial involving 137 postmenopausal women with CVI. Following one week run-in with placebo, the patients were treated with either 1000 mg/d oxerutin or 600 mg/d horse chestnut extract for 12 weeks and observed for further 6 weeks. Volume reduction of the leg and subjective symptoms were evaluated [46].

Equivalence to oxerutin

Both substances proved to be equivalent in volume reduction of leg edema and improvement of subjective symptoms. The improvement was visible even 6 weeks after the end of the treatment. Only 2 of 62 patients in the horse chestnut group reported having side-effects and none of the patients withdrew from the study.

In a randomized double-blind study 40 CVI patients were given aescin (150 mg /day) or hydroxyethylrutoside (2000 mg/day) for 8 weeks [19]. The outcome was measured by the following parameters: leg circumference before and after edema provocation, symptoms such as feeling of pain, tiredness and tenseness of the legs, swollen legs and itching. Both treatments improved leg edema and subjective symptoms, though only the group treated by aescin experienced a significant improvement. The tolerance was equally good in both groups.

7.2 Open Studies

Long term treatment well tolerated

In a recent open, multi-centered study including over 5000 patients with CVI the effect of horse chestnut extract on symptoms and the tolerance to drug therapy were investigated. Most of the patients were treated for 4 to 10 weeks with 150 mg aescin/day. The following symptoms were evaluated: pain, tiredness, tenseness, swollen or itchy legs and edema.

Of 3,321 patients who indicated having strong or unbearable pain before starting treatment (62.9 % of total), the situation remained unchanged in only 190 (3.6 %) after treatment (Fig. 18). Other symptoms such as leg tenseness (Fig. 19) or swollen legs improved markedly or disappeared completely. Most of the symptoms disappeared during the first week of drug therapy. The treatment was well tolerated. Only 24 out of 5000 patients had some gastro-intestinal complaints, four patients complained of leg cramps [26].

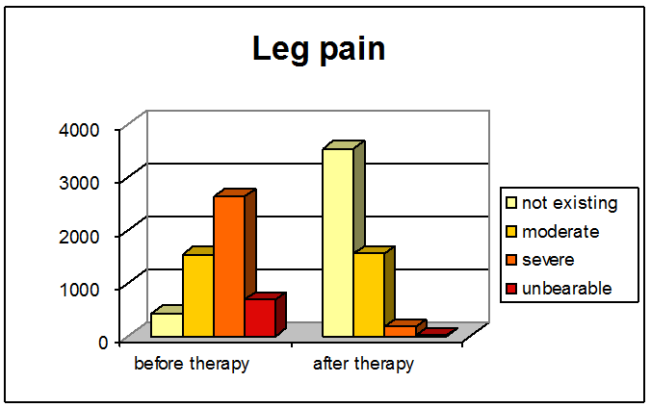

Fig. 18: Leg pain before and after treatment with horse chestnut extract [26]

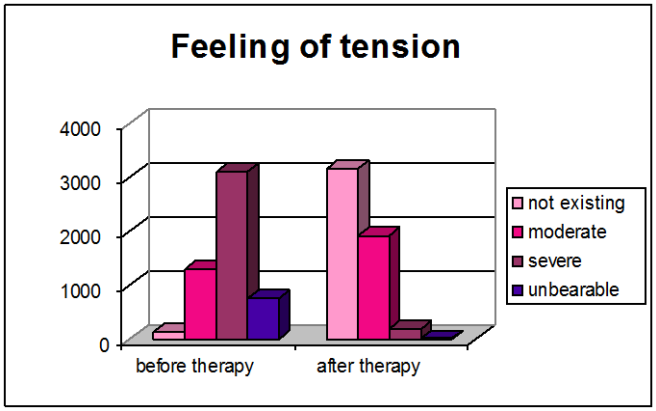

Fig. 19: Feeling of tension in the legs before and after treatment [26]

Treatment effective after one week

The effect of a short-term treatment with 700 mg horse chestnut seed extract was studied in 85 women in different stages of CVI. *Hippocastani semen* extract was efficient in postpartum or postoperative deep venous thrombosis and varicosis after 2 or 3 days of treatment. Out of 85 patients, 74 had no more complaints after 1 week of treatment. The treatment was generally well tolerated; one patient developed an allergy and another nosebleeding [3].

7.3 Multi-Center Studies

In a multi-center open study a total of 4,113 patients suffering from CVI were included. Most of the patients received 200 mg horse chestnut extract daily. 45 % of these patients were also treated with compression therapy. The participants of the study were questioned about symptoms of CVI such as pain, heaviness, edema and nocturne cramps [40].

Efficacy judged "good" to "very good" by patients and physicians

The above-mentioned symptoms had improved or disappeared in app. 85 % of the patients after an average of 87 days of treatment. The efficacy of the treatment was judged as being "very good" or "good" by 89 % of their physicians. A total of 3,743 of the patients (91 %) declared that life quality was improved by horse chestnut extract treatment.

High level of compliance

Only 0.4 % of the patients experienced some slight gastro-intestinal side-effects. A large majority of the participants (91 %) continued the treatment after the end of the study.

The beneficial effect of horse chestnut extract was confirmed in an open study conducted with 1183 patients over 5 months. After the treatment with horse chestnut extract containing 40 mg aescin three times daily, objective and subjective symptoms were markedly reduced (Fig. 20). A total of 43 % of the patients found a reduction of the size of the varicose veins.

Adverse effects were recorded in only 10 patients, of whom 7 were of gastro-intestinal nature. The treatment was interrupted in only one case [35].

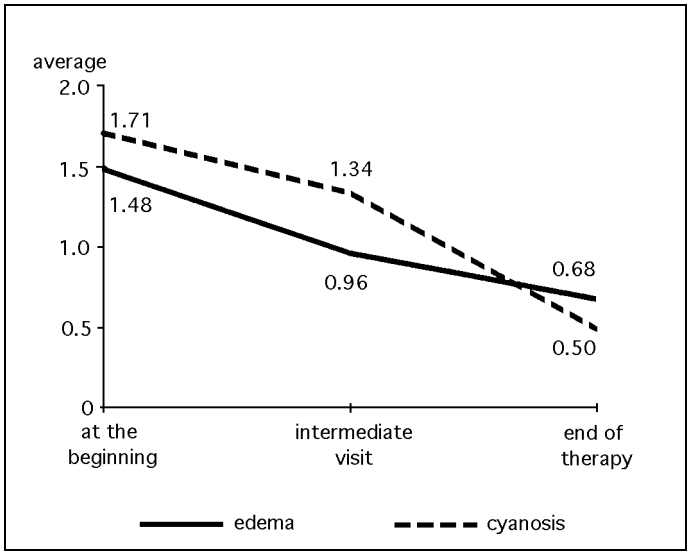

Fig. 20: Scores for edema and cyanosis of the legs during the treatment with horse chestnut extract [35]

7.3 Therapeutic Safety

High level of therapeutic safety

Horse chestnut extract is notable for its particularly high level of clinical safety. To-date acute cases of *Hippocastani semen* extract poisoning have not been reported.

Particular emphasis should be put on the high tolerance of *Hippocastani semen* preparations leading to a high level of treatment compliance because of the almost total absence of side-effects.

Summary

The treatment with horse chestnut extract is effective for the treatment of chronic venous insufficiency. Symptoms such as pain, heaviness, tenseness and edema of the legs improve under treatment. Horse chestnut extract is well tolerated.

Hence horse chestnut extract (as available from EUROMED) is of great importance to phytotherapy. The evaluation of the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) on efficacy and safety of *Hippocastani semen* in treating CVI resulted in a positive Commission E-Monograph [42].

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