Clinical Studies on Horse Chestnut (*Aesculus hippocastanum* L.)

Chronic Venous Insufficiency (CVI)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Geissbühler and Degenring, 1999	Venous insufficiency	U, MC n=71 patients (61 women and 10 men) with chronic venous insufficiency and edema	6 weeks	Morning and evening massage gel into lower leg including ankles and the inner side of the thighs	Aesculaforce® Venen-Gel (1g of gel contains 54–117 mg dry extract standardized to 2% escin)	After 6 weeks of treatment, ankle circumference was reduced significantly ($p<0.001$) by 0.7 cm compared with baseline. Patients symptoms score also decreased significantly ($p<0.001$) by 60%. Over 85% of the cases reported good to medium efficacy. [Note: the principal author was employed by the manufacturer.]
Shah *et al.*, 1997	Venous insufficiency	DB, PC, MC n=52 males and females with CVI (mean age test group 54 years; mean age placebo group 56 years)	6 weeks	2 tablets 3x/day (120 mg escin/day)	Aesculaforce® tablet (Each enteric coated tablet contains 63–90 mg native dry extract standardized to 20 mg escin per tablet)	After 2 weeks treatment there was significant ($p<0.05$) reduction in edema of the ankles and venous filling rate ($p=0.03$). There was no significant improvement in subjective symptoms. HCSE was well tolerated. [Note: the principal author was employed by the manufacturer.]
Diehm *et al.*, 1996	Venous insufficiency	R, SB, PC, Cm, PG n=240 men and women with CVI (mean age 52 years)	12 weeks preceded by a 2-week placebo run-in	1 capsule 2x/day (100 mg escin/day) vs. mechanical compression with bandages and class II elastic stocking	Venostasin® retard extract capsule (Each capsule contains 240–290 mg native dry extract standardized to 50 mg triterpene glycosides, calculated as escin, with 10–60 mg dextrin)	Lower-leg volumes were significantly reduced in both HCSE ($p=0.005$) and compression therapy ($p=0.002$) groups. HCSE decreased lower-leg volume by an average of 43.8 ml compared to 46.7 ml with compression therapy and an increase of 9.8 ml with placebo. HSCE was well-tolerated (98% compliance), whereas compression treatment was reported as uncomfortable, inconvenient and subject to poor (90%) compliance.
Rehn *et al.*, 1996	Grade II CVI	R, DB, Cm, MC, PG n=137 postmenopausal patients with grade II chronic venous insufficiency	12 weeks, preceded by 1 week placebo run-in, follow-up period of 6 weeks without treatment	One 300 mg capsule 2x/day (100 mg escin/day) vs. 1,000 mg/day O- (β-hydroxyethyl)-rutosides for 4 weeks, then 500 mg/day for 8 weeks	HCSE capsules standardized to 50 mg escin each or oxerutin (brand not stated)	Both HCSE and oxerutin significantly reduced leg volume compared to baseline with mean leg volume reduction of 100 ml after 12 weeks. HCSE alleviated subjective symptoms. After 6-week follow-up period both treatments exhibited substantial carry-over effect. Authors concluded that both therapies are effective in treatment of CVI.
Masuhr *et al.*, 1994	Venous insufficiency	S n=4,113 (treated in 842 practices)	87 days	Two, 100 mg tablets per day (100 mg escin/day)	Venoplant® retard, with 100 mg dry extract adjusted to 50 mg escin	In more than 84% of the patients, symptoms either improved or disappeared, with the "good" tolerance in 90% of the cases. The authors concluded that CVI can be successfully treated with a symptom-based therapy using horse chestnut seed extract.
Diehm *et al.*, 1992	Venous insufficiency	R, DB, PC, PG n=39 men and women with venous edema in chronic deep-vein incompetence	6 weeks	One, 300 mg capsule 2x/day (150 mg escin/day)	HCSE capsules standardized to 75 mg escin each (brand not stated)	Compared with baseline, HCSE significantly reduced ($p<0.01$) leg volume by an average 84 ml compared to 4 ml with placebo. HCSE caused dramatic improvement in feelings of heaviness, tension, fatigue, and paresthesia in the legs. Itching was not helped. Authors conclude that HCSE is a safe and effective adjunct to compression therapy.

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Erler, 1991	Venous insufficiency	R, DB, Cm, PG n=40 patients with CVI and peripheral venous edema	2 months	One, 300 mg capsule 2x/day (150 mg escin/day) vs. 2000 mg/day O-(β-hydroxyethyl)-rutosides	HCSE capsules standardized to 75 mg escin each (brand not stated)	Compared with baseline, HCSE significantly protected calf and ankle from edema provocation. Both HCSE and rutin preparations were comparable in reducing edema, but HCSE had a more pronounced protective effect.
Pilz, 1990	Venous insufficiency	R, DB, PC, PG n=28 patients with CVI	20 days	One, 300 mg capsule 2x/day (100 mg escin/day)	HCSE capsules standardized to 50 mg of escin (brand not stated)	HCSE treatment caused significant reduction ($p<0.05$) of 0.08 cm in leg circumference and decreased edema compared with placebo. Subjective symptoms were also significantly decreased ($p<0.05$).
Steiner, 1990	Venous insufficiency	R, DB, PC, CO n=20 female patients with varicosis during pregnancy	2 weeks	One, 300 mg capsule 2x/day (100 mg escin/day)	Venostasin® Retardkapsel	Compared to placebo, HCSE caused significant reduction ($p=0.009$) of 114 ml in leg volume. Leg circumferences and subjective symptoms were also significantly reduced ($p<0.05$) during HCSE treatment period. HCSE was rated as significantly better than placebo by physicians ($p<0.01$) and patients ($p<0.05$).
Steiner and Hillemanns, 1990	Edema due to venous insufficiency	R, DB, PC, CO n=52 pregnant women with edema due to CVI	20 days	One, 300 mg capsule 2x/day (100 mg escin/day)	Venostasin® Retardkapsel each capsule contains 240–290 mg native dry extract standardized to 50 mg triterpene glycosides, calculated as escin, with 10–60 mg dextrin	Significant reductions ($p<0.01$) in foot volume before and after edema provocation and greater resistance to edema provocation demonstrated in HCSE group compared with placebo. Reductions in foot circumference and less severe subjective symptoms of pain, fatigue, swelling, and itching were also significant in HCSE group.
Erdlen, 1989	Venous insufficiency	R, DB, Cm, PG n=30 patients with CVI	1 month	One, 300 mg capsule 2x/day (100 mg escin/day) or reference medication (type not clearly indicated, presumably rutosides)	HCSE capsules standardized to 50 mg escin each (brand not stated)	HCSE significantly reduced ankle circumference by 0.4 cm and improved subjective symptoms compared with baseline.
Kalbfleisch and Pfalzgraf, 1989	Venous insufficiency	R, DB, Cm, PG n=30 (33) patients with CVI	2 months	One, 300 mg capsule/day (50 mg escin/day) vs. 500 mg O- (β-hydroxyethyl)-rutosides/day	HCSE capsules standardized to 50 mg escin each (brand not stated)	HCSE reduced ankle and calf circumference by 0.2 and 0.18 cm, respectively, compared to baseline. Values were not significantly different from the rutoside.
Rudofsky *et al.*, 1986	Venous insufficiency	R, DB, PC, PG n=39 patients (67% women) with grade I or II chronic venous insufficiency	1 month	One, 300 mg capsule 2x/day (100 mg escin/day)	HCSE capsules standardized to 50 mg escin each (brand not stated)	HCSE treatment resulted in statistically significant ($p<0.001$) reduction by 78 ml in leg volume compared with 34 ml increase with placebo. At 28 days, HCSE caused a significant change in calf and foot circumference ($p<0.01$). Additionally, significant improvement in subjective parameters (pain, tiredness, tension, and pruritus in legs) were reported. No difference with respect to venous capacity or venous drainage when leg was elevated.

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Lohr *et al.*, 1986	Venous insufficiency	R, DB, PC, PG n=74 patients (57 women and 17 men) with CVI	2 months (preceded by a 12-day washout phase with placebo)	One, 300 mg capsule 2x/day (morning and evening) (100 mg escin/day)	Venostasin® Retardkapsel	HCSE treatment resulted in leg volume reduction of 16.5 ml compared to 3.8 ml reduction with placebo. Formation of edema was decreased (– 21.0 ml) with HCSE and increased (+ 0.2) ml with placebo during edema-provoking period. Authors concluded that HCSE therapy showed statistically significant activity in inhibiting progression of edematous disease conditions and was well-tolerated.
Bisler *et al.*, 1986	Venous insufficiency	R, DB, PC, CO n=22 patients with CVI	Single dose of HCSE or placebo followed by 4-week study period	Two, 300 mg capsules/day (100 mg escin/day)	Venostasin® Retardkapsel	Three hours after administration, an acute dose of HCSE had an anti-edematous effect with a statistically significant (p=0.006) decrease (22%) in the capillary filtration coefficient compared with placebo, which caused an increase. Authors conclude that HCSE inhibits edema in CVI of leg by reducing transcapillary filtration.
Kreysel *et al.*, 1983	Varicosis	DB n=15 varicose patients	12 days	One, 300 mg capsule 3x/day (150 mg escin/day)	Venostasin® Retardkapsel	After 12 days of treatment, significant reduction in activity of glycosaminoglycan hydrolase enzymes. Serum activity of 3 lysosomal glycosaminoglycan hydrolases were significantly reduced by 29.1%, 25.7%, and 28.7% respectively, compared to placebo. The authors hypothesize that HCSE acts at the site of enzyme release, exerting a stabilizing effect on the lysosomal membrane.
Friederich *et al.*, 1978	Venous insufficiency or varicosis	R, DB, PC, CO n=95 patients with varicosis or CVI	20 days	One, 300 mg capsule 2x/day (100 mg escin/day)	HCSE capsules standardized to 50 mg escin each (brand not stated)	HCSE caused significant reduction ($p<0.05$) in CVI-related symptoms including calf spasm, pain, fatigue, and tenseness compared to placebo. No effect on pruritus.
Knoche and Knoche, 1978	Venous complaints	S n=61	9 months	One, 100 mg tablet 2x/day	Venoplant® retard standardized to 50 mg escin and 15 mg milk thistle (*Carduus marianus*) extract	A reduction in lower leg pain was demonstrated as early as 3 days after treatment. Edema formation declined after 7-14 days. Only 3 patients complained of minor side effects, including stomach complaints and dizziness.
de Rossi et al., 1977	Venous complaints (varicosis, thrombophlebitis, phlebothrombosis)	S n=1,236	28 days (average)	One, 100 mg tablet 2x/day	Venoplant® retard tablet containing 100 mg horse chestnut and 15 mg milk thistle (providing 50 mg escin and 7.5 mg silymarin per tablet)	Rapid effect (21% reported improvement by day 4, 52% by day 8, and 70% by day 10) and good gastric tolerance were emphasized by 90% of the physicians.
Neiss and Böhm, 1976	Varicosis	R, DB, PC, CO n=226 (233) predominantly women with varicosis	20 days	One, 300 mg capsule 2x/day (100 mg escin/day)	HCSE capsules standardized to 50 mg escin each (brand not stated)	Compared to placebo, HCSE caused significant ($p<0.05$) reduction in edema, leg pain, and pruritus.

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Other

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Oschmann *et al.*, 1996	Bio-equivalence as determined by pharmaco-kinetics	R, CO n=24	3 days each phase with 1-week washout between pases	Single dose of one tablet or one capsule (50 mg escin)	Venoplant® retard 263.2 mg tablet or Venostasin® retard 240–290 mg capsule (providing 50 mg escin per tablet or capsule)	Bioequivalence was established between the 2 dosage forms.
Calabrese and Preston, 1993	Experimentally induced injury with hematomas	R, DB, PC n=70 healthy volunteers	9-hour study period	1 time acute topical application	Topical gel containing HCSE standardized to 2% escin (brand not stated)	Using tonometric sensitivity measurements, escin gel significantly reduced ($p<0.001$) tenderness to pressure of experimentally induced hematomas. The effect was observed from 1 hour after treatment lasting until the end of the 9-hour study period.
Put, 1979	Severe cranio-cerebral trauma	C, Cm n=142 accident victims with severe cranio-cerebral trauma	Treatment periods varied on an individual basis from 1–56 weeks with follow-ups at 2–3.5 years after accident and treatment	Days 1–5: 20 mg/day escin i.v.; Days 6–9: 10 mg/day escin i.v.; Beginning on day 10: 1 tablet/day vs. corticosteroid i.v. (type not specified)	Purified escin i.v. in the form of sodium escinate (first 10 days) followed by Reparil®-coated tablets	Regaining of consciousness was more rapid in the escin group than the corticosteroid group. Escin was more effective than steroid therapy at reducing intracranial pressure and lowering mortality rates. Follow-up examinations 2–3.5 years after the accident showed significantly higher rehabilitation rate in escin group (49 of 71) compared with steroid group (36 of 71).

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