Eur J Clin Pharmacol (1996) 50: 443–447

CLINICAL TRIALS

N. Ihme · H. Kiesewetter · F. Jung · K. H· Hoffmann
A. Birk · A. Müller · K. I. Grützner

Leg oedema protection from a buckwheat herb tea in patients with chronic venous insufficiency: a single-centre, randomised, double-blind, placebo-controlled clinical trial

Received: 25 April 1995 / Accepted in revised form: 29 February 1996

Abstract *Objectives*: The efficacy of a buckwheat herb tea was determined in patients with chronic venous insufficiency (CVI) in a single-centre, randomised, double-blind, placebo-controlled clinical trial.
Methods: Sixty-seven male and female patients (22–74 years) with CVI were randomly divided into two groups after a 2-week run-in period. They received either buckwheat herb tea (*Fagopyrum esculentum*) or a placebo tea for a period of 3 months. The main outcome measure was the lower leg volume determined by ultrasound. Subjective symptoms were assessed by a clinical symptom score system. The femoral vein diameters were measured by B-scan sonography. In a subgroup of patients capillary permeability was determined by cutaneous fluorescence angiography.
Results: Although the mean partial leg volume did not change in the treatment group (from 2041 to 2073 ml), it increased in the placebo group by 110 ml (from 1972 to 2082 ml) according to intent to treat. The difference between the groups was significant. The subjective clinical symptoms were significantly reduced in both groups. The mean diameters of the femoral veins were reduced and capillary permeability was improved, but neither change was statistically significant. No drug-related adverse effects were observed.
Conclusion: CVI is a very placebo-sensitive condition. The treatment with buckwheat herb tea is safe and could have a favourable influence on patients with CVI such that further oedema development is prevented.

N. Ihme · H. Kiesewetter (✉) · K. H· Hoffmann · A. Birk
A. Müller · K. I. Grützner
Universitätsklinikum Charité, Medizinische Fakultät der
Humboldt Universität zu Berlin, Institut für Transfusionsmedizin
und Immunhämatologie, Schumannstrasse 20/21,
D-10117 Berlin, Germany

Key words Buckwheat herb, Oedema protection; chronic venous insufficiency, *Fagopyrum esculentum*, microcirculation

Introduction

Venous disorders are not uncommon in modern society and several studies on venous disorders have been carried out [1]. In Germany alone, about 10 million people are affected and 5 million suffer from advanced venous insufficiency [2].

Chronic venous insufficiency (CVI) includes disorders due to varicose veins or thrombosis (post-thrombotic syndrome). Three major stages of severity are distinguished. Early stage I is characterised by daytime ankle and lower leg oedema with dilated veins. The next stage II is distinguished by chronic oedema with additional hyper- and depigmentation of the skin and/or induration of the hypodermis. These changes can lead to the development of ulcer, which marks stage III of chronic venous insufficiency. The standard treatment of CVI is physical therapy with compression stockings and exercise. However, in contrast to drug therapy, compliance is very low [3]. Drug treatment is considered effective if the effects of venous occlusion, such as oedema and ulcer are improved or the progression of the disease is slowed or halted. In Germany several phytotherapeutic products are popular and are being widely used, among which buckwheat herb is of interest.

Buckwheat herb (*Fagopyrum esculentum*) has a high content of rutin (quercetin-3-rutinoside), a flavonoid that is partially metabolised in the intestine and excreted in the urine [4]. Pharmacological studies have demonstrated the following effects of rutin: normalisation of an increased vascular permeability and fragility [5, 6], oedema protection [7], hyaluronidase inhibition [5], vasoconstriction [8, 5], epinephrine potentiation [8, 9], and an antioxidative effect [10, 11].

From these actions a normalisation of capillary function, a reduction in oedema and inflammation, which are thought to correlate with clinical symptoms, is expected from the therapy of CVI with rutosides on theoretical grounds. This was demonstrated for *O*-(*β*-hydroxyethyl)-rutosides, semisynthetic derivatives chemically similar to rutin [12–14].

Only one uncontrolled study with buckwheat herb treatment has been published, which demonstrated an improvement in 64% of the 166 patients examined [15]. Therefore, this double-blind trial was conducted to substantiate the clinical experience with buckwheat herb tea with emphasis on oedema protection. The purpose was to evaluate the effect of buckwheat herb tea on the lower leg volume and the subjective symptoms due to CVI.

Materials, methods, and subjects

Seventy-seven male and female patients, aged 22–74 years, suffering from chronic venous insufficiency stages I and II entered the study after giving their informed consent. All of them were previously known to the trial centre, an outpatient centre for vascular and circulation disorders. The inclusion criteria were: ankle and/or lower leg oedema, a clinical subjective symptom score of at least 3, stem varicosis and/or post-thrombotic syndrome and/or valvular insufficiency of the deep veins. The major exclusion criteria were stem and branch varicosis, as well as perforating veins with a surgical indication, active or healed ulcers cruris, acute thrombosis or venous inflammation, oedema due to cardiac or renal insufficiency, concomitant therapy with diuretics, dihydroergotamine drugs or any other drugs for venous therapy, and other severe disorders.

All inclusion and exclusion criteria, including the main efficacy parameter and clinical symptom score, were assessed by a thorough physical entrance examination. Eligible patients entered the 2-week run-in phase, during which all patients received the placebo tea 3 times daily. Then all patients were randomly allocated to a group receiving either the buckwheat herb or placebo tea. The randomisation was carried out by Rancode computer software (IDV Gauting, Germany). During the active treatment phase all patients took the study medication 3 times a day before meals and reported to the study centre after 2, 4, 6, 8 and 12 weeks. A 4-week postobservation period followed, during which all patients received the placebo tea again.

The main efficacy parameter was the lower leg volume of the more seriously affected leg. It was determined by the sum of the foot volumetric measurement by a Gutmann volumeter and the ultrasound volumetric measurement of the lower leg above the ankle [16]. The femoral vein diameters were assessed as a secondary parameter by B-scan sonography. A descriptive evaluation of the venous status was performed by a venous Doppler examination. The clinical score of the subjective symptoms was determined by the sum of the first degree symptom scores where tenseness, sensation of heaviness and swelling were scored according to intensity on a scale of 0, 1 or 2; and of second-degree symptom scores where pain, paresthesia, nightly calf cramps, "burning feet" and "restless legs" were scored according to intensity on a scale of 0, 1/2 or 1. Since the first-degree symptoms are more characteristic of CVI, they received a higher numerical value. The second-degree symptoms are less specific for the disease, but are frequently described by patients.

As a safety measure standard laboratory tests (serum analysis, haematology, urinalysis) with validated procedures were carried out.

A subgroup of 20 patients were selected randomly (a block randomisation method was carried out using Rancode software, IDV Gauting, Germany) to determine capillary permeability. Participation was voluntary, and a sample size estimation was not carried out. Capillary permeability was measured by using cutaneous fluorescence angiography. Sodium fluorescein 0.2 ml (20%) l^{-1} estimated blood volume was injected into the antecubital vein. Subsequently, its appearance in skin capillaries of the medial malleolus was recorded per microscope and video recorder for 5 min. For analysis, the fluorescence intensity of the observed skin area was determined over the video time of 5 min, the maximum was found and the basic skin fluorescence was subtracted. This value was set in relation to the one found 60 s after injection of the sodium fluorescein. This relative intensity (%) was chosen as the study parameter, because 60 s after the injection the largest differences between healthy volunteers and patients with microcirculation disorders can be found [17, 18]. For the video capillary microscopy of the microcirculation of the skin, a microscope with video was used as an optical system using a method published by Jung [19]. This fluorescence angiography technique has already been used in other microcirculation studies with CVI patients [20–22]

The active treatment consisted of a buckwheat herb tea (100% dried herb of *Fagopyrum esculentum*, Fagorutin) with a standardised total flavonoid content of 5%. The tea was packed in tea bags containing 1.8 g buckwheat herb per bag. One tea bag was used for one cup of tea. The daily rutin intake amounted to about 270 mg. The substance rutin is easily extractable from buckwheat herb when prepared as a hot tea and has better in vitro absorption properties than pure rutin [23]. The placebo tea was prepared from mallow leaves (*Malva sylvestris* L. and/or *M. neglecta* Wallr.) without determinable amounts of flavonoids. A blinded taste test with pharmacists demonstrated that the teas were similar in taste and appearance and hard to distinguish.

The sample size was estimated assuming an expected decrease in lower leg volume of 25 ml with the active treatment. It was calculated to be $n = 32$ per treatment group (program N of IDV Gauting, Germany). The change in lower leg volume was assessed as the difference between the initial value (week 0) and the last value of active medication (week 12). The evaluation was made by the *t*-test for equally distributed variables, and the result was significant if the *P* value was below 0.05 (two-tailed). Confidence intervals were calculated at the 95% level. For an assessment of the efficacy, the main efficacy parameter was evaluated twice, by the intent-to-treat and completers' analysis. Secondary parameters were tested by the *t*-test, and *P* values were calculated for the completers.

The study was carried out according to the principles stated in the Declaration of Helsinki/Hongkong 1989, the GCP guidelines, the requirements of the German drug law, and the currently accepted scientific standard in Germany [24]. The protocol was approved by the ethics committees of the regional medical associations of Norththine-Westphalia and Saarland.

Results

Seventy-seven patients complied with the inclusion and exclusion criteria and entered the randomisation phase, and 67 patients completed the study and qualified for the completers' analysis. Six dropouts were from the placebo group, of which one experienced a deep phlebothrombosis. Four dropouts were from the active treatment group, of which one patient had to withdraw due to a hip operation. There were no dropouts due to suspected drug-related adverse effects.

Table 1 Lower leg volume: partial leg volume of the more seriously affected leg. Intent-to-treat analysis. Values are given as means with (standard deviation)

Week	−2 Placebo	0	12	16 Placebo
		Active treatment		
Active treatment group	2042 (298)	2041 (312)	2073 (309)* (P = 0.1907)	2176 (333)
Placebo treatment group	1993 (270)	1972 (275)	2082 (339)* (P = 0.0009)	2097 (346)

* Difference in total volume (week 0 minus week 12) between treatment groups, P = 0.0449

The active treatment group consisted of 10 male and 30 female patients with a mean age of 57.3(9.6) years, a mean weight of 71.5(10.4) kg and a mean height of 167.5(7.5) cm. In this group 17 patients suffered from CVI stage I, 22 had CVI stage II and 1 was classified as stage III. The placebo group included 14 male and 23 female patients with a mean age of 59.8(7.3) years, a mean weight of 73.4(11.8) kg and a mean height of 168.6(8.0) cm. Nineteen patients of the placebo group suffered from CVI stage I and 18 from stage II.

The intent-to-treat analysis and the completers' analysis resulted in the same outcome. The mean partial leg volume did not change significantly after 12 weeks of treatment with buckwheat herb tea ($P > 0.1$). According to intent-to-treat, a significant increase was observed in the placebo group in mean partial leg volume of 110 ml ($P > 0.001$, 95% confidence interval: 172–49) after 12 weeks (see Table 1). The difference of total volumes (initial value minus value after 12 weeks treatment) between the treatment groups was statistically significant ($P > 0.05$). Also, the completers' analysis did not show a significant volume change in the treatment group [from 2045(307) to 2080(304) ml ($P > 0.1$)]. However, an increase of mean partial leg volume of 131 ml from 1943(243) to 2074(333) ml was observed in the placebo group ($P < 0.001$, 95% confidence interval: 203–60). The difference between the groups was significant ($P < 0.05$).

The individual evaluation in the active treatment group showed that 16 patients experienced a decrease in leg volume compared to only 6 in the placebo group. The mean intraindividual volume change in the active group was 4(88) ml, whereas in the placebo group it amounted to 66(102) ml.

Figure 1 shows the relative fluorescence intensity (% FLI) observed 60 s after injection of sodium fluorescein at the medial malleolus before and after 12 weeks of therapy. In the active treatment group the mean values for the relative capillary permeability decreased by 15% ($P < 0.03$) from 30.3(6.6)% to 25.8(8.6)% after 12 weeks, whereas in the placebo group no change was observed [30.0(4.1) to 30.3(3.0)%]. Although a pharmacological effect is assumed, it did not reach statistical significance when both groups were compared ($P < 0.08$).

In Table 2 the femoral vein diameters are listed. The mean diameter of the right femoral vein was reduced by 0.35 mm ($P < 0.02$) and the mean diameter of the left femoral vein decreased by 0.33 mm ($P < 0.02$) after 12 weeks of active treatment. In contrast there were no changes observed with placebo. The differences in venous diameters before and after therapy compared to placebo were statistically not significant ($P > 0.1$ right side, $P > 0.2$ left side).

Table 2 Diameters of the femoral veins. The diameters were determined by B-scan sonography. Values are given as means with (standard deviation)

	Right femoral vein	Left femoral vein
Active treatment (n = 36)		
Week 0	11.7 (1.69)	11.8 (1.67)
Week 12	11.4 (1.64) (P = 0.0186)	11.4 (1.66) (P = 0.0136)
Placebo (n = 30)		
Week 0	11.4 (1.81)	11.5 (1.82)
Week 12	11.34 (1.75) (P = 0.8353)	11.5 (1.80) (P = 0.9443)

Table 3 Clinical symptom score values: sum of first- and second-degree symptom score values. During the run-in (weeks-2 to 0) and postobservation (weeks 12–16) periods all patients received placebo treatment. Values are given as means with (standard deviation)

Week	Active treatment (n = 36)	Placebo (n = 31)
−2	6.4 (1.2)	5.9 (0.9)
0	5.8 (1.6)	5.4 (1.1)
2	5.0 (1.6)	4.5 (1.6)
4	4.2 (1.6)	3.7 (1.7)
6	3.2 (1.6)	3.2 (1.5)
8	2.9 (1.7)	2.7 (1.4)
12	2.2 (1.4)	2.4 (1.7)
16	2.0 (1.1)	1.6 (1.3)

As can be seen from Table 3, the subjective symptoms were reduced during both treatments. The score values decreased by 3.6 points due to active treatment ($P = 0.0001$) and by 3.0 points due to placebo ($P = 0.0001$). Only in three patients of each group there was no change in symptom score. The differences from week 0 and the end of treatment (week 12) were compared between the two groups, they did not reach statistical significance ($P > 0.2$).

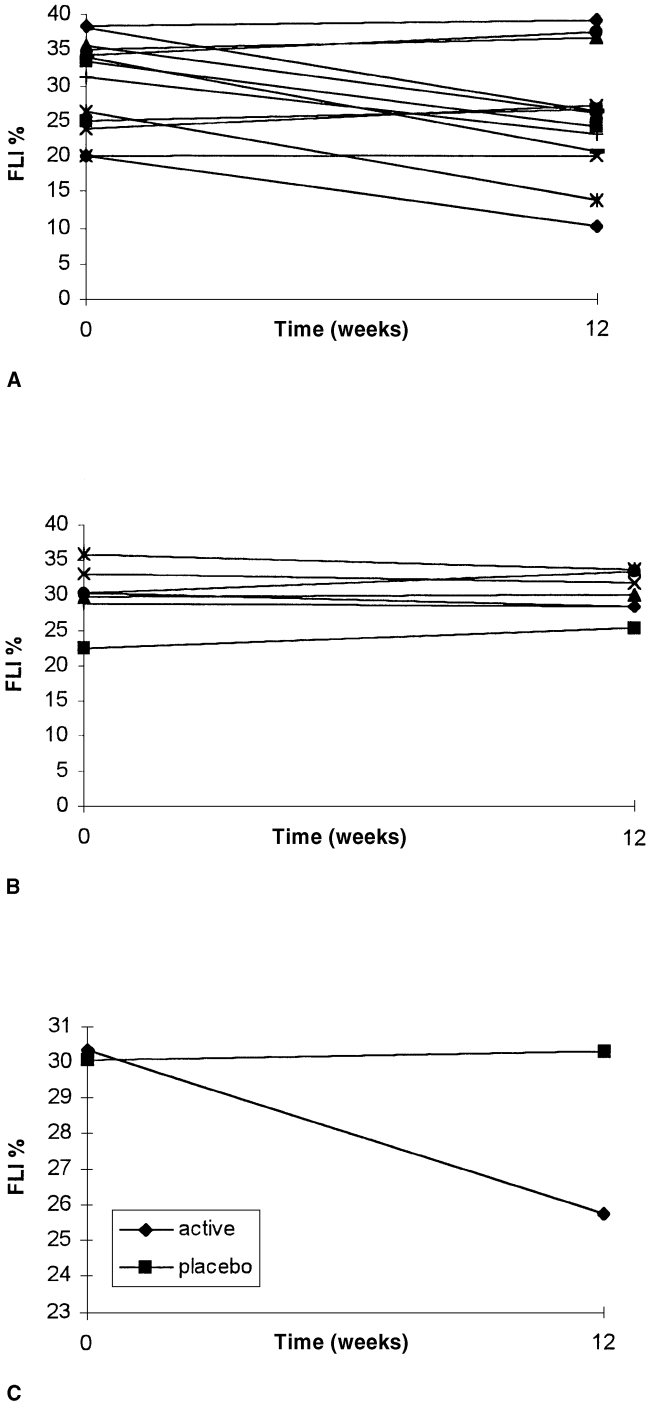

Fig. 1A–C Capillary permeability: percentage relative fluorescence 60s after injection of sodium fluorescein at the medial malleolus. **A** Individual data of capillary permeability active treatment; **B** Individual data of capillary permeability placebo treatment; **C** Mean capillary permeability

All laboratory parameters remained unchanged throughout the study period, except for a slight decrease in potassium concentration and an increase in partial thromboplastin time by 2 s during the active treatment, the differences were statistically not significant.

Discussion and conclusions

The main finding of this clinical trial is the temporary arrest of the presumably continuous increase in leg volume. The difference between the groups was statistically significant. The additional accumulation of about 100 ml fluid on average was prevented. It is difficult to define the clinical relevance of an oedema protective effect, since there are no studies published in which volume limits were defined or established. Studies with healthy volunteers examining the oedema development of the lower limbs on long-distance air flights show that a 100 ml increase in lower leg volume is meaningful in the sense that it marks the difference between healthy and diseased [25]. With regard to these results, the prevention of an additional 100 ml fluid is considered clinically relevant in patients with CVI In other studies with venous active phytotherapeutics volume effects of around 45 ml were found [26], similarly with hydroxyethyl rutosides [12–14, 27].

The reduction of the partial leg volume is thought to be due to effects within the macro- and microcirculation. Particularly in the femoral vein, a reduction of about 1 mm in venous diameter was observed in almost half of the patients. This 10% reduction in diameter is a pharmacological effect that may have positive clinical implications in CVI. Effects on the venous macrocirculation were also found for hydroxyethyl rutosides [28].

It is postulated that capillaries and venules in the microcirculatory system are annealed by rutin. This is supported by the finding that the fluorescence intensity in the skin tended to decrease after the intake of the buckwheat herb tea. The capillary action of rutin was also found in different patient groups with microcirculatory disorders treated with buckwheat herb tea [15].

The clinical symptoms, such as tenseness, a feeling of heaviness, swelling, pain, paresthesias, calf cramps, burning feet, restless legs and pruritus, were improved by both buckwheat herb and placebo. The study showed that CVI is an extremely placebo sensitive condition with regard to these symptoms. It is important to note that, although the placebo effect is very high, it tends to decrease with increasing stages of disease severity.

The study demonstrated that the buckwheat herb tea used to influenced the relevant parameters of CVI, but further studies are needed to substantiate this claim. In conclusion, buckwheat herb tea was well tolerated and can be considered safe in the supportive treatment of chronic venous insufficiency.

Acknowledgement The study was carried out at the Zentrum für Gefäβ- und Kreislauferkrankungen, Rottstrasse 19, D-52068 Aachen, Germany.

References

1. Wienert V, Willer H (1991) Epidemiologie der Venenerkrankungen – eine Synopsis Z Hautkr 66:758–761
2. Fischer H (1983) Sozioepidemiologische Studie über die Venenleiden bei einer erwachsenen Wohnbevölkerung in der Bundesrepublik Deutschland. In: Voelter W, Jung G (eds) *O*-(*β*-Hydroxyethyl)-rutoside: Neue Ergebnisse in Experiment und Klinik. Springer, Berlin Heidelberg New York
3. Glaeske G, Müller B (1991) Fortschrittliche Phlebologie weist Varizen in die Schranken. MMW 133:10–11
4. Baba S, Furuta T, Fujioka M, Goromaru T (1983) Studies on drug metabolism by use of isotopes XXVII: Urinary metabolites of rutin in rats and the role of intestinal microflora in the metabolism of rutin. J Pharm Sci 72:1155–1158
5. Leibetseder J (1963) Tierexperimentelle Untersuchungen zum Problem Kapillarpermeabilität unter Verwendung von Flavonoiden und Radioisotopen. Zbl f Veterinärmedizin 7: 599–649
6. Graebner HF, Derichsweiler P, Barth G (1973) Rasch ablaufende Erholung radiogener Permeabilitätsänderung an der Subkutis nach örtlicher Bestrahlung und deren Beeinflussung durch Rutin. Strahlentherapie 146:226–240
7. Wanderka H (1981) Prüfung des Phytotherapeutikums "Fagorutin" am künstlich erzeugten Stauungsödem. Z Phytotherapie 22:225–233
8. Schiller AA (1951) Mechanism of action of vitamin P flavonoid (Rutin) on the cutaneous circulation. Am J Physiol. 165: 293–305
9. Clark WG, Geissman TA (1949) Potentiation of effects of epinephrine by flavonoid ("vitamin P"-like) comounds. Relation of structure to activity. J Pharmacol Exp Ther 95: 363–381
10. Afanasev IB, Dorozhko AI, Brodskii AV, Kostyuk A Potapovitch AI (1989) Chelating and free radical scavenging mechanisms of inhibitory action of rutin and quercetin in lipid peroxidation. Biochem Pharmacol 38:1763–1769
11. Wojcicki J, Gonet B, Dabrowska-Zamojcin S, Juzwiak L, Samochowiec L, Tustanoweski S (1994) Effect of buckwheat extract on free radical generation. Planta Medica (in press)
12. Balmer A, Limoni C (1983) Placebo-kontrollierter klinischer Doppelblindversuch mit Venoruton bei der Behandlung von Zeichen und Symptomen der chronisch-venösen Insuffizienz (CVI). In: Voelter W, Jung G (eds) *O*-(*β*-Hydroxyethyl)-rutoside: Neue Ergebnisse in Experiment und Klinik. Springer, Berlin Heidelberg New York
13. Kranendonk SE, Koster AM (1993) A double-blind clinical trial of the efficacy and to lerability of *O*-(*β*-hydroxyethyl)-rutosides and compression stocking in the treatment of leg oedema and symptoms following surgery for varicose veins. Phlebology 8:77–81
14. MacLennan WJ, Wilson J, Rattenhuber V, Dikland WJ, Vanderdonckt J, Moriau M (1994) Hydroxyethylrutosides in elderly patients with chronic venous insufficiency: its efficacy and tolerability. Gerontology 40:45–52
15. Schilcher H, Patz B, Schimmel K (1990) Klinische Studie mit einem Phytopharmakon zur Behandlung von Mikrozirkulationsstörungen. Ärztezeitschrift für Naturheilverfahren 11: 819–826
16. Baisch F, Plath G, Buckey J, Blomqvist G, Klein M, Schmitt R (1990) Ultrasound measurement techniques for determination of limb volume. Annual International Conference of the IEEE Engineering in Medicine and Biology Society 12: 0285–0286
17. Jünger M, Hahn U, Bort S, Geiger B, Hahn M (1982) Distribution of microangiopathy in chronic venous insufficiency. Int J Microcirc Clin Exp (Suppl) 11:109
18. Baer-Suryadinata C, Bollinger A (1985) Transcapillary diffusion of Na-fluorescein by a "large window technique" in skin areas of forefoot. Int J Microcirc Clin Exp 4:227–228
19. Jung F, Kiesewetter H, Nüttgens HP, Toonen H, Müller G (1992) Interactive image processing system for cutaneous video capillary microscopy: methodology and clinical application. Biomed Optronics 1:27–35
20. Luetolf O, Bull RH, Bates DO, Mortimer PS (1993) Capillary underperfusion in chronic venous insufficiency: a cause for leg ulceration ? Br J Dermatology 128:249–254
21. Jünger M, Hahn U, Bort S, Klyscz T, Hahn M, Rassner G (1994) Bedeutung der kutanen Mikroangiopathie für die Entstehung von Stauungsdermatosen bei chronischer Veneninsuffizienz (CVI). Wien Med Wschr 144:206–210
22. Leu A J, Franzeck UK, Bollinger A (1991) Mikroangiopathie bei chronisch-venöser Insuffizienz (CVI). Therapeutische Umschau 48:715–721
23. Schilcher H, Müller A (1981) *Fagopyrum esculentum* Moench – a new pharmaceutically useful flavonoid plant. Proc Int Bioflav Symp:523–528
24. Landgraf H, Vanselow B, Schulte-Huermann D, Mülmann MV, Bergau L (1994) Economy class syndrome: Rheology, fluid balance, and lower leg edema during a simulated 12-hour long distance flight. Aviat Space Environ Med 5:930–935
25. Marshall M, Loew D (1994) Diagnostische Maßnahmen zum Nachweis der Wirksamkeit von Venenpharmaka. Phlebologie 23:85–91
26. Rudofski G, Diehm C, Gruß JD, Hartmann M, Schultz-Ehrenburg HK, Bisler H (1990) Chronisch venöse Insuffizienz: Behandlung mit Ruscus-Extrakt und Trimethylhesperidinchalkon. MMW 132:205–210
27. Küster HH (1983) Offene Studie mit Venoruton-intens bei Patienten mit chronisch venöser Insuffizienz. In: Voelter W, Jung G (eds.), *O*-(*β*-Hydroxyethyl)-rutoside: Neue Ergebnisse in Experiment und Klinik. Springer, Berlin Heidelberg New York
28. Bergqvist D, Hallböök T (1983) Die Wirkung von *O*-(*β*-Hydroxyethyl)-rutosiden auf die Symptomatik bei Patienten mit chronisch-venöser Insuffizienz in einer schwedischen Gemeinde – Ein Doppelblindversuch. In: Voelter W, Jung G (eds) *O*-(*β*-Hydroxyethyl)-rutoside: Neue Ergebnisse in Experiment und Klinik. Springer, Berlin Heidelberg NewYork