Effect of Pycnogenol on the Healing of Venous Ulcers

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Background: Venous ulcers are common complications of chronic venous insufficiency that result in severe physical and mental suffering to patients. The oral administration of diosmin/hesperidin has been used as adjuvant therapy in the treatment of chronic venous insufficiency. The purpose of this study was to evaluate and compare the effect of pycnogenol and diosmin/hesperidin on the healing of venous ulcers.

Methods: This longitudinal, prospective, randomized clinical trial was conducted with 30 adult patients with venous ulcers from a vascular surgery outpatient clinic of a university hospital. The patients were randomly allocated to 2 groups: Group 1 ($n = 15$) was treated with pycnogenol (50 mg orally, 3 times daily) and Group 2 ($n = 15$) was treated with diosmin/hesperidin (450/50 mg orally, twice daily). They were assessed every 15 days for 90 days. During follow-up visits, photo-documentation was obtained and the ulcer area and circumference of the affected limb were measured. Friedman's test and Mann–Whitney test were used to compare ulcer areas and circumference of affected limbs between and within groups at different time points. The level of significance was set at 5% ($P < 0.05$) for all tests.

Results: Both the pycnogenol and diosmin/hesperidin treatments had a similar effect on the healing of venous ulcers and led to a significant decrease in the circumference of affected limbs ($P < 0.0001$).

Conclusion: The results suggest that pycnogenol has an adjuvant effect on the healing of venous ulcers, similar to diosmin/hesperidin.

INTRODUCTION

Chronic venous disease has a high prevalence, affecting about 30% of the adult population worldwide. It can also be found among 20-year-olds and is highly prevalent in women at a ratio of women to man of 4:1. The main initial anatomical change associated with chronic venous disease is the dilation of vein walls with formation of varicose veins.[1–4]

Chronic venous insufficiency corresponds to the later stages of chronic venous disease and is mainly characterized by skin changes. Complications associated with chronic venous insufficiency may lead to increased loss of workdays, early retirement, and high costs in secondary care, framing this condition as a public health problem. It is estimated that 1% of the global working population has complications related to chronic venous insufficiency,

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including varicose hemorrhage, thrombophlebitis, and especially ulcerations, which are the most serious complications, resulting in severe physical and mental suffering to the patient.[5–8] Venous ulcers correspond to 70% of all leg ulcers. About 1.5% of adults throughout the world are expected to develop this complication. It has been estimated that 30% and 78% of healed venous ulcers recur within the first year and after 2 years, respectively.[5–8]

Phlebotropic drugs are used in the symptomatic treatment of chronic venous disease in the lower limbs and act on the microcirculatory system, especially on capillary permeability.[9,10] Some phlebotropic drugs are effective against symptoms of chronic venous disease. Micronized purified flavonoid fraction, consisting of 90% micronized diosmin (synthetized from hesperidin) and 10% flavonoids expressed as hesperidin, acts by reducing endothelial activation, edema, and the inflammatory response to the leukocyte–endothelial adhesion cascade. The combination diosmin/hesperidin has shown to be active and effective in different pathophysiological and biochemical pathways leading to chronic venous hypertension at all clinical stages, especially in improving venous tone. This medication has also been found efficacious in protecting endothelial cells and the extracellular matrix against inflammatory chemical mediators.[11] Micronized diosmin/hesperidin has been reported to act as adjuvant to promote the rapid healing of venous ulcers.[12,13]

Pycnogenol is an extract of bark from the French maritime pine (*Pinus pinaster* Aiton subsp. *atlantica*) standardized to contain 70 ± 5% procyanidins, which have significant antioxidant activity and anti-inflammatory actions. It is administered orally in the treatment of chronic venous insufficiency and has shown to be very effective in relieving signs and symptoms of this disease, with a safety profile that allows its broad use as an herbal medication.[14,15] According to a previous study,[16] oral pycnogenol is superior to diosmin/hesperidin in alleviating the signs and symptoms of chronic venous insufficiency, and its topical use in varying concentrations has also shown to be effective.[17,18]

Few studies were found in the PubMed, MEDLINE, Cochrane Library, EBSCO, LILACS, and SciELO databases regarding the effect of pycnogenol in patients with venous ulcers. The search for a medication that acts on the microcirculation decreasing edema and that could be used in the prevention and adjuvant treatment of venous ulcers justifies this study. Pycnogenol is an herbal medicine with a high safety profile and low degree of sensitivity or adverse effects.

The aims of this study were to evaluate and compare the effect of pycnogenol and diosmin/hesperidin on the healing of venous ulcers.

MATERIALS AND METHODS

This is a longitudinal, prospective, analytical, interventional, randomized clinical trial conducted with 30 adult patients with venous ulcers from the Vascular Surgery Outpatient Clinic of the Samuel Libânio General Hospital (Hospital das Clínicas Samuel Libânio, HCSL), Pouso Alegre, MG, Brazil. The study was approved by the Research Ethics Committee of the Sapucaí Valley University (UNIVÁS) (approval number 303.386) and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all patients before their inclusion in the study and after the procedures had been fully explained.

Eligibility criteria included adult patients of both genders, with open venous ulcers Class C6 according to the Clinical–Etiology–Anatomy–Pathophysiology classification, who signed the written informed consent and agreed to participate in follow-up assessments every 15 days during 90 days, and to receive only the proposed treatment, not taking other medications that could affect treatment outcome.

Exclusion criteria were infectious or immunosuppressive diseases. Patients participating in other clinical study that could affect the treatment outcome were not included. Also, patients who used dressings different from those of the study, who failed to attend the scheduled visits, who took other phlebotropic drugs, and who dropped out from the study were excluded from the sample.

Setting the significance level α at 5% and the power of the sample at 90%, the sample size of 15 patients in each group would be required to detect this difference. Therefore, a total of 30 consecutive patients who met study criteria were selected for the study. The patients were randomly allocated to 2 groups: Group 1 ($n = 15$) was treated with pycnogenol (50 mg orally, 3 times daily; Laboratório Farmoquímica S/A, Rio de Janeiro, Brazil), and Group 2 ($n = 15$) was treated with diosmin/hesperidin (450/50 mg orally, twice daily; Daflon 500, Servier do Brasil, Rio de Janeiro, Brazil). All patients received the same type of wound dressing.

The allocation sequence was generated using a computer-generated randomization chart (http://www.randomization.com) and concealed in sequentially numbered, opaque, sealed envelopes until the patient was randomized. The sealed envelopes were held by the principal investigator.

After inclusion in the study, medical history, family history, lifestyle habits, and anthropometric measurements were obtained, and clinical examination was performed to detect symptoms of venous insufficiency, including heavy pain, fatigue, pruritus, and leg edema. All patients were assessed for the presence of arterial, venous, and lymphatic changes in the upper and lower limbs, cervical region, and abdomen. Palpation and auscultation were performed and vascular dilations, pulsatility changes, thrills, and murmurs were detected, as well as the existence of ulcerations, trophic changes in the skin, and alterations in skin color and perfusion.

All patients underwent color Doppler ultrasound (GE Vivid 3, General Electric Ultrasound, Milwaukee, WI) using 7.5-MHz linear transducers to assess the anatomical location of functional changes in the superficial and deep venous systems.

Daily dressing changes and wound debridement of venous ulcers were performed in all patients at the Nursing Care and Education Center of the HCSL. After cleaning the ulcers with running water and chlorhexidine as a degerming agent, a debriding ointment was used in the wound bed, oil containing essential fatty acids was applied to hydrate the skin surrounding the wound bed, the dressing was covered with gauze, and the limb was wrapped with crepe bandage. Mechanical debridement was carried out when necessary to remove devitalized tissue, fibrin deposits, and debris from the wound bed. Patients were treated with relative rest, avoiding prolonged standing.

The same investigator assessed all participants at follow-up visits every 15 days for 90 days or until the ulcer was healed. During the follow-up visits, photo-documentation was obtained and the ulcer area and circumference of the affected limb were measured. Photographs were taken 10 cm from the ulcer, without zoom, using a digital camera (DSC-W90, Cybershot 8.1 Megapixel; Sony, Tokyo, Japan). Ulcer area was measured with the Image Tool version 3.0 software (University of Texas Health Science Center, San Antonio, TX). The circumference of the affected limb was measured at the proximal third (distal portion of the tibial tuberosity) and distal third of the ankle (adjacent to the medial malleolus) to evaluate the effects of the medication on edema.

Statistical Analysis

The Mann–Whitney test was used for comparisons between groups. The Friedman analysis of variance was applied for comparisons within groups over time. A chi-squared test was carried out to assess associations between variables. Fisher's exact test was used for small numbers, when the chi-squared test was inappropriate.

All statistical tests were performed at a significance level of 0.05 ($P < 0.05$).

RESULTS

Thirty patients were included in the study, but 2 of them (one from each group) were lost to follow-up and 1 patient from Group 2 took other phlebotropic drugs. All 3 patients were excluded from the study. The statistical analysis was based on a final sample of 27 patients, of whom 14 were allocated to Group 1 (pycnogenol treatment) and 13 were allocated to Group 2 (diosmin/hesperidin treatment).

Of the 27 remaining patients, 22 (81.5%) were women and 23 (85.2%) were Caucasians. The 2 groups were similar in age and body mass index (BMI), as shown in Table I. Overall, 22 (81.42%) patients had hypertension, 11 (40.7%) had ulcer history, 7 (25.9%) had diabetes mellitus, 4 (14.8%) were obese (BMI > 30), and 2 (7.4%) had history of cardiopathy. No significant differences were found in the distribution of the clinical characteristics of patients between groups (Table I).

The mean length of ulcer history was 34 months (range 20 days to 15 years) for the whole sample. Patients in Group 1 (pycnogenol) reported a mean length of ulcer history of 7.35 months (median 5.5 months), and those in Group 2 (diosmin/hesperidin) reported a mean length of 23.94 months (median 7.0 months). This difference was attributed to a patient in Group 2 with an ulcer history of 180 months; however, when excluding this patient, the length of ulcer history was similar in both groups.

No significant between-group differences were found in the results of color Doppler ultrasound (Table I).

There was a significant decrease in ulcer area ($P < 0.001$) over time within both treatment groups during the study period (Tables II and III). A significant decrease in ulcer area from baseline was observed earlier in patients treated with pycnogenol (after 45 days of treatment) than in patients treated with diosmin/hesperidin (after 60 days of treatment). Patients in Group 1 showed a trend toward a more favorable treatment effect on ulcer healing compared with those in Group 2 (Fig. 1), but

Table I. Age, body mass index, clinical characteristics, and color Doppler ultrasound results according to group

Variables	Group 1: pycnogenol ($n = 14$)	Group 2: diosmin/hesperidin ($n = 13$)	Mann–Whitney test
Age (years)			
Median	55	63	$P = 0.560$
Mean	57.85	60.51	$z = 0.58$
SD	9.45	12.03	
BMI (kg/m^2)			
Median	26.43	26.44	$P = 0.9227$
Mean	26.44	27.29	$z = 0.10$
SD	4.30	5.45	
Clinical characteristics			Fisher's test
Systemic arterial hypertension (%)	71	69	$P = 0.6483$
Ulcer history (%)	36	46	$P = 0.7035$
Diabetes mellitus (%)	14	31	$P = 0.6483$
Obesity (%)	7	23	$P = 0.3259$
Cardiopathy (%)	7	8	$P = 1.0$
Color Doppler ultrasound			Chi-squared test
Reflux in collateral/perforating veins (%)	29	23	$P = 0.8496$
Reflux in saphenous veins (%)	50	46	$\chi^2 = 0.326$
Reflux in the deep venous system (%)	21	31	
Total (%)	100	100	

For Mann–Whitney test, Fisher's test, and chi-squared test, $P < 0.05$.
SD, standard deviation.

without significant differences between groups at all time points within the 90-day study period.

For both treatment groups, there was a significant decrease over time in the circumference of the affected limb measured at both the proximal (Group 1, $P < 0.0001$; Group 2, $P = 0.0126$) and distal (Group 1, $P = 0.0023$; Group 2, $P = 0.0130$) thirds of the ankle (Table IV). A significant decrease from baseline in the circumference of the proximal third of the ankle was observed earlier in patients treated with pycnogenol (after 45 days of treatment) than in patients treated with diosmin/hesperidin (after 90 days of treatment). No significant between-group differences in the circumference of the proximal and distal thirds of the ankle were observed at all time points within the 90-day study period.

Changes in the circumference of the proximal and distal thirds of the ankle over time in both groups are shown in Figures 2 and 3.

DISCUSSION

The healing of venous ulcers is a great challenge for patients and health professionals. The numerous treatments available are often ineffective[19,20] and, even in cases where the ulcer heals, recurrence rates tend to be high.[21] Surgical treatment is the most effective option and should always be used in patients with venous ulcers caused by varicose veins, usually occurring in the lower limbs. However, in some countries, most patients have only access to the public health service, which unfortunately is commonly characterized by long waiting periods for treatment, leading to the perpetuation and consequent worsening of the disease.

Clinical measures including the use of dressings and elastic or inelastic compression therapy combined with postural changes are especially important in the treatment of venous ulcers of different etiologies, such as deep vein thrombosis, congenital or acquired arteriovenous fistulas, and venous malformation, because complete wound healing is difficult to achieve in these cases. Thus, treatments or adjunct therapies that can improve or accelerate the healing process are essential to relieve the suffering of such patients.

The effective relief of symptoms of ulcers caused by chronic venous insufficiency using natural and

Table II. Ulcer area at different time points for Group 1 (pycnogenol)

Patient no. ($n = 14$) Ulcer area (cm^2)	Days of treatment						
	Baseline	15	30	45	60	75	90
1	15.15	14.24	14.11	14	13.87	13.18	13.05
4	5.72	5.43	5.38	5.35	5.29	5.14	5.09
5	12.08	11.54	10.9	9.85	8.74	7.35	6.28
6	23.04	22.75	22.38	22.07	21.82	21.6	20.96
9	9.05	8.45	8.04	7.26	6.54	6.35	5.8
12	5.84	5.16	4.35	3.12	2.4	1.76	0
14	1.14	0.93	0.47	0	0	0	0
15	4.34	3.75	2.98	2.07	1.24	0	0
17	2.37	1.8	1.71	1.19	1.02	0	0
19	3.16	2.55	1.54	0.12	0	0	0
23	1.26	1.56	1.15	0.92	0.97	0.98	0.62
25	3.34	3.14	2.92	2.75	2.4	2.16	1.78
26	4.78	4.35	3.78	3.24	2.98	2.7	2.54
Mean	7.02	6.58	6.13	5.53	5.17	4.70	4.31
Median	4.78	4.35	3.78	3.12	2.4	2.16	1.78
Friedman ANOVA	$\chi^2 = 72.94$, $P < 0.0001$						

ANOVA, analysis of variance.

Table III. Ulcer area at different time points for Group 2 (diosmin/hesperidin)

Patient no. ($n = 13$) Ulcer area (cm^2)	Days of treatment						
	Baseline	15	30	45	60	75	90
2	15.55	14.86	14.7	14.85	14.6	14.58	14.65
3	4.05	3.73	3.46	3.27	2.9	2.64	2.38
7	18.14	18.02	17.93	18.24	18.1	17.98	17.84
8	8.09	7.34	5.97	4.78	2.34	1.92	0
10	16.74	17.98	17.35	16.8	15.42	14.76	13.47
11	9.15	8.74	8.3	7.98	7.59	7.15	6.74
13	1.38	1.31	0.64	0	0	0	0
16	3.98	3.04	2.35	1.94	0.95	0	0
18	3.32	3.07	2.4	2.03	1.72	1.75	1.54
20	0.19	0.23	0.22	0.22	0.8	2.87	1.34
21	1.11	0.54	0.54	0.83	2.43	1.82	1.34
22	1.29	1.08	0.76	0.38	0.32	0.34	0
24	1.37	0.75	0.68	0.61	0.26	0.49	0.4
27	10.48	9.74	9.18	7.76	6.48	5.96	5.38
Mean	6.77	6.45	6.03	5.69	5.27	5.16	4.64
Median	4.01	3.4	2.93	2.65	2.38	2.28	1.44
Friedman ANOVA	$\chi^2 = 37.65$, $P < 0.0001$						

ANOVA, analysis of variance.

synthetic drugs is an attractive and desirable goal that has given rise to various studies.[22,23] Micronized diosmin/hesperidin is a phlebotropic drug widely used in the treatment of venous insufficiency from the first clinical symptoms. At present, it is the phlebotropic drug most studied and used and, according to some studies and guidelines, has Level 1B evidence regarding its adjuvant effect on the healing of venous ulcers.[4] Pycnogenol is an herbal medicine easily accessible and with a low degree of sensitivity or adverse effects that has shown significant results in the treatment of venous insufficiency.[15]

The social and clinical characteristics of patients participating in this study, such as gender, age, BMI, ethnicity, and risk factors, are consistent to those from previous studies. The presence of comorbidities among the participants of the study was

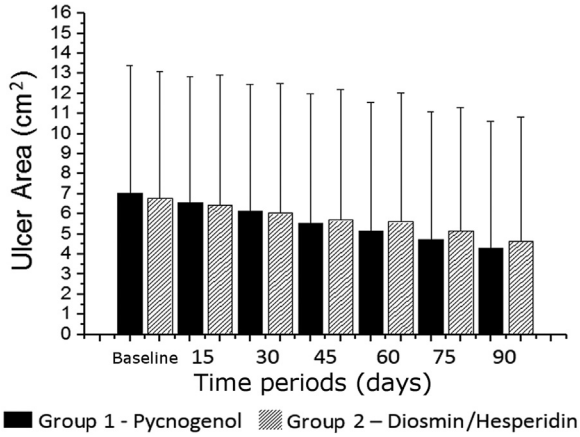

Fig. 1. Frequency distribution of ulcer area at different time points for both groups.

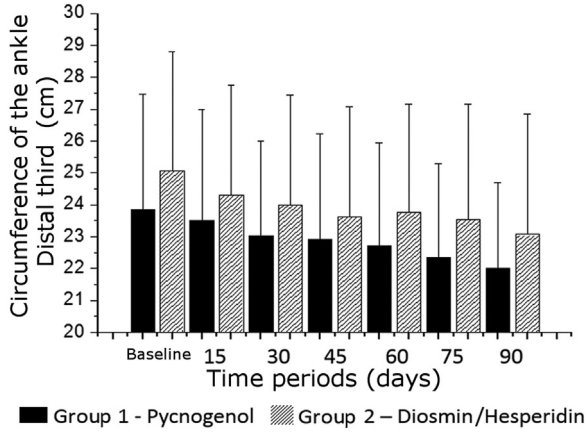

Fig. 2. Circumference of the proximal third of the ankle at different time points for both groups.

Table IV. Circumference of the proximal and distal thirds of the ankle at different time points for both groups

Group	Circumference (cm)	Days of treatment						
		Baseline	15	30	45	60	75	90
Proximal third								
Group 1 ($n = 14$)	Mean	36.64	35.71	35.14	34.67	34.71	34.14	33.85
	Median	36.5	35.5	35	33.75	34	33.5	33
	Friedman ANOVA $\chi^2 = 33.17$, $P < 0.0001$							
Group 2 ($n = 13$)	Mean	37.46	36.53	36.07	35.61	35.61	35.53	35.38
	Median	37	37	35	35	35	35	35
	Friedman ANOVA $\chi^2 = 16.22$, $P = 0.0126$							
Distal third								
Group 1 ($n = 14$)	Mean	23.85	23.5	23.03	22.92	22.71	22.35	22
	Median	24	23.5	22.75	22.5	22	21.5	21
	Friedman ANOVA $\chi^2 = 20.41$, $P = 0.0023$							
Group 2 ($n = 13$)	Mean	25.07	24.30	24	23.61	23.76	23.53	23.07
	Median	24	24	24	23	23	23	23
	Friedman ANOVA $\chi^2 = 16.15$, $P = 0.0130$							

ANOVA, analysis of variance.

expected because all patients were 40 years of age or older, which is an age group with a high prevalence of comorbid conditions. Various patients had a history of recurrent ulcers, which is consistent with the natural development of venous ulcers, characterized by frequent recurrence. Ulcer recurrence was possibly associated with nonadherence to the elastic compression therapy after ulcer healing and a long waiting period without access to surgery to treat venous insufficiency.[24–26]

The results indicated that diosmin/hesperidin and pycnogenol, when used as adjuvant treatments, have a similar effect on the healing of venous ulcers. They also showed that these drugs significantly decreased edema in limbs affected by ulceration. A meta-analysis found a significant increase in healing rates of venous ulcers and decrease in edema in patients with chronic venous disease treated with diosmin/hesperidin, and also a better response to treatment in patients who received the phlebotropic drug combined with elastic compression.[27,28]

Patients in Group 1 showed a significant decrease from baseline in ulcer area and in the circumference of the proximal third of the ankle of the affected limb after 45 days of pycnogenol treatment, whereas patients in Group 2 showed significant improvement in the same parameters from baseline after 60 days of treatment with diosmin/hesperidin. This suggests an early effect of the pycnogenol

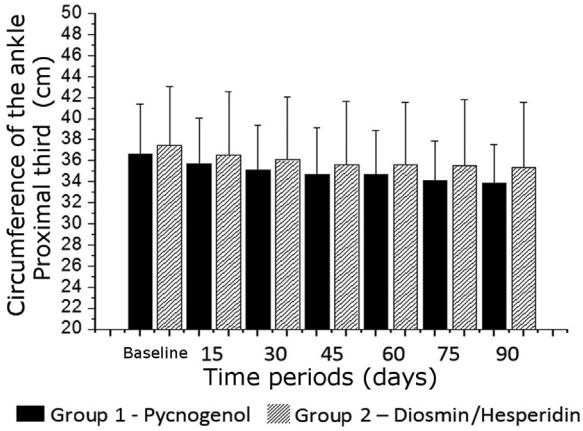

Fig. 3. Circumference of the distal third of the ankle at different time points for both groups.

therapy, which may relieve the symptoms of patients with venous ulcer in a shorter period of time compared with the treatment with diosmin/hesperidin. However, no significant differences in reduction of ulcer area and circumference of the proximal third of the ankle were observed between groups at the different time points, possibly due to the small size of the study sample.

Pycnogenol as an herbal drug has a higher safety profile and lower degree of sensitivity or adverse effects compared with synthetic drugs, such as diosmin/hesperidin.[29] In addition, the cost for a 1-month supply of pycnogenol is equivalent to that of diosmin/hesperidin. Pycnogenol is easily accessible, may be prepared by a compounding pharmacy at lower costs, and our findings indicate that it may be used as a novel adjunct to the many existing protocols for the management of patients with venous ulcers. The benefits arising from the use of herbal medicines are numerous and related mainly to efficiency, low cost, and reduced adverse effects, as well as stimulation of a healthy lifestyle. Herbal medicines allow a better use of natural resources, besides promoting the country's economic, scientific, and cultural development.

Although a placebo-controlled clinical trial of pycnogenol would be desirable, the Institutional Ethics Committee would not approve a study failing to offer benefits to a group of patients when it was possible to compare pycnogenol with a medication having Level 1B evidence for the same purpose.

The small sample size was the major limitation of this study. Further studies with a larger number of patients and involving multiple centers are necessary to confirm the beneficial effects of pycnogenol on the healing of venous ulcers and extend our results.

CONCLUSION

The results indicated that pycnogenol has an adjuvant effect on the healing of venous ulcers equivalent to that of diosmin/hesperidin.

REFERENCES

1. Meissner MH, Gloviczki P, Bergan J, et al. Primary chronic venous disorders. J Vasc Surg 2007;46:54S–67S.
2. Meissner MH, Moneta G, Burnand K, et al. The hemodynamics and diagnosis of venous disease. J Vasc Surg 2007;46:4S–24S.
3. Maffei FHA, Lastória S, Yoshida WB, et al. Insuficiência venosa crônica diagnóstico e tratamento clínico. In: Silva MC ed. Doenças Vasculares Periféricas. 4th ed. Rio de Janeiro: Medsi, 2008. pp 1804–14.
4. O'Donnell TF Jr, Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum. J Vasc Surg 2014;60:3S–59S.
5. Fowkes FG, Evans CJ, Lee AJ. Prevalence and risk factors of chronic venous insufficiency. Angiology 2001;52:S5–15.
6. Briggs M, Closs SJ. The prevalence of leg ulceration: a review of the literature. EWMA J 2003;3:14–20.
7. Bergan JJ, Schmid-Schönbein GW, Smith PD, et al. Chronic venous disease. N Engl J Med 2006;355:488–98.
8. Mayer W, Jochmann W, Partsch H. Varicose ulcer: healing in conservative therapy. A prospective study. Wien Med Wochenschr 1994;144:250–2.
9. Gohel MS, Davies AH. Pharmacological agents in the treatment of venous disease: an update of the available evidence. Curr Vasc Pharmacol 2009;7:303–8.
10. Collins L, Seraj S. Diagnosis and treatment of venous ulcers. Am Fam Physician 2010;81:989–96.
11. Coleridge Smith PD. From skin disorders to venous leg ulcers: pathophysiology and efficacy of Daflon 500 mg in ulcer healing. Angiology 2003;54:S45–50.
12. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. Drugs 2003;63:71–100.
13. Coleridge-Smith P, Lok C, Ramelet AA. Venous leg ulcer: a meta-analysis of adjunctive therapy with micronized purified flavonoid fraction. Eur J Vasc Endovasc Surg 2005;30:198–208.
14. Blazsó G, Gábor M, Rohdewald P. Antiinflammatory activities of procyanidin-containing extracts from *Pinus pinaster* Ait. after oral and cutaneous application. Pharmazie 1997;52:380–2.
15. Gulati OP. Pycnogenol® in chronic venous insufficiency and related venous disorders. Phytother Res 2014;28:348–62.
16. Cesarone MR, Belcaro G, Rohdewald P, et al. Comparison of Pycnogenol and Daflon in treating chronic venous insufficiency: a prospective, controlled study. Clin Appl Thromb Hemost 2006;12:205–12.
17. Blazsó G, Gábor M, Schönlau F, et al. Pycnogenol accelerates wound healing and reduces scar formation. Phytother Res 2004;18:579–81.
18. Belcaro G, Cesarone MR, Errichi BM, et al. Venous ulcers: microcirculatory improvement and faster healing with local use of Pycnogenol. Angiology 2005;56:699–705.
19. Bergqvist D, Lindholm C, Nelzén O. Chronic leg ulcers: the impact of venous disease. J Vasc Surg 1999;29:752–5.

20. Bryant RA, Nix DP. Acute & Chronic Wounds: Current Management Concepts. 4th ed. St. Louis, MO: Mosby, 2012.
21. Robertson L, Evans C, Fowkes FG. Epidemiology of chronic venous disease. Phlebology 2008;23:103–11.
22. van Gent WB, Wilschut ED, Wittens C. Management of venous ulcer disease. BMJ 2010;341:c6045.
23. Word R. Medical and surgical therapy for advanced chronic venous insufficiency. Surg Clin North Am 2010;90:1195–214.
24. Nelson EA, Bell-Syer SE, Cullum NA. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev 2000;4:CD002303.
25. Nicolaides AN, Allegra C, Bergan J, et al. Management of chronic venous disorders of the lower limbs: guidelines according to scientific evidence. Int Angiol 2008;27:1–59.
26. Abbade LP, Lastória S, de Almeida Rollo H, et al. A sociodemographic, clinical study of patients with venous ulcer. Int J Dermatol 2005;44:989–92.
27. Smith PC. Daflon 500 mg and venous leg ulcer: new results from a meta-analysis. Angiology 2005;56:S33–9.
28. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53:2S–48.
29. Cesarone MR, Belcaro G, Rohdewald P, et al. Improvement of signs and symptoms of chronic venous insufficiency and microangiopathy with Pycnogenol: a prospective, controlled study. Phytomedicine 2010;17:835–9.