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Review

Treating intermittent claudication with Tibetan medicine Padma 28: Does it work?

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Abstract

Herbal drugs are being increasingly used in medical practice, often without appropriate scrutiny of their safety and efficacy. The medicinal product Padma 28 is a fixed combination with Tibetan origin, used in Europe since the 1960s for the symptomatic treatment of circulatory disorders, including those of peripheral arterial occlusive disease (PAOD). We have conducted an analysis of all available data on this herbal drug from published literature as well as from original data we obtained from contacting the authors of published papers, reports and the manufacturer. A total of 19 trials have reported on 2084 patients to date, 444 of whom were in six controlled clinical studies on PAOD. A meta-analysis of five trials showed Padma 28 to increase walking distance by >100 m in 18.2% of the patients with verum, versus 2.1% with placebo ($P < 0.001$; odds ratio: 10 [95% CI 3.03, 33.33]; RR: 0.12; number needed to treat = 6.2). The safety profile appears to be favourable. Available evidence shows that Padma 28 provides significant relief from PAOD-related symptoms (i.e. walking distance), probably of the same order of magnitude as other employed medications. However, larger confirmatory RCTs are desirable.

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Keywords: Peripheral arterial occlusive disease (PAOD); Maximum walking distance; Tibetan herbal drug; Phytotherapy; Meta-analysis; CAM; Padma 28

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1. Introduction

The most common symptom of peripheral arterial disease is intermittent claudication [1]. Its prevalence increases with age, affecting about 2.5% of those aged <60 years, up to 8.3% of those aged 60–70 years and can reach 18.8% of those aged 70 years or more [2]. Peripheral arterial occlusive disease (PAOD) is usually due to generalised atherosclerosis leading to occlusion of the leg arteries; claudication and the associated trophic lesions being ischaemic manifestations. At walking, the patient locally incurs a major oxygen debt with a metabolic breakdown of the muscle that can be compensated by rest, thus reducing the metabolic demand, although at the cost of producing reactive oxygen species (ROS). Both atherosclerosis and the damage induced by ischaemia-reperfusion are probably related to increased activity of ROS [3].

Atherosclerosis is a complex process, involving the accumulation of oxidised cholesterol, which causes a cascade of inflammatory processes, resulting in an unstable atherosclerotic plaque that ultimately ruptures. Many plants contain antioxidant constituents that can reduce low-density lipoprotein oxidation [4] and therefore should slow down the progression and/or prevent vascular disease. The “oxidative modification hypothesis” of atherogenesis is actively discussed [5], although many questions remain unanswered.

Acute extremity ischaemia and reperfusion initiates a complex inflammatory cascade that can result in injury to both the ischaemic extremity (local injury) and tissues outside the ischaemic field (distant injury). The pathogenesis of injury in sustained ischaemia involves the production of unstable intermediates during ischaemia and free radical production during reperfusion [6]. Several lines of evidence support the importance of the antioxidative status in the protection from ischaemic damage, e.g. protecting lower limb skeletal muscle during aortic reconstruction surgery [7], and after femorodistal bypass (lower incidence of systemic inflammatory response syndromes) [8]. Furthermore, significantly increased free-radical activity has been shown in patients with peripheral arterial disease undergoing balloon angioplasty [3] or with diabetes mellitus [9].

In the 8th century, Yuthog Yongten Gonpo compiled the four main standard texts, known as rGyud bzhi, which still form the basis of the Tibetan medicinal system called Sowa Rigpa. In later centuries Tibetan medicine spread to China, Mongolia and Eastern Siberia. In the 1960s, descendants of the Siberian physician Sul Tim Badma brought a collection of formulas to Switzerland. This included the fixed combination Padma 28, a mixture of 20 herbal drugs, a mineral and camphor, which have been used in circulatory problems and as an anti-inflammatory agent [10]. The constituents of Padma 28 [11] include terpenes, flavonoids, polysaccharides, saponines and tannins, and the medicine was registered in Switzerland in 1977 for symptomatic treatment of circulatory disorders. The product information approved by the Swiss Agency for

Therapeutic Products confirmed the efficacy of Padma 28 in PAOD (Fontaine Stage II) in 2002 [12]. In view of the use of Padma 28 in several other countries, it is our department’s aim to analyse the evidence concerning its efficacy and safety. The focus of the current work was to evaluate the current evidence of efficacy and safety of Padma 28 in the light of an ever-increasing use of herbal medicines in our daily practice, through a systematic meta-analysis of all published evidence and a report, rather than to explore its mechanism of action, and to highlight the shortcomings in our current knowledge of this herbal drug for the management of PAOD.

2. Materials and methods

2.1. The review protocol

To perform a systematic review of Padma 28, we conducted the following search strategy: (1) search period from inception to June 2004; (2); the databases to be searched were: TOXLINE, MEDLINE, HealthSTAR, The Cochrane Collaborative Library, US National Library of Medicine (PubMed), AMED, Embase, AIDSLINE and CANCERLIT; (3) search terms were “Padma 28, herbal, peripheral arterial disease, Tibetan medicine, phytotherapy”. Additionally, we checked reference lists from pertinent articles obtained from the search lists for secondary papers and multiple publications of the same trial, and experts in the area as well as the manufacturer.

Regarding eligibility criteria, the protocol based the selection of studies on De Backer’s [13] minimum criteria for evaluation of studies of drugs in intermittent claudication, namely (a) randomised placebo-controlled trial; (b) patients with Fontaine stage II disease; (c) pain-free and/or maximum walking distance measured by standardised treadmill test; (d) treatment duration of at least 12 weeks; (e) additionally a sample size of at least 30 patients. Although all trials were conducted prior to these criteria were in place, we still felt it important to apply them as they give an idea of a more disease specific quality ranking. In case of multiple publications of the same study, we selected the one which had been published in a peer-review journal and if these were multiples we chose the most recent publication.

All trials were to be summarised independently by one reviewer according to a pre-established non-validated tabulated format that included: full reference, quality rating, stage of PAOD, demographic data, description of treatments groups, mean haematology and biochemistry laboratory data on admission and end of trial, end-points (maximum and/or pain-free treadmill walking distance) and adverse events. Trials in non-PAOD patients were to be excluded. The data summaries were to be verified and approved by the other authors who consented and agreed with the tabulated data.

2.2. Statistics

The protocol followed the guidelines of the Cochrane Collaboration Handbook for reviews [14]. The studies were re-analysed following current standards and reported on an intention-to-treat (ITT) basis, whenever possible. Appropriate software [15] was employed for the analysis of the results. Analysis of treatment groups was to include odds ratio and risk difference according to Peto Mantel-Haenszel [16]; and sensitivity analyses were performed in the event of significant results. In the case of continuous data, pooling as weighted mean difference was used. The Last Observation Carried Forward method was employed for missing values [17]. Testing

was to be two-sided, the significance level set at 5%, non-significance at 10% and values in between were set as trends.

3. Results

We found 19 ‘hits’ for unique studies with reliable data, consisting of pharmacological and clinical trials (Fig. 1). These trials reported a total of 2084 patients, which was a higher overall figure than we had expected and highlights the extent of use of this treatment and amply justified our aim to undertake a critical review of the evidence in PAOD. Of these, six trials [18–23] fulfilled the criteria for inclusion in

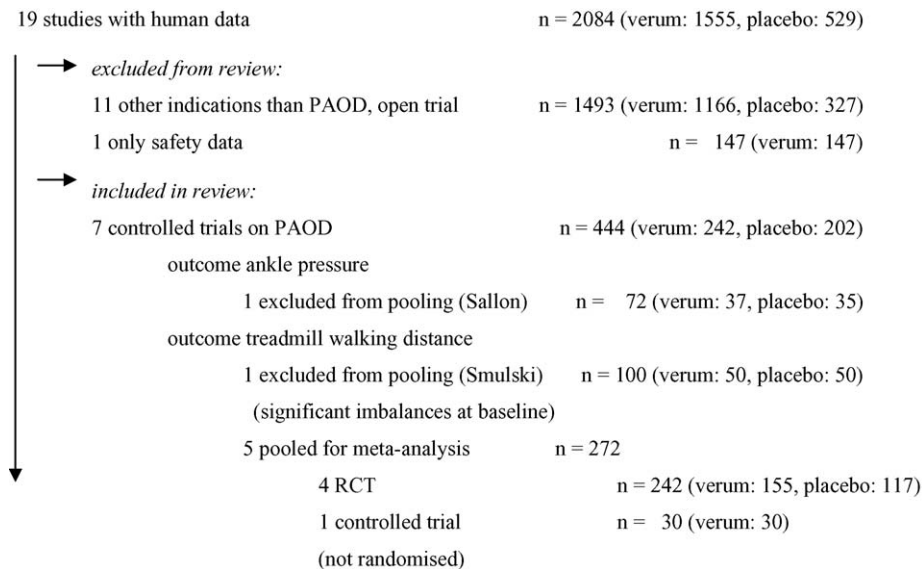


Fig. 1. Clinical studies with Padma 28.

Table 1
Main selection criteria and characteristics of Padma 28 trials prior to re-analysis

	References						
	Schröder et al. [18]	Drabaek et al. [22]	Samochowiec et al. [19]	Samochowiec et al. [24]	Sommoggy and Schleicher [20]	Smulski and Wojcicki [21]	Sallon et al. [23]
Double-blind, parallel group	Yes	Yes	Yes	No	Yes	Yes	Yes
Run-in period (weeks)	2	No	2	2	2	2	No
Steady-state on treadmill	Yes	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	No
Exclude other limiting factors	Yes	Yes	Not recorded	Not recorded	Yes	Yes	Not recorded
Treatment duration (months)	4	4	4	4	4	4	6
1–2 monthly assessments	Yes	Yes	Yes	Yes	Yes	Yes	No
Maximum walking distance ^a	Yes	Yes	Yes	Yes	Yes	Yes	No
Pain-free walking distance ^a	No	Yes	No	No	No	No	No
Brachial/ankle blood pressure	Yes	Yes	No	No	Yes	No	Yes
Multiple publications	No	Yes	No	No	No	Yes	No
Raw data obtained ^b	Yes	Yes	Partial	Partial	Partial	Partial	Partial
Re-analysed	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Main endpoint	Walking distance	Walking distance	Walking distance	Walking distance	Walking distance	Walking distance	Other ^c

^a Walking distances on standardised treadmill test.

^b Yes = full data provided for re-analysis; partial = key efficacy and safety data provided, but at least some secondary endpoint data missing.

^c The endpoints were: e.g. systemic and ankle blood pressures, ankle/brachial index and recovery time.

Table 2
Posology, age and anatomical occlusion site

Source reference	Dosing per capsule (mg)	Dosing per day	Mean age \pm S.D.	Location of occlusion		
				Iliac	Ileo-femoral	Femoro-distal
Schröder et al. [18]	380	3 \times 2	68 \pm 8	4.5%	7.5%	65.7%
Drabaek et al. [22]	382.15	2 \times 2	67 \pm 12	NA	NA	NA
Samochowiec et al. [19]	309	2 \times 2	59 \pm 6	72.0%	9.0%	19.0%
Samochowiec et al. [24]	309	2 \times 2	57 \pm 5	63.3%	6.7%	30.0%
Sommogy and Schleicher [20]	309	NA	64 \pm 11	NA	NA	NA
Smulski and Wojcicki [21]	309	2 \times 2	55 \pm 6	NA	NA	NA
Sallon et al. [23]	382.15	2 \times 2	74 \pm 10	18.1%	0.0%	81.9%

S.D., standard deviation; NA, not available or incomplete records.

the review (Table 1). In addition, one other trial [24] had a historical placebo-control (continuation study, used the first-phase placebo group as control) but fulfilled all other criteria and we were given access to the raw data, which contained good-quality treadmill walking distance information, and it was included. Thus, a total of 444 patients yielded data for the review and 272 for the meta-analysis, which was facilitated by the relative uniformity in dosage regimen, all in the range of 309–382 mg per capsule, two taken twice or three times a day (Table 2).

3.1. Pooled analysis of treadmill walking distances

The weight of evidence provided by the clinical studies with Padma 28 is limited by the fact that all studies were conducted before GCP guidelines were enforced for human studies. On the other hand, the raw data lists were available to us, which allowed us to re-analyse all studies and increased the plausibility of the results of the subsequent pooled analyses. In six of seven studies, maximum treadmill walking distance was the primary endpoint (Tables 1 and 4). For transparency,

Table 3
Main characteristics and critique of analysed studies

Schröder et al. [18]	Data partially published. Our re-analysis considered the 67 randomised patients with fully documented disease history and stable symptoms (maximum walking distance <250 m). Re-analysis of the raw data showed in the ITT collective ($n = 51$, after excluding of major protocol violations) a significant increase in the mean maximum treadmill walking distance ($P = 0.004$). The number of patients with improved maximum walking distance (>150 m) was significant ($P < 0.05$). Treatment did not affect ankle/brachial index (ABI). Global assessments by investigators were significantly favourable to verum
Drabaek et al. [22]	Thirty-six patients with documented medical history reported with stable treadmill walking distance (50–300 m) for at least 6 months and ABI of <0.85. In the ITT analysis, a significant improvement in verum-treated patients for pain-free walking distance ($P < 0.05$). Increase in the maximum walking distance (by >100 m) in 7 out of 18 verum-treated patients vs. 0 out of 18 placebo-treated patients ($P < 0.05$). The authors could not demonstrate any significant changes in ABI at any time
Samochowiec et al. [19]	One hundred PAOD patients randomised to placebo or verum, with at least 8-months' documented history and stable maximum walking distance of <150 m (Fontaine stage IIb). After unblinding, there were more patients with cardiovascular diseases in the verum group and more patients with hyperlipidaemia on placebo; the authors considered the imbalances were evened out. The study does not provide information about blinding. Re-analysis showed a greater mean maximum walking distance by +93% on verum, while walking distance increased by >100 m in 18% of the verum patients vs. 0% of the placebo patients ($P < 0.01$). The authors also describe a drop in systolic and in diastolic blood pressure by -7.91 ± 9.57 and -5.73 ± 5.67 mmHg, respectively
Samochowiec et al. [24]	Open comparison using placebo-treated patients from previous series [19] as historic controls and 30 patients also from the previous series who agreed to be re-treated after a 2-month washout interval. Re-analysis confirmed a significant increase in mean maximum walking distance ($P < 0.01$) but not for the proportion of patients with increases of walking distances by more than 100 m
Sommogy and Schleicher [20]	Thirty-nine patients with PAOD randomised to Padma 28 or placebo as an add-on to physical training. Mean increase in walking distance at the end of the study was significant in the verum group and not in the placebo group. However, there was no significant difference between treatments
Smulski and Wojcicki [21]	One hundred patients with PAOD with at least 8 months' documented history and stable maximum walking distance <250 m on treadmill. Although the original paper reported on 93 fully protocol compliant patients, the manufacturer provided us the full data on 100 patients for an ITT re-analysis. There were imbalances between groups at baseline, concerning significant differences in: walking distance, age and concomitant pathologies (angina pectoris, blood pressure and lipid levels). Due to these differences the study was excluded from meta-analysis in a second run. However, the results showed a significant difference in maximum walking distance, and in the number of patients improving their walking distance by more than 100 m ($P < 0.001$)
Sallon et al. [23]	Seventy-two patients with PAOD randomised to verum or placebo, treated for 6 months, with post-exercise ABI measurements, change in exercise-induced pressure and time to pressure recovery. There were fewer decreases in ABI (by >15%) in the verum than in the placebo-treated patients but this difference was not significant. A patient self-assessment questionnaire on improvement in pain-free walking ability was favourable to verum ($P < 0.01$)

Table 4

Mean maximum treadmill walking distance (*m*) at baseline (T_0) and after 16 weeks of treatment (T_{16}) and the difference

Study	Baseline				End of trial (week 16)				Difference between groups	
	Verum		Placebo		Verum		Placebo		Verum – placebo	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Schröder et al. [18] ^a	144.85	(116.3, 173.4)	166.26	(139.82, 192.7)	278.45	(199.16, 357.74)	237.03	(175.35, 298.71)	41.42	(–14.74, 97.58)
Drabaek et al. [22] ^a	115.17	(99.02, 131.32)	125.33	(96.77, 153.89)	239.44	(135.08, 343.8)	128.78	(96.69, 160.87)	110.67	(40.06, 181.28)
Samochowiec et al. [19]	78.78	(69.01, 88.55)	67.53	(56.47, 78.59)	156.24	(131.13, 181.35)	66.64	(55.87, 77.41)	89.60	(58.94, 120.26)
Samochowiec et al. [24]	78.23	(64.31, 92.15)	69.70	(56.37, 83.03)	126.73	(108.25, 145.21)	67.33	(54.49, 80.17)	59.40	(37.81, 80.99)
Smulski and Wojcicki [21] ^b	87.46	(78.96, 95.96)	75.00	(67.15, 82.85)	187.70	(168.01, 207.39)	87.50	(78.14, 96.86)	100.20	(76.28, 124.12)
Sommogy and Schleicher [20] ^c	205.60	(150.2, 261)	202.35	(137.36, 267.34)	300.00	(213.09, 386.91)	277.93	(170.91, 384.95)	22.07	(–28.58, 72.72)
Pooled mean ($P < 0.001$)										
All trials	105.92	(96.3, 115.54)	104.27	(93.19, 115.35)	197.91	(176.88, 218.94)	124.69	(106.41, 142.97)	73.22	(42.59, 103.85)
Without Smulski	111.91	(99.62, 124.2)	114.44	(100.15, 128.73)	201.29	(174.08, 228.5)	137.78	(113.67, 161.89)	63.51	(27.11, 99.91)

^a LOCF.^b Excluded from meta-analysis because of significant differences at admission.^c Data as reported; add on to physical training.

we also present a summary of the main characteristics and critique of the main trials in Table 3. The trial of Smulski was eliminated from the final meta-analysis because of significant differences between the treatment groups at baseline. The pooled analysis of the remaining five trials showed a significant treatment effect relative to placebo (Table 4). Regarding

the percentage of patients who increased their treadmill walking distance by 100 m or more after 4 months of treatment, the pooled analysis shows the treatment to be effective, too (Fig. 2). Eighteen percent of the patients reach this target ($P < 0.001$; odds ratio: 10 [95% CI 3.03, 33.33]; RR: 0.12; number needed to treat = 6.2). Sensitivity analysis by random

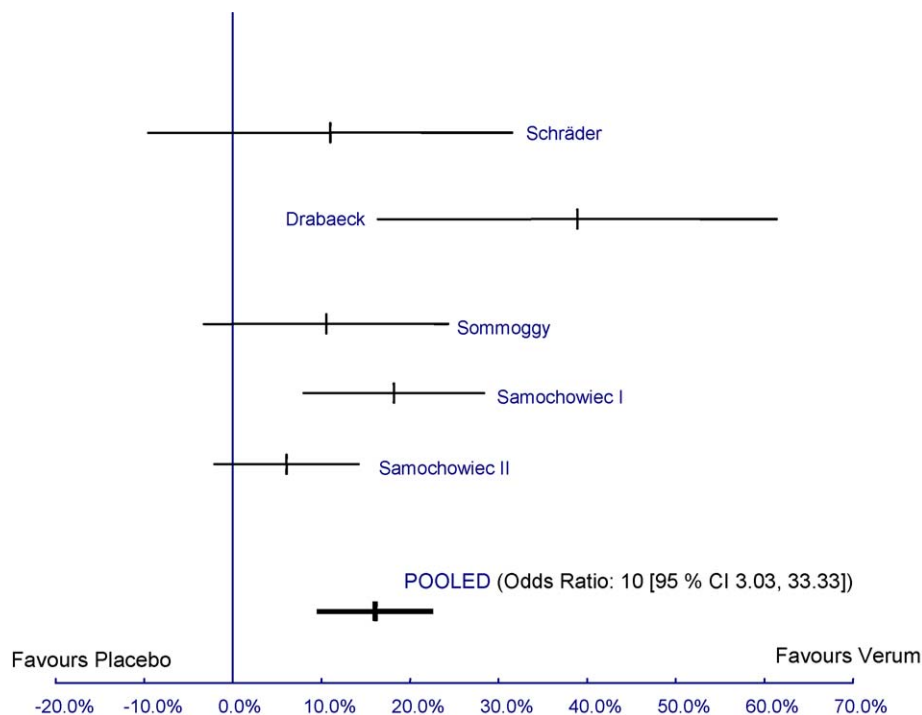


Fig. 2. Rate difference (verum – placebo) of % of patients with an increase in maximum walking distance by >100 m from start to end of treatment (16 weeks).

elimination of trials showed odds ratios between 14.53 and 50.00, indicating that the results are not driven by any one particular trial.

In a stepwise regression analysis of four of the studies with relevant data [18,19,21,24] we tested the variables treatment, age, gender, hypertension, hypercholesterolaemia, hyperlipidaemia, walking distance on admission, concomitant treatment (e.g. anticoagulants or cardiovascular drugs), concomitant cardiac disease, diabetes mellitus and smoking as independent variables with maximum walking distance as the dependent variable. Treatment was the variable with the largest impact on results ($P < 0.001$) although there was heterogeneity between studies ($P = 0.002$). None of the other variables showed a significant correlation with outcome. Additionally, the mean pooled data showed mild but significant reductions of glycaemia, triglycerides and systolic as well as diastolic blood pressure. However, as mentioned above, in the absence of a significant correlation of these parameters with maximum walking distance, the clinical meaningfulness of these mild improvements is debatable. The data on cholesterol levels and on inhibition of platelet aggregation were also inconclusive.

3.2. Safety

In the safety evaluation, we considered “adverse event” any undesired occurrence during a study, regardless of the original classification being adverse event, intercurrent disease or side effect. The safety evaluation took into account

Table 5
Adverse events (from patients with reporting in all 19 studies)

	Placebo	Verum
Patients with reporting	184	371
Serious events	6 (3.3%)	9 (2.4%)
Non-serious events: unrelated ^b to treatment	18 (9.7%)	25 (6.7%)
Non-serious events: related ^b to treatment	5 (2.7%)	12 (3.2%)
Treatment withdrawals	19 (10.3%)	28 (7.6%)
Summary of adverse events by body system (regardless of relationship to treatment)		
Gastrointestinal system disorders	9 (4.9%)	12 (3.2%)
Vascular disorders (worsening PAOD ^a)	7 (3.8%) ^c	5 (1.4%) ^d
Cardiovascular disorders	1 (0.5%)	7 (1.9%)
Body as a whole—general disorders	2 (2.2%)	6 (1.6%)
Urinary system disorders	2 (1.1%)	2 (0.5%)
Skin and appendages disorders	1 (0.5%)	5 (1.4%)
Central and peripheral nervous system disorders	2 (1%)	2 (0.5%)

^a Verum vs. placebo, $P < 0.1$.

^b As reported by investigators.

^c Includes one amputation of toes (unrelated to treatment).

^d Includes one death due to myocardial infarct and heart failure (unrelated to treatment).

all 19 studies in humans (total patients exposure: verum 1555, placebo 529) and the reported patients are displayed in Table 5. The results suggest that the treatment is very well tolerated, events being relatively few, the commonest having an incidence of 2.4% (dyspepsia).

Serious events were rare and related to the underlying pathology. In the population examined for this review, there were two serious adverse events: one verum-treated patient had a myocardial infarction. On placebo one patient underwent amputation of a toe due to deterioration of his PAOD. Routine haematology and biochemistry screenings did not reveal any systematic change in laboratory values in either group.

4. Discussion

Since the studies reported had a duration of at least 16 weeks and there were no consistent major changes in the lipid profile or in the haemodynamic variables measured, it seems reasonable to assume that the observed results on Padma 28 are not related to a single overriding effect but rather to a combination of minor effects on a number of disease factors. The “multiple small effects” theory matches Tibetan medicine philosophy, where a multifactorial approach with minor concerted interventions meets the needs to regulate the unbalanced state of chronic diseases developed over many years and caused by many factors. Patients with PAOD typically exhibit polymorbidity (with frequently associated diabetes and cardiovascular, pulmonary or other diseases), with intermittent claudication being but one of the clinical manifestations. In daily medical practice this often results in polypharmacy, where the use of several potent drugs aims at treating multifactorial pathophysiological processes. Both patients and physicians should welcome the possibility of providing some relief with a ‘non-aggressive’ medication. The potential antioxidative properties of the preparation may play a prominent role but robust, prospective studies are needed to evaluate these.

The main findings of this meta-analysis are the efficacy and safety of Padma 28 and the pooled analysis shows that this treatment is associated with prolongation of maximum walking distance in patients with intermittent claudication due to PAOD (Fontaine stage II). One in six patients had a clinically relevant improvement. This effect appears to be independent of demographic, clinical and disease-related criteria. The overall evidence on Padma 28 may not be sufficient to fulfil the requirements for new drugs for this condition, thus larger trials according to international guidelines are needed, particularly in view of the apparently favourable safety profile.

While we endeavoured to apply De Backer’s criteria to the studies pooled it has to be pointed out that recently European guidelines for the assessment of new treatments in PAOD have become available [25]. Yet, these European guidelines were not used for exclusion of studies particularly regarding

duration of treatment and follow up. To view our results in the light of those obtained with other treatments in the same type of patients, Girolami's meta-analysis [26] found a significant increase in pain-free (139 m; 95% CI 31.0, 246.9 m) and total treadmill walking distance (179.1 m; 95% CI 60.2, 298.1 m) for studies of physical training while smoking cessation resulted in a non-significant increase in total treadmill walking distance (46.7 m; 95% CI –19.3, 112.7 m). Pentoxifylline increased both pain-free (by 21.0 m; 95% CI 0.7, 41.3 m) and total walking distance (by 43.8 m; 95% CI 14.1, 73.6 m) [26]. Naftidrofuryl significantly increased pain-free walking distance by 58.6 m (95% CI 30.4, 86.8 m) and total walking distance by 71.2 m (95% CI 13.3, 129.0 m) [26]. In another meta-analysis cilostazol, a selective phosphodiesterase inhibitor, increased maximal and pain-free walking distances by 50% and 67%, respectively, and was reported to be better in the two trials that compared it to pentoxifylline [27]. In an overview by Linde et al. [28], Ginkgo biloba was significantly more effective than placebo in increasing walking distance, but the clinical relevance was felt to be moderate (e.g. increase of pain free walking distance 34 m; 95% CI 26, 34 m). A new meta-analysis concerning Ginkgo, with partly different studies, interpreted the findings as clinically relevant [29]. The meta-analysis of Padma 28 suggests that the increases in maximum walking distances are of the same order of magnitude as physical training and may be larger than those reported with pentoxifylline, naftidrofuryl, smoking cessation or Ginkgo biloba.

There is no "gold standard" treatment for intermittent claudication in PAOD, treatment usually comprising a package of measures including lifestyle changes (physical activity, smoking cessation, dietary changes), treatment of underlying diseases (diabetes, hypertension), use of vasoactive drugs to increase perfusion in affected limbs and invasive procedures when all previous steps fail [30]. In this context, Padma 28 may prove to be a useful complementary therapy for the mild to moderate stages of disease (Fontaine stage II), although definitive prospective studies are needed to address this conclusively.

As in all meta-analyses of published literature, two potential limitations of our findings are publication bias and influence by sponsors. The only way to address publication bias is through future large randomised trials conducted according to current guidelines. Regarding potential sponsor's influence we feel we may have overcome this by conducting our own literature searches and by insisting on re-analysing the raw data with kind permission from the original authors, in addition to following the guidelines of the Cochrane Collaboration Handbook for reviews.

5. Conclusions

The meta-analysis of current evidence shows Padma 28 to be significantly effective in the relief of symptoms of PAOD. The data suggest that this herbal medicine is com-

parable to pentoxifylline and naftidrofuryl in treating the symptoms of PAOD. Nevertheless, larger GCP-conforming RCTs are needed to assess the exact therapeutic value in the management of PAOD, as no single trial to date has yielded sufficiently compelling evidence to warrant change in current practice.

Conflict of interests

None declared. The Department of Internal Medicine, Complementary Medicine, University of Zurich (Professor Saller) was responsible for the conduct of the project on the following bases: (1) the protocol design and literature searches were the responsibility of the Institute of Complementary Medicine; (2) all data management and analyses were conducted by the Institute of Complementary Medicine; (3) interpretation of results was the prerogative of our institution; (4) publication of results was to occur regardless of the outcome of the review.

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Contributors: RS conceived the overall project plan. RB performed the re-analysis and statistics. The manufacturer provided the raw data. RS, RB and JM are the guarantors of the paper.

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