PYCNOGENOL FOR THE TREATMENT OF CHRONIC DISORDERS:
A systematic review

by

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DECLARATION OF AUTHENTICITY

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Signature:  Date: March 2011

ABSTRACT

Background

Oxidative stress has been implicated in the development of a number of conditions including amongst others cancer, arthritic disorders and cardiovascular disease. Pycnogenol is a herbal dietary supplement derived from French maritime pine bark extract. Pycnogenol is standardised to contain 70 ± 5% procyanidin which is a powerful antioxidant. Pycnogenol is marketed as a supplement for preventing or treating a wide range of chronic conditions. Although several randomised controlled trials of Pycnogenol have been conducted to date, this evidence has not yet been systematically reviewed.

Objectives

The aim was to carry out a systematic review in order to assess the efficacy and safety of Pycnogenol for the treatment of chronic disorders.

Search methods

The electronic databases CENTRAL (until 18 September 2010), MEDLINE (until 18 September 2010) and EMBASE (until 13 October 2010) were searched, as well as three trial registries. Furthermore the manufacturer of Pycnogenol was contacted and bibliographies of included studies were hand-searched.

Selection criteria

Randomised controlled trials (RCTs) evaluating the effectiveness of Pycnogenol in adults or children with any chronic disorder were included. The primary outcomes were any clinical outcomes directly related to the disorder (stratified as participant- and investigator-reported) as well as all-cause mortality. Adverse events and biomarkers of oxidative stress were also assessed.

Data collection and analysis

Two authors independently assessed trial eligibility, extracted all data and judged methodological quality. A third author additionally extracted information on outcomes and results. With two exceptions, results for outcomes across studies could not be pooled mainly due to poor quality reporting. Study authors were contacted for additional information.

Results

This review includes 15 RCTs with a total of 791 participants that have evaluated Pycnogenol for the treatment of seven different chronic disorders. The disorders included asthma (2 studies; N = 86), attention deficit hyperactivity disorder (1 study; N = 61), chronic venous insufficiency (2 studies; N = 60), diabetes mellitus (4 studies; N = 201), erectile dysfunction (1 study; N = 21), hypertension (2 studies; N = 69) and osteoarthritis of the knee (3 studies; N = 293). Two of the studies were conducted exclusively in children; the others involved adults. Due to small sample size, limited numbers of trials per condition, variation in selected outcomes and outcomes measures and the risk of bias no definitive conclusions regarding the efficacy or safety of Pycnogenol are possible.

Authors' conclusions

Current evidence is insufficient to support Pycnogenol use for the treatment of any chronic disorder. Well designed, adequately powered trials are recommended to establish the value of this treatment.

OPSOMMING

Inleiding

Oksidatiewe stres blyk 'n rol te speel in die ontwikkeling van 'n verskeidenheid siektes onder andere kanker, artritis en kardiovaskulêre siektes. Pycnogenol, 'n kruie-bevattende dieetaanvulling wat uit Franse denneboombas vervaardig word, is gestandaardiseer om 70 ± 5% prosianidien – 'n kragtige anti-oksidant – te bevat. Die produk word bemark om 'n wye reeks chroniese siektes te voorkom of te behandel. Alhoewel daar tot op hede verskeie kliniese proewe op Pycnogenol uitgevoer is, is die uitkomstes nog nie met behulp van 'n stelselmatiese oorsig geëvalueer nie.

Doelwitte

Die doel van hierdie studie was om met behulp van 'n stelselmatiese oorsig die doeltreffendheid en veiligheid van Pycnogenol ten opsigte van die behandeling van chroniese siektes te evalueer.

Soektogstrategie

Die elektroniese databasisse CENTRAL (tot 18 September 2010), MEDLINE (tot 18 September 2010) en EMBASE (tot 13 Oktober 2010) is deursoek, asook drie registers met kliniese proewe. Verder is die vervaardiger van Pycnogenol gekontak en is daar met die hand deur bibliografieë van ingeslote studies gesif.

Keuringskriteria

Ewekansige gekontroleerde proewe (RCT's) is ingesluit waarin die effektiwiteit van Pycnogenol in volwassenes of kinders met enige chroniese siekte geëvalueer is. Enige kliniese uitkomste wat direk aan die chroniese siekte verwant is (gesorteer as deelnemer- of ondersoeker-gerapporteerde uitkomstes) asook mortaliteit (enige oorsake) is as die primêre uitkomstes ondersoek.

Dataversameling en -ontleding

Twee navorsers het onafhanklik van mekaar proewe gekeur, alle relevante data onttrek en gehalte van die metodiek beoordeel. 'n Derde navorser het die resultate van die uitkomstes bykomend onttrek. Met twee uitsonderings, kon resultate van uitkomstes van die verskillende ingeslote studies kon nie statisties saamgevoeg word nie, hoofsaaklik as gevolg van swak rapportering. Skrywers van die ingeslote studies is in verband met die verlangde inligting gekontak.

Resultate

Vyftien RCT's met 'n totaal van 791 deelnemers is ingesluit. In hierdie studies is Pycnogenol vir die behandeling van sewe verskillende chroniese siektes geëvalueer: asma (2 studies; N = 86), aandagafleibaarheid-hiperaktiwiteitsgebreksindroom (1 studie; N = 61), chroniese veneuse ontoereikendheid (2 studies; N = 60), diabetes mellitus (4 studies; N = 201), erektiele disfunksie (1 studie; N = 21), hipertensie (2 studies; N = 69) en osteo-artritis van die knie (3 studies; N = 293). Twee van hierdie studies is uitsluitlik met kinders gedoen; die res was volwassenes. As gevolg van klein steekproewe, 'n beperkte aantal studies per siekte, wisseling in uitkomstes en die risiko vir sydigheid kan geen definitiewe gevolgtrekking oor die doeltreffendheid en veiligheid van Pycnogenol gemaak word nie.

Skrywers se gevolgtrekking

Tans is daar nie voldoende wetenskaplike bewyse om Pycnogenol-gebruik vir die behandeling van enige chroniese siekte aan te beveel nie. Goed ontwerpte proewe met 'n voldoende aantal deelnemers word aanbeveel om die waarde van hierdie behandeling onomwonde vas te stel.

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LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme inhibitor
ADHD	Attention deficit hyperactivity disorder
CAP	Child Attention Problems Teacher Rating Scale
COX-2 inhibitor	Cyclooxygenase-2 inhibitors
CPRS	Conner's Parent Rating Scale
CTRS	Conner's Teacher Rating Scale
CVI	Chronic venous insufficiency
ED	Erectile dysfunction
ELISA	Enzyme-linked immune-absorbent assay
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GSG	Reduced glutathione
GSSG	Oxidized glutathione
HPLC	High performance liquid chromatography
IIEF-5 score	International Index of Erectile function score
IQR	Interquartile range
MD	Mean difference
NSAIDS	Nonsteroidal anti-inflammatory drugs
PEF	Peak expiratory flow
RCT	Randomised controlled trial
ROS	Reactive oxygen species
RR	Risk ratio
SD	Standard deviation
SE	Standard error
USA	United States of America
VAS	Visual analogue scale
WHO	World Health Organization
WOMAC score	Western Ontario and McMaster Universities score

LIST OF DEFINITIONS

Free radicals

Atoms, molecules or ions which contain one or more unpaired electrons and are capable of independent existence.[Cos 2004]

Oxidative stress

Refers to a state of imbalance between the production of reactive oxygen species and the body's ability to defend itself against the deleterious effect of oxidation.[Sies 2005; Whitney 2002]

Proanthocyanidin

A powerful antioxidant found in a variety of foods, especially fruit such as grapes, berries, pomegranates, apples and pears.[Beecher 2003]

Procyanidin

A subtype of proanthocyanidin, a member of the flavonoid subgroup of polyphenols.[Scalbert 2000]

Pycnogenol

A herbal dietary supplement derived from French maritime pine bark extract which is standardised to contain 70 ± 5% procyanidin.[Oliff 2010; Schonlau 2010]

Reactive oxygen species

A collective term for free radicals (e.g. superoxide anion, hydroxyl, nitric oxide) and certain non-radicals (e.g. hydrogen peroxide, hypochlorous acid, ozone) which are both by-products of oxygen metabolism in the body.[Cos 2004]

INTRODUCTION

INTRODUCTION

Every health professional around the world had taken the Hippocratic Oath, promising to treat ill health to the best of his/her ability. In practice this translates to integrating the following three aspects before a clinical decision can be made: the knowledge, expertise and skills of the professional; the patient's values and preferences; and the best available evidence.[1] This task of keeping up to date is not easy as there is vast amount of biomedical literature electronically available.[2] However, this task has been made much simpler by applying clinical epidemiology, the science, explicitly in the form of evidence-based health care.[3] This field of epidemiology arose in the late 1960s due to the growing awareness that laboratory experiments and experience alone are not sufficient for making clinical decisions.[2, 4] Clinical epidemiology and evidence-based health care are umbrella concepts which include all health care fields, including nutrition. The main objective of nutritional epidemiology is thus to provide the best possible scientific evidence to support an understanding of the role of nutrition in the causes and prevention of ill health.[5]

The practice of evidence-based nutrition involves five essential steps: identifying knowledge gaps and converting it into answerable questions; finding the best evidence to answer the question; appraising the evidence critically; and applying the evidence and evaluating performance.[3] The latter involves patient follow-up as well as synthesizing research which build on the principle that science is cumulative.[6] Research synthesis is defined by the World Health Organization as the process through which two or more research studies are assessed with the objective of summarizing the evidence relating to a particular question.[6] Overviews, (traditional) reviews, systematic reviews and meta-analysis are types of research synthesis. The validity of these types of research synthesis is dependent on the methodological quality involved.[7] Overviews and traditional reviews are rarely explicit about how primary studies were selected, assessed and analysed.[7] This directly influences the quality of the findings since readers are not able to assess potential bias in the review process.[7] A systematic review on the other hand, reduces bias by the systematic identification, appraisal, synthesis and, if relevant, statistical aggregation of all relevant studies (meta-analyses) on a specific topic according to a pre-determined and explicit method.[8] The findings of a systematic review depend on the studies that are to be included and since randomised controlled trials are the golden standard of primary research, a systematic review of randomised controlled trials (which may or may not include meta-analyses) is the highest level of evidence, especially when it comes to health care interventions.[9]

In general, systematic reviews are not controlled but resources such as workshops and courses, textbooks, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and Assessment of Multiple Systematic Reviews (AMSTAR) tool are available to ensure transparent and reproducible methodology of high quality. An international non-profit organization that eases this process in various ways is the Cochrane Collaboration which was founded in 1993 in Oxford, England. Its primary aim is to help people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews of the evidence that underpins these reviews.[10] Cochrane reviews are supported by more than 50 different Cochrane Review Groups which core functions are, amongst others, to focus on a particular health care area, avoid duplication of reviews as well as maximising the quality of reviews by assisting in the correctness of the content, putting together search strategies, statistical support and thorough peer reviewing. A unique feature of Cochrane reviews in the Cochrane Database of Systematic Reviews is the fact that regular updates with the latest evidence are required. Updating involves conducting searches for new studies on a regular basis (frequency depends on the specific health care area), followed by all the other systematic steps when relevant studies are found.

Antioxidants in general, and the flavonoid proanthocyanidin in particular, is a very broad and interesting field of research. In the electronic database PubMed alone there are 1131 results (17 January 2011) when searching for titles and/or abstracts containing the terms 'proanthocyanidin OR procyanidin'. These studies include laboratory, animal and human studies that focus on a wide variety of characteristics, from the bioavailability of proanthocyanidin to the clinical effect that this substance may have on various medical conditions. This project's focus is on the latter area of research.

Pycnogenol is a proanthocyanidin-containing supplement that is marketed for its antioxidant properties. There are many such supplements available globally, but Pycnogenol is the best researched one. According to the website of the manufacturer, Horphag Research Ltd, there are more than 230 scientific articles and clinical trials that have confirmed over the past forty years Pycnogenol's safety, absence of toxicity and clinical efficacy.[11] People around the world pay a lot of money for supplements such as Pycnogenol which is marketed to aid in the treatment of an array of conditions including attention deficit hyperactivity disorder, asthma, cholesterol/dyslipidaemia, chronic venous insufficiency, diabetes, dysmenorrhoea, endometriosis, erectile dysfunction, hypertension, melasma, muscle cramps, osteoarthritis, peri-menopause, platelet function and retinopathy.[12] This is a comprehensive claim and as a result it was decided to evaluate the evidence systematically to establish whether these

claims related to Pycnogenol are justified or not. Against this background this Cochrane review was therefore undertaken to assess the efficacy and safety of Pycnogenol for the treatment of chronic disorders.

Another interesting area to explore is, for example, the difference between the clinical efficacy of proanthocyanidin in whole food such as fruit and vegetables versus supplements or extracts in the prevention and/or treatment of medical disorders. Although the proanthocyanidin dosage in the supplements will probably be higher than one can get by eating decent portions of fruit and vegetables daily, the interaction between nutrient and non-nutritive components in fruit and vegetables may be responsible for superior health benefits.[13] However, this would be a project on its own and is beyond the scope of this project.

References to the Introduction and Closing Remarks are presented on the last page of this project.

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PYCNOGENOL FOR THE TREATMENT OF CHRONIC DISORDERS:

A systematic review

According to guidelines and specific format of the Cochrane Collaboration

PYCNOGENOL FOR THE TREATMENT OF CHRONIC DISORDERS

Review information

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Plain language summary

Use of the antioxidant supplement Pycnogenol to treat a variety of chronic disorders

Pycnogenol is a supplement containing approximately 70% procyanidin which is extracted from French pine bark. Procyanidin is a powerful antioxidant which also occurs widely in food such as grapes, berries, pomegranates, red wine and various nuts. There are many procyanidin-containing supplements worldwide which is marketed to neutralise reactive oxygen species (ROS; generally referred to as free radicals in the media). Everyone is bombarded daily by ROS for example through exercise, stress, smoking, air pollution and exposure to ultraviolet light. ROS can cause harm in various ways, but on the other hand it also have several beneficial functions in humans. It is thus possible that excessive amounts of antioxidants may have a negative effect and that a balance between ROS and antioxidants may be critical for maintaining health. The objectives of this systematic review were then to assess the efficacy and safety of Pycnogenol as treatment for any chronic disorder. We included 15 randomised controlled trials which addressed seven different chronic conditions: asthma (2 studies), attention deficit hyperactivity disorder (ADHD) (1 study), chronic venous insufficiency (2 studies), diabetes (4 studies), erectile dysfunction (1 study), hypertension (2 studies) and osteoarthritis (3 studies). Due to small sample size and limited numbers of trials per condition no definite conclusions regarding the efficacy and safety of Pycnogenol are possible.

Background

Description of the condition

Reactive oxygen species (ROS) is a collective term for free radicals (e.g. superoxide anion, hydroxyl, nitric oxide) and certain non-radicals (e.g. hydrogen peroxide, hypochlorous acid, ozone) which are both by-products of oxygen metabolism in the body (Cos 2004). Free radicals are atoms, molecules or ions which contain one or more unpaired electrons and are capable of independent existence (Cos 2004). Sources of ROS include radiation, exercise, stress, smoking, air pollution, ultraviolet light and some foods (Whitney 2002). While ROS performs important functions within cells, most notably the destruction of pathogens phagocytosed by white cells, they may cause significant damage in large amounts. Oxidative

stress refers to a state of imbalance between the production of ROS and the body's ability to defend itself against the deleterious effect of oxidation (Sies 2005; Whitney 2002). Damage to cellular structures may ensue, leading to the development of disease (Ammar 2009; Cos 2004; Watson 2006; Whitney 2002).

Oxidative stress has been implicated in the development of a number of conditions including cardiovascular disease, arthritic and rheumatic disorders, cancer, inflammatory bowel disease, Alzheimer's disease, Parkinson's disease and cataracts (Litchford 2008). While the exact role of ROS in the pathogenesis of these diseases remains unclear, the following are some mechanisms that are thought to be important:

- Oxidative damage to cellular DNA may lead to the development of certain malignancies (Nijveldt 2001; Whitney 2002);
- Oxidation of low density lipoproteins (LDL) may accelerate plaque formation in arteries, increasing the likelihood of developing cardiovascular diseases (Nijveldt 2001; Whitney 2002);
- Oxidation of poly-unsaturated fatty acids in cell membranes may hinder blood flow and contribute to cardiovascular problems (Whitney 2002);
- Oxidative stress encourages telomere (the non-gene terminal end of a chromosome which protects the chromosome from destruction) instability and dysfunction in chondrocytes (cartilage cells), which may result in cartilage ageing and the development of osteoarthritis (Yudoh 2005);
- Dopamine-derived ROS and oxidized dopamine metabolites are toxic to neurons of the substantia nigra (part of the brain stem that release neurotransmitters, such as dopamine, that is important for the control of movement and coordination) which may lead to Parkinson's disease (Hald 2005).

Description of the intervention

Pycnogenol is a herbal dietary supplement derived from French maritime pine bark extract. The trees (*Pinus pinaster* Ait. subsp. *altantica*) are exclusively grown in Landes de Gascogne, Southwest France (Oliff 2010). Fresh pine bark is powdered and extracted with water and ethanol in a process patented by the manufacturer Horphag Research, Geneva, Switzerland (Oliff 2010). Pycnogenol is standardised to contain 70 ± 5% procyanidin (condensed oligomeric catechin and epicatechin) (Oliff 2010; Schonlau 2010).

Procyanidin is a subtype of proanthocyanidin, a member of the flavonoid subgroup of polyphenols (Scalbert 2000). It is a powerful antioxidant found in a variety of fruits such as

grapes, berries, pomegranates, apples and pears, as well as in various nuts, pine bark, red wine, tea and chocolate (Beecher 2003; Cos 2004). Proanthocyanidin containing supplements are sold under a variety of brand names worldwide such as Bioxidin©, ActiVin™, Pycnogenol®, and Procydin®. These differ in terms of the source and quantity of proanthocyanidin contained as well as in the number and types of other ingredients included. We decided to focus our review on Pycnogenol as this is an extensively researched, standardised product widely marketed for its antioxidant effects. It should be kept in mind that dietary supplements such as Pycnogenol may also have non-antioxidant related activity which may account for any observed effects on health.

How the intervention might work

Three antioxidant mechanisms have been attributed to proanthocyanidin:

- Free radical scavenging, i.e. proanthocyanidin is oxidized by free radicals, resulting in more stable, less-reactive radicals (Cos 2004; Nijveldt 2001);
- Proanthocyanidin binding of iron and copper, which are cofactors of several enzymes involved in oxygen metabolism, thus limiting the formation of free radical reactions (Cos 2004);
- Direct inhibition of pro-oxidative enzymes such as lipoxygenase, nitric oxide synthase and xanthine oxidase (Cos 2004).

It is important to recognise that ROS has several important beneficial functions in cells including:

1. Mediation of apoptosis (programmed cell death, also known as cellular suicide);
2. Mediation of detoxification reactions;
3. Defending cells against pathogenic viruses and bacteria;
4. Mediation of other specific biochemical reactions (Salganik 2001; Whitney 2002).

It is therefore possible that excessive amounts of antioxidants may negatively affect these important physiological processes (Bjelakovic 2007). This implies that a balance between ROS and antioxidants may be critical for maintaining health.

Why it is important to do this review

Dietary supplements have expanded into a multi-billion dollar industry worldwide. However, the efficacy and safety of antioxidant supplements have not been sufficiently clarified (Bjelakovic 2007; Donma 2005; Lichtenstein 2005; Tonks 2007). Pycnogenol is marketed as a supplement for preventing the onset, alleviating symptoms or limiting progression of a wide

range of chronic clinical disorders. The manufacturer of Pycnogenol strongly promotes research and claims that its products are based on results of scientific research (American Botanical Council 2010). Although several randomised trials of Pycnogenol have been conducted to date, this evidence has not yet been evaluated in a systematic review.

Objectives

To assess the efficacy and safety of Pycnogenol for the treatment of chronic disorders.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) investigating the efficacy or safety (or both) of Pycnogenol.

Types of participants

Adults and children with any chronic disorder, regardless of geographical location or setting. We defined a chronic disorder as a disease (e.g. heart disease, stroke, cancer, diabetes, HIV/AIDS etc.) or non-specific illness (e.g. fatigue, pain etc.) of more than three months duration.

Types of interventions

Experimental

Pycnogenol, alone or in combination with other supplements, as long as the comparison group(s) received the same treatment apart from Pycnogenol. Any dose or route of administration was deemed acceptable, but Pycnogenol should have been used for at least one month (four weeks).

Control

- Placebo;
- No intervention;
- Other supplement(s) (excluding those with antioxidant properties).

Types of outcome measures

For each chronic disorder we assessed the following outcomes:

Primary outcomes

1. Any clinical outcome directly related to the disorder, stratified as:
    - Participant-reported outcomes (e.g. joint pain in patients with osteoarthritis);
    - Investigator-reported outcomes (e.g. serum cholesterol levels in patients with hyperlipidaemia, retinal blood flow with diabetic retinopathy).
2. All-cause mortality.

Secondary outcomes

1. Adverse events, stratified as:
    - Serious (causing death, hospitalisation or cessation of use);
    - Not serious.
2. Biomarkers of oxidative stress (e.g. antioxidant activity in plasma, oxidized glutathione concentration).

Studies reporting only on antioxidant biomarkers were not included.

Search methods for identification of studies

AS used a comprehensive and exhaustive search strategy in order to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

Electronic searches

Journals and trials databases

We searched the following databases:

- MEDLINE (accessed via PubMed), until 18 September 2010;
- Clinical Trials (CENTRAL) database, The Cochrane Library until 18 September 2010;
- EMBASE (accessed via Ovid), until 13 October 2010.

Detailed search strategies with the main terms 'Pycnogenol' and 'pine bark', are presented in Appendix 1, Appendix 2 and Appendix 3.

Trials registries

The following trial registries were searched for ongoing trials using the phrase "Pycnogenol OR pine bark":

- ClinicalTrials.gov, until 18 September 2010;
- Current Controlled Trials, until 18 September 2010;
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), until 18 September 2010.

Searching other resources

We contacted the manufacturer of Pycnogenol, Horphag Research (UK) Ltd, via email to request a list of completed clinical trials. This was received on 21 July 2010. We also hand-searched the reference lists of included studies in order to identify additional relevant studies.

Data collection and analysis

Selection of studies

The authors AS and JV independently screened the title and abstract of studies identified by the search and applied the pre-specified criteria in order to identify eligible studies. Where at least one author considered a study to be relevant, we obtained the full-text and independently assessed it for eligibility. Where there was missing information or where clarity was needed, we contacted the authors of the primary studies. We resolved any remaining disagreement by consensus among the four authors. We listed studies at first thought to be relevant but which were later excluded in the table 'Characteristics of excluded studies' together with reasons for exclusion.

Data extraction and management

The authors AS and JV independently extracted data using a standardized, pre-piloted extraction form. For each study we collected the following items: administrative details, study methodology, participant characteristics, interventions, outcomes, study findings, ethical approval and funding sources. The outcomes and results were also independently extracted by AM. Disagreements were resolved by consensus. Where reported information was unclear or contradictory, or where important data were missing, we contacted the study author(s) via email.

We planned to group data based on duration of follow-up as follows:

- Short term (less than three months);
- Medium term (three months to twelve months);
- Long term (thirteen months onwards).

However, this was not done as no study involved a follow-up period of more than three months. Where multiple time points were reported for one category (e.g. two week intervals for a period of eight weeks of treatment) we used only the longest time point data.

Assessment of risk of bias in included studies

The authors AS and JV independently assessed each included study for risk of bias using the guidelines provided in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2008). The specific criteria appear in Appendix 4. The components of the methodology that were assessed are sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential threats to validity. Each included study was rated 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear' (uncertain risk of bias) for each of the six domains. Disagreements were resolved by consensus.

Crossover trials were additionally assessed, in a separate table (Table 1), to determine (Higgins 2008):

1. Whether the crossover design was suitable;
2. Whether there was a carry-over effect;
3. Whether only first period data are available;
4. Whether a correct analysis (paired analysis) had been used;
5. Whether the results are comparable to those from parallel-group trials.

Measures of treatment effect

We used Review Manager Version 5 (RevMan 2008) to conduct the analyses. We calculated risk ratios (RRs) for dichotomous data and mean differences (MDs) for continuous data. All results are presented with 95% confidence intervals except where data were reported as medians and ranges. Where results were reported insufficiently for analysis (e.g. where standard deviation (SD) of change was not provided and the contact authors of the studies have not yet responded to our requests), we presented the available results in a table.

Unit of analysis issues

The two crossover trials in the included studies were not included in any meta-analysis as one did not report results for the placebo group and the other reported results insufficiently. One included study had three intervention groups (local plus oral Pycnogenol; oral Pycnogenol; local Pycnogenol) and one control group (no treatment). Since the intervention group of all the other included studies involved oral Pycnogenol only, we decided to select this group from the above trial and exclude the other two groups from the analysis.

Dealing with missing data

We attempted to obtain essential missing data by contacting the original authors whenever possible (Appendix 5). Where there was no missing data we used the intention-to-treat principle. In the presence of missing dichotomous data we still used the intention-to-treat principle but assumed that the missing participants did not experience the event. In the case of missing continuous data we used the available-case analysis.

Assessment of heterogeneity

We assessed heterogeneity in our two meta-analyses using visual inspection of the forest plots. If confidence intervals for the results of individual studies had poor overlap, we took this as an indication of statistical heterogeneity. Furthermore, we used the Chi^2 test for heterogeneity (significance level $P < 0.1$) and quantified the degree of heterogeneity by means of the I^2 statistic (Higgins 2003). The following guidelines were used for the interpretation of the I^2 values (Higgins 2008):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

It was not appropriate to draw funnel plots as the number of studies was insufficient. Therefore it was not possible to explore the possibility of small study bias.

Data synthesis

We used a fixed effects model to combine the results of studies where appropriate. Only two studies presented outcomes that allowed for pooling of results. However, should

considerable statistical heterogeneity ($I^2 \geq 75\%$) existed we would not have pooled the study results in a meta-analysis but reported it separately.

Subgroup analysis and investigation of heterogeneity

We planned to further investigate statistical heterogeneity by conducting the following subgroup analyses:

- Age: adults (over 16 years versus children (16 years and younger);
- Dose of Pycnogenol used: high dose (150 mg/day and above) versus low dose (up to 150 mg/day);
- Type of disorder (e.g. cardiovascular disease, cancers, chronic obstructive pulmonary disease, metabolic disorders).

However, the data available was insufficient to undertake subgroup analysis.

Sensitivity analysis

We planned to perform a sensitivity analysis if appropriate in order to assess the influence of study quality (using adequacy of allocation concealment as a marker) and funding source on the findings. Due to insufficient data this was not possible in this review, but may be appropriate in future updates.

Results

Description of studies

Results of the search

Figure 1 summarises the search results. In total we screened 246 records of which 36 were identified as potentially eligible. The full-text articles of these were obtained for further assessment. Fifteen studies met our eligibility criteria and the rest were excluded with reasons which are displayed in the table of 'Characteristics of excluded studies'. Another completed study is awaiting classification as the information from this study is currently available only as a conference abstract and poster (see table of 'Characteristics of studies awaiting classification'). We identified four ongoing studies, the available details of which are provided in the table of 'Characteristics of ongoing studies'.

Included studies

Fifteen RCTs with a total number of 791 participants were included in the review and full details of these studies are provided in the table 'Characteristics of included studies'. All studies employed a parallel group design, except for Hosseini 2001a and Hosseini 2001b which were crossover trials. The studies assessed the effects of Pycnogenol in patients suffering from seven different chronic disorders:

- Asthma: two trials with a total of 86 participants conducted in Iran and the USA (Hosseini 2001a, Lau 2004);
- Attention deficit hyperactivity disorder (ADHD): one study with 61 participants conducted in Slovakia (Trebatická 2006);
- Chronic venous insufficiency (CVI): two trials with a total of 60 participants both conducted in Italy (Arcangeli 2000, Petrassi 2000);
- Diabetes mellitus: four trials with a total of 201 participants conducted in Italy (2), China and the USA (Belcaro 2006a, Liu 2004a, Steigerwalt 2009, Zibadi 2008);
- Erectile dysfunction (ED): one study with 21 participants conducted in Slovak Republic (Duracková 2003);
- Hypertension: two trials with a total of 69 participants conducted in the USA and China (Hosseini 2001b, Liu 2004c);
- Osteoarthritis: three trials with a total of 293 participants conducted in Slovakia, Iran and China (Belcaro 2008b, Cisár 2008, Farid 2007).

Two of the 15 studies were conducted exclusively in children (Lau 2004, Trebatická 2006); the rest included only adults. In all studies Pycnogenol was consumed orally, except for Belcaro 2006a in which Pycnogenol was also applied locally to skin ulcers. The duration and dosages varied across studies and chronic conditions:

- Asthma: in both studies the dosage of Pycnogenol depended on individual body weight (1 mg/lb/day). In Hosseini 2001a the treatment duration was four weeks while in Lau 2004 it was three months.
- ADHD: dosage of Pycnogenol depended on individual body weight (1 mg/kg/day); treatment duration was one month.
- CVI: in both studies participants received 300 mg Pycnogenol per day; treatment duration was two months.
- Diabetes mellitus: treatment duration in Belcaro 2006a was six weeks; there were three treatment groups. The group that received Pycnogenol orally got 150 mg/day and the group that applied Pycnogenol locally used 100 mg/day; the third group (oral

plus local Pycnogenol) thus used a total of 250 mg Pycnogenol daily. The treatment duration in Liu 2004a and Zibadi 2008 was 12 weeks and the participants consumed 100 mg and 125 mg Pycnogenol per day respectively. The participants in Steigerwalt 2009 received 150 mg Pycnogenol daily for two months.

- ED: the Pycnogenol group consumed 120 mg Pycnogenol daily for three months.
- Hypertension: the treatment period in Hosseini 2001b was eight weeks compared to 12 weeks in Liu 2004c. Participants in Liu 2004c received 100 mg Pycnogenol per day and those in Hosseini 2001b twice as much.
- Osteoarthritis: in Cisár 2008 and Farid 2007 the participants in the Pycnogenol group received 150 mg Pycnogenol daily, while those in Belcaro 2008b received 100 mg/day. The treatment duration in all three studies was three months.

Excluded studies

Eighteen studies were excluded with reasons (see the table 'Characteristics of excluded studies'). The most common reason for exclusion was that the study was not randomised (8/18). Other reasons were: the treated condition was not a chronic disorder (2/18), prevention rather than treatment (2/18), an inappropriate control group (4/18) and inappropriate outcomes (2/18).

Risk of bias in included studies

Our judgements regarding the risk of bias in each of the included studies can be found in the table 'Characteristics of included studies'. Figure 2 and Figure 3 provides a graphical summary of the risk of bias assessments. Table 1 presents additional information regarding the risk of bias in the two crossover trials included in the review (Hosseini 2001a, Hosseini 2001b).

Allocation

Allocation refers to both the generation of the random allocation sequence and concealment of the allocation code.

While all included trials reported that allocation had been randomised, the method used for generating the allocation sequence was judged to be adequate in only five (Belcaro 2008b, Hosseini 2001b, Petrassi 2000, Steigerwalt 2009, Trebatická 2006). The other ten studies provided insufficient information regarding this component of the study design.

None of the included trials described the method used for concealing allocation except for Lau 2004. In this study the authors reported that the treatment was "identified by preassigned codes prepared by an independent laboratory" but the coding is not described. The risk of bias for all 15 studies was therefore judged as 'unclear'.

Blinding

Fourteen included trials were reported to be "double-blind". However, only three (Lau 2004, Petrassi 2000, Trebatická 2006) mentioned who was blinded (e.g. participants, providers or outcome assessor) or that the placebo was indistinguishable from the test drug. Therefore we judged these three studies to have a low risk of bias.

Eleven studies were judged as having an unclear risk of bias. Of these, five (Arcangeli 2000, Belcaro 2008b, Cisár 2008, Farid 2007, Zibadi 2008) reported that the placebo was identical to the test drug in terms of appearance. However, it is not clear whether the placebo was also matched in terms of other characteristics such as weight and taste. Pycnogenol is known to have a bitter, astringent taste. The other six studies provided no further details other than the use of a double-blind design (Hosseini 2001a, Hosseini 2001b, Liu 2004a, Liu 2004c, Steigerwalt 2009, Duracková 2003).

In Belcaro 2006a blinding did not occur because of the nature of the interventions. There were four groups in this study: one group consumed Pycnogenol orally, the second group applied Pycnogenol locally (on the ulcer), the third group used Pycnogenol both orally and applied it locally while the fourth group did not receive any medical treatment. This study is judged to have a high risk of bias.

Incomplete outcome data

Seven of the 15 included trials were judged to have adequately addressed incomplete outcome data because no participants were lost to follow-up during the study period (Belcaro 2006a, Hosseini 2001b, Liu 2004a, Liu 2004c, Petrassi 2000, Steigerwalt 2009, Duracková 2003). In Cisár 2008 more than twice as many participants were lost to follow-up in the control group than in the group receiving the test drug. Therefore this study was judged to have a high risk of bias.

The remaining seven included trials were judged as having an unclear risk of bias. In three studies (Farid 2007, Trebatická 2006, Zibadi 2008) an "intention-to-treat" analysis was performed. However, it is not clear what the authors mean by the term e.g. whether missing

data were imputed. The other four studies that were judged as unclear are Arcangeli 2000, Belcaro 2008b, Hosseini 2001a, and Lau 2004. Hosseini 2001a used a crossover design but it is not reported whether the analyses were performed with first or second period data or both, or how participants who were lost to follow-up were dealt with in the analysis. In Arcangeli 2000 and Lau 2004 it is not reported whether all randomised participants completed the study and whether analyses were done on data from all outcomes for all participants. In Belcaro 2008b it is stated that 11 participants were lost to follow-up but it is not reported how this was addressed in the analysis.

Selective reporting

The protocol for each included trial was searched for in the trials registries mentioned under 'Search methods for identification of studies'. Studies that do not have a protocol available can at best be judged as having an unclear risk of bias with regards to selective reporting. This was the case in all studies except Zibadi 2008. In addition, we assessed whether reports stated the pre-specified study outcomes in the Methods section and judged those that did not as having a high risk of bias. This was the case in 13 studies (all except for Cisár 2008 and Hosseini 2001a which pre-specified their outcomes). All outcomes pre-specified in Zibadi 2008's protocol were addressed in the study, but there were outcomes reported in the study that were not pre-specified in the protocol. No outcomes were reported in the Methods section of the study. This trial was judged to have a high risk of bias.

Other potential sources of bias

For the judgement of this domain, we focused on the reporting of baseline characteristics (not relevant for the two crossover studies) and source of funding.

All studies except Duracková 2003 reported baseline characteristics separately for the treatment and control groups and we therefore judged them to have a low risk of bias. Duracková 2003 was judged to have an unclear risk of bias because the age of the participants was not reported separately for the treatment and control groups.

Horphag Research Ltd, the manufacturer and holder of Pycnogenol's registered trademark, funded seven of the studies included in this review (Belcaro 2006a, Cisár 2008, Farid 2007, Hosseini 2001b, Lau 2004, Trebatická 2006, Zibadi 2008). These were judged to have an unclear risk of bias. The source of funding was not reported in six of the included studies (Arcangeli 2000, Belcaro 2008b, Liu 2004a, Liu 2004c, Petrassi 2000, Steigerwalt 2009) and

they were also judged as having an unclear risk of bias. Hosseini 2001a was funded by companies other than Horphag Research Ltd and was judged to have a low risk of bias.

Effects of interventions

We grouped the included studies according to the type of chronic disorders involved and reported findings for the outcomes as pre-specified in our review protocol, when available. Our primary outcome 'all-cause mortality' was not addressed in any of the studies. While we would have liked to report on the change in symptoms or signs from baseline for several outcomes, this was often not possible as studies did not provide the information required to calculate this (e.g. SD of change). In such cases, if the baseline characteristics were balanced across the comparison groups, we assessed the difference in outcomes at the end of treatment. This is not ideal since the studies are all small (ranging from 11 to 156 participants). Furthermore, in some studies key results were missing from some or all relevant outcomes, for example results were reported only for the treatment group but not for controls, or no measure of variation (or exact p-value) was reported to allow for calculation of SD. Outcomes for which results are in part missing and estimates of effect that could not be calculated are presented in additional tables which show only the results as reported in the studies (Table 2; Table 3; Table 4; Table 5; Table 6; Table 7; Table 8; Table 9; Table 10; Table 11; Table 12; Table 13; Table 14).

Efficacy: Asthma

One crossover study (N = 26) conducted in Iran assessed the effect of four weeks treatment with Pycnogenol versus placebo in adults (Hosseini 2001a). In another study (parallel group design, N = 60) in the USA, Pycnogenol was compared with placebo in children over a period of three months (Lau 2004).

Participant-reported clinical outcomes

Asthma symptom scores were measured by both Hosseini 2001a and Lau 2004, but due to insufficient information results could not be evaluated (Table 2). We have contacted the study authors for additional information and are awaiting their response. In Lau 2004 all 30 participants in the Pycnogenol group reported a decrease in asthma symptoms at the end of the treatment period compared to 16/30 in the control group, risk ratio (RR) 1.85 (95% CI 1.32 to 2.58). In the same study the number of participants who stopped use of an albuterol inhaler at the end of the treatment period was 18/30 in the Pycnogenol and 3/30 in the control group (RR 6.0; 95% CI 1.97 to 18.25). The mean number of albuterol inhaler puffs per 24 hours was also measured in Lau 2004. The SD of change was not provided; we've

contacted the study authors and are awaiting their response. We could however compare the final values (at the end of the three months treatment period) and found that a significantly lower number of puffs were needed per 24 hours with Pycnogenol compared to placebo, mean difference (MD) -2.1 (95% CI -2.53 to -1.67). The baseline values were similar (Table 2).

Investigator-reported clinical outcomes

Peak expiratory flow was measured in Lau 2004, but results were not evaluable (Table 2). We have contacted the authors for additional information and are awaiting their response. In Hosseini 2001a there was a statistically significant improvement in pulmonary function at the end of the one month treatment period when comparing Pycnogenol with placebo. The MD for the forced expiratory volume in one second (FEV_1) was 7.0 (95% CI 0.10 to 13.90) and for FEV_1/forced vital capacity (FVC) the MD was 7.70 (95% CI 3.19 to 12.21).

Efficacy: Attention deficit hyperactivity disorder

One study (N = 61) in which Pycnogenol versus placebo treatment was given to children for a month was conducted in Slovakia (Trebatická 2006).

Participant-reported clinical outcomes

Parents and teachers evaluated hyperactivity and inattention: teachers by means of CAP (Child Attention Problems Teacher Rating Scale) and CTRS (Conner's Teacher Rating Scale) and parents by means of CPRS (Conner's Parent Rating Scale). Results were only reported in a figure together with exact p-values comparing final values (end of month one) of Pycnogenol versus placebo. Since the baseline CAP scores (inattention and hyperactivity) of the Pycnogenol and placebo groups were the same, and the percentage change at the end of the one month treatment period relative to baseline was reported for CTRS, we could compare the change in each group for these two outcomes. However, for CPRS only the final values could be compared. We've contacted the authors for additional information and are awaiting their response. In the mean time, where relevant, we've extracted the mean scores or percentages from the figures and used the p-values to calculate the relevant standard errors. A decrease in CAP, CTRS and CPRS represent an improvement in inattention and hyperactivity. The Pycnogenol group reported a significant improvement in inattention at the end of treatment compared to control [CAP score MD 2.0 (95% CI 0.61 to 3.39); CTRS (% change) MD 14.0 (95% CI 0.34 to 27.66)]. With regards to the CPRS score for inattention, the study only reported that non-significant changes occurred in both groups. The Pycnogenol group also reported an improvement in hyperactivity compared to control, but this was only statistically significant for CAP [CAP score MD 2.0 (95% CI 0.10 to 3.90)]

and not for CTRS (% change) MD 4.0 (95% CI -3.19 to 11.19). The difference in end of month one CPRS scores between the Pycnogenol and placebo groups was not significant, MD -3.50 (95% CI -7.15 to 0.15).

Investigator-reported clinical outcomes

Psychologists evaluated the children's visual-motoric coordination and concentration and found an improvement with Pycnogenol (MD 8.0; 95% CI 0.16 to 15.84).

Biomarkers of oxidative stress

Glutathione formed from amino acids in human cells can occur either in a reduced (GSH) or oxidized form (GSSG). A decrease in oxidative stress will be reflected in an increased GSH/GSSG. The percentage change in GSH/GSSG was obtained from Dvoráková 2007 which reports on the same study as Trebatická 2006. Results were not reported sufficiently to calculate an effect size (Table 3); study authors have been contacted and we are awaiting their response.

Efficacy: Chronic venous insufficiency

In two studies (Arcangeli 2000 N = 40; Petrassi 2000 N = 20) conducted in Italy, adults were treated with Pycnogenol versus placebo for a period of two months (60 days).

Participant-reported clinical outcomes

Both studies evaluated the change in scores of heaviness, swelling and pain of the legs by using the same four-point symptom scale where 0 = symptom absent and 3 = symptom severe (see table of 'Characteristics of included studies'). While Petrassi 2000 stated in their Methods section that they also evaluated the change in scores for the symptoms night cramps and paraesthesiae, no results for these two symptoms were reported. We have contacted the study authors for this information and are awaiting their response.

Because the SD of change is not provided in either study we could not compare the change in symptoms in the comparison groups (Table 4). We have contacted the corresponding author of Petrassi 2000 and are awaiting their response; the author of Arcangeli 2000 is not contactable. We conducted a meta-analysis of the final results (end of month two) of the two studies (60 participants). The heaviness score (MD -0.72; 95% CI -0.91 to -0.54; fixed effect, heterogeneity $Chi^2 = 0.0$, $I^2 = 0\%$) (Analysis 3.1; Figure 4) as well as swelling (MD -0.46; 95% CI -0.67 to -0.25; fixed effect, heterogeneity $Chi^2 = 2.31$, $I^2 = 57\%$) (Analysis 3.2; Figure 5) was significantly lower in the Pycnogenol group compared to placebo. Pains scores in Arcangeli 2000 were also lower with Pycnogenol (MD -0.59; 95% CI -1.02 to -0.16). Petrassi

2000 reported that "the pain parameter could not be evaluated because of the small number of participants who showed a positive score". It is important to note that when comparing only final values (and not the change in each group) it is assumed that the baseline values are balanced which would be expected to be the case in RCTs that are sufficiently large. This was not the case in Arcangeli 2000 and Petrassi 2000. In Arcangeli 2000 heaviness score was 19.8% greater, legs were 12% more swollen and patients experienced 13.4% more pain at baseline in the Pycnogenol group compared to placebo. In Petrassi 2000 mean heaviness score was 21.3% greater and there was 25% more leg swelling in the Pycnogenol group. Baseline values for pain were not reported in this study.

Both studies reported the percentage of participants that had disappearance of the symptoms heaviness and swelling at the end of the treatment period, and Arcangeli 2000 also reported on pain. However, only effect sizes for Arcangeli 2000 could be calculated because Petrassi 2000 did not report results for the placebo group. We have contacted the study authors for this information and are awaiting their response. In Arcangeli 2000 the RR for disappearance of heaviness was 15.0 (95% CI 0.91 to 246.20), disappearance of swelling (27.0; 95% CI 1.71 to 425.36) and disappearance of pain (25.0; 95% CI 1.58 to 395.48) in the Pycnogenol group versus the placebo.

Investigator-reported clinical outcomes

In Arcangeli 2000 physicians judged the efficacy of the treatment on a pre-specified scale where 1 = poor and 4 = very good. We found Pycnogenol to be significantly more efficacious compared to placebo (RR 4.75; 95% CI 1.97 to 11.48). This same outcome was assessed in Petrassi 2000 but the combined result of both the randomised and non-randomised arm of the study was reported. This was also the case for the other eligible outcome namely change in ambulatory venous pressure. We've contacted the study authors for the additional information we require and are awaiting their response. Arcangeli 2000 measured venous blood flow and reported simply that no difference in either of the groups was found at the end of the treatment period compared to baseline.

Efficacy: Diabetes mellitus

Four studies (N = 201) were performed on adults with diabetes (Belcaro 2006a, Liu 2004a, Steigerwalt 2009, Zibadi 2008) but none of them had the same primary outcomes. Belcaro 2006a conducted a study in Italy on 30 insulin-dependent diabetics. They evaluated the effect of Pycnogenol (orally, locally, and both orally and locally) versus no medical treatment on foot ulcers for six weeks. In Liu 2004a the effect of a 12 week Pycnogenol versus placebo treatment on blood glucose levels was assessed in China on 77 type II diabetics. Steigerwalt

2009 conducted a study in Italy evaluating the two months treatment effect of Pycnogenol versus placebo on retinopathy in 46 type II diabetics, whereas Zibadi 2008 assessed the effect of a 12 week Pycnogenol versus placebo treatment on 48 hypertensive type II diabetics in the USA.

Participant-reported clinical outcomes

In Belcaro 2006a participants reported on the change in symptoms related to the microcirculation where a score of 0 represents absence of symptoms and a score of 10 very severe symptoms. The SD of change was not given (we have contacted the study authors and await their response), hence we used the final values (Table 5). The baseline values were similar (Table 5). This study had three intervention groups (local plus oral Pycnogenol; oral Pycnogenol; local Pycnogenol) and one control group (no treatment). Since the intervention group of all the other included studies involved oral Pycnogenol, we decided to select this group and exclude the other two groups from the analysis. The microcirculation-related symptoms were not significantly lower in the Pycnogenol group compared to the control, MD -1.30 (95% CI -4.02 to 1.42).

Steigerwalt 2009 assessed the change in visual acuity as subjectively reported by participants. However, no results for the placebo group are reported. We have contacted the study authors and are awaiting their response.

Investigator-reported clinical outcomes

In Belcaro 2006a the final values of area of ulceration (mm^2) for Pycnogenol (oral) were not significantly lower compared to control, MD -4.0 (95% CI -9.92 to 1.92). However, the transcutaneous PO_2 (mm Hg) was significantly higher in the Pycnogenol (oral) group compared to the control (MD 7.0; 95% CI 3.18 to 10.82) but not significantly lower for transcutaneous PCO_2 (mm Hg) (MD -1.0; 95% CI -3.79 to 1.79). Results for the outcome skin flux at rest were reported insufficiently (Table 5); we have contacted the study authors and are awaiting their response. The outcome venoarteriolar response (LDF units) was reported in medians and ranges (Table 6).

Liu 2004a measured the change in blood glucose (mmol/l) and plasma $HbA1_c$ (%) between baseline and week 12 and analysed it with the Mann-Whitney rank sum test. The results of this change were therefore reported as medians and interquartile ranges (Table 7).

Zibadi 2008 also measured change in blood glucose (mg/dl) and $HbA1_c$ (%), and in addition urinary albumin levels (mg/l) (Table 8). Because the SD of change was not reported (we've

contacted the study authors for this information and are awaiting their response), we compared the final values (end of week 12) of the two groups. Blood glucose levels in the Pycnogenol group were not significantly lower compared to control (MD -26.70; 95% CI -55.79 to 2.39). Baseline values were not quite balanced as glucose levels (mg/dl) in the Pycnogenol group was 6.8% less compared to placebo. Furthermore, in Zibadi 2008 the $HbA1_c$ was lower in the Pycnogenol versus placebo group at the end of week 12 (MD -0.9; 95% CI -1.78 to -0.02) but urinary albumin levels was not significantly lower (MD -13.90; 95% CI -31.09 to 3.29). The mean $HbA1_c$ at baseline in the Pycnogenol group was 2.5% less than placebo while the mean urinary albumin value at baseline were 20.8% less than placebo.

In Steigerwalt 2009 change in visual acuity was also evaluated using a Snellen chart. However, the results were reported separately for participants with moderate and mild edema (not pre-specified in the Methods section), thereby making it impossible to compare Pycnogenol and placebo for all randomised participants. For the same reason we could not analyse results for the outcomes change in retinal blood flow, diastolic blood flow relative to maximum systolic blood flow, retinal edema score and retinal thickness. We have contacted the study authors for the required information and are awaiting their response.

Biomarkers of oxidative stress

The concentration of nitric monoxide (nmol/l), a type of free radical that also has important functions in the body such as vasodilation, was measured in Liu 2004a. No results were reported, only that the difference between Pycnogenol and placebo was not statistically significant.

Efficacy: Erectile dysfunction

One small study (N = 21) conducted in Slovak Republic assessed the effect of three months treatment with Pycnogenol versus placebo in adult men (Duracková 2003).

Participant-reported clinical outcomes

ED symptom scores were measured with the help of the International Index of Erectile Function (IIEF-5) questionnaire (maximum score = 25; normal erectile function scores between 21 and 25) (see the table 'Characteristics of included studies'). The SD of change was not reported (Table 9). We have contacted the study authors for this information and are awaiting their response. Comparing the final values (end of month three) we found a significantly higher score with Pycnogenol treatment, MD 7.90 (95% CI 5.08 to 10.72). Comparison of the baseline mean ED symptom scores showed an 11.5% higher score in the

Pycnogenol group compared to placebo. A further reason for caution is the lack of comparative baseline data regarding age of participants which could be a potential confounder in ED studies.

Biomarkers of oxidative stress

Antioxidant activity in the blood was measured but results were not reported sufficiently (Table 9). We have contacted the authors for additional information and are awaiting their response.

Efficacy: Hypertension

Two studies with a total of 68 participants - Hosseini 2001b (crossover trial; USA; N = 11) and Liu 2004c (parallel-group trial; China; N = 58) - investigated the treatment effect of Pycnogenol versus placebo for a period of eight and 12 weeks respectively, in adults.

Investigator-reported clinical outcomes

Change in blood pressure was only measured directly by Hosseini 2001b; however no results were reported for the placebo group (Table 10). In Liu 2004c blood pressure changes were indirectly evaluated by monitoring the nifedipine dose needed to control participants' blood pressure. All participants received 20 mg nifedipine at the start of the treatment period and adjustments to the dose was made as necessary at each visit. The number of participants who used a reduced nifedipine dose at the end of the treatment period (week 12) was not significantly higher in the Pycnogenol group compared to placebo (RR 1.12; 95% CI 0.83 to 1.52). However, the number of participants in the Pycnogenol group who reduced nifedipine dose to 10 mg at the end of the 12th week of treatment was significantly higher compared to placebo (RR 4.29; 95% CI 1.63 to 11.27).

Biomarkers of oxidative stress

The concentration of nitric monoxide was measured in Liu 2004c; results were reported as medians and interquartile ranges (Table 11).

Efficacy: Osteoarthritis of the knee

In three studies with a total of 293 participants (Belcaro 2008b N = 156; Cisár 2008 N = 100; Farid 2007 N = 37) adults were treated with Pycnogenol versus placebo for a period of three months (12 weeks or 90 days). The studies were conducted in Italy, Slovakia and Iran respectively.

Participant-reported clinical outcomes

All three studies evaluated the effect of Pycnogenol on pain, stiffness, physical function (referred to as 'daily activities' in Cisár 2008) and overall effect by means of WOMAC (Western Ontario and McMaster Universities) scores. Additionally, in Belcaro 2008b, negative alterations in social functions and the sum of emotional parameters were also evaluated as osteoarthritis symptoms with the WOMAC instrument. According to Bellamy 2001 the WOMAC instrument is available either in a Likert scale or in a visual analogue format. Cisár 2008 used a Likert scale and Farid 2007 a visual analogue scale (VAS). It is not reported what type of scale Belcaro 2008b used, but the interpretation of the scale is reported (see 'Characteristics of included studies'). The results of these three studies could not be pooled due to Cisár 2008 who reported results in median WOMAC scores and Belcaro 2008b and Farid 2007 who reported the results insufficiently (Table 12). However, in Farid 2007, the final values of each group (end of month three) could be compared. Pain scores (MD -142.0; 95% CI -199.55 to -84.45), physical function scores (MD -529.0; 95% CI -741.59 to -316.41) and composite WOMAC scores (MD -730.0; 95% CI -1011.95 to -448.05) were significantly lower in the Pycnogenol group compared to placebo. However, stiffness scores were not significantly lower (MD -33.0; 95% CI -68.48 to 2.48). Inspecting the baseline values indicated that the Pycnogenol group had 3% less pain, 8.3% less stiffness, 4.3% less physical function and had overall 4.3% less osteoarthritis symptoms than the placebo group. In Cisár 2008 medians were presented graphically together with p-values but no range were reported to indicate the spread (Table 13). We have contacted the study authors for this information and are awaiting their response.

Change in the use of concomitant medication [or specific concomitant medication such as nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors (COX-2)] was monitored in each of the three studies. In Belcaro 2008b results for the reduction of NSAIDs use was reported as 58% for the Pycnogenol and 1% for the placebo group. We have contacted the study authors for clarification and interpretation of this outcome and are awaiting their response. Cisár 2008 reported that 38% in the Pycnogenol and 8% in the placebo group (50 participants in both groups) used a decreased analgesic dosage at the end of the three months treatment period, compared to start. This translates into a significant difference of 19/50 versus 4/50 events, RR 4.75 (95% CI 1.74 to 12.97). Farid 2007 reported on the change in frequency and dosage of NSAIDs and COX-2 inhibitor usage during the treatment period. Results were reported only in a figure from which we could not extract data accurately; we have contacted the study authors for the required information and are awaiting their response.

Investigator-reported clinical outcomes

In Belcaro 2008b physical performance at baseline and after three months of treatment was evaluated on a treadmill. Results were reported as means and ranges (Table 14).

Safety

Results for safety of the treatment across all seven chronic disorders, stratified as serious and non-serious, are presented in Table 15. None of the fifteen included studies assessed safety as a main outcome. All of the studies, except Duracková 2003 (which did not assess this outcome), evaluated safety of the treatment by asking participants to report on adverse events they experienced during the treatment period, and/or by reports from the caretaker (if participants were children) or investigator, and/or by analysing the levels of various biochemical parameters in order to assess whether or not the levels stayed within the range of physiological values during the treatment period.

Cessation of treatment use was classified as a serious adverse event. The only study that clearly reported that the reason for withdrawal from the study was related to the received treatment was Cisár 2008 where 2/50 participants from the Pycnogenol group left compared to 5/50 from the placebo group.

Non-serious adverse events were reported in the following studies: Hosseini 2001a, Liu 2004a, Liu 2004c, Trebatická 2006. The most frequently found adverse event was gastro-intestinal discomfort.

Discussion

Summary of main results

Our objectives were to assess both the efficacy and safety of Pycnogenol for the treatment of chronic disorders. The main finding of this review is that the current evidence-base is both incomplete and inadequate and therefore definitive conclusions about the effects of this intervention are not possible at this stage.

Overall completeness and applicability of evidence

Only fifteen studies, comprising 791 participants, were eligible for inclusion in this review. These addressed seven different disorders. Even for the same disorder outcomes assessed either differed, were measured in different ways or failed to provide sufficient information to

conduct an appropriate analysis. Sample size per study ranged from 11 to 156 participants. A major problem with small studies is that findings are unreliable due to the play of chance. Moore 1998 demonstrated that for results to be statistically accurate and clinically relevant a researcher requires nearly 500 people per group which can be obtained by either conducting such large trials or by pooling results from multiple studies of small size. They stress that single small trials are highly likely to provide misleading results. Thus despite the apparent positive findings of studies in this review the small sample size per study and limited number of studies per disorder precludes firm conclusions regarding the effects of Pycnogenol.

Another complicating issue is the heterogeneity in the way outcomes are presented across studies. In general, with the exception of participant-reported symptom scores, the outcomes per disorder varied across the different studies making it impossible to pool results from different studies. In some cases outcomes were not measured in an optimal manner. For example, in one of the two studies on hypertension, systolic and diastolic blood pressure was not reported directly but by the change in nifedipine dosage at the end of the treatment period, compared to baseline. Achieving standardisation of outcomes in trials that evaluate the same intervention for the same condition should be an important goal (Clarke 2007). Examples of such initiatives exist for cancer, rheumatology and chronic pain (Clarke 2007). Similarly the dosage and duration of Pycnogenol treatment across studies should be standardised.

Lastly, all studies were conducted in affluent countries and it is therefore not known to what extent the results can be applied to people in developing countries.

Quality of the evidence

A major problem with the current evidence-base is the potential risk of bias across studies (Figure 3). It is worth mentioning that the overall quality of reporting was poor which made judgements about study quality difficult. We have contacted authors of all of the included studies (except for one study of which the authors passed away) to ask for additional information (Appendix 5). We await their response which will hopefully allow us to make clearer judgements about the risk of bias.

Potential biases in the review process

It is unlikely that we have missed any relevant RCTs that have assessed the clinical efficacy or safety of Pycnogenol since apart from our electronic and manual searches we have contacted and obtained information about studies from the manufacturer of Pycnogenol. No

language restriction was applied to studies considered for our review. We included adults and children with any chronic disorder and used wide criteria for interventions and outcomes.

Our review highlights the inadequate reporting of study details by authors which makes judgements of study quality challenging. Reporting standards such as the Consolidated Standards of Reporting Trials (CONSORT) have been established for reporting studies and journal editors should ensure that these are applied as a condition for publishing.

We were unable to formally assess the likelihood of publication bias (selective reporting of positive findings) in this review as this was not possible due to the small number of studies per condition. However, as publication bias is more likely with small studies this could be a possible explanation of the positive findings seen in the studies we identified.

Agreements and disagreements with other studies or reviews

This is the first systematic review to specifically evaluate Pycnogenol's efficacy and safety for the treatment of chronic disorders. However, three systematic reviews explored the use of a variety of supplements, including Pycnogenol, on type II diabetes, asthma and osteoarthritis respectively (Bartlett 2008; Clark 2010; Henrotin 2010).

Bartlett 2008 examined the effects of nutritional supplementation for the treatment of type II diabetes. Of the three studies focusing on Pycnogenol only Liu 2004a was included in our review. Another study Spadea 2001 did not meet our eligibility criteria because the results for randomised participants were not reported separately (see table of 'Characteristics of excluded studies'). An additional article authored by W. Leydhecker in 1986 seems to be an unpublished study from the University Clinic of Wurzburg (Germany). Although we didn't come across this study in our search, this study was ineligible for inclusion in our review since the control Dexium has antioxidant properties. Bartlett 2008 only presented the findings as reporting in these studies and did not attempt to recalculate the estimates or synthesise the results quantitatively.

Clark 2010 assessed the efficacy of herb and plant extracts, including Pycnogenol, in the management of asthma. Two studies with Pycnogenol as the intervention were included (Hosseini 2001b; Lau 2004) and both are included studies in our review as well. Like us Clark 2010 noted the problem with variation in outcome measures across different studies. As an example they pointed out that FEV_1 was measured in five different ways across 17 of their included studies. In the two Pycnogenol studies Clark 2010 calculated an effect size for

the use of albuterol inhaler by measuring the number of puffs needed per 24 hours at the end of the treatment period and got the same results as we did. Regarding the risk of bias assessments Clark 2010 assessed only sequence generation, allocation concealment and blinding. For Hosseini 2001b their judgements were the same as ours but for Lau 2004 they judged allocation concealment as adequate compared to ours which was 'unclear'.

Henrotin 2010 aimed to "synthesize and evaluate scientific relevant data" on nutraceuticals that can "support health and physiological or functional benefit on osteoarthritis". Four clinical trials of Pycnogenol were included, three of which we have as included studies (Belcaro 2008b; Cisár 2008; Farid 2007). We excluded Belcaro 2008a as this reported on a non-random subsample of trial participants (see table of 'Characteristics of excluded studies' for reason of exclusion). Henrotin 2010 only stated what was reported in the various studies. Direct comparisons with our findings are therefore not possible. In contrast with our review (Figure 3), Henrotin 2010 judged Belcaro 2008b, Cisár 2008 and Farid 2007 to be of good to very good quality using a different instrument to ours. The criteria for this instrument, as described by Henrotin 2010, are presented in Table 16 (number 7).

We assessed the methodological quality of the abovementioned systematic reviews with the validated AMSTAR tool (Shea 2007) and present our findings in Table 16. The quality was poor, with the exception of Clark 2010.

Authors' conclusions

Implications for practice

Pycnogenol is marketed to aid in the treatment of the following conditions: ADHD, asthma, cholesterol/dyslipidaemia, CVI, diabetes, dysmenorrhoea, endometriosis, erectile dysfunction, hypertension, melasma, muscle cramps, osteoarthritis, peri-menopause, platelet function and retinopathy (American Botanical Council 2010). Our review shows that currently available evidence is not sufficient to support or cordone the use of Pycnogenol for the treatment of chronic conditions. Concern about long-term safety of antioxidant supplements exists (Bjelakovic 2007; Bjelakovic 2008a; Bjelakovic 2008b); the available evidence provides no assurance of the safety of Pycnogenol.

Implications for research

Well-designed, adequately powered randomised controlled trials of Pycnogenol are needed. Careful attention should be given to the outcomes to be assessed in future trials to ensure that selected outcomes are important to patients and are measured in a standardised manner.

Contributions of authors

AS developed the idea. AS wrote the protocol and review under the guidance of JV. AS and JV extracted all the data; AM extracted the results for all relevant outcomes. AM and AS summarised and analysed the results, with input from JV. JVi provided input at all stages and revised the protocol and review.

Declarations of interest

None known.

Characteristics of studies

Characteristics of included studies

Arcangeli 2000

Methods	RCT; parallel group design. Ethics approval by the "Ministry of Health". Treatment duration: two months after a two week run in period. During the run in period neither drugs acting on the cardiovascular system nor diuretics, analgesics or anti-inflammatory compounds were allowed. No follow-up after end of treatment.
Participants	Total participants: 40 (20 in each group). Country and setting: Italy; clinical centre. Inclusion criteria: adults with chronic venous insufficiency (CVI) as a result of deep vein thrombosis or idiopathic venous lymphatic deficiency. Diagnosis was based on clinical judgement. Exclusion criteria: not reported. Baseline characteristics: Treatment group: 25% males; age range 34 to 74 years, mean age 57.95 (SD 12.78) years. Control group: 40% males; age range 30 to 70 years, mean age 61.40 (SD 10.62) years. Concomitant medication: participants were not allowed to take drugs which act upon the cardiovascular system, diuretics, or analgesic and anti-inflammatory combinations during the treatment period. Diet: a standard diet determined according to participants' energy requirements had to be followed.
Interventions	Treatment: Pycnogenol; 100 mg three times per day for two months. Control: "visually matched" placebo; three times per day for two months. Route of administration: not reported; assumed to be oral.
Outcomes	Symptom scores (heaviness; swelling; pain of legs): collected at baseline, after 30 days and after 60 days of treatment; assessed by a clinical symptomatology score system where 0 = absent, 1 = light, 2 = moderate and 3 =

	severe; the percentage of participants who had disappearance of each symptom was also calculated. Venous blood flow: collected at baseline, after 30 and after 60 days of treatment; measured with a hand-held Doppler ultrasound. Clinical assessment of efficacy: collected at 60 days after treatment; assessed by a semi-qualitative scale where 1 = poor, 2 = moderate, 3 = good and 4 = very good. Clinical tolerability: participants were asked to report "adverse effects" anytime during treatment. Biochemical tolerability: blood samples were collected at baseline and after 60 days of treatment for blood tests (haematology, blood chemistry, liver functions, renal function); the unit of measurement for each blood test is specified in the article.
Notes	Funding source: not reported. Study date: 1989.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"...patients were randomly divided". However, the randomisation method is not reported.
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind". Although it is reported that the placebo "visually matched" the test drug, it is not clear whether the placebo was also matched in terms of other characteristics such as weight and taste. Pycnogenol is known to have a bitter, astringent taste.
Incomplete outcome data addressed?	Unclear	Not reported whether all randomised participants completed the study, i.e. whether data from all participants for all outcomes were collected.
Free of selective	No	Protocol not available; pre-specified outcomes not stated in the Methods section.

reporting?		
Free of other bias?	Unclear	Funding source not reported.

Belcaro 2006a

Methods	RCT; parallel group design. Treatment duration: six weeks. No follow-up after end of treatment.
Participants	Total participants: 30 (divided into three treatment- and one control group). Country and setting: not reported, assumed to be Italy; setting not reported. Inclusion criteria: insulin-dependent diabetics with foot ulcers appearing for the first time and had been present for at least two months; severe diabetic microangiopathy based on blood flow in tibial arteries exceeding 60 mm Hg as measured by Laser Doppler skin perfusion pressure. Exclusion criteria: severe stenosis or obstruction at the femoral or iliac artery level or recent venous thrombosis as indicated by colour duplex imaging; any clinical disease requiring treatment; severe bone or joint problems or limited mobility; uncontrolled diabetes; severe hypertension; signs of systemic infections; obesity; recent thrombosis (less than six months); and the presence of aneurysms or thrombi. *Baseline characteristics* Treatment groups: Pycnogenol oral and local treatment: 37.5% males; assumed mean age 54.3 (SD 4.4) years; assumed mean duration of disorder 11.3 (SD 2.6) years. Pycnogenol local treatment: 37.5% males; assumed mean age 55.0 (SD 5.0) years; assumed mean duration of disorder 11.0 (SD 2.4) years. Pycnogenol oral treatment: 66.7% males; assumed mean age 55.0 (SD 3.0) years; assumed mean duration of disorder 11.2 (SD 4.0) years. Control group: 50% males; assumed mean age 52.4 (SD 6.1) years; assumed mean duration of disorder 12.0 (SD 3.0) years. Concomitant treatment: all participants received general ulcer care daily that included washing and cleaning in water

	and a mild disinfectant (Citrosil, Italy), drying with soft paper tissue and dressed with nonallergic paper and an elastic-adhesive bandage (Tensoplast, South Africa). Exercise: an exercise plan that included an educational video explaining foot protection for diabetics during exercise was given to all participants. Friction-free socks were provided that also kept the medication in place during the study period.
Interventions	*Treatment* Pycnogenol oral and local treatment: Pycnogenol; 50 mg capsule three times per day orally for six weeks together with 100 mg powder from two 50 mg capsules placed on ulcerated area daily for six weeks. Pycnogenol local treatment: Pycnogenol; 100 mg powder from two 50 mg capsules placed on ulcerated area daily for six weeks. Pycnogenol oral treatment: Pycnogenol; 50 mg capsule three times per day orally for six weeks. Control: no Pycnogenol or other medication, standard ulcer care only as received by the three active treatment groups; for six weeks.
Outcomes	Microcirculation-related symptoms (e.g. pain): collected at baseline and after six weeks of treatment; signs and symptoms were measured by means of a clinical scale where 0 = absence of symptoms and 10 = very severe signs or symptoms. Area of ulceration: collected at baseline and after six weeks of treatment; the area of ulceration was copied on a transparent plastic sheet and the relative integral of the area recorded in a computerized Logitech (Palo, Alto, Calif) system; measured in mm^2. Percentage complete healing: collected after six weeks of treatment; no further detail reported. Microcirculatory parameters (transcutaneous PO_2 and PCO_2; skin flux at rest; venoarteriolar response): collected at baseline and after six weeks of treatment; transcutaneous PO_2 and PCO_2 were measured in mm Hg with a combined measurement (CombiuSensor Kontron, United Kingdom) after heating the skin to 44℃, the measurements were recorded after a period of 20 minutes of stabilization and capillarization of the area, and it was made at one centimetre away from the ulcer edge in non-inflamed or infected area where the skin was intact; skin flux at rest was measured by a Laser Doppler in LDF (laser Doppler flux) units; venoarteriolar response was also measured by a Laser Doppler. Because of high cost these parameters were only measured in the group receiving both the oral and local Pycnogenol

	treatment, the group receiving only the oral Pycnogenol as well as the control group. "Side effects": reported during the six week intervention period; measured by direct questioning about tolerability and compliance - particularly gastrointestinal problems, systemic and local skin alterations, signs of allergic reaction and any other manifestation.
Notes	Funding source: "The study was not sponsored by companies producing materials and products quoted in the article. The compound was supplied, without conditions, by Horphag Research Management SA, Geneva, Switzerland." Ethics approval: not reported. Percentage complete healing: there could have been more than one ulcer per patient. It is not clear whether all ulcers of a patient were completely healed in order to be counted as 'complete healed', or whether one ulcer healed was counted. The unit of randomisation was participants, not ulcers.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"Patients were randomly assigned to four groups." However, the randomisation method is not reported.
Allocation concealment?	Unclear	Not reported.
Blinding?	No	The control group received no treatment (also no placebo) while the three treatment groups got capsules for oral or local (or both) use.
Incomplete outcome data addressed?	Yes	No participants were lost to follow-up.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section.
Free of other bias?	Unclear	The study was funded by Horphag Research Ltd. This company is the manufacturer and holder of Pycnogenol's registered trademark.

Belcaro 2008b

Methods	RCT; parallel group design. Ethics approval by the ethical committee of the University of Pescara. Treatment duration: three months. No follow-up after end of treatment.
Participants	Total participants: 156 (77 in the treatment- and 79 in the control group). Country and setting: Italy; community setting (Cesarone 2002). Inclusion criteria: people with grade I or II osteoarthritis of one or both knees (classified by the American Rheumatism Association system), confirmed by x-ray performed by a qualified orthopaedist (Belcaro 2008a); WOMAC (Western Ontario and McMaster Universities) pain subscale index of at least 10 out of 20 (Belcaro 2008a); intermittent or constant pain in the target knee for at least 50% of the time during the last three months which required medical treatment with selective cyclooxygenase-2 (COX-2) inhibitors or other nonsteroidal anti-inflammatory drugs (NSAIDs) (Belcaro 2008a); able to perform the treadmill test; understand all questions from the WOMAC questionnaire. Exclusion criteria: secondary osteoarthritis due to a known disorder (Belcaro 2008a); joint injection of the target knee within the last six months (Belcaro 2008a); cardiovascular disease requiring drug treatment; diabetes; overweight; severe metabolic disorders; surgery or arthroscopy three months before inclusion; radiotherapy or chemotherapy; pregnant, breastfeeding or planned conception. Baseline characteristics: Treatment group: 50.6% males; mean age 48.6 (SD 8.0) years; mean global WOMAC score 79.2; mean of treadmill test 68 meters; distance (range) achieved with treadmill test 0 to 133 meters. Control group: 49.4% males; mean age 47.8 (SD 7.7) years; mean global WOMAC score 76.9; mean of treadmill test 65 meters; distance (range) achieved with treadmill test 12 to 98 meters. Concomitant medication: associated treatments prescribed by the participant's general practitioner were to be reported in a diary.
Interventions	Treatment: Pycnogenol; 50 mg capsule two times per day (after breakfast and dinner) for three months. Control: placebo that matched the test drug by appearance, size and shape; two capsules daily (after breakfast and dinner) for three months. Route of administration: orally.

Outcomes	Symptom scores [pain; stiffness; physical function; global score (sum of previous three scores); negative alterations in social functions; sum of emotional parameters]: collected at baseline and after three months of treatment; measured by the WOMAC index. The interpretation of the WOMAC scores: total score ranges from 0 (no symptoms) to 96; pain score ranges from 0 (no symptoms) to 20; stiffness score ranges from 0 (no symptoms) to 8; and physical function score ranges from 0 (no symptoms) to 68. Use of concomitant medication: participants kept a diary of medication prescribed by their general practitioner during the treatment period; expressed in percentage reduction at the end of the three months treatment period. Physical performance: collected at baseline and after three months of treatment; measured as the total distance in meters on the treadmill that could be covered at 3 km/hour or 8 km/h (inconsistently reported) with an inclination of 10% without pain. Vascular problems (clinical assessment of ankle and foot edema; ankle and foot edema measured by foot volumetry on randomly selected subsample): data for the clinical assessment was collected at baseline and after three months of treatment, whereas data on ankle and foot edema measured by foot volumetry was only collected after three months of treatment; edema was scored by the investigator as 0 = not visible, 1 = only visible after standing for a "long" time or in the evening, 2 = visible during the day but resolves overnight, 3 = visible during the day but only partially resolves overnight, 4 = present all the time; the actual foot volume at inclusion was defined as 100%. Reduction in health care costs (drugs and treatments besides NSAIDs; average management; hospital admissions; days hospitalised; indirect costs): information was recorded in a specific costing file during the treatment period; expressed in percentage reduction at the end of the three months treatment period. "Unwanted effects": reported by participants in diaries during the treatment period.
Notes	Funding source: not reported. However, in another article (Belcaro 2008a) in which a subset of the participants used for this study was evaluated for change in certain biochemical parameters, it is reported that the study was supported by Horphag Research Ltd.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Computer generated blocked randomisation.
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind". Although it is reported that the placebo was identical to the test drug in terms of appearance, it is not clear whether the placebo was also identical in terms of other characteristics such as weight and taste. The test drug is known to have a bitter, astringent taste.
Incomplete outcome data addressed?	Unclear	It is not clear what number of participants was included in the analysis or whether participants were analysed according to the group to which they were randomised. 6/77 participants were lost to follow-up from the treatment group and 5/79 from the control group.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section.
Free of other bias?	Unclear	Funding source not reported in Belcaro 2008b, but another linked study (Belcaro 2008a) suggests that Horphag Research was a sponsor. This company is the manufacturer and holder of Pycnogenol's registered trademark.

Cisár 2008

Methods	RCT; parallel group design. Ethics approval by the Local Ethical Committee of the University Hospital in Bratislava, Slovakia. Treatment duration: 12 weeks. Follow-up: assumed to be two weeks after end of treatment, at week 14.
Participants	Total participants: 100 (50 in each group). Country and setting: Slovakia; outpatients attending the Orthopaedics Department of the University Hospital Ružinov in Bratislava.

	Inclusion criteria: adults (> 25 years) with stage I or II osteoarthritis according to Kellgren-Lawrence in standard AP X-ray view in at least one target knee; mild to moderate pain in the target knee for at least three months preceding the study, and/or morning knee stiffness and/or knee crepitus; females must confirm that they are not presently pregnant and do not plan to get pregnant for at least one year after the end of the trial; postmenopausal women must have been amenorrhoeic for at least one year. Exclusion criteria: participation in another study less than 30 days before the start of the study; moderate or severe osteoarthritis (Kellgren-Lawrence stage III or IV); rheumatoid arthritis or other chronic inflammatory disease affecting the target joint; secondary osteoarthritis; arthroscopic surgery or other major surgery of the target knee; major trauma of the target knee; intra articular injection of corticosteroids or symptomatic slow acting drugs of osteoarthritis (SYSADOA) in target knee in the past three months prior to the study; acute infection of the target knee in the last six months, or if the participants started any form of physiotherapy in the three weeks prior to the study; having a significant psychiatric disorder (including depression) or receiving antipsychotic medication; breastfeeding. Baseline characteristics: Treatment group: 28% males; "average" age 54 (range 25 to 65) years; "average" body mass index (BMI) 27.3 (range 16.9 to 35.4) kg/m^2. Control group: 36% males; "average" age 54 (range 30 to 65) years; "average" BMI 27.2 (range 20.7 to 37.2) kg/m^2. Concomitant medication: participants could use NSAIDs or other analgesics prescribed prior to the start of the study and could change the dose and frequency of drug intake, but they had to report changes at each visit.
Interventions	Treatment: Pycnogenol; 50 mg pills three times per day with meals for 12 weeks. Control: placebo that matched the test drug in terms of appearance; three pills per day with meals for 12 weeks. Route of administration: orally.
Outcomes	Symptom scores (pain; stiffness; ability to perform daily activity; total WOMAC score): collected at baseline and then every two weeks of treatment until the end of the study at week 14; measured by the WOMAC questionnaire (in Slovakian language) that rates pain, stiffness and ability to perform daily activity on a five-point Likert scale. Measuring pain with a visual analogue scale (VAS): "filled in by the patients each week during the whole study (14 weeks)"; intensity of pain is rated on a visual analogue scale where 0 = no pain and 100 = very severe pain. Change in analgesic use: collected at baseline and then "at each visit" (assumed to be every four weeks); reported in percentage reduction or increase.

	"Adverse effects": "Patients were asked every 2 weeks to report any unwanted or unusual effects". Safety by means of basic biochemical parameters (glucose; uric acid; total cholesterol; HDL-cholesterol; LDL-cholesterol; triacylglycerol; high sensitivity C-reactive protein; gamma-glutamyl transferase; alkaline phosphatase; aspartate aminotransferase; alanine aminotransferase): collected at baseline, after three months of treatment and at the end of the study (week 14); fasting venous blood were drawn in the mornings and the serum were analysed by "standard biochemical procedures using the Hitachi 911 automatic analyser and kits, Roche, Switzerland".
Notes	Funding source: : "This study was supported by Horphag Research Ltd, partly by VEGA Grant No. 1/2294/05, 1/1157/04 and 1/3037/06 of Ministry of Education of Slovakia and Mind and Health, civil association." Duration of the trial: not clear from the article. "Patients were investigated at the start, at 3 months and 4 weeks after finishing treatment." From this quote it looks as if the treatment was given for three months (12 weeks) after which there was a four week wash-out period before the final follow-up data collection was performed (in other words a total study duration of 16 weeks). However, the results are reported, inter alia, at weeks 12 and 14 as well as at week 15. This does not correspond with the above quote.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"The subjects were randomly allocated..." However, the randomisation method is not reported.
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind" and that the placebo was identical to the test drug in terms of appearance. However, it is not reported whether the placebo was also identical in terms of other characteristics such as weight and taste. The test drug is known to have a bitter, astringent taste.
Incomplete outcome data addressed?	No	"Data of all patients were evaluated in the intention-to-treat analysis." However, it is not described what the primary study authors mean with the term "intention-to-treat analysis" and how they handled the missing data from participants who were lost to follow-up. 6/50 participants were lost to follow-up from the treatment group and 13/50 from the control group - big difference.

Free of selective reporting?	Unclear	Protocol not available.
Free of other bias?	Unclear	The study was, amongst others, funded by Horphag Research Ltd. This company is the manufacturer and holder of Pycnogenol's registered trademark.

Duracková 2003

Methods	RCT; parallel group design. Ethics approval by the Ethical Committee of the Comenius University Hospital, Slovak Republic. Treatment duration: three months. Follow-up: one month after end of treatment, at the end of month four.
Participants	Total participants: 21 (13 in the treatment- and 8 in the control group). Country and setting: not reported, assumed to be Slovak Republic; setting not reported. Inclusion criteria: men with erectile dysfunction (ED) as determined by means of the International Index of Erectile Function (IIEF-5) which consists of a questionnaire of five questions where 25 points is the maximum score. Exclusion criteria: acute inflammatory cardiovascular disease; renal failure; hepatic insufficiency; endocrine abnormalities (testosterone deficit); psychiatric disorders; no concomitant use of other therapies for ED. Baseline characteristics: Treatment group: 100% males; "average" ED score (as measured by IIEF-5) 12.6 (unspecified measure of variation 1.1). Control group: 100% males; "average" ED score (as measured by IIEF-5) 11.3 (unspecified measure of variation 1.3). No further detail per group is reported. Overall age (n=21): "average" age 46.5 (unspecified measure of variation 12.5) years, range 22 to 69 years. Concomitant medication: none permitted (also no vitamin C and E supplements).
Interventions	Treatment: Pycnogenol; two 20 mg pills three times per day (total of 120 mg/day) for three months. Control: placebo; two pills three times per day for three months. Route of administration: orally.
Outcomes	Symptom scores: collected at baseline, and at the end of the first, second and third month of treatment, as well as at the end of month four (one month after end of treatment); assessed using IIEF-5 questionnaire where normal function

	= 21 to 25 points, mild ED = 16 to 20 points, moderate ED = 11 to 15 points and severe ED = "less than 10 points". Total cholesterol levels: collected at baseline, at the end of the first and third month as well as at the end of month four (one month after end of treatment); analysed by standard biochemical procedures using a Hitachi 911 automatic analyser (Roche, Switzerland); measured in mmol/l. LDL-cholesterol levels: collected at baseline, at the end of the first and third month as well as at the end of month four (one month after end of treatment); analysed by standard biochemical procedures using a Hitachi 911 automatic analyser (Roche, Switzerland); measured in mmol/l. HDL-cholesterol levels: collected at baseline, at the end of the first and third month as well as at the end of month four (one month after end of treatment); analysed by standard biochemical procedures using a Hitachi 911 automatic analyser (Roche, Switzerland); measured in mmol/l. LDL/HDL ratio: collected at baseline, at the end of the first and third month as well as at the end of month four (one month after end of treatment). Triacylglycerol (TAG) levels: no detail reported. Antioxidant activity in the blood: collected at baseline, at the end of the first and third month as well as at the end of month four (one month after end of treatment); determined by the ferric reducing ability of plasma (FRAP) method; measured in mmol of trolox/l; reported in percentage where 100% is the antioxidative activity of plasma before the trial.
Notes	Funding source: "This study was supported partly by VEGA grants No. 1/8303/01, 1/9243/02 of Ministry of Education of the Slovak Republic and by Drug Research Institute, Modra, Slovak Republic."

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"Selection to the different groups was randomised." However, the randomisation method is not reported.

Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind". However, it is not reported whether the placebo was identical to the test drug in all important aspects (i.e. matched in terms of shape, size, colour, taste, and weight).
Incomplete outcome data addressed?	Yes	No participants were lost to follow-up.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section.
Free of other bias?	Unclear	Incomplete baseline characteristics, i.e. unclear whether the participants of the treatment and control groups were similar with respect to various important baseline characteristics.

Farid 2007

Methods	RCT; parallel group design. Ethics approval by the ethical committee of Mashhad Medical University. Treatment duration: three months. No follow-up after end of treatment.
Participants	Total participants: 37 (19 in the treatment- and 18 in the control group). Country and setting: Iran; Rheumatology Department of Mashhad Medical University. Inclusion criteria: adults (25 to 65 years old) with primary osteoarthritis in the knee (according to the American College Rheumatology criteria grade I or II); WOMAC pain subscale index of at least 40 at baseline; intermittent or constant pain in the target knee for at least 50% of the time in the last three months that required medical treatment in the form of COX-2 inhibitors or other NSAIDs on most days. Exclusion criteria: secondary osteoarthritis; arthroscopy, surgery, or a joint injection of the target knee within the previous six months; prior history of knee joint replacement; any serious systemic disease; any other chronic inflammatory disease; use of any supplement apart from a multivitamin daily. Baseline characteristics: Treatment group: 11.1% males; mean age 47.5 (SD 7.4) years; mean BMI 22.7 (SD 3.2)

	kg/m^2; mean duration of disorder symptoms 3.8 (SD 5.1) years; 38.9% participants had knee osteoarthritis grade I; mean NSAIDs or COX-2 inhibitors use 15.6 (SD 4.3) days per month; mean pain WOMAC score 292 (SD 101); mean stiffness WOMAC score 110 (SD 66); mean physical function WOMAC score 997 (SD 352); mean composite WOMAC score 1400 (SD 482). Control group: 5.9% males; mean age 48.9 (SD 9.6) years; mean BMI 23.5 (SD 2.8) kg/m^2; mean duration of disorder symptoms 4.5 (SD 4.7) years; 41.2% participants had knee osteoarthritis grade I; mean NSAIDs or COX-2 inhibitors use 14.8 (SD 5.6) days per month; mean pain WOMAC score 301 (SD 119); mean stiffness WOMAC score 120 (SD 63); mean physical function WOMAC score 1042 (SD 420); mean composite WOMAC score 1463 (SD 552). Concomitant medication: COX-2 and other NSAIDs as medical treatment for pain in the target knee.
Interventions	Treatment: Pycnogenol; 50 mg pills three times per day for three months. Control: placebo that matched the test drug in terms of appearance; three times per day for three months. Route of administration: orally.
Outcomes	Symptom scores (pain; stiffness; physical function; composite WOMAC score): collected at baseline and then after 30, 60 and 90 days of treatment; measured by the WOMAC index which consists out of a total of 24 visual analogue scales. Use of concomitant medication (NSAIDs and COX-2): collected after 30, 60 and 90 days of treatment; participants were asked to keep a diary of medication usage (frequency and dose); data are reported as change in the number of pills per patient per month. Participants' treatment compliance: collected after 30, 60, and 90 days of treatment; measured by means of pill counting. Clinical adverse events: collected after 30, 60 and 90 days of treatment; volunteered reporting by participants or data are extracted by questioning. Safety by means of biochemical parameters (fasting blood glucose; alanine aminotransferase; aspartate aminotransferase; urea; creatinine; complete blood count; haemoglobin levels; hematocrit levels): collected at baseline and after 90 days of treatment; assessed by the clinical laboratory of Mashhad Medical School.
Notes	Funding source: "This research was supported by Horphag Research, Inc which also provided the supplement and

	placebo pills." Title: the claim made about stiffness in the title of this study is not reflected in the results.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"...patients...were allocated randomly to either..." However, the randomisation method is not reported.
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind" and that the placebo was identical to the test drug in terms of appearance. However, it is not reported whether the placebo was also identical in terms of other characteristics such as weight and taste. The test drug is known to have a bitter, astringent taste.
Incomplete outcome data addressed?	Unclear	"Analysis was performed according to the intention-to-treat principle." However, it is not described what the primary study authors mean with the term "intention-to-treat analysis" and how they handled the missing data from participants who were lost to follow-up. 1/19 participants were lost to follow-up from the treatment group and 1/18 from the control group.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section.
Free of other bias?	Unclear	The study was funded by Horphag Research Ltd. This company is the manufacturer and holder of Pycnogenol's registered trademark.

Hosseini 2001a

Methods	RCT; crossover design. Ethics approval by the Human Subjects Committee of Mashhad University of Medical Sciences, Mashhad, Iran. Treatment duration: four weeks per arm. No follow-up after end of treatment.

Participants	Total participants: 26 enrolled; 22 completed the first period and 19 completed the second period. Country and setting: Iran; Allergy Clinic of Mashhad University of Medical Sciences. Inclusion criteria: adults (18 to 60 years old) with asthma according to the American Thoraic Society criteria; baseline forced expiratory volume in one second (FEV_1) should be 30 to 75% of predicted normal value, with an increase in FEV_1 of > 15% of pretreatment value after two puffs of a beta-adrenergic agonist. Exclusion criteria: having emphysema, bronchitis, renal, hepatic, cardiac, or endocrine disease; pregnant women and women of childbearing potential; NSAIDs use (including aspirin); vitamin supplement use; unwilling to exclude wine from their diet during the study period. Baseline characteristics: 45.5% males (10/22); mean age 32 (range 18 to 50) years; mean duration of disorder 8 (range 1 to 16) years. Concomitant medication: usual medications could be used except for glucocorticoids, leukotriene antagonists, multivitamins, aspirin and any other NSAIDs.
Interventions	Treatment: Pycnogenol; 1 mg/lb/day (maximum 200 mg/day) for four weeks. Control: placebo pills for four weeks. Wash-out period: none. Route of administration: orally.
Outcomes	Symptom scores: collected at baseline, at the end of the fourth week (after treatment with either the test drug or placebo) and at the end of the eighth week (after four weeks on the remaining treatment option); measured by means of a symptom severity scale where 1 = mild intermittent, 2 = mild persistent, 3 = moderate persistent, and 4 = severe persistent. Pulmonary functions [% predicted FEV_1; FEV_1/forced vital capacity (FVC)]: collected at baseline, at the end of the fourth week (after treatment with either the test drug or placebo) and at the end of the eighth week (after four weeks on the remaining treatment option); measured by means of spirometry Cysteinyl-leukotrienes C_4, D_4, and E_4 levels: collected at baseline, at the end of the fourth week (after treatment with either the test drug or placebo) and at the end of the eighth week (after four weeks on the remaining treatment option); assayed in triplicate with the use of a Cayman Chemical Cysteinyl-Leukotriene Enzyme Immunoassay Kit (Ann Arbor, MI); expressed in pg/ml.

	"Adverse experiences": all symptoms that were not observed to be present at baseline were recorded as "adverse experiences"; it is not reported whether the participants or investigators or both recorded the symptoms.
Notes	Funding source: the test drug and placebo was a "kind gift" of Cognis Corporation (Kankakee, IL). The study was also funded by Arizona Foundation and other unspecified grants.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"Subjects were randomly assigned to receive Pycnogenol...or placebo pills..." However, the randomisation method is not reported.
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind". However, it is not reported whether the placebo was identical to the test drug in all important aspects (i.e. matched in terms of shape, size, colour, taste, and weight).
Incomplete outcome data addressed?	Unclear	It is not clear what number of participants was included in the analysis. In total, 7/26 participants were lost to follow-up of which four were from the first period and three from the second period. Furthermore, it is not reported whether the analysis was based on the first period data only, or both.
Free of selective reporting?	Unclear	Protocol not available.
Free of other bias?	Yes	Trial was not sponsored by the manufacturer of Pycnogenol.

Hosseini 2001b

Methods	RCT; crossover design. Ethics approval by the Institutional Review Board of the University of Arizona, United States of America (USA). Treatment duration: eight weeks per arm, after a one week run in period. During the run in period all participants took

	placebo pills. No follow-up after end of treatment.
Participants	Total participants: 11. Country and setting: not reported, assumed to be the USA; setting not reported. Inclusion criteria: non-smoking people with mild hypertension (stage I) who complied fully to take the provided placebo pills during the run in period; blood pressure measured three times in sitting patients after a fifteen minute rest should give a systolic blood pressure of between 140 and 159 mm Hg, and/or diastolic blood pressure between 90 and 99 mm Hg. Exclusion criteria: taking antihypertensive medication; taking NSAIDs, including aspirin; use of tobacco; taking any vitamin supplements other than one multivitamin tablet daily. Baseline characteristics: 63.6% males; mean age 50.3 (SD 9.3) years. Concomitant medication: permitted, but not specified. Diet: participants were asked to exclude wine from their diets for the duration of the study.
Interventions	Treatment: Pycnogenol; four 50 mg pills per day (encouraged to be taken in the morning); for eight weeks. Control: four placebo pills per day (encouraged to be taken in the morning); for eight weeks. Wash-out period: none. The following reason was reported: "...we have previously shown that Pycnogenol's effects on platelet aggregation in smokers disappeared three days after the cessation of its use." Route of administration: orally.
Outcomes	Concomitant medication use: not reported when collected, assumed to be only after the 16 week study period; data obtained by questioning participants. Blood pressure (systolic and diastolic): collected at baseline (data from run in period and week 0 combined), and then at the end of week seven and eight as well as at the end of week 15 and 16; the results of week seven and eight as well as of week 15 and 16 were combined to produce the final result after each period; measured in triplicate in a sitting position after a fifteen minute rest; measured in mm Hg. Participants' treatment compliance: collected after the one week run in period as well as after week eight and week 16;

	measured by means of pill counting. Thromboxane B2 levels: collected at baseline and then at the end of week seven and eight as well as at the end of week 15 and 16; the results of week seven and eight as well as of week 15 and 16 were combined to produce the final result after each period; assayed in triplicate by Neogen Corportaion (Lexington, KY) thromboxane B2 enzyme-linked immuno-absorbent assay (ELISA) kit; measured in ng/ml. Adverse events: not reported when collected, assumed to be after each eight weeks arm; data collected by questioning participants. Safety by means of blood tests: collected at baseline and then at the end of week seven and (assumed) eight as well as at the end of week 15 and 16; the results of week seven and eight as well as of week 15 and 16 were combined to produce the final result after each period; no further detail was provided.
Notes	Funding source: "The Pycnogenol pills and placebo were obtained from the Cognis Corporation (LaGrange, Illinois)." The study was "supported by a grant from Horphag, Inc".

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	"...randomized using a statistical formula prepared by the Biostatistics department..."
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind". However, it is not reported whether the placebo was identical to the test drug in all important aspects (i.e. matched in terms of shape, size, colour, taste, and weight).
Incomplete outcome data addressed?	Yes	No participants were lost to follow-up.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section.

Free of other bias?	Unclear	The study was funded by Horphag Research Ltd. This company is the manufacturer and holder of Pycnogenol's registered trademark.

Lau 2004

Methods	RCT; parallel group design. Ethics approval by the Loma Linda University Institutional Review Board for Human Studies, California, USA. Treatment duration: three months after a one week run in period. It is not reported what the purpose of the run in period was. No follow-up after end of treatment.
Participants	Total participants: 60 (30 in each group). Country and setting: USA; recruited from the Pediatric Teaching Office of Loma Linda University Children's Hospital (California) and from local physicians' clinics. Inclusion criteria: children (6 to 18 years old) with mild to moderate asthma as defined by the American Thoracic Society criteria; 50 - 85% of predicted normal FEV_1 and increase of 12% or more after two puffs of rescue inhaler; a severe asthma attack or lower respiratory tract infection in one month before the start of the trial. Exclusion criteria: unable to co-operate with pulmonary function and/or laboratory tests; unable to follow instructions; unable to swallow pills; taking steriodal- or nonsteroidal anti-inflammatory drugs. Baseline characteristics: Treatment group: 57% males; mean age 14 (range 6 to 16) years; % predicted peak expiratory flow (PEF) 69.7 [standard error of the mean (SEM) 1.7]; number of participants using rescue inhaler as needed 30; number of participants using Accolate 5. Control group: 60% males; mean age 14 (range 7 to 18) years; % predicted PEF 69.9 (SEM 1.6); number of participants using rescue inhaler as needed 30; number of participants using oral medication (Accolate) 4. Concomitant medication: not reported whether specific medication was not permitted; however, change in use of rescue inhaler (albuterol) and oral medication Accolate (zafirlukast; leukotriene receptor antagonist) were reported as outcomes in the trial, therefore we know that these specifically were permitted.
Interventions	Treatment: Pycnogenol; 1 mg/lb body weight in two divided dosages daily for three months.

	Control: placebo "indistinguishable" from the test drug; two times per day for three months. Route of administration: orally.
Outcomes	PEF rate: collected at baseline and then at the end of the first, second and third month of treatment; measured with an Assess Peak Flow Meter (Respironics, Cedar Grove, New Jersey); participants were asked to take three PEF rate readings every evening and record the best one on a diary card which was collected by an investigator at the end of each month of treatment; values are expressed in percentage predicted values. Symptom scores: collected at baseline and then at the end of the first, second and third month of treatment; participants reported their scores every evening on diary cards which was collected by an investigator at the end of each month of treatment; measured on a scale from 0 to 4 where 0 = no symptoms, 1 = mild symptoms - not disturbing, 2 = moderate symptoms - somewhat disturbing, 3 = severe symptoms - interfered with daily activities, 4 = very severe symptoms - could not go anywhere. Results were also expressed in the number of participants with a decrease in symptom scores. Use of oral medication (Accolate): collected at baseline and then at the end of the first, second and third month of treatment; recorded by participants every evening in their diary cards and collected by an investigator at the end of each month of treatment; measured as number of participants using oral medication. Use of rescue inhaler (albuterol): collected at baseline and then at the end of the first, second and third month of treatment; recorded by participants every evening in their diary cards and collected by an investigator at the end of each month of treatment; recorded as the number of puffs per 24 hours as well as the number of participants off the rescue inhaler. Participants' treatment compliance: collected at the end of the first, second and third month of treatment; the bottles of capsules were collected and the capsules counted to ascertain compliance; reported in terms of percentage compliance. Urinary leukotriene $C_4/D_4/E_4$ levels: collected at baseline and then at the end of the first, second and third month of treatment; assayed in duplicate by an enzyme immunoassay system (Biotrak, Amersham Pharmacia Biotech, United Kindgom); unit of measurement is pg/ml. "Adverse side effects": not reported when it was collected, assumed to be during the three months treatment period

	via their diary cards; reported by participants.
Notes	Funding source: "This study was supported by the Chan Shun International Foundation, San Francisco, CA, and Horphag Research, Geneva, Switzerland. Neither of the sponsors is the manufacturer of the Pycnogenol capsules used in this study."

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"Sixty patients were randomized so that..." However, the randomisation method is not reported.
Allocation concealment?	Unclear	The treatment was "identified by preassigned codes prepared by an independent laboratory that was not involved in conducting the experiment". It is not clear whether the coding was sufficient to protect sequence generation and whether this above quote refers to blinding rather than to allocation concealment.
Blinding?	Yes	It is reported that the study was "double-blind". This is confirmed by the following quotes: "Neither the subjects nor the persons who evaluated the symptoms had knowledge of the identity of the supplement." "...placebo capsules indistinguishable from Pycnogenol...".
Incomplete outcome data addressed?	Unclear	Not reported whether all randomised participants completed the study, i.e. whether data from all participants for all outcomes were collected.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section.
Free of other bias?	Unclear	The study was, amongst others, funded by Horphag Research Ltd. This company is the manufacturer and holder of Pycnogenol's registered trademark.

Liu 2004a

Methods	RCT; parallel group design. Treatment duration: 12 weeks. No follow-up after end of treatment.
Participants	Total participants: 77 (34 in the treatment- and 43 in the control group). Country and setting: China (Beijing and ShanDong); recruited from three hospital outpatient departments. Inclusion criteria: diabetes mellitus type II according to the WHO 1999 diagnostic criteria for diabetes. Exclusion criteria: pregnant or breastfeeding; use of vitamin supplements during the study period. Baseline characteristics: Treatment group: 52.9% males; median age 54 (interquartile range 45 to 62) years; median weight 69 (interquartile range 64 to 77) kg; median height 168 (interquartile range 162 to 172) cm. Control group: 60.5% males; median age 58 (interquartile range 47 to 66) years; median weight 68 (interquartile range 62 to 75) kg; median height 165 (interquartile range 162 to 171) cm. Concomitant medication: conventional oral antidiabetic medication as needed was permitted.
Interventions	Treatment: Pycnogenol; 100 mg for 12 weeks. Control: placebo; for 12 weeks. Route of administration: not reported, assumed to be oral.
Outcomes	Blood glucose levels: collected at baseline and then in two week intervals until the end of the 12 week treatment; measured enzymatically; measured in mmol/l and reported as percentage decrease relative to pretreatment levels. HbA1c levels: collected at baseline and then at the end of the first, second and third month of treatment; measured by high performance liquid chromatography (HPLC) and reported as percentage decrease relative to pretreatment levels. Endothelin-1 levels: collected at baseline and then at the end of the first, second and third month of treatment; measured by immuno-assay and reported as percentage decrease relative to pretreatment levels. 6-keto-prostaglandin $F1_a$ levels: collected at baseline and then at the end of the first, second and third month of

	treatment; measured by immuno-assay and reported as percentage decrease relative to pretreatment levels. Change in nitrogen monoxide levels: assumed to be collected at baseline and then at the end of the first, second and third month of treatment; measured by colorimetric assay for nitrite/nitrate and reported in nmol/l. "Unwanted effects": not reported when it was collected, assumed to be during the 12 week study period; it is not reported whether the participants or investigators recorded the symptoms. Safety [vital signs, ECG (electrocardiography), blood urea nitrogen, electrolytes and creatinine concentration]: collected at baseline and again at the end of the 12 week treatment period.
Notes	Funding source: not reported. Ethics approval: not reported.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"The treatment groups were randomized in respect to gender, age and anti-diabetic medication." However, the randomisation method is not reported.
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind". However, it is not reported whether the placebo was identical to the test drug in all important aspects (i.e. matched in terms of shape, size, colour, taste, and weight).
Incomplete outcome data addressed?	Yes	No participants were lost to follow-up.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section.
Free of other bias?	Unclear	Funding source not reported.

Liu 2004c

Methods	RCT; parallel group design. Treatment duration: 12 weeks after a two week run in period. During the run in period all participants received placebo instead of their usual medication to confirm diagnosis. No follow-up after end of treatment.
Participants	Total participants: 58 (28 in the treatment- and 30 in the control group). Country and setting: China (Beijing and ShanDong); recruited from three hospital outpatient departments. Inclusion criteria: hypertension according to the WHO 1999 diagnostic criteria for diabetes mellitus; complied fully to take the provided placebo during the run in period. Exclusion criteria: pregnant or breastfeeding; malignant hypertension; use of vitamin supplements during the study period. Baseline characteristics: Treatment group: 53.6% males; median age 56 (interquartile range 46 to 64) years; median weight 69 (interquartile range 64 to 76) kg; median "stature" 168 (interquartile range 162 to 172) cm. Control group: 60% males; median age 58 (interquartile range 46 to 66) years; median weight 68 (interquartile range 62 to 75) kg; median "stature" 164 (interquartile range 160 to 171) cm. Concomitant medication: after the two week run in period on placebo, all participants were put on a calcium antagonist (nifedipine, sustained release tablets, 5 mg, Shanghai Pharmaceuticals Co, Ltd.) The dose nifedipine was 20 mg (frequency not reported, assumed to be daily) initially, and then adjusted at two week intervals (either reduced or increased with 5 mg) as needed to sustain "stable blood pressure".
Interventions	Treatment: Pycnogenol; 100 mg; for 12 weeks. Control: placebo; for 12 weeks. Route of administration: not reported, assumed to be oral.
Outcomes	Nifedipine dose needed to control blood pressure: collected at the end of the 12 week treatment period; measured in terms of the number of participants using a specific dose nifedipine (10 mg, 15 mg, or "20 + 30 mg"). This outcome is dependent on the blood pressure measurements during the treatment period since the nifedipine dose was adjusted every two weeks as needed to sustain "stable blood pressure". Blood pressure was collected at baseline and then at two week intervals until the end of the 12 week treatment period; measured at 08:30 a.m., 90 minutes after intake of medication, after which they rested for 15 minutes followed by a measurement in the sitting upright position; the mean

	of the two measurements was recorded. Endothelin-1 levels: collected at baseline and then at the end of the first, second and third month of treatment; quantified in plasma by radio-immunoassay (Beijing Huaying Biological Technology Company); reported as percentage decrease relative to pretreatment levels. 6-keto-prostaglandin $F1_a$ levels: collected at baseline and then at the end of the first, second and third month of treatment; quantified in plasma by radio-immunoassay (Beijing Huaying Biological Technology Company); reported as percentage decrease relative to pretreatment levels. Angiotensin II levels: collected at baseline and then at the end of the first, second and third month of treatment; quantified in plasma by radio-immunoassay (Beijing Huaying Biological Technology Company); reported as percentage decrease relative to pretreatment levels. Nitrogen monoxide levels: collected at baseline and then at the end of the first, second and third month of treatment; analysed using a calorimetric assay for nitrite/nitrate (Nanjing Jiancheng Biological Technology Company); measured in nmol/l. "Unwanted effects": not reported when it was collected, assumed to be during the 12 week treatment period; reported by participants. Safety by means of determining electrolytes, creatinine, and blood urea nitrogen levels: collected at baseline and again at the end of the 12 week treatment period, no further detail reported. Safety by means of measuring heart rate: collected at baseline and then at two week intervals until the end of the 12 week treatment period; no further detail reported.
Notes	Funding source: not reported. Ethics approval: not reported.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"Patients were randomized to receive either...". However, the randomisation method is not reported.
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind". However, it is not reported whether the placebo was identical to the test drug in all important aspects (i.e. matched in terms of shape, size, colour, taste, and weight).
Incomplete outcome data addressed?	Yes	No participants were lost to follow-up.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section.
Free of other bias?	Unclear	Funding source not reported.

Petrassi 2000

Methods	RCT; parallel group design. Treatment duration: two months after a two week run in period. During the run in period participants were not allowed to take drugs acting on the cardiovascular system, diuretics, analgesics or anti-inflammatory compounds. No follow-up after end of treatment.
Participants	Total participants: 20 (10 in each group). Country and setting: not reported, assumed to be Italy; setting not reported. Inclusion criteria: participants with symptoms of chronic venous insufficiency (CVI) ("heaviness and subcutaneous swelling") and a venous blood pressure higher than 40 mm Hg. Exclusion criteria: none reported. Baseline characteristics: Treatment group: 20% males; mean age 47.7 (assumed SD 3.65) years. Control group: 10%

	males; mean age 36.7 (assumed SD 3.66) years. Concomitant medication: during the two month treatment period participants were not allowed to take drugs affecting the cardiovascular system, diuretics, analgesics or anti-inflammatory compounds. Diet: a "standard diet" according to participants' energy needs was prescribed by a dietary service.
Interventions	Treatment: Pycnogenol; 100 mg three times per day for two months. Control: placebo indistinguishable from the test drug; three times per day for two months. Route of administration: orally.
Outcomes	Symptom scores (feeling of heaviness, swelling and evening edema, localized or diffuse leg pain, night cramps, paraesthesiae): collected at baseline and then at the end of the first and second month of treatment; assessed clinically using a "4-item scale" where 0 = absent, 1 = light, 2 = moderate, and 3 = severe; the percentage of participants showing disappearance of each symptom was also calculated and analysed. Ambulatory venous pressure*: collected at baseline and then at the end of the first and second month of treatment; measured on each leg in a standing position after a 30 minute acclimatization period at room temperature (21 to 23 ºC); measured in mm Hg. Physician's judgement of efficacy and safety of the treatment*: collected at the end of the two month treatment period; assessed by a "semi-quantitative 4-point scale" where 1 = poor, 2 = moderate, 3 = good, and 4 = very good. Safety evaluated by means of biochemical tests (haematology, blood chemistry, hepatic functions, renal functions)*: collected at baseline and at the end of the two month treatment period; analysed by various laboratory tests; the unit of measurement for each blood test is specified in the article. Clinical tolerability*: collected during the trial; not reported whether participants or investigator reported the "side effects".
Notes	Ethics approval: not reported. Funding source: not reported. Study design and results: after the two month treatment 20 additional patients with CVI were added to the study without randomisation. They received the same Pycnogenol or placebo (same dose) for the same time period (60 days).

	Results of many outcomes were pooled so that we could not extract the results from the randomised arm of the trial separately. We have reported all the outcomes, but indicated with an asterisk (*) those outcomes of which the results were pooled. We did not extract pooled results.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	"...according to a computer-elaborated simple randomization table."
Allocation concealment?	Unclear	Not reported.
Blinding?	Yes	It is reported that the study was "double-blind". Furthermore, "the drugs were prepared in white opaque capsules in order to make the lightly pinkish-coloured Pycnogenol indistinct from placebo (lactose)".
Incomplete outcome data addressed?	Yes	For the outcomes of which the results were reported separately for the randomised and non-randomised phase of the trial, all participants were included into the analyses.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section; no results were reported for the outcomes 'change in night cramps' and 'change in paraesthesiae'.
Free of other bias?	Unclear	Funding source not reported.

Steigerwalt 2009

Methods	RCT; parallel group design. Treatment duration: two months. Follow-up: one month after end of treatment, at the end of month three.
Participants	Total participants: 46 (24 in the treatment- and 22 in the control group). Country and setting: not reported, Italy; setting not reported. Inclusion criteria: moderate diabetic retinopathy as judged by existence of macular edema and retinal swelling and

	presence of minor exudates and haemorrhages; diabetes mellitus type II for at least four years; well controlled blood glucose levels by diet and oral antidiabetic medication ($HbA1_c$ < 7%). Exclusion criteria: proliferative retinopathy, severe exudates, progressive haemorrhage and previous haemorrhage; any other ophthalmologic condition than diabetic retinopathy, including intraocular hypertension ≥ 21 mm Hg; those who had previous surgical or laser treatment or other invasive interventions; those with systemic hypertension requiring medical treatment. Baseline characteristics: Treatment group: 58.3% males; assumed mean age 51.2 (SD 5.4) years; assumed mean duration of disorder 6.4 (SD 0.6) years; assumed mean $HbA1_c$ levels 6.9 (SD 0.1) %. Control group: 68.2% males; assumed mean age 52.3 (SD 6.1) years; assumed mean duration of disorder 6.5 (SD 0.5) years; assumed mean $HbA1_c$ 6.8 (SD 0.2) %. Concomitant medication: not reported, but control of blood glucose levels by oral antidiabetic medication was part of the inclusion criteria and thus permitted.
Interventions	Treatment: Pycnogenol; three 50 mg tablets per day after breakfast for two months. Control: placebo; three tablets per day after breakfast for two months. Route of administration: orally.
Outcomes	Visual acuity as perceived by participants: "...subjectively perceived visual improvement..."; no detail reported. Visual acuity as measured by a professional: collected at baseline, after two months of treatment as well as one month after end of treatment; measured by means of the standard Snellen chart. Retinal blood flow: collected at baseline, after two months of treatment as well as one month after end of treatment; measured quantitatively and noninvasively by colour duplex scanning; expressed in cm/s. Diastolic retinal blood flow relative to maximum systolic flow: collected at baseline, after two months of treatment as well as one month after end of treatment; "expressed as flow velocity at the central retinal artery". Retinal edema score: collected at baseline, after two months of treatment as well as one month after end of treatment; measured on a scale ranged from 0 to 6 where 0 = no diabetic macular edema, 2 = mild diabetic macular edema, 4 = moderate diabetic macular edema, and 6 = severe diabetic macular edema. Retinal thickness: collected at baseline, after two months of treatment as well as one month after end of treatment;

	measured in µm by means of resolution ultrasound at 14 MHz from Esaote (Genoa, Italy); ultrasound was conducted twice by two experienced physicians and the average of the two measurements is presented as percentage change from baseline set at 100%. "Side effects": not reported how and by whom side effects were monitored.
Notes	Ethics approval: not reported. Funding source: not reported. Contact author: the contact author is a director of Horphag Research, the manufacturing company of Pycnogenol.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	"Patients were allocated to treatment groups using randomization by blocks. Block allocation sequences were created by using randomly generated numbers from a computer program."
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind". However, it is not reported whether the placebo was identical to the test drug in all important aspects (i.e. matched in terms of shape, size, colour, taste, and weight).
Incomplete outcome data addressed?	Yes	No participants were lost to follow-up.
Free of selective reporting?	No	Protocol not available; pre-specified outcomes not stated in the Methods section.
Free of other bias?	Unclear	Funding source not reported.

Trebatická 2006

Methods	RCT; parallel group design. Ethics approval by the Ethical Committee of the Children University Hospital, Slovakia. Treatment duration: one month. Follow-up: one month after end of treatment, at the end of month two.
Participants	Total participants: 61 (44 in the treatment- and 17 in the control group). Country and setting: Slovakia, outpatients from the Department of Child Psychiatry at the Child University Hospital. Inclusion criteria: children with attention deficit hyperactivity disorder (ADHD) according to the International Statistical Classification of Diseases (ICD-10) which includes Hyperkinetic Disorder, Hyperkinetic Conduct Disorder, Attention Deficit without Hyperactivity; early onset of ADHD - chronicity by six to seven years of age; ADHD symptoms for at least six months; general disposition as restless, inattentive, distractible and disorganized; disorders of cognitive function ("inattention, distractibility, difficulty to persist with any task, difficulty in selective process to information, disturbance of the executive functions, disturbance of motivation, effort and fortitude, visuospacial and memory disturbance"); disorders in control of activity ("inability to suppress activity, abnormality in control of activity, disorganisation and discontinuation of motoric activity"); impulsiveness ("acting without due reflection, engaging in rash and sometimes dangerous behaviour, disturbances or emotions and affectivity"). Exclusion criteria: situational hyperactivity; pervasive developmental disorders; schizophrenia; other psychotic disorders e.g. mood, anxiety, personality disorder as unsocial behaviour; personality change due to medical conditions; mental retardation; living in understimulating environments; conduct disorders; tics; chorea and other dyskinesias; acute inflammatory diseases; renal disorders; cardiovascular disorders; diabetes mellitus. Baseline characteristics: Treatment group: 84% males; "average" age 9.5 (range 6 to 14) years; "average" weight 35.28 (unspecified measure of variation 10.13) kg; assumed mean BMI 17.41 (unspecified measure of variation 3.13) kg/m^2. Control group: 76.5% males; "average" age 8.8 (range 6 to 12) years; "average" weight 34.80 (unspecified measure of variation 10.05) kg; assumed mean BMI 16.77 (unspecified measure of variation 2.61) kg/m^2. Concomitant medication: none were permitted - neither psychotropic drugs nor vitamins E and C supplements during the study period. Diet: "Patients had a standard diet".
Interventions	Treatment: Pycnogenol; 1 mg/kg body weight at breakfast daily for one month.

	Control: placebo identical in shape and appearance as the test drug; the same number of tablets as the test drug per day for one month. Route of administration: orally.
Outcomes	Inattention symptom scores: collected at baseline, after one month of treatment, as well as at the end of the second month (one month after end of treatment); measured by teachers and parents by means of three different scales (i) Child Attention Problems Teacher Rating Scale (CAP), (ii) Conner's Teacher Rating Scale (CTRS), and (iii) the Conner's Parent Rating Scale (CPRS); the score at baseline for the CTRS were put to 100%, the raw scores were reported for CAP and CPRS. Hyperactivity symptom scores: collected at baseline, after one month of treatment, as well as at the end of the second month (one month after end of treatment); measured by teachers and parents by means of three different scales (i) CAP, (ii) CTRS, and (iii) CPRS; the score at baseline for the CTRS were put to 100%, the raw scores were reported for CAP and CPRS. Visual-motoric coordination and concentration: collected at baseline, after one month of treatment, as well as at the end of the second month (one month after end of treatment); "weight score" percentage were evaluated by psychologists and the score at baseline were put to 100%; "weight score" is the sum of values of five subtests of the Performance Scale for each participant, where a higher score represents a better psychological state. Urine catecholamine concentration (adrenaline, noradrenaline, dopamine): collected at baseline, after one month of treatment, as well as at the end of the second month (one month after end of treatment); analysed by HPLC using electrochemical detection; expressed in percentage. Urine creatinine concentration: collected at baseline, after one month of treatment, as well as at the end of the second month (one month after end of treatment); analysed using a commercial kit (DOT Diagnostics, Czech Republic) on Hitachi 911 automatic analyser (Roche); expressed in mmol/l. Total glutathione concentration, oxidized glutathione concentration (GSSG) and GSH (reduced glutathione)/GSSG: total glutathione and GSSG in whole blood was determined by gradient HPLC; GSH was calculated according to the following formula: [GSH] = [total glutathione] - (2 × [GSSG]). Safety by means of basic biochemical parameters (bilirubin, glucose, gamma-glutamyl transferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, uric acid and lipid profile): collected at baseline,

	after one month of treatment, as well as at the end of the second month (one month after end of treatment); analysed in plasma by standard biochemical procedures using the Hitachi 911 automatic analyser (Roche, Switzerland). "Side effects": not reported how it were monitored, we assumed that the parent, care-taker or teacher reported observed "side effects" to the investigator during the two months study period.
Notes	Funding source: "This study was supported by Horphag Res. Ltd. grant, partly by VEGA Grants No. 1/1157/04, 1/3037/06, Grant VV MVTS 03/LF of Ministry of Education of SR, by Drug Research Institute, Modra, SR and Mind&Health, civil association."

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Computer generated random numbers; ratio of Pycnogenol:placebo was 2.5:1.
Allocation concealment?	Unclear	Not reported.
Blinding?	Yes	It is reported that the study was "double-blind". This was confirmed by the following quote: "Teachers, parents and physicians were not aware of results of randomization."
Incomplete outcome data addressed?	Unclear	"Data of all patients were evaluated according ‘intention-to-treat’ analysis". However, it is not reported what they mean with 'intention-to-treat' analysis, i.e. how they handled the missing data. 3/44 participants of the treatment group and 1/17 of the control group were lost to follow-up. No reasons for withdrawal were reported.
Free of selective reporting?	No	No protocol available; pre-specified outcomes no stated in the Methods section.
Free of other bias?	Unclear	The study was, amongst others, funded by Horphag Research Ltd. This company is the manufacturer and holder of Pycnogenol's registered trademark.

Zibadi 2008

Methods	RCT; parallel group design. Ethics approval by the institutional review board of the University of Arizona, USA. Treatment duration: 12 weeks. No follow-up after end of treatment.
Participants	Total participants: 48 (24 in each group). Country and setting: Tuscon, Arizona, USA; participants recruited through newspaper advertising. Inclusion criteria: adult type II diabetics (40 to 75 years old) with hypertension (baseline systolic blood pressure of 130 to 150 mm Hg); receiving angiotensin-converting enzyme (ACE) inhibitor for hypertension. Exclusion criteria: type I diabetes; on insulin treatment; use of supplements apart from one multivitamin daily; other major diseases e.g. cancer, asthma, heart failure; previous heart problems; pregnant or breastfeeding. Baseline characteristics: Treatment group: 54% males; mean age 61.3 (SEM 9.1) years; mean duration of diabetes mellitus 12.9 (SEM 11.6) years; mean pretrial systolic blood pressure 139.0 (SEM 1.3) mm Hg. Control group: 58% males; mean age 58.4 (SEM 11.5) years; mean duration of diabetes mellitus 14.2 (SEM 8.5) years; mean pretrial systolic blood pressure 137.0 (SEM 1.0) mm Hg. Concomitant medication: first generation sulfonylureas, second generation sulfonylureas, metformin, and thiazolidinediones for glucose control were permitted.
Interventions	Treatment: Pycnogenol; 25 mg tablets five times per day for 12 weeks. Control: placebo that "matched" the test drug; for 12 weeks. Route of administration: orally.
Outcomes	ACE inhibitor dosage: dosage were either left unchanged (equal to baseline dose), reduced by 50% or brought back to the baseline dosage until a "stable blood pressure" was obtained; adjustments were made every two weeks after the systolic and diastolic blood pressure measurements were taken; expressed in percentage participants who could achieve blood pressure control with a 50% reduction in pretrial dose of ACE inhibitors at week 12. Blood pressure was measured at baseline and then at two week intervals up to week 12; measured in mm Hg on the left arm after a ten minute rest; three repeated readings at an interval of two minutes were taken while sitting, and the average recorded; Korotkoff I and V were taken as the systolic and diastolic blood pressures respectively; dosage of ACE inhibitor was

	changed according to the systolic blood pressure measurements. Heart rate: collected at baseline and then at two week intervals up to week 12; heart rate was "measured on the left arm after 10-minute rest". Participants' treatment compliance: collected at the end of week four, eight and 12; unused pills were collected from participants and counted; reported in percentage. Endothelin-1 levels: collected at baseline and at the end of week four, eight and 12 after fasting for eight hours; quantified in duplicate samples by ELISA (R&D Systems, Minneapolis, Minn); measured in pg/dl. LDL-cholesterol levels: collected at baseline and at the end of week four, eight and 12 after fasting for eight hours; measured by the cholesterol esterase-cholesterol peroxidase coupling method; measured in mg/dl. $HbA1_c$ levels: collected at baseline and at the end of week four, eight and 12 after fasting for eight hours; measured by inhibition of latex agglutination; reported in percentage. Blood glucose levels: collected at baseline and at the end of week four, eight and 12 after fasting for eight hours; measured by double-enzyme assay with hexokinase and glucose-6-phosphate dehydrogenase using an Olympus AU640 analyser (Olympus America, Inc, Melville, New York); measured in mg/dl. Urinary albumin concentration: data at baseline and at the end of week four, eight and 12; the semi-qualitative screening dipstick test were used on spot urine samples; reported in mg/l. Adverse events: collected at "follow-up visits" (at the end of week four, eight and 12); collected from participants by means of questioning. Safety monitoring: heart rate and change in use of concomitant antidiabetic medication were monitored to make sure that it stayed the same and had no effect on the study outcomes as confounder.
Notes	Funding source: "This study was supported by a research grant of Horphag Research. This funding had no role in the collection, analysis, and interpretation of data or in the writing of the manuscript."

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"...subjects were randomly assigned...". However, the randomisation method is not reported.
Allocation concealment?	Unclear	Not reported.
Blinding?	Unclear	It is reported that the study was "double-blind" and that the placebo "matched" the test drug. It is not clear what characteristics were matched. The test drug is known to have a bitter, astringent taste.
Incomplete outcome data addressed?	Unclear	"Analysis was performed according to the intention to treat principle. Thus, all randomized patients who received at least 1 dose of study treatment and who had both a baseline and at least 1 postbaseline measurement were analyzed." However, it is not reported how missing data were handled. 1/24 participants from the treatment and 2/24 from the control group were lost to follow-up.
Free of selective reporting?	No	Protocol is available on the WHO's International Clinical Trials Registry Platform under the ID ISRCTN44961472. All outcomes specified in the protocol are addressed in the published article. However, there are outcomes in the article that are not pre-specified in the protocol: ACE inhibitor dosage (as the indirect measurement of systolic blood pressure) and adverse events.
Free of other bias?	Unclear	The study was funded by Horphag Research Ltd. This company is the manufacturer and holder of Pycnogenol's registered trademark.

Characteristics of excluded studies

Belcaro 2006b

Reason for exclusion	Prevention.

Belcaro 2008a

Reason for exclusion	Not a RCT (although the participants are a subsample of a RCT, they are chosen according to their C-reactive protein status and not at random).

Cesarone 2006a

Reason for exclusion	Not a RCT.

Cesarone 2006b

Reason for exclusion	Inappropriate control.

Cesarone 2006c

Reason for exclusion	Not a RCT.

Cesarone 2010

Reason for exclusion	Inappropriate control.

Chovanová 2006

Reason for exclusion	Inappropriate outcomes (only antioxidant biomarkers were assessed).

Dvořáková 2006

Reason for exclusion	Inappropriate outcomes (only antioxidant biomarkers were assessed).

Koch 2002

Reason for exclusion	Inappropriate control.

Kohama 2004

Reason for exclusion	Not a chronic disorder.

Kohama 2007

Reason for exclusion	Inappropriate control.

Liu 2004b

Reason for exclusion	Not a RCT.

Ni 2002

Reason for exclusion	Not a RCT (no control group).

Spadea 2001

Reason for exclusion	Not a RCT (only half of the participants were randomised; results were not reported separately).

Stefanescu 2001

Reason for exclusion	Not a RCT.

Suzuki 2008

Reason for exclusion	Not a chronic disorder.

Wilson 2010

Reason for exclusion	Prevention.

Yang 2007

Reason for exclusion	Not a RCT.

Characteristics of studies awaiting classification

Enseleit 2010

Methods	"Randomized, double-blind, placebo-controlled crossover study". Treatment duration: eight weeks per arm. Wash-out period: two weeks.
Participants	"25 patients with coronary artery disease".
Interventions	Treatment: Pycnogenol (200 mg per day) plus standard cardiovascular therapy. Control: placebo plus standard cardiovascular therapy.
Outcomes	At baseline and after each treatment arm the following outcomes were assessed: endothelial function, non-invasively assessed by flow-mediated dilation of the brachial artery; platelet adhesion; baroreceptor function; 24-hour blood pressure; plasma 8-isoprostanes (index of oxidative stress).
Notes	As far as we are aware, only the abstract and accompanying poster is available. Therefore the information we have for this study is limited.

Characteristics of ongoing studies

ISRCTN22412590

Study name	Pilot study for the treatment of heart failure with Pycnogenol.
Methods	"...randomised, double-blind placebo-controlled matched pairs study". Target sample size: 30.
Participants	*Inclusion criteria* Patients > 40 years of age with chronic congestive heart failure [New York Heart Association (NYHA) class II], known for at least six months which were previously untreated or treated with a diuretic and/or a low dose of an ACE inhibitor; must have an exercise capacity of at least 75 watts (W) as assessed by seated bicycle ergometry. *Exclusion criteria* NYHA class I, III, or IV; treatment with digitalis within the previous six months; exercise capacity of > 75 W for two minutes at the test during run in; unstable angina or myocardial infarction within the last six months; atrial fibrillation or ventricular arrhythmia greater than or equal to "Lown III"; cardiac valvular disease or hypertrophic cardiomyopathy; significant hypertension or hypotension (diastolic blood pressure < 60 mm Hg or ≥ 105 mm Hg, or systolic blood pressure < 90 mm Hg or > 175 mm Hg); electrolyte disturbances, hyperuricaemia, hypovolaemia; impaired renal function (creatinine levels > 1.8 mg/dl) or impaired hepatic function; obstructive airways disease; insulin-dependent diabetes mellitus; malignant or other serious disease; hypersensitivity to the study drug Pycnogenol; pregnant, unreliable contraception, breastfeeding; participation in another clinical trial within the last six weeks.
Interventions	Intervention: Pycnogenol, 200 mg (assumed) daily; for 12 weeks. Control: placebo; for 12 weeks.
Outcomes	*Primary outcomes* Tests for maximal workload and pressure-heart product at baseline, as well as the end of week four, eight and 12 of treatment. Maximal workload will be determined by a symptom-limited bicycle exercise test in the seated position. Pressure-heart rate product entails the measurement of systolic blood pressure and heart rate immediately after two minutes of work at 50 W; it is calculated by units of systolic blood pressure (mm Hg) × heart rate per minute divided by 100. *Secondary outcomes*

	Participant-reported symptom scores for dyspnoea and fatigue for the foregoing four weeks upon enrolment (baseline), as well as at the end of week four, eight and 12 of treatment. Symptom scores will be evaluated by asking patients about the severity of the following symptoms: early fatigability, dyspnoea, general capability, lassitude, feeling depressed, and anxiety. The scores range as follows: 0 = not present, 1 = occasionally mild, 2 = frequently mild, 3 = moderate, 4 = severe. Biochemical tests: C-reactive protein, troponin T, and B-type natriuretic peptide (BNP) (specifically NT-proBNP); not reported how frequent these blood analysis were to be done.
Starting date	10 August 2007.
Contact information	A Matsumori; no email address reported; Kyoto University Graduate School of Medicine, Department of Cardiovascular Medicine, Sakyo-ku, Kyoto, Japan, 6068507.
Notes	Country: Japan. Status of study: "Completed". Sponsor: Kyoto University Graduate School of Medicine, Cardiomyopathy and Myocarditis Research Fund, Japan; website http://www.kyoto-u.ac.jp/index-e.html.

NCT00064857

Study name	Pycnogenol for the treatment of lymphedema of the arm in breast cancer survivors.
Methods	"Randomized, placebo control, efficacy study, parallel assignment, double-blind". Estimated enrolment: 26.
Participants	*Inclusion criteria* Both genders 18 years and older with unilateral (ipsilateral to breast cancer resection side) lymphedema of the upper extremity; extravascular water ration of > 1.07/1 between affected versus normal arm using multiple frequency bioelectric impedence; last surgical or radiation treatment to the affected axilla was more than two months ago; the following renal and hepatic function: creatinine clearance > 50 ml/min, total bilirubin < 2 mg/dl, transaminases < 1.5 × ULN (upper limit of normal); not pregnant or breastfeeding, and use of barrier contraception if sexually active; Eastern Cooperative Oncology Group (ECOG) performance of 0 to 2; not allergic to Pycnogenol.

	Exclusion criteria Treated with first course of chemotherapy or radiation; chemotherapy or radiation to axillary lymph node will exclude patients for eight weeks following treatment; more than one episode of arm cellulitis, venous clot, or woody fibrosis of the affected arm (antibiotics used to treat cellulitis must be completed at least four weeks prior to initial screening); patients with a defibrillator Midazolam study only: patiens requiring or benefiting from supplemental oxygen, patients allergic to cherries.
Interventions	Intervention: Pycnogenol; no detail reported. Control: placebo; no detail reported.
Outcomes	Outcomes are not explicitly reported nor grouped into primary and secondary outcomes. However, the planned measurements are reported: Comparison of the correlation of both a single- and a multiple-frequency bioelectric impedance instrument in measuring change in arm volume to a standard assessment using water displacement; Use a small oral dose of midazolam and single blood sampling to screen for effects of Pycnogenol on the activity of the common drug metabolizing enzyme CYP3A4; Use digoxin urine excretion to screen for effects of the test drug upon the activity of P-glycoprotein in the subjects already receiving digoxin; and Evaluation of a new questionnaire of lymphedema symptoms presently begin tested as a tool for assessing the severity and improvement of symptoms with treatment.
Starting date	August 2003.
Contact information	JF Cleary; no email address provided; University of Wisconsin, Madison, Wisconsin, United States, 53706.
Notes	Country: USA. Status of study: "This study has been completed." Sponsors and collaborators: National Center for Complementary and Alternative Medicine (NCCAM).

NCT00214032

Study name	Pycnogenol for the treatment of lymphedema.
Methods	"Randomized, active control, safety/efficacy study, single group assignment, double blind". Enrolment: "2"; we suppose this is a mistake.
Participants	*Inclusion criteria* Females of 18 years and older who have unilateral lymphedema of the upper extremity; received more than six months ago surgical and/or radiation treatment to the effected axilla. Exclusion criteria Participants may not receive or be scheduled to receive cytotoxic or radiation chemotherapy treatment while part of the study.
Interventions	Intervention: Pycnogenol; 300 mg daily; duration not reported. Control: placebo; 3 capsules daily; duration not reported.
Outcomes	*Primary outcome* Reduction of arm lymphedema: measured monthly. *Secondary outcomes* "Comparison/validation of bioelectric impedance to measure lymphedema changes, validation of lymphedema questionnaire": evaluated monthly.
Starting date	March 2002.
Contact information	PR Hutson; no email address provided; University of Wisconsin, Madison, Wisconsin, USA, 53792.
Notes	Country: USA. Status of study: "This study has been completed." Sponsors and collaborators: University of Wisconsin, Madison; National Center for Complementary and Alternative Medicine (NCCAM).

NCT00952627

Study name	Effects of Pycnogenol on cardiac fibrosis and diastolic dysfunction in aged hypertensive subjects.
Methods	"Randomized, placebo control, efficacy study, parallel assignment, double blind". Estimated enrolment: 40.
Participants	*Inclusion criteria* Both genders aged between 50 and 75 years of any race diagnosed with hypertension (diagnosis made over six months) and echocardiographic evidence of grade I or II diastolic dysfunction. "There is no need for standardization of hypertension treatment, as we select only patients who have diastolic dysfunction during treatment." *Exclusion criteria* Unstable angina or myocardial infarction in the past three months; biochemical evidence of renal or hepatic failure; severe anaemia (defined as haemoglobin levels < 7 g/dl); current cancer or other major illness not associated with the heart; bleeding disorders; taking anticoagulants including low dose aspirin; diabetes; known allergy to Pycnogenol; pregnant or breastfeeding; systolic blood pressure > 180 mm Hg or < 100 mm Hg, and diastolic blood pressure >110 mm Hg or < 50 mm Hg; current smoking; having breast implants; taking any of the following: birth control pills, diethylstilbestrol, Ephedra, ephedrine or pseudoephedrine (except where used in prescription products), hormone replacement products, Isotretinoin, any product containing mercury, Phentermine in combination with fenfluramine (including but not limited to Pondimin), or dexfenfluramine (Redux).
Interventions	Intervention: Pycnogenol; 50 mg tablets, four tablets per day; for four months. Control: placebo; no detail provided; for four months.
Outcomes	*Primary outcomes* Cardiac fibrosis: measured as the serum markers of myocardial fibrosis and collagen turnover; collected at baseline and after four months of treatment. Diastolic dysfunction: measured by transthoracic echocardiogram; collected at baseline and after four months of treatment. *Secondary outcomes* Liver and kidney function tests: collected at baseline and after four months of treatment.

	Immunological measurements including the cytokine profile in serum (interleukin-4, interleukin-10, interferon-gamma, C-reactive protein): collected at baseline and after four months of treatment.
Starting date	July 2009.
Contact information	RR Watson; rwatson@u.arizona.edu; University of Arizona, USA, 85724.
Notes	Country: USA. Status of study: "This study is currently [August 2009] recruiting participants". Sponsors and collaborators: University of Arizona; Horphag Research, Switzerland.

Additional tables

Table 1: Additional assessment of risk of bias in included crossover trials

Study ID	Criteria	Yes/No/Unclear	Comments
Hosseini 2001a	Is the crossover design suitable?	Yes	
	Was there no carry-over effect?	Unclear	There was no wash-out period between the treatment and control periods; no tests were performed for assessing period effect, treatment-period interaction, or carry-over effect.
	Are data of both periods available?	Unclear	Not reported.
	Was a paired analysis being used?	Yes	"Paired two-tailed t-test", "Friedman measures analysis of variance on ranks", "student-Newman-Keuls".
	Are the results comparable to those from parallel group trials?	Unclear	There is one included parallel group design RCT on asthma. However, the participants in that trial were children between 6 and 18 years old. We cannot compare that results with the results of this crossover trial on asthmatic adults (18 to 60 years old).
Hosseini 2001b	Is the crossover design suitable?	Yes	

	Was there no carry-over effect?	Unclear	There was no wash-out period between the treatment and control periods; no tests were performed for assessing period effect, treatment-period interaction, or carry-over effect.
	Are data of both periods available?	Yes	Not reported directly, but it is mentioned in the small print beneath the figures that "all 11 subjects data are analysed".
	Was a paired analysis being used?	Yes	Paired t-test.
	Are the results comparable to those from parallel group trials?	Unclear	The same outcomes were not addressed.

Table 2: Incomplete results: Hosseini 2001a and Lau 2004

Study ID	Outcome	Pycnogenol		Placebo		Pycnogenol versus placebo
		Baseline Mean (SE)	Month 3 Mean (SE)	Baseline Mean (SE)	Month 3 Mean (SE)	Mean difference (SE)
Hosseini 2001a	Asthma symptom scores	#	1.75* (#)	#	2.15* (#)	#
Lau 2004	Asthma symptom scores	2.25 (0.13)	0.27 (0.06)	#	#	#
Lau 2004	Peak expiratory flow	69.7 (1.7)	♣	69.9 (1.6)	♣	#
Lau 2004	Use of albuterol inhaler (puffs/24 hours)	2.57 (0.16)	0.22 (0.07)	2.59 (0.14)	2.32 (0.21)	#

Not reported

* Extracted from figure

♣ Only reported in figure from which results cannot be extracted accurately

Table 3: Incomplete results: Dvořáková 2007

Outcome	Pycnogenol		Placebo		Pycnogenol versus placebo
	Baseline Mean (SE)	Month 1 Mean (SE)	Baseline Mean (SE)	Month 1 Mean (SE)	Mean difference (SE)
GSH/GSSG	35.93 (4.27)^	52.26 (3.81)	35.93 (4.27)^	✠	#

✠ "No changes in GSH/GSSG ratio were found in response to placebo treatment."

Not reported

^ "In patients with ADHD, the calculated GSH/GSSG ratio was 35.93±4.27 at the beginning of the trial."

Table 4: Incomplete results: Arcangeli 2000 and Petrassi 2000

Study ID	Outcome	Pycnogenol		Placebo		Pycnogenol versus placebo
		Baseline Mean (SE)	Month 2 Mean (SE)	Baseline Mean (SE)	Month 2 Mean (SE)	Mean difference (SE)
Arcangeli 2000	Heaviness score	2.06 (0.13)	0.94 (0.19)	1.72 (0.11)	1.67 (0.11)	1.07 (#)
	Swelling score	1.68 (0.13)	0.60 (0.21)	1.50 (0.12)	1.39 (0.12)	0.97 (#)
	Pain score	1.61 (0.12)	0.58 (0.19)	1.42 (0.15)	1.17 (0.11)	0.78 (#)
Petrassi 2000	Heaviness score	2.22 (0.222)	0.88 (0.227)	1.83 (0.167)	1.60 (0.245)	1.11 (#)
	Swelling score	1.25 (0.164)	0.33 (0.333)	1.00 (0.00)	0.71 (0.184)	0.63 (#)
	Pain score	#	#	#	#	#

Not reported

Table 5: Incomplete results: Belcaro 2006a

Outcome	Pycnogenol (oral & local)		Pycnogenol (local)		Pycnogenol (oral)		Control		Pycnogenol versus control
	Baseline Mean (SD)	Week 6 Mean (SD)	Baseline Mean (SD)	Week 6 Mean (SD)	Baseline Mean (SD)	Week 6 Mean (SD)	Baseline Mean (SD)	Week 6 Mean (SD)	Mean difference (SD)
Microcirculation-related symptom scores	7.0 (3.0)	2.2 (2.0)	7.1 (3.0)	4.0 (2.0)	7.2 (2.2)	3.8 (2.2)	7.1 (2.0)	5.1 (3.0)	#
Change in area of ulceration (mm^2)	43.0 (4.0)	11.0 (4.0)	46.0 (6)	27.0 (7.0)	45.0 (4.0)	30.0 (6.0)	44.0 (5.2)	35.0 (5.0)	#
Transcutaneous PO_2	47.0 (4.0)	58.0 (3.0)	-	-	46.0 (3.0)	55.0 (4.0)	48.0 (4.2)	48.0 (3.0)	#
Transcutaneous PCO_2	33.0 (2.0)	27.0 (3.0)	-	-	32.0 (3.0)	28.8 (2.0)	32.0 (2.2)	29.8 (3.3)	#
Skin flux at rest	3.6 (1.0)	2.0 (0.7)	-	-	3.5 (0.7)	2.1 (1.0)	3.8 (0.2)	★	#

Not reported

- Not assessed

★ Reported with an error (as "3.3.8"). We contacted the study authors and are awaiting their response.

Table 6: Venoarteriolar response (LDF units): Belcaro 2006a

Time point	Pycnogenol (oral + local) Median (range)	Pycnogenol (oral) Median (range)	Control Median (range)
Baseline	8 (0 to 20)	9 (0 to 21)	9 (0 to 19)
Week 6	22 (5 to 38)	12 (4 to 32)	8 (3 to 23)

Table 7: Blood glucose (mmol/l) and plasma HbA1c (%): Liu 2004a

Outcome	Period	Pycnogenol Median (IQR)	Placebo Median (IQR)	Pycnogenol versus placebo
Blood glucose (mmol/l)	Decrease at the end of week 12 relative to baseline	-1.96 (-3.25 to -1.24)	-1.11 (-2.00 to -0.44)	P < 0.01
HbA1c (%)		-0.69 (-1.07 to -0.43)	-0.53 (-0.75 to -0.16)	P > 0.05

Table 8: Incomplete results: Zibadi 2008

Outcome	Pycnogenol		Placebo		Pycnogenol versus placebo
	Baseline Mean (SE)	Week 12 Mean (SE)	Baseline Mean (SE)	Week 12 Mean (SE)	Mean difference (SE)
Glucose levels (mg/dl)	142.3 (9.8)	118.6 (9.5)	151.1 (12.1)	145.3 (11.4)	17.9 (#)
HbA1c levels (%)	7.9 (0.3)	7.1 (0.2)	8.1 (0.4)	8.0 (0.4)	0.7 (#)
Urinary albumin levels (mg/l)	29.6 (5.9)	22.2 (6.1)	37.4 (7.0)	36.1 (6.3)	6.1 (#)

Not reported

Table 9: Incomplete results: Ďuračková 2003

Outcome	Pycnogenol		Placebo		Pycnogenol versus placebo
	Baseline Mean (SE)	Month 3 Mean (SE)	Baseline Mean (SE)	Month 3 Mean (SE)	Mean difference (SE)
Erectile dysfunction score	12.6 (1.1)	16.8 (0.8)	11.3 (1.3)	8.9 (1.2)	6.6 (#)
Antioxidant activity in the blood (%)	100	118* (#)	100	105* (#)	#

Not reported

* Extracted from figure

Table 10: Incomplete results: Hosseini 2001b

Outcome	Pycnogenol		Placebo		Pycnogenol versus placebo
	Baseline Mean (SE)	Week 8 Mean (SE)	Baseline Mean (SE)	Week 8 Mean (SE)	Mean Difference (SE)
Systolic blood pressure (mm Hg)	139.9 (3.3)	132.7 (4.18)	#	#	#
Diastolic blood pressure (mm Hg)	93.8 (1.23)	92.0 (1.7)	#	#	#

Not reported

Table 11: Change in nitric oxide levels (nmol/l): Liu 2004c

Period	Pycnogenol Median (IQR)	Placebo Median (IQR)	Pycnogenol versus placebo
% change in nitric oxide concentration at end of month 3 relative to baseline	11.75 (-1.44 to 32.08)	10.50 (-2.07 to 29.11)	Ns (p-value not reported)

Ns = Reported to be statistically non-significant

Table 12: Incomplete results: Belcaro 2008b and Farid 2007

Study ID	Outcome	Pycnogenol		Placebo		Pycnogenol versus placebo
		Baseline Mean (SD)	Month 3 Mean (SD)	Baseline Mean (SD)	Month 3 Mean (SD)	Mean difference (SD)
Belcaro 2008b	Sum of pain scores	17.3 (#)	7.7 (#)	17.1 (#)	15.2 (#)	#
Farid 2007	Pain score	292 (101)	164 (72)	301 (119)	306 (103)	133 (#)
Belcaro 2008b	Sum of stiffness scores	6.6 (#)	3.1 (#)	6.7 (#)	6.7 (#)	#
Farid 2007	Stiffness score	110 (66)	75 (54)	120 (63)	108 (56)	23 (#)
Belcaro 2008b	Sum of physical function scores	55.3 (#)	23.8 (#)	53.1 (#)	47.6 (#)	#
Farid 2007	Physical function score	997 (352)	485 (259)	1042 (420)	1014 (385)	484 (#)
Belcaro 2008b	Global WOMAC score	79.2 (#))	34.6 (#)	76.9 (#)	69.5 (#)	#
Farid 2007	Composite WOMAC score	1400 (482)	725 (346)	1463 (552)	1455 (509)	667 (#)
Belcaro 2008b	Negative alterations in social functions	23.1 (#)	9.9 (#)	21.3 (#)	20.4 (#)	#
Belcaro 2008b	Emotional parameters	31.4 (#)	11.5 (#)	28.2 (#)	24.4 (#)	#

Not reported

Table 13: Incomplete results: Cisár 2008

Outcome	Pycnogenol			Placebo			Pycnogenol versus placebo	
	Baseline Median (IQR)	Week 12 Median (IQR)	Median change (p-value)	Baseline Median (IQR)	Week 12 Median (IQR)	Median change (p-value)	Mean change	Statistical significance
Pain reduction (WOMAC A score)	14* (#)	16* (#)	2 (p = 0.001)	14* (#)	16* (#)	2 (#)	0	Ns
Pain reduction (VAS)	37.5* (#)	22.5 (#)	15 (p = 0.058)	43.5* (#)	27* (#)	16.5 (#)	-1.5	Ns
Stiffness reduction in % (WOMAC B score)	100*	120*	20 (P < 0.01)	100*	100*	0 (Ns)	20	#
Ability to perform daily activities (WOMAC C score)	46* (#)	53* (#)	7 (p = 0.01)	44* (#)	50* (#)	6 (Ns)	1	#
Overall reduction in osteoarthritis symptoms (WOMAC overall score)	65* (#)	75* (#)	10 (p = 0.03)	64* (#)	72* (#)	8 (p = 0.02)	2	#

* Extracted from figure

Not reported

Ns = Reported to be statistically non-significant

Table 14: Physical performance on treadmill (meters): Belcaro 2008b

Time point	Pycnogenol Mean (range)	Placebo Mean (range)	Pycnogenol versus placebo
Baseline	68 (0 to 133)	65 (12 to 98)	Ns
Month 3	198 (55 to 374)	88 (25 to 102)	P < 0.05

Ns = Reported to be statistically non-significant

Table 15: Safety

Study ID	Country	Number of participants	Adults or children	Chronic disorder	Treatment duration	Serious adverse events	Non-serious adverse events
Arcangeli 2000	Italy	40	Adults	CVI	2 months	None found	None found
Belcaro 2006a	Italy	30	Adults	Diabetes	6 weeks	None found	None found
Belcaro 2008b	Italy	156	Adults	Osteoarthritis of the knee	3 months	Only the perceived protective effect that the treatment had on "unwanted effects" attributed to NSAIDs use was measured.	
Cisár 2008	Slovakia	100	Adults	Osteoarthritis of the knee	12 weeks	2/50 participants from the Pycnogenol group and 5/50 from the placebo group left the study because they didn't want to use the treatment they've received anymore. 1 participant (with previous myocardial infarction) from the Pycnogenol group left the study because of chest pain; another left because of bad breath. 3 participants from the placebo group left because of worsening pain, 1 because of gastric pain and another 1 felt ill.	None found
Farid 2007	Iran	37	Adults	Osteoarthritis of the knee	3 months	None found	None found
Hosseini 2001a	Iran	26	Adults	Asthma	four weeks	None found	One participant complained of gastrointestinal disturbances which occurred within the first 3 to 4 days of treatment (assumed to be

							Pycnogenol).
Hosseini 2001b	USA	11	Adults	Hypertension	8 weeks	None found	None found
Lau 2004	USA	60	Children	Asthma	3 months	None found	None found
Liu 2004a	China	77	Adults	Diabetes	12 weeks	None found	7/34 participants in the Pycnogenol group complained about dizziness compared to 4/43 in the placebo group. 5/34 participants in the Pycnogenol group reported gastro-intestinal problems compared to 2/43 in the placebo group. "Other complaints of headache, nausea and sleepiness occurred only in one or two patients in both groups."
Liu 2004c	China	58	Adults	Hypertension	12 weeks	None found	"Gastrointestinal problems, nausea, dizziness, headache and sleepiness had been reported. The difference in the rate of side effects in Pycnogenol group (39%) and in placebo group (27%) was not statistically significant."
Petrassi 2000	Italy	20	Adults	CVI	2 months	None found	None found
Steigerwalt 2009	Italy	46	Adults	Diabetes	2 months	None found	None found
Trebatická 2006	Slovakia	61	Children	ADHD	1 month	None found although 2/43 participants withdraw from the study "even though they received medication" (Pycnogenol). 1/17 participant from the placebo group	1/44 participant in the Pycnogenol group reported a "rise in slowness"; another reported moderate gastric discomfort. No adverse events in the placebo group (N = 17) were reported.

						discontinued participation in the study. It is not reported what the reason(s) for withdrawal were.	
Zibadi 2008	USA	48	Adults	Diabetes	12 weeks	None found	None found
Ďuračková 2003	Slovak Republic	21	Adults	ED	3 months	Not assessed	Not assessed

Table 16: Evaluating the methodological quality of systematic reviews with the AMSTAR tool (Shea 2007)

Criteria	**Yes/No/Can't answer/Not applicable**			
	Bartlett 2008	Clark 2010	Henrotin 2010	Our Pycnogenol review
1. Was an 'a priori' design provided? - The research question and inclusion criteria should be established before the conduct of the review.	Yes	Yes	Yes	Yes
2. Was there duplicate study selection and data extraction? - There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	No	Yes	No	Yes
3. Was a comprehensive literature search performed? - At least two electronic sources should be searched. The report must include	Yes	Yes	No	Yes

years and databases used (e.g. CENTRAL, EMBASE and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers or experts in the particular field of study, and by reviewing the references in the studies found.				
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? - The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	No	Can't answer	Yes	No
5. Was a list of studies (included and excluded) provided? - A list of included and excluded studies should be provided.	No	Yes. A list of excluded studies was not provided, but they've presented the number of excluded studies per reason in a flow chart.	No	Yes
6. Were the characteristics of the included studies provided? - In an aggregated from such as a table, data from the original studies should be	No, it is incomplete.	Yes	No, it is incomplete.	Yes

provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity or other diseases should be reported.				
7. Was the scientific quality of the included studies assessed and documented? - 'A priori' methods of assessment should be provided (e.g. for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	No. It is reported that only "double-masked randomised controlled trials" were selected, but one of the three included studies (Spadea 2001) on Pycnogenol was not fully randomised.	Yes. The Cochrane risk of bias assessment tool was used to evaluated adequate sequence generation, allocation concealment and blinding.	Yes. "The methodological quality of each clinical...was determined according to an assessment model adapted from EFSA and FDA recommendations; AFSSA guidelines and other relevant references." This entails that the "quality is scored according to a set of 14 criteria...one point is marked for each criterion presented in the description of the clinical trial." The total scores allow classification as follows: < 6 poor; 7 to 9 medium; 10 to 11 good; and 12 to 14 very good methodological quality.	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusion? - The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	No	Yes	Yes, however we do not agree with their judgement of "good to very good" methodological quality.	Yes
9. Were the methods used to combine the findings of studies appropriate? - For the pooled results, a test should be done to ensure the studies were	Not applicable	Yes	Not applicable	Yes

combinable, to assess their homogeneity (i.e. Chi^2 test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).				
10. Was the likelihood of publication bias assessed? - An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) and/or statistical tests (e.g. Egger regression test).	Not applicable	Not applicable	Not applicable	Not applicable
11. Was the conflict of interest stated? - Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	No	Yes	Yes	Yes

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Data and analyses

Comparison 1: Pycnogenol versus placebo: Asthma

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Decrease of asthma symptoms	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.32, 2.58]
1.2 Patients off albuterol inhaler	1	60	Risk Ratio (M-H, Fixed, 95% CI)	6.00 [1.97, 18.25]
1.3 Number of albuterol inhaler puffs per 24 hours	1	60	Mean Difference (IV, Fixed, 95% CI)	-2.10 [-2.53, -1.67]
1.4 Change in FEV1	1		Mean Difference (IV, Fixed, 95% CI)	7.00 [0.10, 13.90]
1.5 Change in FEV1/FVC	1		Mean Difference (IV, Fixed, 95% CI)	7.70 [3.19, 12.21]

Comparison 2: Pycnogenol versus placebo: Attention deficit hyperactivity disorder

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Change in inattention as measured by CAP scores	1		Mean Difference (IV, Fixed, 95% CI)	2.00 [0.61, 3.39]
2.2 Change in hyperactivity as measured by CAP scores	1		Mean Difference (IV, Fixed, 95% CI)	2.00 [0.10, 3.90]
2.3 % change in inattention as measured by CTRS	1		Mean Difference (IV, Fixed, 95% CI)	14.00 [0.34, 27.66]
2.4 % change in hyperactivity as measured by CTRS	1		Mean Difference (IV, Fixed, 95% CI)	4.00 [-3.19, 11.19]
2.5 Hyperactivity as measured by CPRS scores	1		Mean Difference (IV, Fixed, 95% CI)	-3.50 [-7.15, 0.15]
2.6 % change in visual-motoric coordination and concentration	1		Mean Difference (IV, Fixed, 95% CI)	8.00 [0.16, 15.84]

Comparison 3: Pycnogenol versus placebo: Chronic venous insufficiency

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Heaviness scores	2	60	Mean Difference (IV, Fixed, 95% CI)	-0.72 [-0.91, -0.54]
3.2 Swelling scores	2	60	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.67, -0.25]
3.3 Pain scores	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.02, -0.16]
3.4 Disappearance of heaviness	1	40	Risk Ratio (M-H, Fixed, 95% CI)	15.00 [0.91, 246.20]
3.5 Disappearance of swelling	1	40	Risk Ratio (M-H, Fixed, 95% CI)	27.00 [1.71, 425.36]
3.6 Disappearance of pain	1	40	Risk Ratio (M-H, Fixed, 95% CI)	25.00 [1.58, 395.48]
3.7 Treatment efficacy as judged by physician	1	40	Risk Ratio (M-H, Fixed, 95% CI)	4.75 [1.97, 11.48]

Comparison 4: Pycnogenol (oral) versus control: Insulin-dependent diabetes mellitus

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Microcirculation-related symptom scores	1	14	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-4.02, 1.42]
4.2 Area of ulceration	1	14	Mean Difference (IV, Fixed, 95% CI)	-4.00 [-9.92, 1.92]
4.3 Transcutaneous PO2	1	14	Mean Difference (IV, Fixed, 95% CI)	7.00 [3.18, 10.82]
4.4 Transcutaneous PCO2	1	14	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-3.79, 1.79]

Comparison 5: Pycnogenol versus placebo: Diabetes mellitus type II

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.3 Glucose levels (mg/dl)	1	48	Mean Difference (IV, Fixed, 95% CI)	-26.70 [-55.79, 2.39]
5.4 HbA1c levels (%)	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.78, -0.02]
5.5 Urinary albumin levels (mg/l)	1	48	Mean Difference (IV, Fixed, 95% CI)	-13.90 [-31.09, 3.29]

Comparison 6: Pycnogenol versus placebo: Erectile dysfunction

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 ED symptom scores	1	21	Mean Difference (IV, Fixed, 95% CI)	7.90 [5.08, 10.72]

Comparison 7: Pycnogenol versus placebo: Hypertension

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Reduction of nifedipine dose	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.83, 1.52]
7.2 Using 10 mg nifedipine	1	58	Risk Ratio (M-H, Fixed, 95% CI)	4.29 [1.63, 11.27]

Comparison 8: Pycnogenol versus placebo: Osteoarthritis of the knee

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Pain scores	1	37	Mean Difference (IV, Fixed, 95% CI)	-142.00 [-199.55, -84.45]
8.2 Stiffness scores	1	37	Mean Difference (IV, Fixed, 95% CI)	-33.00 [-68.48, 2.48]
8.3 Physical function score	1	37	Mean Difference (IV, Fixed, 95% CI)	-529.00 [-741.59, -316.41]
8.4 Composite WOMAC score	1	37	Mean Difference (IV, Fixed, 95% CI)	-730.00 [-1011.95, -448.05]
8.5 Reduction of NSAIDS	1	100	Risk Ratio (M-H, Fixed, 95% CI)	4.75 [1.74, 12.97]

Figures

Figure 1: Flow diagram of search results

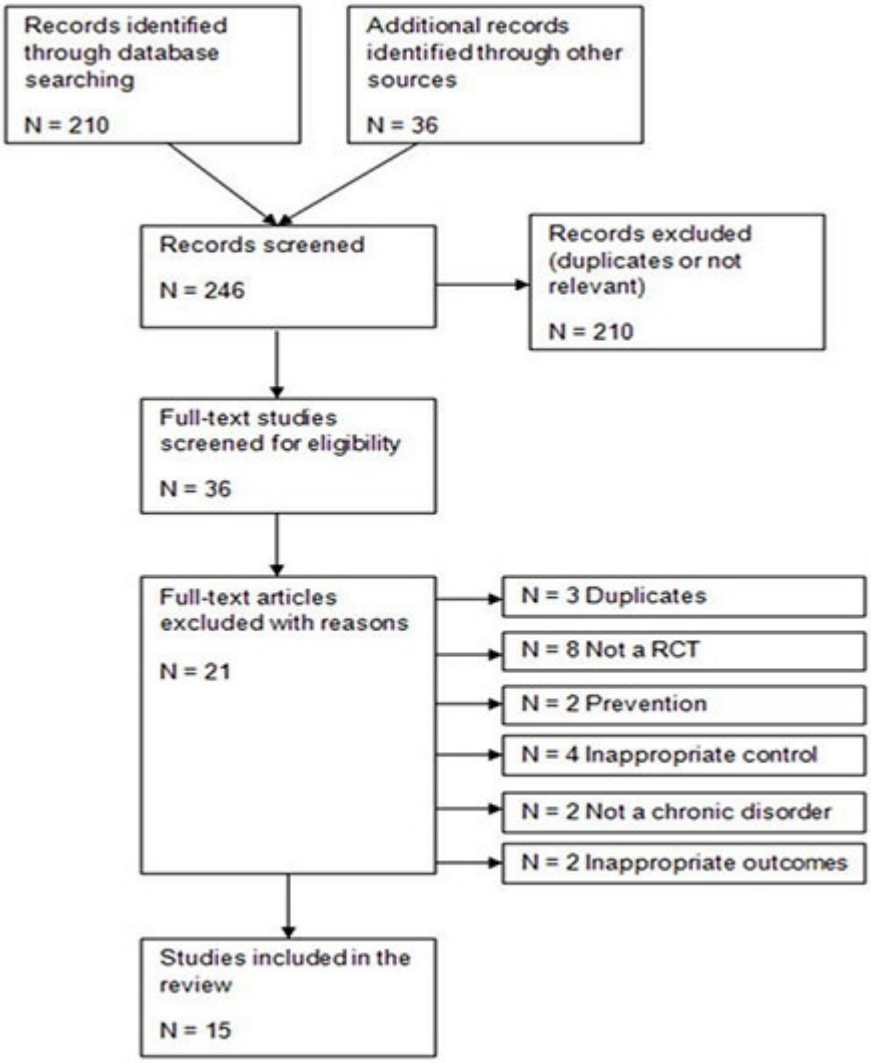


Figure 2: Review authors' judgements about each risk of bias item presented as percentages across all included studies

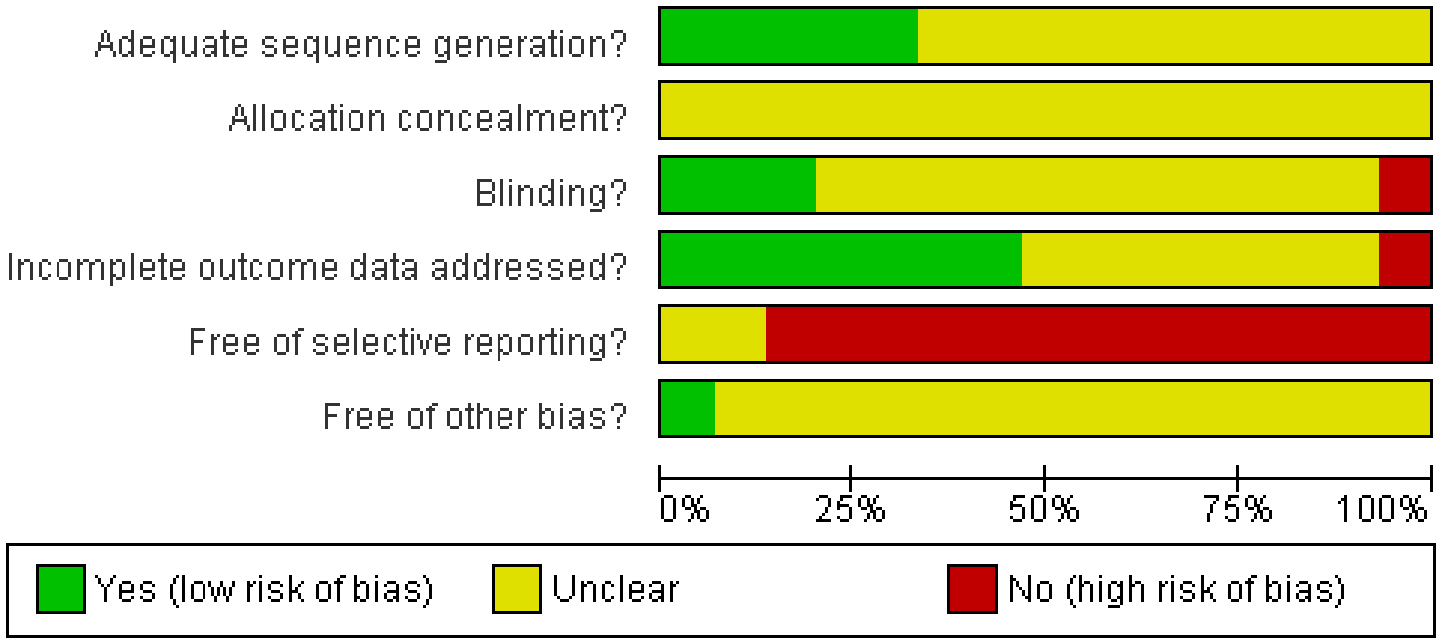


Figure 3: Review authors' judgements about each risk of bias item for each included study

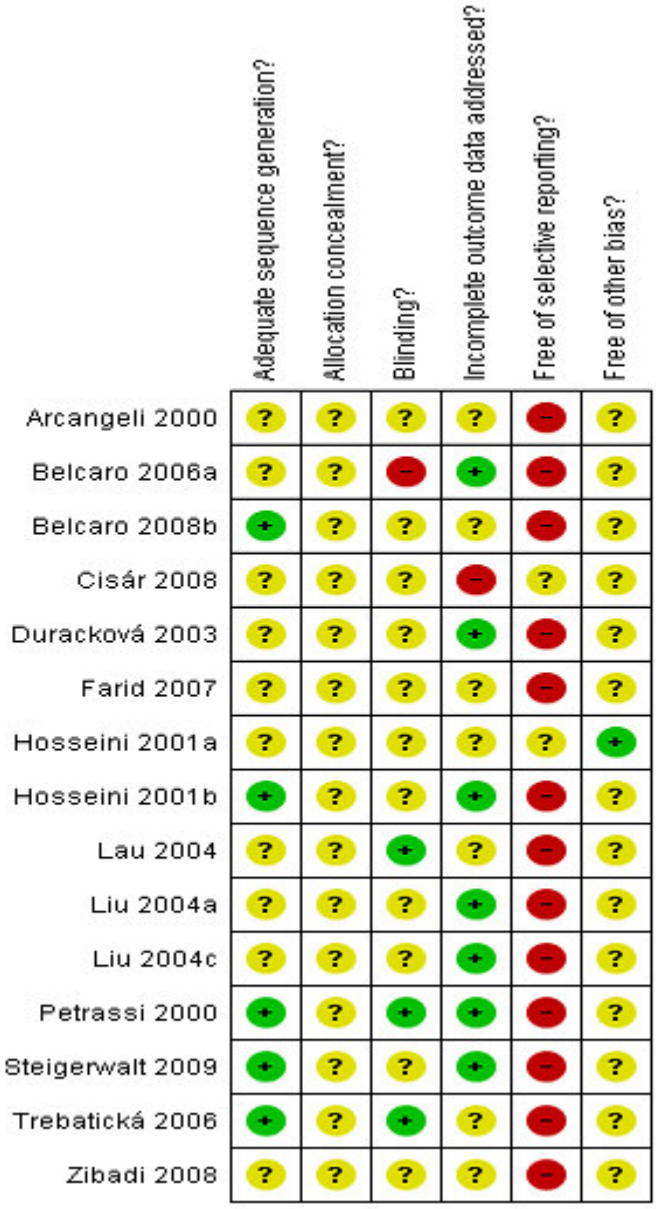


Figure 4 (Analysis 3.1): Forest plot of comparison: 3 Pycnogenol versus placebo: Chronic venous insufficiency, outcome: 3.1 Change in heaviness scores

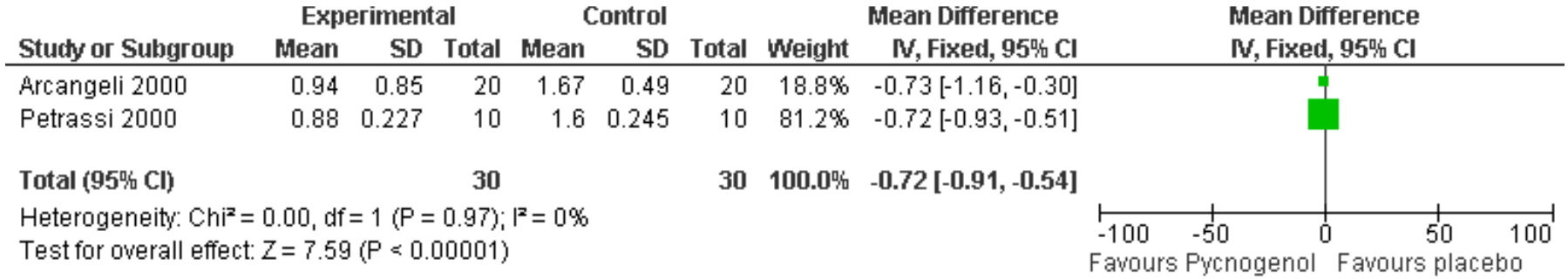
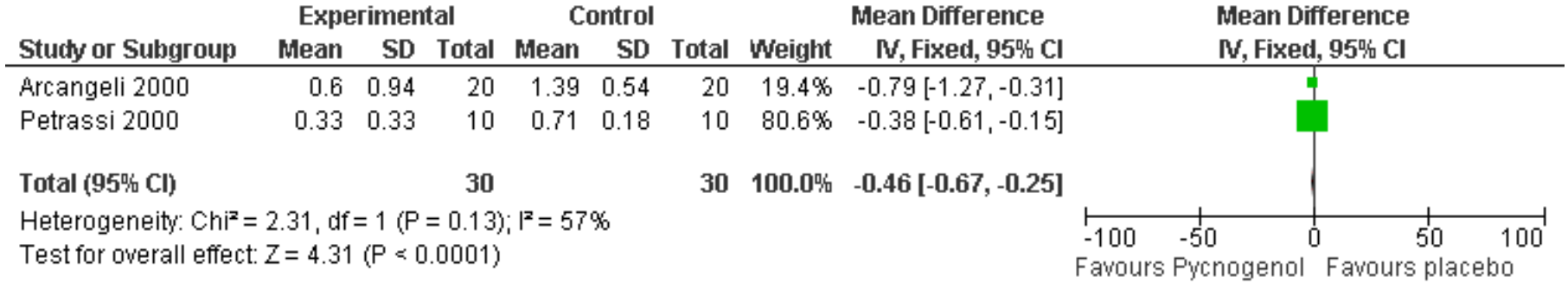


Figure 5 (Analysis 3.2): Forest plot of comparison: 3 Pycnogenol versus placebo: Chronic venous insufficiency, outcome: 3.2 Change in swelling scores



Appendices

Appendix 1: MEDLINE search strategy

1 Pycnogenol [tiab]

2 pine bark [tiab]

3 #1 OR #2

4 randomized controlled trial [pt]

5 controlled clinical trial [pt]

6 randomized [tiab]

7 placebo [tiab]

8 drug therapy [sh]

9 randomly [tiab]

10 trial [tiab]

11 groups [tiab]

12 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

13 animals [mh] NOT (humans [mh] AND animals [mh])

14 #12 NOT #13

15 #3 AND #14

Appendix 2: CENTRAL search strategy

1 (Pycnogenol):ti,ab,kw in Clinical Trials

2 (pine bark):ti,ab,kw in Clinical Trials

3 (#1 OR #2)

4 (randomized controlled trial):pt in Clinical Trials

5 (controlled clinical trial):pt in Clinical Trials

6 (randomized):ti,ab,kw in Clinical Trials

7 (placebo):ti,ab,kw in Clinical Trials

8 (drug therapy):ti,ab,kw in Clinical Trials

9 (randomly):ti,ab,kw in Clinical Trials

10 (trial):ti,ab,kw in Clinical Trials

11 (groups):ti,ab,kw in Clinical Trials

12 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)

13 (#3 AND #12)

Appendix 3: EMBASE search strategy

1 random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over:ti OR cross?over:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'single-blind procedure'/exp OR 'randomized controlled trial'/exp OR allocat*:ti OR allocat*:ab AND [embase]/lim

2 'pycnogenol'/exp OR 'pine bark' AND [embase]/lim

3 'pine'/exp AND 'bark'/exp AND [embase]/lim

4 #2 OR #3

5 #1 AND #4

Appendix 4: Assessment of risk of bias in included studies (Higgins 2008)

Domain 1: Sequence generation

Adequate: investigators described a random component in the sequence generation process such as the use of:

- A random number table;
- Coin tossing;
- Throwing dice;
- Shuffling cards or envelopes.

Inadequate: investigators described a non-random component in the sequence generation process such as the use of:

- Odd or even date of birth;
- The day or date of admission;
- The hospital or clinic record number;
- Preference of the participant;
- The results of a laboratory test or series of tests.

Unclear: there is insufficient information to permit judgement of the way in which sequence generation was performed.

Domain 2: Allocation concealment

Adequate: neither participants nor investigators enrolling participants could foresee assignment due to:

- Central allocation (e.g. via the telephone or pharmacy-controlled);
- Sequentially numbered drug containers of a matching appearance;
- Sequentially numbered, opaque and sealed envelopes.

Inadequate: both participants and investigators enrolling participants could foresee upcoming assignment based on, for example:

- Using an open random allocation schedule;
- Assigned envelopes were unsealed, non-opaque or not numbered appropriately;
- Date of birth;
- Case record number.

Unclear: there is insufficient information to permit judgement to the sequence generation process.

Domain 3: Blinding

Adequate: when anyone of the following are applicable:

- No blinding, but the review judge that the outcome would not be influenced by a lack of blinding;
- Blinding of both the key study personnel and participants are ensured, and it is unlikely that blinding could have been broken;
- Either participants or some key study personnel were not blinded, but the outcome measurement was blinded and the non-blinding of others are not likely to introduce bias.

Inadequate: when anyone of the following are applicable:

- No blinding or incomplete blinding;
- Blinding of key study personnel and participants were attempted, but it is likely that the blinding could have been broken;
- Either key study personnel or participants were not blinded which is likely to introduce bias.

Unclear: there is insufficient information to permit judgement, or the study did not address this outcome at all.

Domain 4: Incomplete outcome data

Adequate: when anyone of the following are applicable:

- No missing outcome data;
- The reasons for missing outcome data are unlikely to be related to the true outcome;
- Missing outcome data are balanced in numbers across intervention groups;
- Missing data have been imputed using appropriate methods;
- For dichotomous data, the proportion of missing outcomes compared with the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous data, the plausible effect size among missing outcomes is not enough to have a clinically relevant impact on the observed effect size.

Inadequate: when anyone of the following are applicable:

- The reason for missing outcome data is likely to be related to true outcome;
- The application of simple imputation is potentially inappropriate;
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;
- For dichotomous data, the proportion of missing outcomes compared with the observed event risk is enough to introduce clinically relevant bias in the intervention effect estimate;
- For dichotomous outcome data, the plausible effect size among missing outcomes is enough to induce clinically relevant bias in the observed effect size.

Unclear: there is insufficient reporting of exclusions to permit judgement, or the study did not address this outcome at all.

Domain 5: Selective outcome reporting

Adequate: when anyone of the following are applicable:

- The study protocol is available and all of the pre-specified outcomes are addressed in the review in the pre-specified way;
- The study protocol is not available, but it is clear that the published reports include all the pre-specified and expected outcomes.

Inadequate: when anyone of the following are applicable:

- Not all of the pre-specified primary outcomes have been reported;
- One or more of the primary outcomes is reported using measurements of analysis methods that were not pre-specified;
- One or more reported primary outcomes were not pre-specified;
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: there is insufficient information to permit judgement of compliance.

Domain 6: Other potential threats to validity

Adequate: when the study seems to be free of other sources of bias.

Inadequate: when there is the possibility of at least one important risk of bias such as:

- The quality of the specific study design is in question;
- The study is stopped early due to some data-dependent process;
- The study has been claimed to have been fraudulent.

Unclear: when there may be a risk of bias, but there is either:

- Insufficient information to assess whether an important risk of bias exists;
- Insufficient rationale or evidence that an identified problem will introduce bias.

Appendix 5: Letters to contact authors of relevant included studies

This letters were sent via email on 19 November 2010 and to date we have received three replies. The responses will be incorporated into the Cochrane review.

Belcaro 2006a

Dear Dr G Belcaro

We are conducting a systematic review with the title "Pycnogenol for the treatment of chronic disorders". Your article published in Clin Appl Thrombosis/Hemostasis 2006;12(3):1-6 with the title "Diabetic ulcers: microcirculatory improvement and faster healing with Pycnogenol" met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Was the trial conducted in Italy?
- With regards to the baseline information of the four different groups in Table 1: is the age and duration of disease expressed as means, i.e. the 54.3, 11.3, 55, 11, etc?
- Can you please describe to us how randomisation was done, in other words how were participants divided into the Pycnogenol or placebo group?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- It is reported in the text that the evaluation of microcirculatory parameters was firstly collected at baseline (week 0). However, in Table 3 it seems like if the first data collection was done at week 1 (and thus not at baseline). Which one is correct?
- With regards to the outcome 'skin flux at rest' in Table 3: the result of the control group at week 6 is given as "3.3.8". What is the correct value (e.g. 3.8 or 3.3)?
- With regards to the outcome 'change in area of ulceration': can you please provide the standard deviation of change between baseline and week 6 for each of the four groups, or at least for the oral plus local Pycnogenol versus control group?

- With regards to the outcome ‘change in symptom score’ (Table 2): can you please provide the standard deviation of change between baseline and week 6 of each of the four groups, or at least for the oral plus local Pycnogenol versus control group?
- With regards to the outcome ‘percentage healing’ (Table 2): can we please get the exact numbers for the 89%, 84%, 85% and 61%, because for example, 89% equates to ‘7.12’ people. Furthermore, can you please explain to us what is meant with “percentage healing”? For example, did all the participants had at least one ulcer that healed, or should all ulcers be healed per participant before he/she was counted?
- With regards to the outcome ‘microcirculatory parameters’ (Table 3): can you please provide the standard deviation of change between week 1 (or baseline?) and week 6 for each of the three relevant groups (or at least for the oral plus local Pycnogenol group and control) for PO_2, PCO_2 and skin flux at rest?

Thank you very much for your time.

Belcaro 2008b

Dear Dr G Belcaro

We are conducting a systematic review with the title "Pycnogenol for the treatment of chronic disorders". Your article published in Phytotherapy Research 2008;22:518-523 with the title "Treatment of osteoarthritis with Pycnogenol. The SVOS (San Valentino Osteo-arthrosis Study). Evaluation of signs, symptoms, physical performance and vascular aspects." met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- We know from the article that the placebo was identical in terms of appearance to the test drug Pycnogenol. Were there other characteristics that were also matched?
- Was the treadmill test performed at 3 km/h as in the text or at 8 km/h as in Tables 1 and 4?
- On what scale was the WOMAC scores measured (e.g. 5 point Likert scale, visual analogue scale etc.)?
- Do all the reported results include all of the available participants, i.e. 71 in the Pycnogenol and 74 in the control group? If not, can you please tell us how many per group?
- How was the analyses performed, i.e. were the missing data just omitted and were the participants analysed according to the group to which they were randomised?
- With regards to Table 2 (sum of the pain, stiffness, physical function and global scores): can you please provide the standard deviation at baseline and at month 3, as well as the standard deviation of change (between baseline and month 3), for each of the abovementioned outcomes for both the Pycnogenol and placebo groups?
- With regards to Table 3 (negative alterations in social functions and sum of emotional parameters outcomes): can you please provide the standard deviation at baseline and at month 3, as well as the standard deviation of change (between baseline and month 3), for these two outcomes for both the Pycnogenol and placebo groups?
- With regards to the totals of the placebo group for the outcome 'sum of emotional parameters' in Table 3: for inclusion the mean is reported as 28.4 and for month 3 as

24.1. How did you calculate these figures? If we add up all individual means for inclusion and month 3, we get 28.2 and 24.4 respectively.

- With regards to 'physical performance' in Table 4: can you please provide the standard deviation of change between baseline and month 3 for both the Pycnogenol and the placebo group?
- With regards to the use of NSAIDs: was NSAIDs the only concomitant medication that was used? What is meant with "the use of NSAIDs dropped by 58% during treatment with Pycnogenol, whereas under placebo NSAIDs use was reduced by only 1%."? Can you please provide the actual numbers per group that experienced a reduction as well as the total number of participants in each group?
- With regards to the clinical assessment of ankle and foot edema: can you please give us the number of participants in each group, for baseline and at the end of the three months treatment period, that relate to the 76%, 79%, 79% and 1%, as well as the total number of participants that were assessed in each group?
- It is reported that "unwanted effects of treatment were reported by patients in diaries". Can you please explain the results that were reported for this outcome, i.e. "evaluation of data demonstrated a decrease of gastrointestinal complications of 63% in the Pycnogenol group versus 3% in the placebo group"?
- In the article published in Redox Report 2008;13(6):271-9 with the title "Variations in C-reactive protein, plasma free radicals and fibrinogen values in patients with osteoarthritis treated with Pycnogenol" it is reported that the study was sponsored by Horphag Research Ltd (UK). Did they only sponsored the study on the subsample (N = 29 + 26 = 55) of participants with CRP-levels ≥ 3 mg/l, or did they sponsor the whole study (in other words the one reported in Phytotherapy Research 2008;22:518-523)?

Thank you very much for your time.

Cisár 2008

Dear Dr P Rohdewald

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. Your article published in Phytotherapy Research 2008;22:1087-92 with the title “Effect of pine bark extract (Pycnogenol) on symptoms of knee osteoarthritis” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Can you please describe to us how randomisation was done, in other words how were participants divided into the Pycnogenol or placebo group?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- We know from the article that the placebo was identical in terms of appearance to the test drug Pycnogenol. Were there other characteristics that also matched?
- We are not quite sure of the total duration of the trial. It is reported that "patients were investigated at the start, at 3 months and 4 weeks after finishing treatment." From this quote we understand that the treatment was given for three months (12 weeks) after which there was a four week wash-out period before the final follow-up data collection was performed (in other words a total study duration of 16 weeks). However, the results are reported, amongst other time points, at weeks 12 and 14 as well as at week 15 (Figure 5). Can you please point out the total duration of the trial as well as the treatment period (e.g. 12 weeks) and the duration of the wash-out period (e.g. 2 weeks or 4 weeks)?
- In the analysis, how was the missing data from the participants lost to follow-up handled? Was it imputed and entered in the analysis or was it omitted (available case analysis)?
- With regards to the results of the two primary outcomes (reduction of symptoms of osteoarthritis using WOMAC scores – for pain, stiffness, ability to perform daily activity, and total WOMAC score; and reduction of pain using VAS) that are only reported in graph form (Figures 1 to 5): can you please provide either the means and standard deviations as well as the standard deviation of change, or the medians and

interquartile ranges for baseline and the end of the treatment period separately for the Pycnogenol and placebo groups?

Thank you very much for your time.

Duracková 2003

Dear Dr Z Durackova

We are conducting a systematic review with the title "Pycnogenol for the treatment of chronic disorders". Your article published in Nutrition Research 2003;23:1189-98 with the title "Lipid metabolism and erectile function improvement by Pycnogenol, extract from the bark of *Pinus pinaster* in patients suffering from erectile dysfunction – a pilot study" met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Was the study conducted in Slovak Republic?
- Can you please describe to us how randomisation was done, in other words how were participants divided into the Pycnogenol or placebo group?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- How did the placebo pill looked with respect to the test drug Pycnogenol, i.e. were they identical in some respects?
- The overall age of the two groups were reported as "average age 46.5 ± 12.5 years". What kind of measure of variation is the 12.5, i.e. standard deviation (SD), standard error of the mean (SEM) etc.? Is it possible to give us the mean age ± SD of each group separately?
- The 'average ED score' (measured by IIEF-5) is reported as 12.6 ± 1.1. What measure of variation is the '1.1', i.e. SD or SEM? Can you please provide the mean baseline scores and the SD or SEM for the Pycnogenol and placebo group separately?
- Can you perhaps provide baseline characteristics of the two groups (separately) e.g. age, mean duration of disorder, weight or body mass index, smoking habits?
- It is reported that moderate ED = 11 to 15 points and severe ED = "less than 10 points". In what category does a score of 10 fit into?
- With regards to the outcome 'change in IIEF-5 scores': can you please provide the mean of the placebo group at the end of the three months treatment period as well as the SEM of change for the period between baseline and month 3 for both the

Pycnogenol and placebo groups? Otherwise the exact p-value of the change between the two groups will also help.

- With regards to the outcome ‘change in antioxidant activity’ (measured by FRAP): can you please provide the mean difference for both the Pycnogenol and the placebo group, as well as the SEM of change between baseline and month 3 for the two groups?

Thank you very much for your time.

Farid 2007

Dear Dr RR Watson

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. Your article published in Nutrition Research 2007;27:692-97 with the title “Pycnogenol supplementation reduces pain and stiffness and improves physical function in adults with knee osteoarthritis” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Can you please describe to us how randomisation was done, in other words how were participants allocated to the Pycnogenol or placebo group?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- We know from the article that the placebo was identical in terms of appearance to the test drug Pycnogenol. Were there other characteristics that also matched?
- For the outcomes ‘change in pain, ‘change in stiffness’, ‘change in physical function’ and ‘change in composite WOMAC score’: can you please provide the standard deviation of change between baseline and day 90 for both the Pycnogenol and the placebo groups?
- For the outcome ‘frequency and dose of additional medication usage (NSAIDs and COX-2)’: can you please provide the actual numbers of Fig.3A and Fig.3B of baseline and month 3, as well as the standard deviation of change between baseline and month 3 for both the Pycnogenol and the placebo groups?
- There were two missing participants at the end of the treatment period. Can you please describe how you have dealt with it in the intention-to-treat analysis?

Thank you very much for your time.

Hosseini 2001a

Dear Dr RR Watson

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. Your article published in the Journal of Medicinal Food 2001;4(4): 201-209 with the title “Pycnogenol in the management of asthma” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Can you please describe to us how randomisation was done, in other words how were participants divided into the Pycnogenol or placebo group?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- How did the placebo pill looked with respect to the test drug Pycnogenol, i.e. were they identical in some respects?
- Did you perform any tests for carry-over effect? If yes, how was it performed?
- Is it possible to please provide the reason why each of the seven participants withdrew from the study?
- With regards to results for the outcome ‘asthma symptom scores’ (Figure 3): can you please provide the mean and standard error of the differences between Pycnogenol and placebo measurements? If it is possible, can you please also tell us how many people in each group showed a decrease of symptoms at the end of the treatment period, compared to baseline? We will then also need the number of participants that were assessed in each of the Pycnogenol and placebo periods.
- With regards to the outcomes ‘FEV_1’ and ‘FEV_1/FVC’: can you please provide the standard deviation of change for each of these two outcomes, for the Pycnogenol and placebo periods?

Thank you very much for your time.

Hosseini 2001b

Dear Dr RR Watson

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. The article published in Nutrition Research 2001;21:1251-60 with the title “A randomized, double-blind, placebo-controlled, prospective, 16 week crossover study to determine the role of Pycnogenol in modifying blood pressure in mildly hypertensive patients” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Was the study conducted in the USA?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- How did the placebo pill looked with respect to the test drug Pycnogenol, i.e. were they identical in some respects?
- Did you perform any tests for carry-over effect? If yes, how was it performed?
- With regards to the outcome ‘systolic and diastolic blood pressure’: can you please provide the mean and standard error of the differences between the Pycnogenol and placebo measurements?
- Was ‘change in use of concomitant medication’ an outcome that was measured? Or was it only monitored to make sure that the usage stayed the same throughout the treatment period?
- There are no results reported for the blood tests for safety which was specified in the Methods section of the article. What parameters were tested with these blood chemical tests and what were the results? It is reported that blood collection occurred at the end of week 7, week 15 and 16. Was it collected at the end of week 8 as well?

Thank you very much for your time.

Lau 2004

Dear Dr BHS Lau

We are conducting a systematic review with the title "Pycnogenol for the treatment of chronic disorders". Your article published in the Journal of Asthma 2004;41(8):825-32 with the title "Pycnogenol as an adjunct in the management of childhood asthma" met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Can you please describe to us how randomisation was done, in other words how were participants divided into the Pycnogenol or placebo group?
- Can you please tell us more about the coding of the bottles of placebo and Pycnogenol: were there two different codes - one for placebo and one for Pycnogenol - or did every one of the sixty bottles had a different code? What was the code like, e.g. how many numbers per code?
- What happened during the one week run-in period before the start of the study?
- Were only rescue inhaler (albuterol) and oral medication (Accolate) permitted during the trial as concomitant medication?
- Did all 60 participants finished the three months intervention period and was data of all outcomes for every participant collected? If not, how was the missing data accounted for in the analyses?
- With regards to the outcome 'change in peak expiratory flow rate (PEF)': can you please provide the mean ± standard error of the mean (SEM) for the Pycnogenol and the placebo group at the three months time point; as well as the standard deviation of change (between baseline and end of month 3) for both the Pycnogenol and the placebo group? In addition we would like to know why, in Figure 2, is the y-axis labeled "median symptom scores" but in the text beneath the figure it is reported as "means ± SEM"?
- With regards to the outcome 'change in symptom scores': can you please provide the mean ± SEM for the placebo group for both the baseline and the three months time point; as well as the standard deviation of change (between baseline and end of month 3) for both the Pycnogenol and the placebo group?

- With regards to the outcome ‘change in use of rescue inhaler’: can you please provide us, for the period between baseline and month 3, with the standard deviation of change for both the Pycnogenol and placebo groups?
- The following quote comes from the article’s Methods section: "Bottles of Pycnogenol or placebo (provided by Horphag Research, Geneva, Switzerland) were identified by preassigned codes..." However, the following quote comes from the Acknowledgement section: “This study was supported by the Chan Shun International Foundation, San Francisco, CA, and Horphag Research, Geneva, Switzerland. Neither of the sponsors is the manufacturer of the Pycnogenol capsules used in this study." Now we are unsure whether Horphag Research provided the Pycnogenol and placebo capsules or not?

Thank you very much for your time.

Liu 2004a

Dear Dr P Rohdewald

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. Your article published in Life Sciences 2004;75:2505-13 with the title “Antidiabetic effect of Pycnogenol French maritime pine bark extract in patients with diabetes type II” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Can you please describe to us how randomisation was done, in other words how were participants divided into the Pycnogenol or placebo group?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- How did the placebo pill looked with respect to the test drug Pycnogenol, i.e. were they identical in some respects?
- Was the Pycnogenol and placebo consumed orally, and how frequent was the Pycnogenol and placebo consumed?
- With regards to the outcome ‘change in nitrogen monoxide levels’: it is reported on page 2509 that “concentrations of nitric monoxide in plasma increased over the treatment period in both groups, with a tendency to higher values in the Pycnogenol group...”. Can you please provide the mean ± standard deviation for baseline and week 12 for the Pycnogenol and placebo groups, as well as the standard deviation of change for the two groups separately?
- Was the study funded? If yes, can you please provide us with the name(s) of the company or institution?

Thank you very much for your time.

Liu 2001c

Dear Dr P Rohdewald

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. The article published in Life Sciences 2004;74:855-62 with the title “Pycnogenol, French maritime pine bark extract, improves endothelial function of hypertensive patients” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Can you please describe to us how randomisation was done, in other words how were participants divided into the Pycnogenol or placebo group?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- How did the placebo pill looked with respect to the test drug Pycnogenol, i.e. were they identical in some respects?
- Was the Pycnogenol and placebo consumed orally, and how frequent was the Pycnogenol and placebo consumed?
- With regards to the outcome ‘change in nitrogen monoxide levels’: it is reported on page 860 that “concentrations of nitric monoxide in plasma increased over the treatment period in both groups...differences in comparison to placebo failed to reach statistical significance.”. Can you please provide the mean ± standard deviation for baseline and week 12 for the Pycnogenol and placebo groups, as well as the standard deviation of change for the two groups separately?
- Was the study funded? If yes, can you please tell us who the funder(s) were?

Thank you very much for your time.

Petrassi 2000

Dear Dr C Petrassi

We are conducting a systematic review with the title "Pycnogenol for the treatment of chronic disorders". Your article published in Phytomedicine 2000;7(5):383-88 with the title "Pycnogenol in chronic venous insufficiency" met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Was the study conducted in Italy?
- The mean age together with a unit of variation is given for the Pycnogenol and placebo groups: "47.7 ± 3.65 years" and "36.7 ± 3.66 years" respectively. What measure of variation is used (e.g. standard deviation)?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- Were the values in Table 1 reported as mean ± standard deviation as mean ± standard error?
- For the outcome 'change in heaviness score': can you please provide the standard deviation of change between baseline and day 60 for both the Pycnogenol and placebo groups?
- For the outcome 'change in swelling score': can you please provide the standard deviation of change between baseline and day 60 for the Pycnogenol and placebo groups?
- For the outcome 'change in pain score': can you please provide the mean and standard deviation of baseline and Day 60 for both groups, as well as the standard deviation of change between baseline and day 60 for both the placebo and Pycnogenol groups?
- Results for the outcomes 'change in night cramps' and 'change in paraesthesiae' are not reported. Can you please provide the mean and standard deviation for baseline and day 60 for both groups, as well as the standard deviation of change between baseline and day 60 for both the placebo and Pycnogenol groups?
- For the outcomes 'change in heaviness', 'change in swelling', 'change in night cramps', 'change in pain', and 'change in parasthesiae': can you perhaps also tell us

how many people per group experienced disappearance of each symptom at the end of the treatment period compared to baseline; as well as the total number of participants in each group for each symptom?

- Can you perhaps provide the data for only the randomised phase of the trial (n = 20) for the outcomes 'ambulatory venous pressure' and 'physician's judgement of efficacy and safety of treatment'? Since we only include randomised controlled trials in our systematic review we unfortunately cannot use the results if it is pooled with the non-randomised arm of the study.
- Was the study funded? If yes, can you please tell us who the funder(s) were?

Thank you very much for your time.

Steigerwalt 2009

Dear Dr F Schönlau

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. The article published in Journal of Ocular Pharmacology and Therapeutics 2009;25(6):537-540 with the title “Pycnogenol improves microcirculation, retinal edema, and visual acuity in early diabetic retinopathy” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Was the study conducted in Italy?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- How did the placebo pill looked with respect to the test drug Pycnogenol, i.e. were they identical in some respects?
- Is the baseline data in Table 1 reported as the mean ± standard deviation?
- Can you please provide the mean ± standard deviation as well as the standard deviation of change (mild and moderate retinal edema cases combined) between baseline and month 2 for both the Pycnogenol and the placebo groups for the following outcomes: retinal thickness, retinal edema score, diastolic flow relative to max systolic flow, retinal blood flow, and visual acuity (Snellen chart)?
- With regard to the outcome ‘diastolic flow relative to max systolic flow’: can you please give us the median of change and the range of change between baseline and month 2 for both the Pycnogenol and the placebo groups?
- On page 539 (Results section) it is reported that "eighteen out of a total of 23 patients taking Pycnogenol reported subjectively perceived visual improvement." But on page 540 (Discussion section) it is reported that "the degree of visual improvement, however, was impressive as patient's themselves, 18 out of a total of 24 taking Pycnogenol, perceived this effect." Should it be 23 of 24? If it should be 23, why? It is reported that no participants were lost to follow-up. Furthermore, nothing about the

placebo group is reported. Can you please provide the results for the placebo group?

- Nothing about the funding source was reported. Was the study funded? If yes, by whom?

Thank you very much for you time.

Trebatická 2006

Dear Dr J Trebatická

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. Your article published in Eur Child Adolesc Psychiatry 2006:15:329-335 with the title “Treatment of ADHD with French maritime pine bark extract, Pycnogenol” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- How was “double-blinding” achieved?
- With regards to the baseline characteristics that are reported in Table 1: are the “average” weight reported together with its standard deviation, or what measure of variation is reported? Is the BMI reported as a mean ± standard deviation?
- With regards to the outcome ‘change in inattention’: can you please provide the mean difference and standard deviation of change between the Pycnogenol and placebo groups for the period between baseline and month 1 for the CAP, CTRS and CPRS tests? Otherwise the final means of each group at the end of month 1 and the exact p-value comparing the final values of the two groups are also fine.
- With regards to the outcome ‘change in hyperactivity’: can you please provide the mean difference and standard deviation of change between the Pycnogenol and placebo groups for the period between baseline and month one for the CAP, CTRS and CPRS tests? Otherwise the final means of each group at the end of month 1 and the exact p-value comparing the final values of the two groups are also fine.
- With regards to the outcome ‘visual-motoric coordination and concentration’: can you please provide the mean difference and standard deviation of change between the Pycnogenol and placebo groups for the period between baseline and month 1? Otherwise the final means of each group at the end of month 1 and the exact p-value comparing the final values of the two groups are also fine.
- Can you please explain what you mean with an “intention-to-treat analysis”? Were values for the four participants that dropped out of the study included in the analysis?

Thank you very much for your time.

Dear Dr Z Ďuračková

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. Your article published in Nutritional Neuroscience 2007;10(3/4):151-157 with the title “Urinary catecholamines in children with attention deficit hyperactivity disorder (ADHD): Modulation by a polyphenolic extract from pine bark (Pycnogenol)” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- At what time point(s) were GSSG and GSH tested? It is reported that “whole blood was used for determination of total and oxidized glutathione”. What is the name of the laboratory process used for the analysis of GSSG and how was reduced glutathione (GSH) determined?
- With regards to the outcome ‘GSH/GSSG’: can you please provide the mean at baseline and mean at month 1 for the Pycnogenol and placebo groups, as well as the standard deviation of change from baseline to month 1 for both the placebo and Pycnogenol groups? Can you please also explain why you used n = 28 (Pycnogenol) and n = 13 (placebo) instead of n = 44 and n = 17 respectively?

Thank you very much for your time.

Zibadi 2008

Dear Dr RR Watson

We are conducting a systematic review with the title “Pycnogenol for the treatment of chronic disorders”. Your article published in Nutrition Research 2008;28:315-20 with the title “Reduction of cardiovascular risk factors in subjects with type 2 diabetes by Pycnogenol supplementation” met our eligibility criteria and is therefore one of our included studies.

In order to get more insight into the study, we will appreciate it if you can help us by answering the following questions:

- Was the study conducted in the USA?
- Can you please describe to us how randomisation was done, in other words how were participants divided into the Pycnogenol or placebo group?
- Was allocation of participants to either of the two groups concealed, in other words was something done to protect the investigator from knowing to which group the next participant will be allocated? If yes, how was it done?
- In terms of what characteristics was the placebo “matched” with the test drug Pycnogenol?
- A total of three participants were lost to follow-up, 2 from the placebo and 1 from the Pycnogenol group. How were data for these participants handled, e.g. the data you had for them, were it part of the analyses and the missing data just omitted, or were the missing data imputed? If imputed, how?
- In Table 1 where the percentage participants in each group that used different types of antidiabetic medications were reported: can you please give us the numbers that relates to the percentages? Because if we take 6% × 24 participants we get ‘1.44’ participants. Also, if one sums the percentages of the Pycnogenol group you get 100%, but for the placebo group it only adds up to 95%. Were there some participants who used other kinds of oral antidiabetic medication?
- Was ‘change in use of concomitant antidiabetic medication’ an outcome, or was it only monitored to make sure that the usage stayed the same throughout the treatment period?
- With regards to the outcome ‘change in glucose levels’: can you please provide the standard error of the mean (SEM) of change between baseline and week 12 for the placebo group?

- With regards to the outcome ‘change in Hb1Ac levels’: can you please provide the SEM of change between baseline and week 12 for both the Pycnogenol and placebo groups?
- With regards to the outcome ‘change in urinary albumin levels’’: can you please provide the SEM of change between baseline and week 12 for the placebo group?
- With regards to the outcome ‘compliance with the test drug or placebo’: can you please provide the number of participants that relates to the following percentages: 94% of the Pycnogenol group and 96% of the placebo group? Does this outcome include those participants that were lost to follow-up?
- With regards to the measurement ‘heart rate’: there are no results reported. Was heart rate measured as a safety measure? Is it possible to give us results for it?

Thank you very much for your time.

CLOSING REMARKS

CLOSING REMARKS

Complementary medicine refers to any substance which originates from a plant, mineral or animal which is used for complementing the healing power of the human body.[14] Nutritional supplements, a type of complementary medicine, is defined as a product intended to increase the total dietary intake, containing at least one of the following: a vitamin, mineral, herb or amino acid.[15] Seventy to eighty percent of people in developing countries have used some form of complementary medicine.[16] In recent years the South African market has been flooded by complementary medicines. This extremely profitable market are today largely unregulated.[17] This raises concern about the efficacy and safety of these products.

Nutritional supplements, amongst other complementary medicines, are advertised widely in South Africa, especially in the printed media. Often these advertisements contain a variety of claims, especially health claims. People not familiar with the field of science can easily be influenced to buy nutritional supplements because of advertisements containing promising claims. Claims should be supported by good research evidence.

Procydin, with proanthocyanidin as the main ingredient, is a popular nutritional supplement in South Africa. Pamphlets in pharmacies and advertisements in newspapers and magazines promote Procydin to benefit people who suffer from “diabetes, arthritis, cardiovascular diseases, high cholesterol, high blood pressure and arteriosclerosis”. Because many family members and friends use this antioxidant supplement it was decided to investigate what the evidence behind this product is.

The researchers are not aware of any clinical trials with Procydin as the intervention, and therefore the title of the initial protocol was ‘Proanthocyanidin supplements for the treatment of chronic disorders’. However, when conducting the search it was found that the majority of studies involve Pycnogenol, a standardised formulation of French maritime pine bark extract. Secondly it was realised that there is a lack of specificity of proanthocyanidin-containing products. Apart from proanthocyanidin, the majority of these supplements also contain a variety of other compounds and the various supplements vary widely in content. Furthermore the source of proanthocyanidin varies (pine bark, grape seed, cranberries etc.) as do the additional ingredients across the various supplements. Since Pycnogenol is the most researched proanthocyanidin-containing product and the manufacturer believes that their product is a “well-researched, evidence-based product” it was decided that a systematic review focusing on Pycnogenol would be more useful. As a consequence of this change in

title, we have revised the following sections of the initial protocol: 'Description of the intervention', 'Objectives' and 'Criteria for considering studies for this review'.

The conclusion of this systematic review is that current evidence is insufficient to support Pycnogenol use for the treatment of any chronic disorder. The impact of this finding is far reaching as this conclusion is not only applicable to Pycnogenol but also to all the other proanthocyanidin-containing supplements available worldwide, including Procydin, whose health claims are based on the clinical evidence of Pycnogenol. Furthermore, this example can strengthen the rationale for the need of an effective international regulating authority. Well-designed, adequately powered randomised controlled trials of Pycnogenol are needed to accurately assess the efficacy and safety of this product for the treatment of chronic disorders.

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