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REVIEW ARTICLE

Phytotherapeutics: an evaluation of the potential of 1000 plants

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SUMMARY

Objective: **The aim of this review is to evaluate and summarize the available scientific information on the commonest plant extracts marketed in Western countries. In view of the intense, ongoing search for new plant extracts with powerful anti-inflammatory activity, we paid particular attention to this topic. The aim is to provide broad coverage of as many potentially useful plants as possible and then to focus on those with the greatest therapeutic potential.**

Methods: **Our bibliographic sources were the SciFinder databases: CAPLUS, MEDLINE, REGISTRY, CASREACT, CHEMLIST, CHEMCATS (update to October 2007). In order to assess the value of clinical trials, we focused a specific search on clinical investigations concerning nine plants with the most trial data, viz., *Althaea officinalis*, *Calendula officinalis*, *Centella asiatica*, *Echinacea purpurea*, *Passiflora incarnata*, *Punica granatum*, *Vaccinium macrocarpon*, *Vaccinium myrtillus*, *Valeriana officinalis*. This was carried out in several databases (update to June 2008): ISI Web of Knowledge[SM] (ISI WoK), SciFinder (CAPLUS, MEDLINE, REGISTRY, CASREACT, CHEMLIST, CHEMCATS) and PubMed (indexed for MEDLINE).**

Results: **Our survey covers roughly a 1000 plants, although clinical trials have been published only for 156 plants supporting specific pharmacological activities and therapeutic applications. However, for about half of the plants, *in vitro* and *in vivo* studies provide some support for therapeutic use. For one-fifth of the plants included in our search, only phytochemical studies were found. Their properties and indications were often attributed to the presence of certain compounds, but no evidence concerning the activities of the whole extracts was presented. We found that for about 12% of the plants, currently available on the Western market, no substantial studies on their properties had been published, while there was strong evidence that 1 in 200 were toxic or allergenic, so that their use ought to be discouraged or forbidden. Nine plants had considerable evidence of therapeutic effect, viz., *A. officinalis*, *Calendula officinalis*, *Centella asiatica*, *E. purpurea*, *Passiflora incarnata*, *Punica granatum*, *Vaccinium macrocarpon*, *Vaccinium myrtillus*, *Valeriana officinalis*.**

Conclusion: **The present review provides a baseline on the level of evidence available on many herbal preparations and should be of help to those intending to research further on these topics.**

***Keywords*: clinical studies, evidence-based medicine, medicinal plants, phytotherapy, plant extracts**

INTRODUCTION

Phytotherapy is considered as a complementary approach for treating and preventing disease; although well grounded in medical tradition, it often lacks proper scientific validation. Rational use of phytopharmaceuticals should be supported by proper laboratory investigations and clinical trials. The often-repeated statement that herbal extracts, while usually exerting a broad spectrum of effects, show fewer undesirable ones than the single active substances is an old tale that has been substantiated in only a few cases. Many publications on the subject claim that phytotherapeuticals are especially suitable for long-term treatment of chronic

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diseases, in geriatric and convalescent patients, for follow-up treatment, and in the prophylaxis of infectious, degenerative and metabolic diseases. It is unfortunate that these claims are often taken for granted. The actual state of the art could be made more scientific by proper evaluation as well as the application of innovative research such as genomics, proteomics and metabolomics (1).

Phytotherapy also has a long standing in veterinary practice, often in the form of remedies that are not evidence-based in relation to quality, efficacy, and safety, or in terms of well-defined dose/effect relationships. The supporting evidence should include well-controlled trials, including placebo-controlled (PC) trials, where appropriate, and bioavailability and pharmacokinetic studies. The pressing need for such validation is highlighted by the current, steady growth of the world market for phytopharmaceuticals, with an estimated turnover of US $12·4 billion in 1995 (2). Today, the herbal industry with a turnover of about US $62 billions retains strong growth potential (3). In US alone, sales of herbal supplements, including dietary supplements and functional foods, in 1998, increased by 101% within 1 year to a total of US $587 million (2). The World Bank reported that trade in medicinal plants, botanical raw materials and drug products, was growing at an annual rate of 5–15% (3, 4). Nevertheless, Nature's biodiversity in potential herbal remedies remains largely unexplored (5).

We present a detailed survey of available scientific information on the commonest plant extracts marketed in Western countries. As our aim was to record the state of the art, our literature search was extended to cover roughly 1000 plants. On the basis of our broad comparative investigation, we attributed a ranking value (−1 to 3) to each plant to express the weight of factual knowledge available on it.

MATERIALS AND METHODS

Our bibliographic sources were the SciFinder databases: CAPLUS, MEDLINE, REGISTRY, CASREACT, CHEMLIST, CHEMCATS (update to October 2007). We used the search words as the Latin name and the common trivial name of the plant, then we refined the results by using 'pharmaceutical', 'therapeutic', 'activity', 'biological', 'medicinal' or 'clinical trial' as topics. English was selected as the document's language, and paper and review as document types. Patents were not reviewed.

In order to assess the data in more detail, we focused the search on clinical investigations concerning nine plants with the most data, viz., *Althaea officinalis*, *Calendula officinalis*, *Centella asiatica*, *Echinacea purpurea*, *Passiflora incarnata*, *Punica granatum*, *Vaccinium macrocarpon*, *Vaccinium myrtillus*, *Valeriana officinalis*. This was carried out in several databases (update to June 2008): ISI Web of Knowledge^{SM} (ISI WoK), SciFinder (CAPLUS, MEDLINE, REGISTRY, CASREACT, CHEMLIST, CHEMCATS) and PubMed (indexed for MEDLINE). On ISI WoK, we searched by using the Latin names of plants and 'clinical trial', 'trial', 'clinical' or 'clinical study' as topics, English and German as languages. On SciFinder, we searched by using the Latin names or the common names of plants; we then refined the results by using 'clinical trial', 'trial', 'clinical' or 'clinical study' as Topic or Clinical Trial as Document type, and English as language. We searched on PubMed by using the Latin names of plants and the following limits: Humans; Clinical Trial, Meta-Analysis, Randomized Controlled Trial as Article type; (English, German, French and Italian as languages). Clinical studies concerning mixtures of extracts and homeopathic remedies were not reviewed.

RESULTS AND DISCUSSION

It is well known that the action of a plant extract (phytocomplex) may substantially differ from that of the pure active molecules used together. Under these circumstances, the search for the active principles in a given plant extract may be unrewarding except for pharmacological interest. The complexity of plant extracts makes the development of evidence-based phytotherapy a difficult task that requires a huge analytical effort and manufacturing skills to produce well-defined, standardized phytopreparations. To the pharmacologist, phytomedicine sets new challenges towards understanding the effects of complex mixtures on biochemical processes in health and disease.

From our survey, an interesting overview emerged as shown in Figs 1 and 2. Only for 156 plants clinical trials have been published

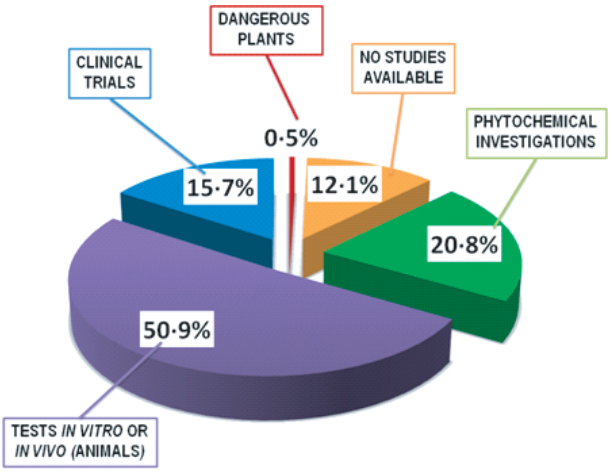

Fig. 1. Types of study performed on the commonest plant extracts being marketed in Western countries.

supporting specific pharmacological activities and therapeutic applications. For half of the approximately 500 plant extracts, *in vitro* and *in vivo* studies provide some validation of their uses, although clinical trials were lacking. For one-fifth of the plants included in our search, only phytochemical studies were found, and their properties and applications were often attributed to the presence of certain compounds, but no evidence concerning the activities of the whole extracts was available.

We found that about 12% of the plants currently on the Western market had no substantial published scientific studies on their properties and about 1 in 200 were toxic or allergenic, so that their use ought to be discouraged or forbidden.

For each category surveyed, a full list is available in Tables S1 and S2. Figure 2 shows that most clinical trials have focused on antimicrobial (antibacterial, antimycotic, antiviral) properties, followed by antioxidant and anti-inflammatory effects.

We reviewed all available published data on plants for which anti-inflammatory activity was claimed (for a total of 215 plants) in order to assess a ranking based on factual knowledge. As shown in Fig. 3, the highest percentage (64%) of plants had rank 2, with only *in vitro* and *in vivo* studies supporting their uses as anti-inflammatory remedies. It is, however, worth mentioning that several clinical trials failed to demonstrate activity for one-third of the plants.

It is disconcerting to find that the widespread use of some phytopreparations is unsupported by any scientific dose/effect assessment, and relevant pharmacokinetic and pharmacodynamic information. For practical purposes, we focused a specific search on clinical investigations concerning nine plants of the highest ranking, viz., *A. officinalis*, *Calendula officinalis*, *Centella asiatica*, *E. purpurea*, *Passiflora incarnata*, *Punica granatum*, *Vaccinium macrocarpon*, *Vaccinium myrtillus*, *Valeriana officinalis*. Tables 1–11 summarize the most recent clinical trials on these plants.

The second study that employs a mixture of natural extracts can hardly be included in a validation protocol for the use of *A. officinalis*.

In 2007, Miyasaka *et al.* (44) published a review on randomized and quasi-randomized controlled trials of *Passiflora incarnata* in the treatment of anxiety disorder. They presented the results of two

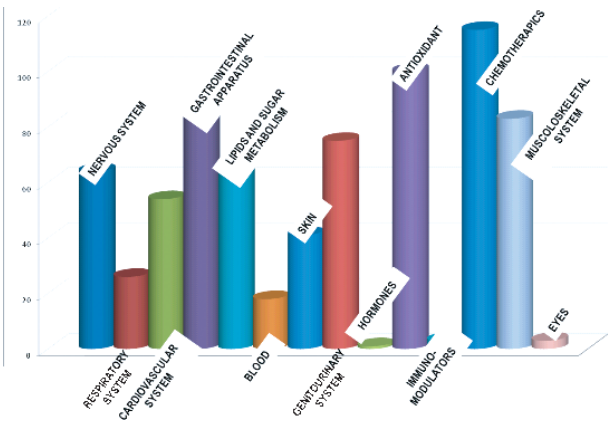

Fig. 2. Topics of investigation in clinical trials of 156 plants.

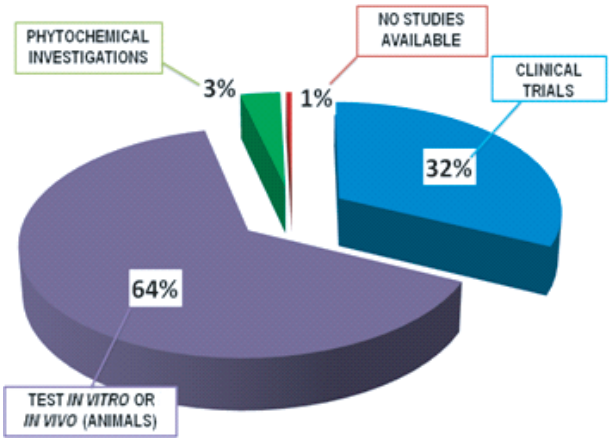

Fig. 3. Ranking subdivion of plants with anti-inflammatory properties.

Table 1. *Althaea officinalis*

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
6	Treatment of the cough as side effect of ACE inhibitor drugs	60 patients (T = 30, P = 30)	Randomized, double-blind, PC	T = 20 mg of *A. officinalis* in 20 drops three times daily. Duration of study = 4 weeks	Mean cough score in T group 2·66 + 0·95 (before treatment) and 1·23 + 1 (after treatment). No significant change in cough scores was found in P group. Eight patients showed al most complete cough suppression in T group, whereas only one patient in P group	There was a significant cough reduction with *A. officinalis*. Studies to determine whether *A. officinalis* reduces ACE-induced cough are recommended
7	Treatment of Old World cutaneous leishmaniasis	171 patients (T1 + P = 86, T2 + P = 85)	Double-blind randomized, comparison with meglumine antimoniate	T1 + P = pure extracts mixture named Z-HE. Time: 5 days (placebo i.v. 20 days). T2 + P = Glucantime 15–20 mg/kg/day i.v. (topical placebo). Duration of study = 20 days	Complete cure was observed in 64 patients, partial cure in 10 patients, and failure in 12 patients	For Glucantime group, complete cure was observed in 23 patients, partial cure in 12 patients, and failure in 50 patients

T1, T2, different treatments; P, placebo; Z-HE, pure extracts mixture of *A. rosa*, *A. officinalis*, and members of Leguminosae, Faliaceae, Malvaceae, and Lythraceae; PC, placebo-controlled.

Table 2. *Calendula officinalis*

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
8	Epithelialization of venous ulcers in the lower leg	34 (T = 21, with 33 venous ulcers, P = 13, with 22 venous ulcers)	Comparative study	T = marigold extract ointment, P = saline solution dressings, posology = twice a day Duration of study = 3 weeks	In T group, the total surface of all the ulcers decreased by 41·7% compared with 14·5% in P group. A complete epi thelialization was ob served in seven patients (T), and four patients in P group	Statistically significant acceleration of wound healing (venous ulcer epithelialization). Results are preliminary
9	Prevention of acute dermatitis induced by X-ray irradiation at the onset radiotherapy	254 (T1 = 126, T2 = 128)	Comparative study, randomized	T1 = calendula (Pommade au Calendula par Digestion, Boiron Ltd), T2 = trolamine (Biafine, Genmedix Ltd), twice a day Duration of study = until radiotherapy completion	The occurrence of acute dermatitis of grade 2 or higher was significantly lower (41% vs. 63%) with the use of calendula than with trolamine	Calendula is highly effective for the prevention of acute dermatitis, it should be proposed for patients undergoing postoperative irradiation for breast cancer

T1, T2, different treatments; P, placebo.

Table 3. *Centella asiatica*

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
10	Effect on cognitive function of healthy elderly volunteers	28 (P, T1, T2, T3)	Randomized, PC, double-blind study	T1 = 250, T2 = 500, T3 = 750 mg, once daily Duration of study = 2 months	T3 treatment enhanced working memory and increased N100 component amplitude of event-related potential. Improvements of self-rated mood were also found in *Centella asiatica* treatment	Attenuation of age-related decline in cognitive function and mood disorders. The mechanisms underlying these effects require further investigation
11	Treatment of oedema and increased CF in venous hypertension	T1 = 20, T2 = 20, P = 12 (with venous hypertension); T3 = 10 (normal subjects)	Clinical, prospective, PC, randomized, dose-ranging trial	T1 = TTFCA 60 mg thrice daily, T2 = 30 mg thrice daily; T3 = 60 mg thrice daily Duration of study = 4 weeks	TTFCA treatment gave a significant decrease of CFR, AC and AET time. No significant change was observed in the P group and in normal subjects treated with TTFCA	180 mg/day was more effective in improving symptoms and CFR
12	Treatment of diabetic microangiopathy	50 (T = 30, P = 10, C = 10)	Clinical prospective PC randomized trial	T = TTFCA 60 mg twice daily Duration of study = 6 months	Significant improvement of microcirculatory parameters in patients treated with TTFCA. RF decreased, VAR improved. PO_2 increased and PCO_2 decreased. The abnormally increased capillary permeability decreased	Improvement of microcirculation and decrease of capillary permeability
13	Prevention of oedema and microcirculation alterations during long flights	66 (T = 33, P = 33)	Randomized PC study	P = no drug or other treatment, T = TTFCA 60 mg thrice daily. Treatment = 2 days before the flight, the day of the flight, and for an other day after the flight	A progressive increase in CO_2, RAS, and oedema score and a progressive decrease in flux and venoarteriolar response with flying time. Alterations of microcirculation and oedema during the flight were weaker in the T group.	Useful for patients prone to oedema and microcirculation disturbances during long flights

Table 3. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
14	Improvement of the microcirculation in venous hypertension and microangiopathy	40 (T = 22, P = 18)	Prospective, PC, randomized trial	T = TTFCA tablets, 60 mg twice daily Duration of study = 8 weeks	A decrease in RF and RAS was observed in T group. The decrease in capillary filtration was associated with improvement in signs and symptoms	No side effects were observed. Venous microangiopathy was improved by TTFCA treatment
15	Part I: effects of TTFCA on different types of arterial plaque. Part II: effects of TTFCA on hypoechoic-echolucent plaques	(I) ITT = 58, TT = 47 (24 with hypoechoic, 23 with hyperechoic plaques) (II) 87 (T = 43, P = 44)	(I) pilot study (II) prospective, randomized, PC trial	(I) T = TTFCA 60 mg tablets thrice daily (II) TTFCA 60 mg tablets thrice daily Duration of studies = 12 months	(I) GSC increased in the hypoechoic group, minor increase in GSM in the hyperechoic group (II) a significant increase in GSM in the T group, improvement in texture and a non-significant decrease in stenosis. No changes were observed in the P group	Events were observed in 6·5% of patients in the TTFCA group and in 11% in the control group. Positive action of TTFCA on the stabilization of hypoechoic, low-density carotid plaques
16	Microcirculatory effects of TTFCA in chronic venous hypertension	40 (T = 20, P = 20)	Prospective, randomized PC study	T = TTFCA tablets, 60 mg twice daily Duration of study = 6 weeks	Decrease in RF (29%) and increase in venoarteriolar response (52%) in T group; PO_2 was increased (7·2%) and PCO_2 decreased (9·6%). Relevant decrease in leg volume (1·3% volume variation)	The effects of TTFCA are observed in a limited sample of patients
17	Improvement of microcirculation in diabetic microangiopathy and neuropathy	T = 50 (diabetic), 50 (diabetic without neuropathy), = 40 (healthy)	Prospective, PC, randomized study	T = TTFCA tablets, 60 mg twice daily, P = similar tablets Duration of study = 2 months	In the neuropathy group: decrease in RF (38%) and RAS (28%), decrease in oedema. In patients without neuropathy decrease in RF (22%) and RAS (9·5%), increase of VAR (22·7%). The variations in normals and the progressive deterioration in untreated patients in both groups indicates the difference between T and P	TTFCA effects on flux, ASR and oedema are important in early stages of microangiopathy to avoid progression to clinical stages

Table 3. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
18	Effects of different doses of TTFCA in patients with venous hypertensive microangiopathy	ITT = 99, TT = 89 (T1 = 33, T2 = 29, P = 27)	Single-blind, PC, randomized study	T1 = TTFCA 120 mg daily, T2 = 60 mg daily	Significant difference between drug-treated groups and P group, higher for 120 mg daily and lower for 60 mg daily dose of TTFCA. Transcutaneous PO_2-PCO_2 measurements significantly modified by TTFCA while no variation detected in the P group	Doses as 120 mg daily may be safe ly used in venous hypertension
19	TTFCA effects on modulation of collagen production and on the echogenicity of echolucent plaques at the femoral bifurcation	50 (T = 26, P = 24)	Prospective, PC, randomized study	T = TTFCA 60 mg thrice daily. Antiplatelet agents in all patients; cholesterol-lowering agents (34% of T group, 36% of P group) Duration of study = 12 months	GSM increased from 14 to 22·8 in the T group and from 14·3 to 15 in controls. No significant changes in texture observed in controls while a qualitative increase in homogenicity was observed in the T group. Plaque size showed a median increase of 23% in controls, less in the T group (7%)	Positive action of TTFCA on the stabilization of hypoechoic, low-density femoral plaques
20	Anxiolytic activity in healthy subjects	40 (T = 20, P = 20)	Double-blind, PC randomized	T = single 12 g orally administered dose	Compared with placebo, *Centella asiatica* significantly attenuated the peak ASR amplitude 30 and 60 min after treatment, showing anxiolytic activity. No significant effect on self-rated mood, heart rate, or blood pressure	Preliminary findings
21	Effect on venous insufficiency	87 (T1, T2, P)	Placebo double-blind study	T1 = FTTCA 30 mg bid, T2 = 60 mg bid Duration of study = 60 days	RF, transcutaneous PO_2 and PCO_2 improved as did the abnormally increased RF, PCO_2 decreased and PO_2 increased in comparison with values measured at inclusion. Efficacy of FTTCA in venous hypertensive microangiopathy	Effects of FTTCA appear to be dose-related

Table 3. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
22	Effects on CFR, AC and AE in patients with venous hypertension and normal subjects	T1 = 20, T2 = 20, P = 12, T3 = 10 (normal subjects)	PC open study	T1 = TTFCA 60 mg t.i.d., T2 = 30 mg t.i.d.; T3 = 60 mg t.i.d. Duration of study = 4 weeks	A significant decrease in CFR, AC, and AECT time in T group (greater in the higher dose group). No significant change in the P and T3 group. Symptoms were also significantly improved in T1 and T2 groups according to the dose. No significant changes were observed in the P group	
23	Effects on venous insufficiency of the lower limbs	94 (T1, T2, P)	Multicentre, double-blind vs. placebo study	T1 = TECA 120 mg/day, T2 = 60 mg/day Duration of study = 2 months	A significant difference in favour of TECA was shown for the symptoms of heaviness in the lower limbs and oedema. The venous distensibility was improved for the TECA groups but aggravated for the P group	

CF, capillary filtration; CFR, capillary filtration rate; AC, ankle circumference; AE, ankle oedema; AET, ankle oedema tester; AECT, ankle oedema coin tester; ASR, acoustic startle response; RF, flux at rest; VAR, venoarteriolar response; RAS, rate of ankle swelling; TTFCA, total triterpenic fraction of *Centella asiatica*; TECA, titrated extract of *Centella asiatica*; ITT, intention to treat; TT, total treatment; T1, T2, T3, different treatments; P, placebo; C, control group; PC, placebo-controlled.

Table 4. *Echinacea purpurea*: reviews and meta-analyses of clinical trials concerning its efficacy in preventing and treating induced or naturally-occurring common cold; its immunomodulating, anticancer, antifungal effects, its role in the prevention and treatment of URI

References	Object of study	Total of participants	Number and Study type	Echinacea preparation	Outcome	Comments and limitations
24	Prevention and treatment of the common cold	1356 for the evaluation of cold incidence, 1630 for the evaluation of cold duration	14 randomized PC (7 evaluating cold incidence, 5 evaluating cold duration, 2 evaluating cold incidence and duration); 2 on children	7 EP, 1 EA, 1 EPP, 1 unspecified, 4 combinations of different species (5 with Echinacin or Echinagard from Madaus AG); 4 of *Echinacea* combined with supplements	*Echinacea* decreased the odds of developing the common cold by 58% and the duration of a cold by 1·4 days *Echinacea* decreases the incidence and duration of common cold	Large-scale randomized prospective studies are needed to take into account important variables such as plant species or variety, quality of preparation, dose, method of cold induction
25	Prevention and treatment of the common cold	1232 (T = 666 among whom 200 were children, P = 566, among whom 207 were children)	Seven double-blind PC randomized studies; one on children	5 EP, 2 EA + EP. No standardized preparations	Results are inconsistent; studies on larger numbers failed to show a significant effect, whereas smaller studies documented positive effects	Evidence on the efficacy of EP is scanty, especially in paediatric patients
26	Comparison of *Echinacea* with either a placebo, no treatment, or another treatment for the prevention or treatment of common cold		16 randomized PC trials, all of them except 1 being double-blind	22 comparisons of an *Echinacea* preparation with a control group (19 with placebo, 2 with no treatment, 1 with another herbal preparation); 3 investigated the prevention of cold and 19 concerned treatment. A variety of different *Echinacea* preparations were used	None of the 3 comparisons in the prevention trials showed an effect over placebo. Comparing an *Echinacea* preparation with placebo as treatment, a significant effect was reported in 9 comparisons, a trend in 1, and no difference in 6	*Echinacea* preparations tested in clinical trials differ greatly. Beneficial effects of other *Echinacea* preparations for cold prevention may exist, but have not been substantiated by independently replicated, rigorous randomized trials

Table 4. (Continued)

References	Object of study	Total of participants	Number and Study type	Echinacea preparation	Outcome	Comments and limitations
27	Prevention of experimentally induced rhinovirus cold	390 (T = 223, P = 167)	Three double-blind PC randomized studies	2 EP (3 × 300 mg, 3 × 176 mg daily), 1 EA (3 × 300 mg daily); prophylactic treatment 7 or 14 days before virus challenge extended to 5 or 7 days after	The likelihood of experiencing a clinical cold was 55% higher with P than with *Echinacea*. Standardized *Echinacea* extracts were effective in prevention of symptoms of common cold after clinical inoculation	Additional clinical studies are needed to confirm this finding
28	Immunomodulating, anticancer and antifungal effects; prevention and treatment of URI	URI (1891), IE (165), AF (203), AC (43), BP (1450)	6 IE, 3 AC, 1 AF, 4 BP, 13 for prevention and treatment of URI, double-blind randomized, some PC	20 EP, 2 EA + EP, 3 EPP, 2 non-specified (9 Echinacin, 2 Echinagard, 1 Echinaforce, 3 Esberitox); 1 *Echinacea* combined with supplements	The immunomodulation activity is only partially understood. Human studies with oral preparation gave disomogeneous results. In the treatment of acute URI reduction (10–40%) of symptoms with early treatment was reported. Benefit as a cold preventive appeared marginal, with an estimated 5–15% effect as best trial to date	Although suggestive of a modest benefit, these rials were limited both in size and in methodological quality. Effectiveness in treating illness or enhancing health has not been proved beyond a reasonable doubt

T, treatments; P, placebo; PC, placebo controlled; EP, *Echinacea purpurea*; EA, *E. angustifolia*; EPP, *E. purpurea* pallida; URI, upper respiratory infection; IE, immunomodulating effects; AF, antifungal; AC, anticancer; BP, bronchitis and pertussis.

Table 5. *Echinacea purpurea*: Still unreviewed clinical trials concerning immunomodulating effects and URI prevention and treatment

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
29	Effects on the frequency of UPT symptoms (preventive efficacy)	ITT = 90, TT = 58 (T = 28, P = 30)	Randomized double-blind, PC	T = 3 caps EP, P = parsley Duration of study = 8 weeks	T group reported 9 sick days per person during the 8-week period, whereas the P group 14 sick days. Prophylactic treatment with commercially available EP capsules did not significantly alter the frequency of UPT symptoms compared with placebo	
30	Alterations of erythroid growth factors and erythropoietic status	24 (T, P)	Double-blind PC	T = 8000 mg/day of either *Echinacea* or placebo in 5 × 400 mg × 4 times per day Duration of study = 28 days	Treatment resulted in an increase in EPO and IL-3 but did not significantly alter RBCs, Hb, or Hct	
31	CD25 expression on T cells after ingestion of *Echinacea purpurea*, *Astragalus membranaceus* and *Glycyrrhiza glabra*	14 (T1 = 4, T2 = 4, T3 = 3, T4 = 3)	Phase 0, double-blind, repeated within subject, randomized pilot study	T1 = EP, T2 = *A. membranaceus*, T3 = *G. glabra*, T4 = combination (7·5 mL of herbal extract twice daily) Duration of study = 7 days	CD25 expression on T cells was significantly increased in subjects ingesting *Echinacea* after 24 h with notable increases in activation from *Astragalus* and *Glycyrrhiza*	With daily use of *Echinacea* CD25 expression remains elevated for at least 7 days

Table 5. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
32	Effects on electrocardio graphic and blood pressure measurements on healthy volunteers	ITT = 17, TT = 16 (both phases)	Randomized PC crossover study	T = single 350 mg dose of EP or placebo in a crossover fashion with a 7-day washout period between treatment phases	A single 350 mg dose of EP had no effect on electrocardiographic and blood pressure measurements of healthy volunteers	
33	Efficacy in controlling low-grade uveitis	T1 = 32, T2 = 20	Pilot study	T1 = echinacea (150 mg twice a day) as add-on therapy, T2 = conventional steroid therapy alone Max duration of the trial = 9 months	19/21 patients with anterior uveitis and 9/11 with intermediate uveitis treated with *Echinacea* presented uveitis settled, with a steroid-off time of 209 and 146 days, respectively. BCVA was stable or improved in 19/21 of anterior uveitis and 9/11 of intermediate uveitis. T2 group required a longer treatment period with steroids with a steroid-off time of 121 and 87 days.	Systemic *Echinacea* proved effective and safe in the control of low-grade autoimmune idiopathic uveitis
34	Effect on CD69 expression and immune cell activation	16 (T1 = 4, T2 = 4, T3 = 3, T4 = 3, P = 2)	PC double-blind study	T1 = EP, T2 = *A. membranaceus*, T3 = *G. glabra*, T4 = combination (7·5 mL of tincture twice daily) Duration of study = 7 days	E. A. and G. herbal tinctures stimulate activation and proliferation of several types of immune cells. *Echinacea* increased total number of CD4, CD8 T and NK cells	The three herbal preparations when combined had an additive effect on immune cell activation, although not on proliferation

Table 5. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
35	Effect on different subpopulations of B- and T-lymphocytes	40 (T = 20, P = 20)	Double-blind PC crossover study	T = Esberitox 12 mL daily Duration of study = 2 treatments, 14 days each, washout period: 4 weeks	No significant changes in the treatment period for T- and B-lymphocytes, CD4+- and CD8+-T-lymphocytes including the subgroups of 'naive' and 'memory' CD4+- and CD8+-T-lymphocytes as well as the natural killer cells	There is no evidence of an *Echinacea* increase in any of the lymphocyte subpopulation investigated
36	Effect on the immune response during a common cold	ITT = 150, TT = 56 (T = 25, P = 31)	Double-blind randomized PC study	T = Echinilin (8 doses of 5 mL on day 1 and 3 doses on other days) Duration of study = 7 days	In T group the monocyte and neutrophil counts were significantly higher at day 8. No significant effects on the distribution of CD3+, CD8+ and CD20+ cells, but a significant decrease in CD4+ cells on day 3 and increase in the NK cells on day 8. By day 8, in the P group an ongoing free-radical generation (oxidative burst capacity of the neutrophils) persisted	Echinilin, by enhancing the non-specific immune response and eliciting free-radical scavenging, may have caused a faster resolution of cold symptoms
37	Effect on the immune response	11	Pilot study	T = EP 675 mg + EA 600 mg twice daily Duration of study = 14 days	*Echinacea* enhances the immune response by altering the expression of leucocyte hsp70 and increasing white cell counts	

Table 5. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
38	Stimulation of phagocytic activity and production of cytokines	40 (T, P)	Double-blind PC crossover study	T = freshly expressed EP juice Duration of study = 2 × 14 days with a washout period of 4 weeks in between	EP neither enhanced the phagocytic activity of polymorphonuclear leukocytes nor that of monocytes. EP did not influence the production of TNF-alpha and IL-1beta by LPS-stimulated monocytes	Other immunomodulatory effects may explain the effects of *Echinacea* preparations in reducing the duration and severity of URT infections as shown by randomized, double-blind clinical trials
39	Immunomodulating effects of EP and EA and larch arabinogalactan from Larix occidentalis	48 (T1, T2, T3, T4, T5, P)	Randomized, double-blind, PC, prospective trial	T1 = EPE, T2 = urEPA, T3 = EPA, T4 = EPALA, T5 = LA Duration of study = 4 weeks	Complement properdin increased by 21% in the EPA group and by 18% in the EPALA group, compared with the placebo group	The increase in complement properdin may be just one aspect of immune system stimulation in patients treated with either EPA and EPALA
40	Influence on genital herpes	50 (T, P)	Single centre, prospective, double-blind, PC crossover	T = Echinaforce Duration of study = 1-year period (6-month placebo and 6-month Echinaforce)	No statistically significant benefit could be detected in this study comparing placebo vs. Echinaforce in the treatment of frequently recurrent genital herpes	

UPT, upper respiratory tract; BCVA, best-corrected visual acuity; RBCs, blood cells; Hct, hematocrit; Hb, haemoglobin; EPO, erythropoietin; IL-3, interleukin 3; T1, T2, T3, T4, T5, different treatments; P, placebo; ITT, intention to treat; TT, total treatment; PC, placebo controlled; EP, *Echinacea purpurea*; EA, *Echinacea angustifolia*; EPE, standardized extract of *E. purpurea*; urEPA, ultra-refined *E. purpurea/E. angustifolia*; EPA, *E. purpurea/E. angustifolia*; EPALA, *E. purpurea/E. angustifolia* plus larch arabinogalactan; LA, larch arabinogalactan.

Table 6. *Passiflora incarnata*

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
41	Treatment of preoperative anxiety	60 (T = 30, P = 30)	Double-blind PC randomized trial	T = *Passiflora incarnata* (500 mg, Passipy Iran Darouk) as premedication 90 min before surgery	The numerical rating scale anxiety scores were significantly lower in the *Passiflora* group than in the control group. In outpatient surgery, a *Passiflora* premedication reduced anxiety without inducing sedation	No significant differences in psychological variables in the post-anaesthesia care unit; the recovery of psy chomotor function was comparable in both groups
42	Adjuvant agent in management of anxiety during opiates detoxification by clonidine	65 (T1, T2 + P)	Double-blind randomized controlled trial	65 opiates addicts assigned randomly to treatments: T1 = *Passiflora* extract (60 drops) + clonidine tablet (0·8 mg), T2 + P = clonidine tablet + placebo drops Duration of study = 14 days	Both protocols were equally effective in treating the physical symptoms of withdrawal syndromes. T1 group showed a significant superiority over T2 in the management of mental symptoms	*Passiflora* extract may be an effective adjuvant agent in the management of opiate withdrawal A larger study to confirm these results is wanted
43	Anxiolytic effect	36 (T1 + P = 18, T2 + P = 18)	Pilot double-blind randomized trial	T1 + P = *Passiflora* extract (45 drops per day) + placebo tablet, T2 + P = oxazepam (30 mg/day) + placebo drops Duration of study = 4 weeks	*Passiflora* extract and oxazepam were effective in the treatment of generalized anxiety disorder. No significant difference was observed between the two protocols	*Passiflora* extract is effective for the management of generalized anxiety disorder; it causes a low incidence of impairment of job performance compared with oxazepam, a distinct advantage. A large-scale trial is justified

T1, T2, different treatments; P, placebo; PC, placebo controlled.

Table 7. *Punica granatum*

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
45	Antioxidant activity of a POMx and its safety as a dietary supplement for overweight individuals	(I) 64 (T1, T2, P), Study (II) 22	(I) safety assessment, PC (II) antioxidant activity assessment	(I) 1/2 POMx caps daily T1 = 710 mg POMx (435 mg GAEs), T2 = 1420 mg POMx (870 mg GAEs) (II) POMx 2caps daily = 1000 mg (610 mg of GAEs)	These studies demonstrate the safety of a POMx dietary supplement and provide evidence of antioxidant activity *in vivo*	No adverse events related to the dietary supplement consumption or changes in haematology, serum chemistry, or urinalyses were observed
46	Erectile dysfunction	53	Randomized, PC, double-blind, cross-over study	T = PJ Duration of study = two 4-week treatment periods separated by a 2-week washout	Of the 42 subjects who demonstrated improvement in GAQ scores after beverage consumption, 25 reported improvement after drinking PJ	Statistical significance was not achieved
47	Protective and ameliorative effects of EA-rich PE on skin pigmentation after UV irradiation	T1 = 13, T2 = 13, P = 13	Double-blind, PC randomized trial	T1 = 200 mg/day EA, T2 = 100 mg/day EA Duration of study = 4 weeks	EA-rich PE, taken orally, has a slight inhibitory effect on skin pigmentation after UV irradiation	
48	Anti-oxidative effects on serum proteins and macrophages of PJ consumption by diabetic patients	T = 10, C = 10	Study with a control group	T = PJ 50 mL per day Duration of study = 3 months	PJ consumption by diabetic patients resulted in anti-oxidative effects on serum and macrophages	These effects could help controlling of atherosclerosis development in these patients
49	Effects of PJ consumption on PSA progression in men with a rising PSA following primary therapy for prostate cancer	48	Open-label, single-arm clinical trial (phase II, Simon two-stage)	T = 237 mL PJ daily (wonderful variety, 570 mg polyphenol GAEs) Duration of study = 13 months	A statistically significant prolongation of PSA doubling time warrants further testing in a PC study	The first clinical trial of PJ in patients with prostate cancer

Table 7. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
50	Effect on dental plaque microorganisms	60 (T1 = 20, T2 = 20, P = 20)	Randomized PC comparative study	P = distilled water, T1 = chlorhexidine (standard), T2 = pomegranate HAE as mouth-rinses	HAE from *Punica granatum* also showed an antibacterial activity against selected microorganisms	May be a possible alternative for the control of dental plaque bacteria
51	Effect of antioxidant polyphenol-rich PJ supplementation on patients with stable COPD	30 (T = 15, P = 15)	Randomized, placebo, double-blind	T = 400 mL PJ daily, P = synthetic orange-flavoured drink Duration of study = 5 weeks	No differences between T and P groups for any of the serobiochemical and haema tological parameters, urinary 8-iso-PGF (2 alpha), respiratory function variables and clinical symptoms of COPD	
52	Effects of PJ on patients with ischemic CHD	45 (T, P)	Randomized, PC, double-blind	T = PJ 240 mL/day, P = beverage of similar caloric content, amount, flavour and colour Duration of study = 3 months	The extent of SDS decreased in the pomegranate group (−0·8 ± 2·7) but increased in the control group (1·2 ± 3·1). Daily consumption of PJ may improve stress-induced myocardial ischemia in patients with CHD	
53	Improvement of lipid profiles in diabetic patients with hyperlipidemia	22	Quasi-experimental study	T = 40 g/day of concentrated PJ Duration of study = 8 weeks	After consumption of PJ, significant reductions in TC, LDL-C, LDL-C/HDL-C, and TC/HDL-C. No significant changes in serum triacylglycerol and HDL-C concentrations	Consumption of conc. PJ may modify heart disease risk factors in hyperlipidemic patients

Table 7. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
54	Antifungal agent against candidosis associated with denture stomatitis	60 (T1 = 30, T2 = 30)	Clinical trial, randomized controlled trial	T1 = miconazole (Daktarin® oral gel), T2 = pomegranate gel, three times daily Duration of study = 15 days	Satisfactory and regular response in 27 and 21 subjects of T1 and T2, respectively. Absence of yeasts observed in 25 subjects of T1 and 23 of T2 group	Pomegranate may be useful as a topical antifungal agent for candidosis associated with denture stomatitis

T1, T2, different treatments; C, control group; P, placebo; PC, placebo controlled; GAQ, Global Assessment Questionnaire; POMx, pomegranate ellagitannin-enriched polyphenol extract; GAEs, gallic acid equivalents; EA, ellargic acid; PJ, pomegranate juice; PE, pomegranate extract; PSA, prostate-specific antigen; GA, gallic acid; HAE, hydroalcoholic extract; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SDS, stress-induced ischemia.

studies using different (non-comparable) doses, regimes, or methods of administration. Data on the effectiveness of the plant on anxiety were too scanty for any firm conclusion to be drawn. The authors concluded that RCTs with larger samples were necessary, comparing the effectiveness of passiflora with placebo and other medications.

The effectiveness of cranberry products in preventing UTIs in susceptible populations has been reviewed by different authors (66–68). The last one reported the results of 10 studies, 5 crossover and 5 parallel-group (all randomized or quasi randomized), where cranberry/cranberry-lingonberry juice were evaluated vs. placebo, other juice or water, and cranberry tablets vs. placebo. One thousand and forty-nine patients were included. Cranberry products significantly reduced the incidence of UTIs over an observation period of 12 months. They were more effective in women with recurrent UTIs. However, the optimum dosage and method of administration were not clear. The author concluded that further properly designed studies were needed.

In 2004, Canter and Ernst (79) systematically reviewed PC trials on anthocyanosides extracted from *Vaccinium myrtillus* on night vision. They identified 30 relevant trials, 12 of which were placebo-controlled. To quote their conclusions: 'negative outcome was associated with more rigorous methodology but also with lower dose level and extracts from geographically distinct sources that may differ in anthocyanoside composition. The hypothesis that *Vaccinium myrtillus* anthocyanosides improves normal night vision is not supported by evidence from rigorous clinical studies'.

In 2006, a systematic review was published of randomized PC trials on the efficacy of valerian for improving sleep (84). Sixteen studies including 1093 patients were reviewed. The authors concluded that most studies were methodologically weak and there was a considerable variety of doses and preparations, as well as lengths of treatment. Available evidence suggests that valerian may improve sleep quality without producing side effects. Future studies employing standard measurements of sleep quality should assess recommended doses and safety of standardized valerian preparations.

In a previous review (85), evidence for the efficacy of valerian against insomnia was also found to

Table 8. *Vaccinium macrocarpon*: clinical trials to evaluate the UTI-related therapeutic properties of cranberry

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
55	Antioxidant status and biosafety after consumption of dried CJ by healthy women	65 (T1 = 20, T2 = 22, P = 23)	Pilot double-blind PC trial	T1 = 400 mg of dried CJ per day, T2 = 1200 mg of dried CJ[a] per day Duration of study = 8 weeks	A statistically significant decrease in the serum level of AOPP was observed in volunteers consuming 1200 mg/day of dried CJ	Cranberry fruits are effective in preventing oxidative stress
56	MH vs. CT in the prevention of UTI in patients with neuropathic bladder following SCI	305 (T1, T2)	Double-blind factorial-design randomized controlled trial	T1 = MH 1 g twice daily. T2 = CT 800 mg twice daily	Prevention of UTI does not benefit from the addition of MH or CT to the usual regimen of patients with neuropathic bladder following SCI	
57	Prevention of UTIs in women	12	Open-label pilot study	T = 1 cap twice daily, 200 mg of concentrated CE (30% phenolics) Duration of study = 12 weeks	A cranberry preparation with a high phenolic content may wholly prevent UTIs in women who are subject to recurrent infections	
58	Efficacy of CJ consumption with regard to the presence of *in vitro* bacterial anti-adherence activity in the urine of healthy volunteers	20 (T1, T2, P1, P2)	Double-blind, randomized, PC, crossover study	P1 = 250 mL placebo + 500 mL mineral water, P2 = 750 mL placebo, T1 = 250 mL CJ[b] + 500 mL min. water, T2 = 750 mL CJ Four regimens successively in a randomly order, with a washout period of 6 days	A dose-dependent significant decrease in bacterial adherence associated with CJ consumption was observed against different *Escherichia coli* uropathogenic strains in the urine compared with placebo	No significant differences in the pH or specific gravity between the urine samples collected after cranberry or placebo consumption

Table 8. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
59	Effectiveness in reducing UTIs in hospitalized older people	376 (T = 187 + P = 189)	Randomized, PC, double-blind trial	T = 300 mL of CJ[b] daily Duration of study = 15 days (P), 16 days (T). Follow-up = 35 days	5·6% participants developed a symptomatic UTI: 14/189 in P and 7/187 in T group. These between-group differences were not significant, although fewer infections with *Escherichia coli* in T	The infection rate observed was lower than anticipated, making the study underpowered Larger trials are now required to determine whether CJ is actually effective in reducing UTIs in older hospitalized patients
60	Effects of CE on bacteriuria and pyuria in patients with SCI	48 (T = 26, P = 22)	Randomized, double-blind, PC study	T = 2 g of concentrated CJ daily Duration of study = 6 months	CE taken in capsule form did not reduce bacteriuria and pyuria in persons with SCI. No differences or trends detected between participants and controls	CE cannot be recommended for treating these conditions
61	Effects of CE on bacteriuria and pyuria in patients with SCI	21 (T, P)	Prospective, double-blinded, PC, crossover study	T = 400 mg CT thrice daily Duration of study = two 4-week treatments, 1-week washout period	CT were not found to affect urinary pH or reduce either bacterial counts or UTIs in individuals with neurogenic bladders	Further long-term studies are needed to relate specific types of bladder management and UTIs
62	Compared prophylactic efficacy of concentrated CT, and CJ against lower UTI in adult women	150 (T1, T2, P)	Randomized, PC, comparative controlled trial	T1 = placebo juice + CT, T2 = CJ + placebo (CT twice daily, CJ 250 mL three times daily) Duration of study = 1 year	Both CJ and CT statistically significantly decreased the number of patients experiencing at least one symptomatic UTI per year (to 20% and 18%, respectively) compared with placebo (to 32%)	CT provided the greater cost-effective prevention of UTI

Table 8. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
63	Effect of CJ on bacterial biofilm load in the bladder	15	Pilot study	T = a 250 mL water thrice daily for 7 days, then a 250 mL CJ[b] thrice daily Duration of study = 15 days	CJ intake significantly reduced the biofilm load compared with baseline, thus reducing the risk of UTI	Results encourage the carrying out of further, larger clinical trials of the use of CJ to reduce UTI risk
64	Effect of cran berry prophylaxis on bacteriuria and rates of symptomatic UTI in children with neurogenic bladder	15 (T, P)	Double-blind, PC, crossover study	T = cranberry concentrate or placebo Duration of study = 6 months (3 months receiving cranberry concentrate, followed by 3 months of placebo)	The frequency of bacteriuria in patients with neurogenic bladder is 70%. Cranberry concentrate had no effect on bacteriuria in this population. No significant difference in the acidification of urine in the P group vs. the cranberry group	
65	Effect of regular intake of a CJ beverage on bacteriuria and pyuria in elderly women	ITT = 192, TT = 153 (T, P)	Quasi-randomized, double-blind, PC trial	T = 300 mL commercially available CJ per day, P = synthetic drink indistinguishable in taste, appearance, and vitamin C	Cranberry beverage reduced the incidence of bacteriuria with pyuria in older women	Current beliefs about the effects of cranberry juice on the urinary tract may have microbiologic justification.

UTI, urinary tract infections; SCI, spinal cord injury; LJ, Lingonberry juice; AOPP, advanced oxidation protein products; MH, Methenamine Hippurate; CE, cranberry extract; CJ, cranberry juice; CT, cranberry tablets; P, placebo treatments; T, treatment; T1, T2, different treatments; C, control group; ITT, intention to treat.

[a]NutriCran90, Decas Botanical Synergies, US.

[b]Ocean Spray Cranberries Inc., Lakeville-Middleboro, USA.

Table 9. *Vaccinium macrocarpon*: clinical trials to evaluate non-UTI-related therapeutic properties of cranberry

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
69	Effect of regular intake of CJ and the probiotic La1 to inhibit *Helicobacter pylori* in asymptomatic colonized children	295 (T1, T2, T3, C)	Multicentre, randomized, PC, double-blind trial	T1 = CJ/La1, T2 = placebo juice/La1, T3 = CJ/heat-killed La1, C = placebo juice/heat-killed La1 (daily CJ 200 mL, La1 80 mL) Duration of study = 3 weeks	*Helicobacter pylori* eradication rates significantly differed in the four groups: 1·5% in C group compared with 14·9%, 16·9%, and 22·9% in the La1, CJ, and CJ/La1 groups, respectively	A regular intake of CJ or La1 may be useful in the management of asymptomatic children colonized by *H. pylori*. No synergistic inhibitory effects in CJ/La1 group
70	Effect of CJ on the eradication of *Helicobacter pylori* in treated patients	177 (T = 89, P = 88) + C = 712	Double-blind randomized clinical study	All treated with OAC (1 week) + T1 = 250 mL CJ[a] twice daily Duration of study = 2 weeks C = OAC alone for 1 week	For females, eradication rate was higher in the CJ-OAC (95·2%) than in the P-OAC arm (86·8%) and significantly higher than in the non-P-OAC group (80%). For males, the rate was non-significantly lower in the CJ-OAC arm (73·9%) than in the P-OAC arm (80%) and non-P-OAC group (85%)	Addition of cranberry to triple therapy improves the rate of *H. pylori* eradication in females
71	Effect of consuming increasing daily doses CJC on the plasma lipid profile of abdominally obese men	31	Blind PC study	P = 4-week run-in period 500 mL/day PJ[a], three 4-week successively periods = 125 mL (T1), 250 mL (T2) and 500 mL (T3) CJC daily Duration of study = 12 weeks	A significant increase in plasma HDL-cholesterol concentration after the consumption of 250 mL CJC per day, plateaued during T3. No variation was observed in total as well as in LDL and VLDL cholesterol	Polyphenolic compounds from cranberries may be responsible for this effect, supporting the notion that the consumption of flavonoid-rich foods can be cardioprotective

Table 9. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
72	Effect of anthocyanin-rich CJ on plasma antioxidant activity and biomarkers of oxidative stress in 20 healthy female volunteers	20 (T + P)		T = 750 mL/day of CJ Duration of study = 2 weeks	Plasma vitamin C increased significantly in volunteers consuming CJ. Total phenols, tHcy, TC, TG, HDL and LDL were unchanged. The plasma antioxidant potential, GSH-Px, CAT and SOD activities, and MDA were similar for both groups. Supplementation with CJ did not affect 8-oxo-dG in urine or endogenous or H_2O_2-induced DNA damage in lymphocytes	CJ consumption did not alter blood or cellular antioxidant status or several biomarkers of lipid status relevant to heart disease. CJ had no effect on basal or induced oxidative DNA damage
73	Efficacy of CJ on neuropsychologic functions of cognitively intact older adults	50 (T = 25, P = 25)	Double-blinded, PC, randomized parallel-group	T = 32 oz/day of a beverage containing 27% CJ per vol Duration of study = 6 weeks	No significant interactions were found between the cranberry and placebo groups and their pretreatment baseline and end-of-treatment phase-standardized neuropsychologic assessments	

Table 9. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
74	Effectiveness in the suppression of *H. pylori*	189 (T = 97, P = 92)	Prospective, randomized, double-blind, PC trial	T = two 250 mL juice boxes of CJ[a] daily Duration of study = 90 days	Regular consumption of CJ can suppress *H. pylori* infection	
75	Effect of CJ on nasopharyngeal and colonic bacterial flora, as well as infectious diseases and related symptoms in children	341 (T = 171, P = 170)	PC randomized trial	T = CJ 5 mL/kg (up to 300 mL) of CJ[a] (41 g cranberry concentrate) or a placebo per day, divided into three doses Duration of study = 3 months	CJ was well accepted by the children, but caused no change in either the respiratory bacterial flora or the fatty acid composition of stool bacteria	Cranberry juice had no effect on common infectious diseases or their symptoms
76	Effect of CJ on urolithiasis risk factors	24 (12 normal, 12 calcium oxalate stone-formers)	Randomized study	T1 = 1 L of CJ[a] daily, T2 = 1 L of deionized water Duration of study = 7-day (T1) + 7-day (T2), washout period between phases of about 3 weeks	It reduces urinary pH likely by providing an acid load and decreasing urinary uric acid perhaps by retarding urate synthesis. Overall, CJ increases the risk of calcium oxalate and uric acid stone formation but decreases the risk of brushite stones	
77	Influence on side effects of diabetes and quality of life of diabetics	27 (T = 14, P = 13)	Randomized PC	T = six capsules CJ concentrate powder daily (240 mL CJ) Duration of study = 12 weeks	No differences were found between the treatment groups in fasting serum glucose, HbA_{1c}, fructosamine, TG, or HDL or LDL levels after 6 and 12 weeks	

Table 9. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
78	Effect of CJ on urinary biochemical and physicochemical risk factors associated with Ca oxalate urolithiasis	20 (T = 10, P = 10) (African men with no previous history of kidney stones)	Randomized PC crossover trial	T = 500 mL of CJ[b] diluted with 1500 mL tap water, P = 2000 mL of tap water Duration of study = 2 weeks, 2-week washout period before the two groups crossed over	The ingestion of CJ significantly and uniquely altered 3 key urinary risk factors: it increased citrate excretion, decreased oxalate and phosphate excretion and relative Ca oxalate supersaturation	CJ has antilithogenic properties, deserving consideration for conservative therapy in Ca oxalate urolithiasis

P, placebo treatment; PJ, placebo juice; T, treatment; T1, T2, T3, different treatments; C, control group; PC, placebo controlled; La1, Lactobacillus johnsonii La1; CJ, cranberry juice; CJC, cranberry juice cocktail; OAC, triple therapy with omeprazole, amoxicillin and clarithromycin; ESR, electron spin resonance spectrometry; tHcy, homocysteine; GSH, reduced glutathione; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein cholesterol; TG, triglycerides; GSH-Px, Glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase; MDA, malondialdehyde, 8-oxo-dG = 8-oxo-deoxyguanosine; HbA_{1c}, emoglobina glicosilata.

[a]Ocean Spray Cranberries Inc., Lakeville-Middleboro, USA.

[b]Crystal Falls, Black Sheep Beverage Distributors, South Africa.

Table 10. *Vaccinium myrtillus*

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
80	Effects of berry consumption on platelet function, blood pressure, and HDL cholesterol	71 (T = 35, C = 36)	Single-blind, randomized, PC trial	T = 2 portions of various berries daily[a] C = 1 of 4 different control products each day[b] Duration of study = 8 weeks	Plasma concentrations of polyphenols and Vitamin C increased in T group significantly more than in C. TC and TG were unaffected by the intervention, while HDL increased significantly more in T group (5·2%) than in C group (0·6%). SBP decreased slightly in T group (1·5 mmHg). Berry consumption significantly inhibited platelet function	The consumption of moderate amounts of berries resulted in favourable changes in platelet function, HDL cholesterol, and blood pressure. A regular consumption of berries may play a role in the prevention of cardiovascular disease
81	Effect of anthocyanin supplementation in the prevention of chronic inflammatory diseases in healthy adults	118 (T = 59, P = 59)	m	T = 2 × 75 mg Medox caps twice daily, providing a total of 300 mg anthocyanins per day (Medpalett Pharm., purified anthocyanins from bilberries and blackcurrant), P = caps with maltodextrin and blue colour additive Duration of study = 3 weeks	Medox anthocyanins decreased the plasma concentration of several NF-κB-regulated pro-inflammatory chemokines and immunoregulatory cytokines	Anthocyanin supplementation may play a role in the treatment of chronic inflammatory diseases

Table 10. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
82	Investigation of the effect of bilberry on night VA and night CS	15 (P = 8, T = 7)	Double-blind, PC, crossover design	T = 1 cap thrice daily (160 mg bilberry extract (25% anthocyanosides), P = inactive ingredients (Mg aspartate and colouring) Duration of study = 2 × 3 weeks, 1-month washout period	No difference in night VA during any of the measurement periods, no difference in night CS during any of the measurement periods	It is doubtful that bilberry supplementation, in the forms currently available and in the recommended doses, is effective in improving night vision
83	Treatment of primary fibromyalgia	12 (T1, T2, T3, P)	Double-blind, crossover trial, PC	T1 = anthocyanidins[§] 120 mg, T2 = 80, T3 = 40 mg, daily Duration of study = 3 months	Small but statistically significant benefits at a dose of 80 mg/day, the recommended one for these substances to be used as a food supplement	Further trials of anthocyanidins in a larger number of patients should probably be undertaken

T1, T2, T3, different treatments; P, placebo; VA, night visual acuity; CS, night contrast sensitivity; TC, total serum cholesterol; HDL, high-density lipoprotein; TG, serum triglycerides; SBP, systolic blood pressure.

[a]Every day, whole bilberries (100 g) and a nectar containing 50 g crushed lingonberries were consumed. Black currant or strawberry purée (100 g, 80% black currants) and cold-pressed chokeberry and raspberry juice (0·7 dL juice, 80% chokeberry) were consumed on the alternating days.

[b]The control products were 2 dL sugar-water, 100 g sweet semolina porridge, 100 g sweet rice porridge, and 40 g marmalade sweets. The aim was to control for the increased energy intake in the berry group. [§] Sources of anthocyanidins: grape seed (*Vitis vinifera*), bilberries (*Vaccinium myrtillus*) cranberries (*Vaccinium macrocarpon*). The product is manufactured under the name of Colladeen® by Lamberts Healthcare Ltd, UK.

Table 11. *Valeriana officinalis*

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
87	Effectiveness of kava for reducing anxiety and of valerian for improving sleep quality	391 (T1 = 121, T2 = 135, P = 135)	Randomized, double-blind, PC trial	T1 = 1 kava softgel caps. (100 mg of total kavalactones) 3 daily, 2 placebo-valerian softgel caps. 1 h before bedtime. T2 = 2 valerian softgel caps (each 3·2 mg of valerenic acids). 1 h before bedtime, and 1 placebo-kava softgel caps. 3 daily Duration of study = 28 days	Neither kava nor valerian relieved anxiety or insomnia more than placebo	
88	Effects of valerian on the sleep, cognitive and psychomotor function of sleep-disturbed older adults	16 (T1, T2, P)	Double-blind PC three-way crossover clinical trial	T1 = a 21:00 hours dose of valerian 300 mg, T2 = valerian 600 mg	No significant effect between valerian 300 mg, valerian 600 mg or placebo on any EEG parameter or psychometric measure. Valerian at these doses is ineffective as an acute dose for sleep problems	More research is required into therapeutic dose, types of valerian preparation, and the optimum period of use for therapeutic effect
89	Effect of valerian on mood and/or psychomotor/ cognitive performance	10 young healthy volunteers (T1, T2, T3, T4, P)	Randomized, PC, double-blind, crossover trial	T = 90 mL of water with 5 identical (colour and size) caps. containing VRE (Lichtwer Pharma, Eatontown, NJ, USA) (T1 = 600, T2 = 1200, T3 = 1800 mg), T4 = 10 mg diazepam, P = cornstarch	No significant effects	Acute administration of valerian does not have mood-altering or psychomotor/ cognitive effects in young healthy volunteers

Table 11. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
90	Effectiveness of valerian for the management of chronic insomnia in general practice	21 (T + P)	Randomized, PC trial	T = 225 mg valerian extract Duration of study = 21 days	Valerian was not shown to be appreciably better than placebo in promoting sleep or sleep-related factors for any individual patient or for all patients as a group	
91	Study of the cognitive and psychomotor effects of single oral doses of valerian	Nine healthy subjects (T1, T2, T3, P)	Double-blind, PC, four-way cross-over study	T1 = valerian 500 mg, T2 = valerian 1000 mg, T3 = triazolam 0·25 mg	Valerian was without effect on either cognitive or psychomotor performance in healthy volunteers at the doses used	
92	Efficacy and tolerability of valerian extract LI 156 compared with oxazepam in the treatment of non-organic insomnia	202 (T1, T2)	Multicentre, double-blind, randomized comparative study	T1 = 600 mg/day VE (LI 156 Sedonium), T2 = 10 mg/day oxazepam Duration of study = 6 weeks	Valerian extract LI 156 (Sedonium) 600 mg/day showed a comparable efficacy to 10 mg/day oxazepam in the therapy of non-organic insomnia	Adverse events occurred in 29 patients (28·4%) receiving valerian extract LI 156 and 36 patients (36·0%) under oxazepam, and were all rated mild to moderate
93	Studied of the sleep of patients with insomnia who complained of poor sleep despite chronic use of benzodiazepines	37 (T = 19 patients with primary insomnia, C = 18 healthy individuals)	Double-blind PC	T = concoction of valepotriates (80% didrovaltrate, 15% valtrate, and 5% acelvaltrate) three times daily in 100 mg doses[a] Duration of study = 15 days	Valerian had a positive effect on withdrawal from BDZ use	

Table 11. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
94	Study on the putative anxiolytic effect of valepotriates	36 outpatients with generalized anxiety disorder (T1 = 12, T2 = 12, P = 12)	Randomized parallel, double-blind, flexible-dose, PC pilot Study	T1 = valepotriates (mean daily dose: 81·3 mg), T2 = diazepam (mean daily dose: 6·5 mg) Duration of study = 4 weeks	The preliminary data obtained in the present study suggest that the valepotriates may have a potential anxiolytic effect on the psychic symptoms of anxiety	As the number of subjects per group was very small, the present results must be viewed as preliminary. Further studies addressing this issue are warranted
95	Effect on sleep difficulties in children with intellectual deficits	Five children with varying intellectual deficits and different primary sleep problems (T, P)	Double-blind, PC and randomized trial	T = 20 mg/kg Duration of study = 14 days	Significant reductions in sleep latencies and nocturnal time awake, lengthened total sleep time and improved sleep quality. The treatment was apparently most effective in children with deficits that involved hyperactivity	Although the findings are preliminary and in need of replication, there is evidence to suggest that valerian may be useful in the safe and effective long-term treatment of intransigent sleep difficulties in children with ID's
96	Improvement of sleep quality when treating non-organic insomniacs with extractum Valerianae radix siccum instead of oxazepam	75 (T, C)	Randomized, double-blind, clinical, comparative study	T = 2 × 300 mg extractum Valerianae radix siccum dragées LI 156, C = 2 × 5 mg oxazepam dragées, daily 30 min before going to bed Duration of study = 28 days	In both groups sleep quality improved significantly, but no statistically significant difference could be found between groups. No differences in the efficacy of valerian and oxazepam	Because of the more favourable adverse effect profile of valerian compared with oxazepam, this hypothesis should be analysed confirmatorily in an equivalence study
97	Effect of valerian extract on sleep structure and sleep quality	16 patients with previously established psycho physiological insomnia (T, P)	Randomized, double-blind, PC, crossover study	T = multiple dosage Duration of study = single dose or 14 days	Treatment with a herbal VRE demonstrated positive effects on sleep structure and sleep perception of insomnia patients	It can therefore be recommended for the treatment of patients with mild psychophysiological insomnia

Table 11. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
98	Influence of valerian on reaction time, alertness and concentration	102 (99 volunteers in Section A, 91 in Section B)	Randomized, controlled, double-blind trial	Section A: T1 = single evening dose of VRE (600 mg LI 156), T2 = FNZ (1 mg). Section B: after 2 weeks of evening administration of VRE (600 mg LI 156)	Neither single nor repeated evening administrations of 600 mg of VRE have a relevant negative impact on reaction time, alertness and concentration the morning after intake	
99	Effect of valerian extract on sleep polygraphy in poor sleepers	14 (T = 8, P = 6)	PC study	T = valerian extract (Valdispert forte, 405 mg t.i.d.) Duration of study = 7 days	Subjects in the valerian group showed an increase in SWS and a decrease in sleep stage 1	No effect on sleep onset time or time awake after sleep onset, on self-rated sleep quality. REM sleep was unaltered
100	Effect of aqueous extract of valerian root on sleep	18 (T1, T2, P)	PC study	T1 = valerian extract 450 mg. T2 = valerian extract 900 mg	The aqueous valerian extract exerts a mild hypnotic action Both doses reduced perceived sleep latency and wake time after sleep onset	The data suggest the dose-dependent effect
101	Pharmacological activity of valepotriates and sesquiterpenes of valerian		Double-blind study	T = Valeriana Natt. preparation containing primarily sesquiterpenes	44% reported perfect sleep and 89% reported improved sleep from the preparation	No side effects were observed

Table 11. (Continued)

References	Object of study	Number of participants	Study type	Preparation, dose, duration of treatment	Outcome	Comments and limitations
102	The effect of an aqueous extract of valerian root on subjectively rated sleep measures	128	Randomized controlled trial	T = 9 samples to test (3 samples containing placebo, 3 samples containing 400 mg valerian extract and 3 samples containing a proprietary over-the-counter valerian preparation)	Valerian produced a significant decrease in subjectively evaluated sleep latency scores and a significant improvement in sleep quality	Night awakenings, dream recall and somnolence the next morning were relatively unaffected by valerian. The only change was a significant increase in reports of feeling more sleepy than normal the next morning

T1, T2, T3, different treatments; P, placebo; C, control group; PC, placebo controlled; VRE, valerian root extract; FNZ, flunitrazepam; SWS, slow-wave sleep; BDZ, benzodiazepines.
[a]Obtained from a commercially available product, Valmane (Whitehall Pharm.).

be inconclusive. In fact, findings were contradictory and there was great inconsistency in trial design (number of patients, experimental procedures and methodological quality). In 2006, Miyasaka *et al.* (86) presented a review on randomized and quasi-randomized controlled trials of *Valeriana officinalis* in the treatment of anxiety disorder. Valerian extract in any dose, regime, or method of administration was tried for general anxiety disorder, anxiety neurosis, chronic anxiety status, or any other disorder in which anxiety was the primary symptom. The authors concluded that there was insufficient evidence about the efficacy or safety of valerian compared with placebo or diazepam. RCTs involving larger samples are needed, comparing valerian with placebo or other means used to treat of anxiety disorders, such as antidepressants.

CONCLUSION

Establishing the efficacy of most phytopreparations and identifying their mechanism(s) of action are major challenges. The present review provides a baseline on the level of evidence available on many of those preparations and should be of help to those intending to research further on these topics.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Plant table.

Table S2. List of plants with anti-inflammatory properties.

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