Forschende Komplementärmedizin und Klassische Naturheilkunde

Forsch Komplementärmed Klass Naturheilkd 2003;10(suppl1):17–27

Systematic Reviews of Herbal Medicines – an Annotated Bibliography*

K. Linde[1,2] G. ter Riet[3,4] M. Hondras[5] A. Vickers[6] R. Saller[7] D. Melchart[1],
for the Cochrane Complementary Medicine Field

[1] Centre for Complementary Medicine Research, Department of Internal Medicine II, Technische Universität, München
[2] Institute for Social Medicine & Epidemiology, Charité Hospital, Humboldt University, Berlin, Germany
[3] NHS Centre for Reviews & Dissemination, University of York, UK
[4] Department of Epidemiology, Maastricht University, The Netherlands
[5] Consortial Center for Chiropractic Research, Davenport, IO
[6] Memorial Sloan-Kettering Cancer Center, New York, NY, USA
[7] Division of Complementary Medicine, Department of Internal Medicine, Universitätsspital Zurich, Switzerland

Key Words
Medicinal plants · Botanical medicines · Meta-analysis

Summary
Objective: To provide a comprehensive collection and a summary of systematic reviews of clinical trials on herbal medicines. **Methods:** Potentially relevant reviews were searched through the register of the Cochrane Complementary Medicine Field, the Cochrane Library, Medline, and bibliographies of articles and books. To be included articles had to review prospective clinical trials of herbal medicines; had to describe review methods explicitly; had to be published; and had to focus on treatment effects. Information on conditions, interventions, methods, results and conclusions was extracted using a pretested form and summarized descriptively. **Results:** From a total of 79 potentially relevant reviews preselected in the screening process 58 met the inclusion criteria. 30 of the reports reviewed ginkgo (for dementia, intermittent claudication, tinnitus, and macular degeneration), hypericum (for depression) or garlic preparations (for cardiovascular risk factors and lower limb atherosclerosis). The quality of primary studies was criticized in the majority of the reviews. Most reviews judged the available evidence as promising but definitive conclusions were rarely possible. **Conclusions:** Systematic reviews are available on a broad range of herbal preparations prescribed for defined conditions. There is very little evidence on the effectiveness of herbalism as practiced by specialist herbalists who combine herbs and use unconventional diagnosis.

Schlüsselwörter
Phytotherapie · Metaanalysen

Zusammenfassung
Ziel: Umfassende Zusammenstellung der vorliegenden systematischen Übersichtsarbeiten klinischer Studien in der Phytotherapie. **Methoden:** Potentiell relevante Übersichtsarbeiten wurden mit Hilfe des Registers des Cochrane Complementary Medicine Field, der Cochrane Library, Medline, und Bibliographien von Artikeln und Büchern identifiziert. Einschlusskriterien waren: Die Übersichtsarbeiten berichteten über prospektive klinische Studien zu therapeutischen Effekten von Phytotherapeutika; beschrieben explizit die verwendete Methodik und waren in Zeitschriften, Büchern oder im Internet publiziert. Informationen zu Patienten, Interventionen, Methoden, Ergebnissen und Schlussfolgerungen wurden standardisiert extrahiert und deskriptiv zusammengefasst. **Ergebnisse:** 58 von 79 in einem Screening-Prozess vorausgewählten Übersichtsarbeiten entsprachen den Einschlusskriterien. Allein 30 berichteten über Studien zu Ginkgo (bei Demenz, Claudicatio intermittens, Tinnitus und Makuladegeneration), Hypericum (bei Depression) oder Knoblauch (in Bezug auf kardiovaskuläre Risikofaktoren und Atherosklerose der unteren Extremitäten). Die Qualität der Primärstudien wurde in der Mehrzahl der Reviews bemängelt. In vielen Fällen wurde die vorhandene Evidenz als vielversprechend bewertet, definitive Schlussfolgerungen wurden jedoch nur in wenigen Reviews gezogen. **Schlussfolgerung:** Systematische Reviews liegen zu einer Reihe von Phytotherapeutika vor. Sehr wenige Untersuchungen liegen dagegen zu traditionelleren Anwendungsformen der Phytotherapie wie z.B. Teeanwendungen vor.

*Originally published in BMC Complementary and Alternative Medicine 2001;1:5 (available at http://www.biomedcentral.com/1472–6882/1/5)as a part of a series of three papers on acupuncture, herbal medicine and homeopathy

KARGER

Fax +49 761 4 52 07 14
E-mail Information@Karger.de
www.karger.com

Accessible online at:
www.karger.com/fkm

PD Dr. Dieter Melchart
Centre for Complementary Medicine Research
Department of Internal Medicine II, Technische Universität
Kaiserstrasse 9, D-80801 München
Tel.+49 89 3-304 10 48, Fax -934 84
E-mail Dieter.Melchart@lrz.tu-muenchen.de

Introduction

Systematic reviews are considered to be the best available method to summarize the existing evidence on a given topic. In recent years an increasing number of such reviews has been performed in a variety of complementary therapies including herbal medicine. The objective of this report is to provide a comprehensive collection and transparent summary of the available systematic reviews of herbal medicines. It was not our primary objective to assess efficacy as we do not consider a review of reviews of a large number of interventions an appropriate tool for this purpose. However, when summarizing the results of systematic reviews it is unavoidable to cite their conclusions on efficacy.

Herbal medicines (defined as preparations derived from plants and fungi, for example by alcoholic extraction or decoction, used to prevent and treat diseases) are an essential part of traditional medicine in almost any culture [1]. In industrialized countries herbal drugs and supplements are an important market. Some countries like Germany have a long tradition in the use of herbal preparations marketed as drugs and figures for prescriptions and sales are stable or slightly declining [2]. In the US and the UK herbal medicinal products are marketed as 'food supplements' or 'botanical medicines'. In recent years sales of such products have been increasing strongly in these countries [3.4]. In the Third World herbs are mainly used by traditional healers [5].

Methods

To be included in this overview reviews had to meet the following criteria: 1) Report reviews prospective (not necessarily controlled) clinical trials of substances extracted from plants in humans. Reviews dealing with single substances (e.g., artemisin derivatives) derived from plants were excluded on the grounds that such agents are comparable to conventional drugs. 2) Reports explicitly describe, at least, one of the following issues: a) methods for searching primary studies *and* eligibility criteria for primary studies; b) methods to assess quality aspects; c) methods to summarize the results of the primary studies. 3) Reports are published in journals, books, theses, or the internet. Reviews published before 1989 and as abstracts only were not included. 4) The primary focus of the report is on treatment effects (not diagnosis, side effects, risks, etc.). There were no language restrictions. Disease-oriented reviews including a variety of interventions were included only if they reviewed at least 4 herbal medicine trials.

The primary source for identification of systematic reviews was the register of the Cochrane Complementary Medicine Field. For the compilation of this register a variety of databases including Medline, Embase, CISCOM, AMED and other sources have been searched. In addition, we searched 1) Medline 1989 to July 2000 using a standard strategy to identify systematic reviews [8] combined with 50 single plant names and the 'exploded' term 'medicinal plants'; 2) the Cochrane Library (last check in issue 2000, 3) Bibliographies of articles obtained and relevant textbooks were screened for further potentially relevant articles. The literature list from the Complementary Medicine Field register was screened in a first step independently by two reviewers who excluded all references for which they were sure that the papers were not systematic reviews. Abstracts of the publications identified by other means were screened by one reviewer. Full copies were obtained for all potentially relevant papers. One (in 46% of papers), two (53%) or three (1%) reviewers checked eligibility and extracted information (bibliographic details, topic, intervention, inclusion criteria, methodological issues, studies and number of patients included, results, and conclusions) from included reviews using pretested forms. For this report the included reviews were summarized in a tabular format giving basic information on the conditions, interventions, comparisons, number of studies reviewed, methodological features, results, and conclusions drawn by the reviewers (if possible in the original wording). We assessed the following methodological features: Comprehensiveness of the literature search (scored if in addition to Medline other databases and non-electronic sources were searched), whether inclusion and exclusion criteria were explicitly listed, whether the quality of primary studies was assessed using formal methods (such as scores or checklists), whether a summary of results was provided for each included study, and whether a quantitative meta-analysis was performed.

If several review publications by the same team of reviewers with the same focus and published within a time span of 3 years were available these were considered as updates unless inclusion criteria for the two versions were clearly different.

Results

From a total of 79 potentially relevant reviews preselected in the literature screening process, 58 (published in 65 papers) met the inclusion criteria [7–71]. Eleven reports were not truly systematic reviews (not meeting inclusion criterion 2) [72–82], 5 dealt with isolated substances of plant origin [83–87] and 4 were excluded for other reasons (one disease-focused review with less than 4 herbal medicine trials [88], one review not on preventative or therapeutic use [89], 2 reviews not truly herbal medicine [90–91]).

More than half of the reports reviewed gingko, hypericum or garlic preparations. No less than 13 systematic reviews dealt with ginkgo (*Ginkgo biloba*) extracts (see table 1). Seven of these reviewed trials (total number of trials covered in any of the reviews 15) in patients with intermittent claudication [7–13]. Most of these reviews concluded that ginkgo extracts were significantly more effective than placebo in increasing measures like walking distance but the clinical relevance of the effects was felt to be moderate by some reviewers. The 5 reviews dealing with dementia and cerebral insufficiency (total number of trials included about 50) all draw positive conclusions [13–17]. However, many of the older trials were in patients with minor cognitive impairment and more evidence is needed to decide whether ginkgo extracts have clinically relevant beneficial effects in more severe forms of dementia. Finally, 1 review found that ginkgo extracts might be effective in the treatment of tinnitus [18] and another found insufficient evidence for efficacy in patients with macular degeneration [19].

The effectiveness of St. John's wort (*Hypericum perforatum*) extracts in depression was investigated in 9 reviews [20–30] (total number of trials covered 29; see table 2). Mainly due to slight differences in the inclusion criteria (for example, restriction to trials with a minimum of 6 weeks observation or with a

minimum quality score) the respective study collections differed to a considerable amount. However, the conclusions were very similar. Hypericum extracts have been shown to be superior to placebo in mild to moderate depressive disorders. There is growing evidence that hypericum is as effective as other antidepressants for mild to moderate depression and causes fewer side effects but further trials are still needed to establish long-term effectiveness and safety.

Eight reviews have been performed on garlic (*Allium sativum*) for cardiovascular risk factors [31–38] (total number of trials covered about 50) and lower limb atherosclerosis [39] (see table 2). A modest short-term effect over placebo on lipid-lowering seems to be established but the clinical relevance of these effects is uncertain. Data from randomized trials on cardiovascular mortality are not available. Effects on blood pressure seem to be at best minor. The available results on fibrinolytic activity and platelet aggregation are promising but insufficient to draw clear conclusions. A specific problem in research on garlic is the great variety of garlic preparations used: the exact content of bioactive ingredients in these is often unclear.

Three reviews (covering a total of about 30 trials) have been performed on preparations containing extracts of *Echinacea* (*Echinacea purpurea, pallida* or *angustifolia*), two of which by the same study group [40–43]. The results suggest that *Echinacea* preparations may have some beneficial effects mainly in the early treatment of common colds. Similar to garlic a major problem is the high variation of bioactive compounds between different *Echinacea* preparations. Cranberries (*Vaccinium macrocarpon*) for urinary tract infections [44, 45], mistletoe (*Viscum album*) for cancer [46–48], peppermint (*Mentha piperita*) oil for irritable bowel syndromes [49, 50] and saw palmetto (*Serenoa repens*) for benign prostate hyperplasia [51–53] have each been subject to 2 reviews. For saw palmetto there is good evidence for efficacy over placebo while for the other three the data are inconclusive (see table 3).

Single systematic reviews have been published on aloe (*Aloe vera*) [54], artichoke (*Cynara scolymus*) leave extract [55], evening primrose (*Oenothera biennis*) oil [56], feverfew (*Tanacetum parthenium*) [57], ginger (*Zingiber officinialis*) [58], ginseng (*Panax ginseng*) [59], horse chestnut (*Aesculus hippocastanum*) seeds [60], kava (*Piper methysticum*) [61], milk thistle (*Silybum marianum*) [62], a fixed combination of three herbal extracts [63], rye-grass pollen (*Secale cereale*) extract [64, 65], tea tree (*Melaleuca alternafolia*) oil [66], and valerian (*Valeriana officinalis*) root [67] (see table 4).The only review which focused on a herbal intervention which is not marketed as a drug or food supplement was on cabbage leaves for breast engorgement and included a single small-scale trial [68]. Chinese herbal therapy for atopic eczema [69] and a variety of herbs for lowering blood glucose [70] and for analgesic and anti-inflammatory purposes [71] have also been reviewed. For some of these herbal preparations the evidence is promising but further studies are considered necessary to establish efficacy in almost every case.

Discussion

Our overview shows that a considerable number of systematic reviews on herbal medicines is available. In the majority of cases the reviewers considered the available evidence as promising but only very rarely as convincing and sufficient as a firm basis for clinical decisions. The methodological quality of the primary studies has been criticized by many reviewers.

Our summary of the existing studies must be interpreted with caution. What we performed is a systematic review of systematic reviews which inherently bears a large risk of oversimplification. Readers who want to reliably assess the evidence for a given herb for a defined condition should read the respective reviews. Our collection – which to the best of our knowledge is complete up to summer 2000 – is aimed at facilitating the access and giving an idea of the amount of the available evidence. Based on the increase of herbal medicine reviews in recent years we expect that at least ten new publications will become available in the year 2001.

Most of the currently available systematic reviews address herbal preparations which are marketed and widely used in industrialized countries. However, the widespread traditional use of herbs in the Third World is rarely ever investigated and has not been subjected to systematic reviews. The many herbs used in folk medicine or other traditional uses of herbs (for example, hypericum is used for a variety of ailments other than depression including enuresis, diarrhea, gastritis, bronchitis, asthma, sleeping disorders etc.) seem to be rarely investigated. Furthermore, practitioners of herbal medicine often combine different herbs and use unconventional diagnostic approaches to adapt prescriptions to single patients. It seems likely that these traditional forms of herbal medicine will remain underresearched relative to single herbal preparations due to the lack of financial incentive for sponsors and due to methodological problems.

Herbal medicines products are not, in general, subject to patent protection. This reduces the motivation for drug companies to invest in trials. Many of the existing herbal medicine manufacturers are comparably small companies, often with limited research resources and expertise. Maybe partly for these reasons, the quality of many older herbal medicine trials is low. Furthermore, negative trials which could threaten the company's survival might not become published.

A fundamental problem in all clinical research of herbal medicines is whether different products, extracts, or even different lots of the same extract are comparable and equivalent. This is a major issue in the expert research community and a major obstacle to a reliable assessment for the non-expert. For example, *Echinacea* products can contain other plant extracts, use different plant species (*Echinacea purpurea, pallida* or *angustifolia*), different parts (herb, root, both), and might have been produced in quite different manners (hydro- or lipophilic extraction). Pooling studies that use different herbal products in a quantitative meta-analysis can be misleading. Health care

Table 1. Systematic reviews of clinical trials of Ginkgo biloba extracts

Reference	Indication	Intervention	Comparisons	Studies	Features[a] 1 / 2 / 3 / 4 / 5	Results	Authors' conclusion
Ginkgo *(Ginkgo biloba)*							
Pittler and Ernst, 2000 [7]	intermittent claudication	ginkgo	placebo	8 RCT	y / y / y / y /y	increase of pain-free walking distance over placebo after 12 or 24 weeks 34m (95% CI 26–43m)	evidence for a modest benefit of uncertain clinical relevance
Moher et al., 2000 [8]	intermittent claudication	ginkgo[b]	placebo	5 RCT	y / y / y / n / y	increase of pain-free walking distance over placebo after 24 weeks 32m (95% CI 14–50m)	inconsistent results from the few available small studies do not allow firm conclusions
Ernst, 1996 [9]	intermittent claudication	ginkgo extract EGb761	placebo, other drugs	10 RCT/CCT	p / p / n / n / n	most studies low quality; increase of walking distance compared to placebo 24 to 160 m; at least similar effectiveness compared to other drugs.	available evidence promising but further high quality research needed
Schneider, 1992 [10]	intermittent claudication	ginkgo	placebo, other treatment	7 RCT/CCT (vs. placebo), 2 RCT/CCT (other)	? / n / n / y / y	mean effect size d = 0.75 (95% CI 0.44–1.07) over placebo	effectiveness over placebo clearly shown
Letzel and Schoop, 1992 [11]	intermittent claudication	ginkgo extract EGb 761	ginkgo vs. placebo, pentoxifyllin vs. placebo	5 RCT ginkgo 9 RCT pentoxifyllin	? / p / n / y / y	pooled increase of walking distance: 45% over placebo for gingko and 57% for pentoxifyllin	ginkgo extract EGb761 more effective than placebo and similarly effective as pentoxifyllin
Kleijnen and Knipschild, 1991 [12]	intermittent claudication	ginkgo	ginkgo vs. placebo, pentoxifyllin vs. placebo	15 RCT/CCT (ginkgo), 5 RCT/CCT pentoxifyllin	y / y / y / n / n	many trials low quality; all trials with positive results; evidence similar as for pentoxifyllin	ginkgo seems effective for intermittent claudication but further high quality studies are needed
Weiss and Kallischnigg, 1991 [13]	cerebral insuffiency, interrmittent claudication	ginkgo extract EGb761	placebo	17 RCT/CCT (cerebral insuffiency), 8 RCT/CCT	? / p / p / n / n	10 of 12 interpretable trials on cerebral insufficieny and all 4 interpretable trials on intermittent claudication with significant positive results	effectiveness for both conditions biometrically shown
Ernst and Pittler, 1999 [14]	dementia	ginkgo	placebo	9 RCT	y / y / y / y / n	results collectively suggest that ginkgo is more effective for dementia than placebo	encouraging findings warranting large scale trials
Oken et al., 1998 15]	Alzheimer dementia	ginkgo	placebo	4 RCT	y / y / n / y / y	significant effect over placebo for cognitive function (hedges g = 0.41, 95% CI 0.22–0.61)	clinical relevance of the observed effects has to be confirmed in further research
Hopfenmüller, 1994 [16]	cerebral insufficiency	ginkgo extract LI 1370	placebo	10 RCT, 1 CCT	n / n / n / y / y	global response (based on symptom scores): OR 1.98 (95% CI 1.39–2.57) in favor of ginkgo	ginkgo extract superior to placebo
Kleijnen and Knipschild, 1992 [17]	cerebral insufficiency	ginkgo	ginkgo vs. placebo hydergine vs. placebo	40 RCT/CCT (ginkgo), 4 RCT/CCT (hydergine)	y / y / y / n / n	many trials low quality; virtually all trials reported positive results; evidence similar as for hydergine	ginkgo seems effective for cerebral insufficiency but further high quality studies are needed
Ernst and Stevinson, 1999 [18]	tinnitus	ginkgo	placebo, other treatment (1 trial)	5 RCT	y / y / y / y / n	3 trials favour ginkgo over placebo, 1 no difference, in one trial ginkgo better than another treatment	results suggest that extracts of Ginkgo biloba are effective in treating tinnitus
Evans, 2000 [19]	macular degeneration	ginkgo	placebo	1 RCT	y / y / y / y / –	one small trial reporting improvement	insufficient evidence to recommend ginkgo for age-related macular degeneration

RCT = Randomized controlled trials, CCT = non-randomized controlled trials, CS = cohort studies, UCS = uncontrolled studies; OR = odds ratio, RR = rate ratio.

[a]Features: 1 = comprehensive search, 2 = explicit inclusion criteria, 3 = formal quality assessment, 4 = summary of results for each included study, 5 = meta-analysis; y = yes, p = partly, n = no, – = not applicable, ? = unclear.

[b]Review on all pharmacologic treatments for the respective condition.

Table 2. Systematic reviews of clinical trials of hypericum and garlic preparations

Reference	Indication	Intervention	Comparisons	Studies	Features[a] 1 / 2 / 3 / 4 / 5	Results	Authors' conclusion
St. John's wort *(Hypericum perforatum)*							
Gaster, 2000 [20]	depression	hypericum	placebo and antidepressants	8 RCT	p / y / p / y / n	4 placebo-controlled trials with positive results, in 4 trials standard antidepressants tended to be slightly better	data suggest that hypericum is superior to placebo, insufficient evidence re equivalence with antidepressants
Williams et al., 2000 [21]; Mulrow et al., 1998 [22]	depression	hypericum (and other drugs)	placebo and antidepressants	14 RCT	y / y / n / y /y	treatment response: RR 1.9 (95% CI 1.2–2.8) vs. placebo and 1.2 (1.0–1.4) vs. antidepressants	data suggest that hypericum is superior to placebo, insuffcient evidence re equivalence with antidepressants
Kim et al., 1999 [23]	depression	hypericum	placebo and antidepressants	6 RCT	p / y / y / y / y	treatment response: RR 1.48 (95% CI 1.03–1.92) vs. placebo and 0.98 (0.67–1.28) vs. antidepressants	hypericum more effective than placebo and similarly effective as low dose antidepressants; quality problems
Stevinson and Ernst, 1999 [24]	depression	hypericum	placebo and antidepressants	6 RCT	y / y / y / y / n	only trials published after Linde 1996; trials show effects better than placebo / similar to antidepressants	data confirm findings of earlier trials, but still insufficient evidence to assess equivalence with antidepressants
Linde et al., 1998, 1996 [25, 26]	depression	hypericum	placebo and antidepressants	27 RCT	y / y / y / y / y	treatment response: RR 2.47 (95% CI 1.69–3.61) vs. placebo and 1.01 (0.87–1.16) vs. antidepressants	hypericum more effective than placebo; inadequate evidence to assess equivalence with antidepressants
Volz, 1997 [27]	depression	hypericum	placebo and antidepressants	15 RCT/CCT	p / p / n / n / n	most placebo-controlled trials positive; similarly effective as (not adequately dosed) antidepressants	a therapy with hypericum of mild and moderate depression can be attempted; further studies needed
Ernst, 1995 [28]	depression	hypericum	placebo and antidepressants	11 RCT	y / y / y / y / n	most of 8 placebo-controlled trials positive; 3 trials against standard medication with similar effects	hypericum is superior to placebo and seems equally effective as standard medication
Volz and Laux, 2000 [29]	mild to moderate depression	hypericum	fluoxetine	17 + 9 CCT	n / y / n / y / n	no direct comparison of hypericum and fluoxetine available; mean depression score (HAMD) reduction in hypericum trials 53%, in fluoxetine trials 55%	response rates are similar; findings difficult to interpret because of the indirect comparison
Friede and Wüstenberg, 1998 [30]	anxiety in depressed patients	hypericum	placebo, amitriptyline	8 RCT	? / y / y / y / n	trials collectively show reduction of anxiety symptoms over placebo; only 1 trial vs. amitriptyline	hypericum is effective for depressed patients with anxiety

Table 2 continuation see next page

Table 2. Continued

Reference	Indication	Intervention	Comparisons	Studies	Features[a] 1 / 2 / 3 / 4 / 5	Results	Authors' conclusion
Garlic *(Allium sativum)*							
Lawrence et al., 2000 [31]	cardiovascular risk factors	hgarlic	mainly placebo; no and other treatment	45 RCT	y / y / y / y / y	37 trials consistently show small short-term effects over placebo for cholesterol reduction; no consistent effects on blood pressure, promising effects re platelet aggregation and fibrinolytic activity	insufficient data to draw conclusion regarding clinical cardiovascular outcomes; garlic preparations may have small, positive, short-term effects on lipids
Stevinson et al., 2000 [32]	hypercholestero-lemia	garlic	placebo	13 RCT	y / y / y / y / y	pooled total cholesterol reduction over placebo 0.41 (95% CI –0.66 to –0.15) mmol/l; when analysis restricted to high quality trials 0.11 (-0.30 to 0.08)	available data suggest that garlic is superior to placebo; the size of the effect is modest; the use of garlic for hypercholesterolemia is therefore of questionable value
Silagy and Neil,1994 [33]; Neil et al., 1996 [34]	cholesterol lowering	garlic	placebo	16 RCT	y / p / y / y / y	pooled cholesterol reduction over placebo 0.65 (95% CI 0.53–0.76) mmol/l	meta-analysis suggests positive effects but reviewers are sceptic (low quality; own replication negative)
Warshafsky et al., 1993 [35]	cholesterol lowering	garlic	placebo	5 RCT	p / y / y / y / y	pooled cholesterol reduction over placebo 0.59 (95% CI 0.44–0.74) mmol/l	available evidence supports the use of garlic as one modality to decrease cholesterol levels
Silagy and Neil, 1994 [36]	lowering blood press.	dried garlic (Kwai)	placebo, other treatment	8 RCT	y / p / y / y / y	pooled reduction over placebo: SBP 7.7 (95% CI 4.3–11.0), DBP 5.0 (2.9–7.1) mm Hg	garlic maybe of some clinical use in subjects with mild hypertension; further research needed
Kleijnen, 1991 [37]	cardiovascular risk factors	garlic supplements	placebo	18 RCT/CCT	p / p / y / y / n	most studies with shortcomings; the majority of trials with positive results but inconsistent effect sizes	no clear conclusion drawn
Kleijnen et al., 1989 [38]	cardiovascular risk factors	garlic and onions	unclear	10 RCT, 8 CCT	y / p / n / y / n	all trials with severe shortcomings; fresh garlic with beneficial effects, onions and commercially available supplements yielded contradictory results	inadequate evidence to justify supplementation, further research needed
Jepson et al., 1997 [39]	lower limb atherosclerosis	garlic	placebo	1 RCT	y / y / y / y / –	walking distance not significantly different between groups	insufficient evidence

RCT = Randomized controlled trials, CCT = non-randomized controlled trials, CS = cohort studies, UCS = uncontrolled studies; OR = odds ratio, RR = rate ratio.
aFeatures: 1 = comprehensive search, 2 = explicit inclusion criteria, 3 = formal quality assessment, 4 = summary of results for each included study, 5 = meta-analysis; y = yes, p = partly, n = no, – = not applicable, ? = unclear.

Table 3. Systematic reviews of clinical trials of herbal medicines (at least 2 reviews per herb)

Reference	Indication	Intervention	Comparisons	Studies	Features[a] 1 / 2 / 3 / 4 / 5	Results	Authors' conclusion
Echinacea *(Echinacea purpurea, angustifolia, and pallida)*							
Barrett et al., 1999 [40]	upper respiratory infections	*Echinacea* (including combinations)	placebo	13 RCT	y / p / y / y / n	overall quality modest; all 4 prevention studies show only minor trends, 8 of 9 treatment studies with generally positive results	*Echinacea* may be beneficial for early treatment of acute upper respiratory infections; little evidence to support the prolonged use for prevention
Melchart et al., 1999 [41]	common cold	*Echinacea* (including combinations)	placebo, no treatment	16 RCT	y / y / y / y / p	minor effects in prevention and treatment, promising effects in early treatment; heterogeneous preparations	*Echinacea* extract can be efficacious for the common cold, but evidence insufficient for recommendations
Melchart et al., 1994 [42, 43]	immunostimulation	*Echinacea* (including)	placebo, no treatment	18 RCT, 8 CCT	y / y / y / y / n	most studies low quality; most studies show immunostimulating effects	*Echinacea* extracts can be efficacious immunostimulators, but evidence insufficient for recommendations
Cranberries *(Vaccinium macrocarpon)*							
Jepson et al., 1998 [44]	urinary tract infection (prevention)	cranberries	placebo	4 RCT	y / y / y / y/ n	in 3 of 4 trials cranberries effective for at least one of the outcomes of interest	insufficient evidence, further research needed
Jepson et al., 1998 [45]	urinary tract infection (treatment)	cranberries		0 RCT	y / y / – / – / –	no trials meeting the inclusion criteria	no evidence available
Mistletoe *(Viscum album)*							
Kleijnen and Knipschild, 1994 [46]	cancer	mistletoe	placebo, no treatment	11 RCT/CCT	y / y / y / n / n	most studies low quality; most studies show longer survival with mistletoe but not the best trial	insufficient evidence to recommend mistletoe outside of clinical trials
Kiene, 1989 [47, 48]	cancer	mistletoe	no treatment, none	2 RCT, 33 CCT, 11 other studies	y / n / n / y / n	most studies low quality. 9 of 12 interpretable studies suggest positive effects on survival	available evidence supports positive effects of mistletoe
Peppermint *(Mentha piperita)*							
Jailwala et al., 2000 [49]b	irritable bowel syndrome	1. peppermint oil 2. Chinese herbal therapy	placebo	1. 3 RCT 2. 1 RCT	p / y / y / n / n	Chinese herbal therapy trial rated as positive, one of three peppermint oil trials rated as positive	in both cases efficacy not clearly established
Pittler and Ernst, 1998 [50]	irritable bowel syndrome	peppermint oil	placebo, other treatment	8 RCT	y / y / y / y / y	global improvement rates significantly higher compared to placebo; quality of trials doubtful	the role of peppermint oil for irritable bowel syndrome has not been established beyond reasonable doubt
Saw palmetto *(Serenoa repens)*							
Boyle et al., 2000 [51]	benign prostate hyperplasia	Permixon" (saw palmetto)	placebo, other treatment	11 RCT, 2 UCS	? / n / n / y / y	peak urine flow 2.20 (95% CI 1.20–3.20) ml/s increase over placebo; significant decrease nocturia	despite some limitations strong evidence that the extract tested has beneficial effects
Wilt et al., 2000 [52], 1998 [53]	benign prostate hyperplasia	saw palmetto	placebo, other treatment	14 RCT (placebo), 5 RCT (other)	y / y / y / y / y	saw palmetto superior to placebo for nocturia, self rating, peak urine flow; similar effects as finasteride	evidence suggests that saw palmetto improves urological symptoms and flow measures; further studies needed

RCT = Randomized controlled trials, CCT = non-randomized controlled trials, CS = cohort studies, UCS = uncontrolled studies; OR = odds ratio, RR = rate ratio.
[a]Features: 1 = comprehensive search, 2 = explicit inclusion criteria, 3 = formal quality assessment, 4 = summary of results for each included study, 5 = meta-analysis; y = yes, p = partly, n = no, – = not applicable, ? = unclear.
[b]Review on all pharmacologic treatments for the respective condition.

Table 4. Systematic reviews of clinical trials of herbal medicines

Reference	Indication	Intervention	Comparisons	Studies	Features[a] 1 / 2 / 3 / 4 / 5	Results	Authors' conclusion
Vogler and Ernst, 1999 [54]	various	aloe	placebo, other and no treatment	6 RCT, 4 CCT	y / y / y / y / n	positive results for genital herpes, psoriasis, hyper-lipidemia, diabetes; contradictory for wound healing	promising results, but overall evidence insufficient
Pittler and Ernst, 1998 [55]	cholesterol lowering	artichoke leave extract	placebo	1 RCT	y / y / y / n / n	effects over placebo only in the subgroup of participants with serum cholesterol > 210 mg/dl	more trials needed
Morse et al., 1989 [56]	atopic eczema	evening primrose oil (Epogam)	placebo	9 RCT/CCT	? / n / n / y / y	epogam significantly better than placebo for most outcomes	no conclusion drawn
Vogler et al., 1998 [57]	migraine	feverfew	placebo	5 RCT	y / y / y / y / n	majority of trials favor feverfew over placebo	effectiveness has not been established beyond reasonable doubt
Ernst and Pittler, 2000 [58]	nausea and vomiting	ginger root	placebo, metoclopramide	6 RCT	y / y / y / y / p	2 of 3 trials on postoperative nausea positive (best negative), trials on seasickness, morning sickness and chemotherapy-induced nausea positive	evidence promising but insufficient to draw firm conclusions
Vogler et al., 1999 [59]	various	ginseng root extract	placebo, other treatment (1 trial)	16 RCT	y / p / y / y / n	contradictory results re. physical performance (7 trials), psychological function (5), immuno-modulation (2), positive results in diabetes and herpes simplex (1 trial respectively)	the efficacy of ginseng root extract is not established beyond reasonable doubt for any of these indications
Pittler and Ernst, 1998 [60]	venous insufficieny	horse chestnut seeds	placebo, other treatment	13 RCT	y / y / y / y / n	significant effects over placebo and similar effects compared to other treatments	horse chestnut seeds seem to be effective; further trials needed (confirmation, long-term results, combination)
Pittler and Ernst, 2000 [61]	anxiety	kava	placebo	7 RCT	y / y / y / p / p	all trials suggest superiority over placebo; 3 trials with data for meta-analysis show sign. superiority	available data suggest that kava is a treatment option for anxiety; further studies needed
Lawrence et al., 2000 [62]	liver diseases	milk thistle	placebo, other and no treatment	33 RCT, 1 CCT	y / y / y / y / y	variety of conditions studied, studies often poor quality; mixed and inconsistent findings	efficacy is not established; possible benefit shown most frequently for aminotransferases.
Ernst, 1999 [63]	musculoskeletal pain	Phytodolor® populus, fraxinus, solidago	placebo, other treatments	10 RCT	y / p / y / y / n	placebo-controlled trials show superiority over placebo and similar effects as NSAIDs	the data suggest that the combination is effective in the symptomatic treatment of musculoskeletal pain
MacDonald et al., 2000 [64]; Wilt et al., 2000 [65]	benign prostata hyperplasia	rye grass pollen extract	placebo, other therapy	4 RCT	y / y / y / y / y	significant improvement over placebo in subjective, but not objective symptoms; no differences compared to tadenan and paraprost	available evidence suggests that Cernilton" is well tolerated and modestly improves subjective symptoms. Further studies needed
Ernst and Huntley, 2000 [66]	dermatologic conditions	tea trea oil	placebo, other treatment	4 RCT	y / y / y / y / n	2 trials vs. placebo positive, 3 trials vs. other treatments similar effects	data promising but insufficient
Stevinson and Ernst, 2000 [67]	insomnia	valerian root	placebo	9 RCT	y / y / y / y / n	highly heterogeneous studies with sometimes contradictory and inconsistent findings	available evidence is promising but not fully conclusive; further, rigorous trials needed
Renfrew and Lang, 1984 [68]	breast engorgement	cabbage leaves	usual care	1 RCT	y / y / n / y / -	fewer women stopping breast feeding among those receiving cabbage leaves	further research desirable
Armstrong and Ernst, 1999 [69]	atopic eczema	Chinese herbal therapy	placebo	2 RCT	y / y / n / y / n	2 positive studies by the same research team; lack of intent-to-treat analysis	evidence encouraging but insufficient given the potential of relevant side effects

Table 2 continuation see next page

Table 4. (continued)

Reference	Indication	Intervention	Comparisons	Studies	Features[a] 1 / 2 / 3 / 4 / 5	Results	Authors' conclusion
Ernst, 1997 [70]	hypoglycemic activity	all plants	no treatment, placebo, none	7 RCT, 4 CCT, 10 UCS	y / p / n / y / n	most studies low quality; most papers report positive effects on a variety of plants	use of hypoglycemic plant remedies not supported by rigorous research; further studies required
Ernst and Chrubasik, 2000 [71]	analgetic or inflammatory treatment	various	placebo	18 RCT	y / y / y / y / n	trials on evening primrose oil, blackcurrant seed oil, borage oil, harpagophytum, willow bark, feverfew, and 3 combinations; almost all trials positive	the results suggest that several herbal remedies have potential in alleviating the pain of rheumatic diseases; more research urgently needed

RCT = Randomized controlled trials, CCT = non-randomized controlled trials, CS = cohort studies, UCS = uncontrolled studies; OR = odds ratio, RR = rate ratio.
[a]Features: 1 = comprehensive search, 2 = explicit inclusion criteria, 3 = formal quality assessment, 4 = summary of results for each included study, 5 = meta-analysis; y = yes, p = partly, n = no, – = not applicable, ? = unclear.

professionals and patients considering to prescribe or take a particular herbal product should check carefully whether the respective product or extract has been tested in the trials included in a review. On the health food store shelf the high quality, standardized products used in the trials might not be available. Only a herbal medicine expert can judge with some certainty whether the results can be extrapolated to the product of interest.

On the level of health care policies the available systematic reviews more often provide insight into the deficiencies of the evidence than guidance for decision making. Trials on hard endpoints are very rarely available and observation periods have generally been short. The clinical relevance of the observed effects is not always clear.

Herbal medicines are generally considered as comparably safe. While this is probably correct case reports show that severe side effects and relevant interactions with other drugs *can* occur. For example, hypericum extracts cause considerably fewer side effects than tricyclic antidepressants [92] but can decrease the concentration of a variety of other drugs by enzyme induction [93]. Several reviews summarizing side effects and interactions have been published [94–98].

Conflict of interest

KL, DM and GtR have been involved in some of the reviews analyzed. These were extracted and assessed by other members of the team.

Contributors

GtR, MH, AV and KL planned the work, searched the literature, and extracted and assessed reviews. KL coordinated the study and wrote the first draft of the manuscript. DM contributed to the protocol and in numerous discussions during the project. RS provided important input as a herbal medicine expert. All authors commented on earlier drafts.

Acknowledgements

KL's work was partly funded by the NIAMS grant 5 U24-AR-43346–02 and by the Carl and Veronica Carstens Foundation, Essen, Germany. We would like to thank Brian Berman for his support, his help to get funding and his patience in awaiting the completion of our work.

References

1 Vickers A, Zollman CE: ABC of complementary medicine: herbal medicine. BMJ 1999;319:1050–1053.
2 Schwabe U: Arzneimittel der besonderen Therapierichtungen (Naturheilmittel); in Schwabe U, Paffrath D (Hrsg): Arzneiverordnungs-Report 1998. Berlin, Springer, 1999, pp 621–656.
3 Brevoort P: The booming US botanical market. A new overview. HerbalGram 1998;44:33–51.
4 Barnes J: Phytotherapy: consumer and pharmacist perspectives; in Ernst E (ed): Herbal Medicine – a Concise Overview for Professionals. Oxford, Butterworth Heinemann, 2000, pp 19–33.
5 Bodeker GC: Editorial. J Altern Complement Med 1996;3:323–326.
6 Linde K, Vickers A, Hondras M, et al: Systematic Reviews of Complementary Therapies – an Annotated Bibliography. Part 1: Acupuncture. BMC Complementary and Alternative Medicine.
7 Pittler MH, Ernst E: *Ginkgo biloba* extract for the treatment of intermittent claudication: A meta-analysis of randomized trials. Am J Med 2000; 108:276–281.
8 Moher D, Pham B, Ausejo M, Saenz A, Hood S, Barber GG: Pharmacological management of intermittent claudication: A meta-analysis of randomised trials. Drugs 2000;59:1057–1070.
9 Ernst E: *Ginkgo biloba* in der Behandlung der Claudicatio intermittens. Fortschr Med 1996;114: 85–87.
10 Schneider B: *Ginkgo-biloba*-Extrakt bei peripheren arteriellen Verschlusskrankheiten. Meta-Analyse von kontrollierten klinischen Studien. Arzneimittelforschung/Drug Res 1992;42:428–436.
11 Letzel H, Schoop W: *Gingko-biloba*-Extrakt EGb 761 und Pentoxifyllin bei Claudicatio intermittens. Sekundäranalyse zur klinischen Wirksamkeit. VASA 1992;21:403–410.
12 Kleijnen J, Knipschild P: *Gingko biloba* for intermittent claudication and cerebral insufficiency; in Kleijnen J (ed): Food Supplements and Their Efficacy. Maastricht, Rijksuniversiteit Limburg, 1991, pp 83–94.
13 Weiss G, Kallischnigg G: *Gingko-biloba*-Extrakt (EGb 761) – Meta-Analyse von Studien zum Nachweis der therapeutischen Wirksamkeit bei Hirnleistungsstörungen bzw. peripherer arterieller Verschlusskrankheit. Münch Med Wochenschr 1991;10: 138–142.
14 Ernst E, Pittler MH: *Ginkgo biloba* for dementia: A systematic review of double-blind, placebo-controlled trials. Clin Drug Invest 1999;17:301–308.
15 Oken BS, Storzbach DM, Kaye JA: The efficacy of *Ginkgo biloba* on cognitive function in Alzheimer disease. Arch Neurol 1998;55:1409–1415.
16 Hopfenmüller W: Nachweis der therapeutischen Wirksamkeit eines *Ginkgo biloba*-Spezialextraktes – Meta-Analyse von 11 klinischen Studien mit Patienten mit Hirnleistungsstörungen im Alter. Arzneimittelforschung/Drug Res 1994;44:1005– 1013.
17 Kleijnen J, Knipschild P: *Gingko biloba* for cerebral insufficiency. Br J Clin Pharmacol 1992;34:352–358.
18 Ernst E, Stevinson C: *Ginkgo biloba* for tinnitus: A review. Clin Otolaryngol 1999;24:164–167.
19 Evans JR: *Ginkgo biloba* extract for age-related macular degeneration (Cochrane Review); in The Cochrane Library, Issue 1, 2000, Oxford, Update Software.
20 Gaster B: St John's wort for depression. A systematic review. Arch Intern Med 2000;160:152–156.
21 Williams JW Jr, Mulrow CD, Chiquette E, Hitchcock Noel P, Aguilar C, Cornell J: A systematic review of newer pharmacotherapies for depression in adults: Evidence report summary. Ann Intern Med 2000;132:743–756.
22 Mulrow CD, Williams JW Jr, Trivedi M, et al: Treatment of depression – newer pharmacotherapies. Psychopharmacol Bull 1998;34:409–795.
23 Kim HL, Streltzer J, Goebert D: St. John's wort for depression: A meta-analysis of well-defined clinical trials. J Nerv Ment Dis 1999;187:532–539.
24 Stevinson C, Ernst E: Hypericum for depression. An update of the clinical evidence. Eur Neuropsychopharmacol 1999;9:501–505.
25 Linde K, Mulrow CD: St John's wort for depression (Cochrane Review); in The Cochrane Library, Issue 4, 1998, Oxford, Update Software.
26 Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D: St John's wort for depression – an overview and meta-analysis of randomised clinical trials. BMJ 1996;313:253–258.
27 Volz HP: Controlled clinical trials of hypericum extract in depressed patients – an overview. Pharmacopsychiatry 1997;30(suppl):72–75.
28 Ernst E: St. John's Wort, an anti-depressant? A systematic, criteria-based review. Phytomedicine 1995; 2:67–71.
29 Volz HP, Laux P: Potential treatment for subthreshold and mild depression: A comparison of St. John's wort extracts and fluoxetine. Compr Psychiatry 2000;41(suppl 1):133–137.
30 Friede M, Wüstenberg P: Johanniskraut zur Therapie von Angstsyndromen bei depressiven Verstimmungen. Z Phytother 1998;19:309–317.
31 Lawrence V, Mulrow C, Ackerman R, et al: Garlic: Effects on cardiovascular risks and disease, protective effects against cancer, and clinical adverse effects. Evidence Report/Technology Assessment: Number 20, 2000. *www.ahcpr.gov/clinic/garlicsum.htm*
32 Stevinson C, Pittler MH, Ernst E: Garlic for treating hypercholesterinemia – a meta-analysis of randomized clinical trials. Ann Intern Med 2000;133: 420–429.
33 Silagy C, Neil A: Garlic as a lipid lowering agent – a meta-analysis. J R Coll Physicians Lond 1994;28: 39–45.
34 Neil HA, Silagy CA, Lancaster T, et al: Garlic powder in the treatment of moderate hyperlipidaemia: A controlled trial and meta-analysis. J R Coll Physicians Lond 1996;30:329–334.
35 Warshafsky S, Kamer RS, Sivak SL: Effect of garlic on total serum cholesterol. Ann Intern Med 1993; 119:599–605.
36 Silagy CA, Neil HA: A meta-analysis of the effect of garlic on blood pressure. J Hypertens 1994;12: 463–468.
37 Kleijnen J: Controlled clinical trials in humans on the effects of garlic supplements; in Kleijnen J. Food supplements and their efficacy. Maastricht, Rijksuniversiteit Limburg, 1991, 73–82.
38 Kleijnen J, Knipschild P, ter Riet G: Garlic, onions and cardiovascular risk factors. A review of the evidence from human experiments with emphasis on commercially available preparations. Br J Clin Pharmacol 1989;28:535–544.
39 Jepson RG, Kleijnen J, Leng GC: Garlic for lower limb atherosclerosis (Cochrane Review); in The Cochrane Library, Issue 4, 1998, Oxford, Update Software.
40 Barrett B, Vohmann M, Calabrese C: *Echinacea* for upper respiratory tract infection. J Fam Pract 1999; 48:628–635.
41 Melchart D, Linde K, Fischer P, Kaesmayr J: *Echinacea* for prevention and treatment of the common cold (Cochrane Review); in The Cochrane Library, Issue 1, 1999, Oxford, Update Software.
42 Melchart D, Linde K, Worku F, Bauer R, Wagner H: Immunmodulation mit *Echinacea*-haltigen Arzneimitteln – eine kriteriengestützte Analyse der kontrollierten klinischen Studien. Forsch Komplementärmed 1994;1:26–36.
43 Melchart D, Linde K, Worku F, Bauer R, Wagner H: Immunomodulation with *Echinacea* – a systematic review of controlled clinical trials. Phytomedicine 1994;1:245–254.
44 Jepson RG, Mihaljevic L, Craig J: Cranberries for the prevention of urinary tract infections (Cochrane Review); in The Cochrane Library, Issue 4, 1998, Oxford, Update Software.
45 Jepson RG, Mihaljevic L, Craig J: Cranberries for the treatment of urinary tract infections (Cochrane Review); in The Cochrane Library, Issue 4, 1998, Oxford, Update Software.
46 Kleijnen J, Knipschild P: Mistletoe treatment for cancer. Review of controlled trials in humans. Phytomedicine 1994;1:255–260.
47 Kiene H: Klinische Studien zur Misteltherapie karzinomatöser Erkrankungen. Therapeutikon 1989;6:347–353.
48 Kiene H: Klinische Studien zur Misteltherapie der Krebserkrankung. Eine kritische Würdigung. Inaugural-Dissertation, Universität Witten-Herdecke, 1989.
49 Jailwala J, Imperiale TF, Kroenke K: Pharmacologic treatment of the irritable bowel syndrome: A systematic review of randomized, controlled trials. Ann Intern Med 2000;133:136–147.
50 Pittler MH, Ernst E: Peppermint oil for irritable bowel syndrome: A critical review and meta-analysis. Am J Gastroenterol 1998;93:1131–1135.
51 Boyle P, Robertson C, Lowe F, Roehborn C: Meta-analysis of clinical trials of permixon in the treatment of symptomatic benign prostatic hyperplasia. Urology 2000;55:533–539.
52 Wilt TJ, Ishani A, MacDonald R, Stark G, Mulrow C, Lau J: *Serenoa repens* for treatment of benign prostatic hyperplasia (Cochrane Review); in The Cochrane Library, Issue 1, 2000, Oxford, Update Software.
53 Wilt TJ, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C: Saw palmetto extracts for treatment of benign prostatic hyperplasia – a systematic review. JAMA 1998;280:1604–1609.
54 Vogler BK, Ernst E: *Aloe vera:* A systematic review of its clinical effectiveness. Br J Gen Pract 1999; 49:823–828.
55 Pittler MH, Ernst E: Artichoke leaf extract for serum cholesterol reduction. Perfusion 1998;11: 338–340.
56 Morse PF, Horrobin DF, Manku MS, et al: Meta-analysis of placebo-controlled studies of the efficacy of epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and responses. Br J Dermatol 1989;121:75–90.
57 Vogler BK, Pittler MH, Ernst E: Feverfew as a preventive treatment for migraine: A systematic review. Cephalalgia 1998;18:704–708.
58 Ernst E, Pittler MH: Efficacy of ginger for nausea and vomiting: A systematic review of randomized clinical trials. Intern J Anesth 2000;84:367–371.

59 Vogler BK, Pittler MH, Ernst E: The efficacy of ginseng. A systematic review of randomised clinical trials. Eur J Clin Pharmacol 1999;55:567–575.
60 Pittler MH, Ernst E: Horse-chestnut seed extract for chronic venous insufficiency. Arch Dermatol 1998;134:1356–1360.
61 Pittler MH, Ernst E: Efficacy of kava extract for treating anxiety: Systematic review and meta-analysis. J Clin Psychopharmacol 2000;20:84–89.
62 Lawrence V, Mulrow C, Jacobs B, et al: Report on milk thistle: Effects on liver disease and cirrhosis and clinical adverse effects. Evidence Report/Technology Assessment, Number 21, *www.ahcpr.gov/clinic/milktsum.htm*
63 Ernst E: The efficacy of phytodolor for the treatment of musculoskeletal pain – a systematic review of randomized clinical trials. Nat Med J 1999 (Summer):14–7.
64 MacDonald R, Ishani A, Rutks I, Wilt TJ: A systematic review of Cernilton for the treatment of benign prostatic hyperplasia. Br J Urol Int 2000;85: 836–841.
65 Wilt TJ, MacDonald R, Ishani A, Rutks I, Stark G: Cernilton for benign prostatic hyperplasia (Cochrane Review); in The Cochrane Library, Issue 2, 2000, Oxford, Update Software.
66 Ernst E, Huntley A: Tea tree oil: A systematic review of randomised clinical trials. Forsch Komplementärmed 2000;7:17–20.
67 Stevinson C, Ernst E: Valerian for insomnia: A systematic review of randomized clinical trials. Sleep Med 2000;1:91–99.
68 Renfrew MJ, Lang S: Do cabbage leaves prevent breast engorgement? (Cochrane Review); in The Cochrane Library, Issue 4, 1998, Oxford, Update Software.
69 Armstrong NC, Ernst E: The treatment of eczema with Chinese herbs: *a* systematic review of randomized controlled trials. Br J Clin Pharmacol 1999;48: 262–264.
70 Ernst E: Plants with hypoglycaemic activity in humans. Phytomedicine 1997;4:73–78.
71 Ernst E, Chrubasik S: Phyto-anti-inflammatories: A systematic review of randomized, placebo-controlled, double-blind trials. Rheum Dis Clin North Am 2000;26:13–27.
72 Budeiri D, Li Wan Po A, Dornan JC: Is Evening Primrose Oil of value in the treatment of premenstrual syndrome? Control Clin Trials 1996;17:60–68.
73 Diehm C: The role of oedema protective drugs in the treatment of venous insufficiency: a review of evidence based on placebo-controlled clinical trials with regard to efficacy and tolerance. Phlebology 1996;11:23–29.
74 Evans MF: Morgenstern K. St. John's wort: A herbal remedy for depression? Can Fam Physician 1997;43:1735–1736.
75 Giles JT, Palat CR, Chien SH, Chang ZG, Kennedy DT: Evaluation of *Echinacea* for treatment of the common cold. Pharmacotherapy 2000;20:690–697.
76 Josey ES, Tackett RL: St. John's wort: a new alternative for depression? Int J Clin Pharmacol Ther 1999;37:111–119.
77 Kleijnen J, ter Riet G, Knipschild P: Teunisbloemolie. Een overzicht van gecontroleerd onderzoek. Pharmaceutisch Weekblad 1989;124:418–423.
78 Knipschild P: Ginseng: pep of nep? Pharmaceutisch Weekblad 1988;123:4–11.
79 McPartland JM, Pruitt PL: Medical marijuana and its use by the immunocompromised. Altern Ther Health Med 1997;3:39–45.
80 Weihmayr T, Ernst E: Die therapeutische Wirksamkeit von Crataegus. Fortschr Med 1996;114: 27–29.
81 Wettstein A: Cholinesterase inhibitors and ginkgo extracts – are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months duration. Phytomedicine 2000;6:393–401.
82 Wong AHC, Smith M, Boon HS: Herbal remedies in psychiatric practice. Arch Gen Psychiatry 1998; 55:1033–1044.
83 Ernst E, Pittler MH: Yohimbine for erectile dysfunction: A systematic review and meta-analysis of randomized clinical trials. J Urol 1998;159:433–436.
84 McIntosh HM, Olliaro P: Artemisin derivatives for treating uncomplicated malaria (Cochrane Review); in The Cochrane Library, Issue 2, 2000, Oxford, Update Software.
85 McIntosh HM, Olliaro P: Artemisin derivatives for treating severe malaria (Cochrane Review); in The Cochrane Library, Issue 2, 2000, Oxford, Update Software.
86 Pittler MH, Ernst E: Artemether for severe malaria: a meta-analysis of randomized clinical trials. Clin Infect Dis 1999;28:597–601.
87 Wilt TJ, Ishani A, MacDonald R, Stark G, Mulrow C, Lau J: Beta-sitosterols for benign prostatic hyperplasia (Cochrane Review); in The Cochrane Library, Issue 1, 2000, Oxford, Update Software.
88 Dumont L, Mardirosoff C, Tramér M: Efficacy and harm of pharmacological prevention of acute mountain sickness: A quantitative systematic review. BMJ 2000;321: 267–272.
89 Ernst E: Can allium vegetables prevent cancer? Phytomedicine 1997;4:79–83.
90 Joy CB, Mumby-Croft R, Joy LA: Polyunsaturated fatty acid (fish or evening primrose oil) for schizophrenia (Cochrane Review); in The Cochrane Library, Issue 2, 2000, Oxford, Update Software.
91 Young GL, Jewell MD: Creams to prevent striae gravidarum (Cochrane Review); in The Cochrane Library, Issue 4, 1998, Oxford, Update Software.
92 Ernst E, Rand JI, Barnes J, Stevinson C: Adverse effects profile of the herbal antidepressant St. John's wort (*Hypericum perforatum* L.). Eur J Clin Pharmacol 1998;54:589–594.
93 Ernst E: Second thoughts about safety of St John's wort. Lancet 1999;354:2014–2015.
94 De Smet PAGM: Health risks of herbal remedies. Drug Saf 1995;13:81–93.
95 Miller LG: Herbal medicine. Selected clinical considerations focusing on known or potential drug-herb interactions. Arch Intern Med 1998;158: 2200–2211.
96 Fugh-Berman A: Herb-drug interactions. Lancet 2000;355:134–138.
97 Ernst E: Possible interactions between synthetic and herbal medicinal products. Part 1: A systematic review of the indirect evidence. Perfusion 2000;13: 4–15.
98 Ernst E: Possible interactions between synthetic and herbal medicinal products. Part 2: A systematic review of the direct evidence. Perfusion 2000;13: 60–70.