Abstract

**Background:** Complementary therapies are widespread but controversial. We aim to provide a comprehensive collection and a summary of systematic reviews of clinical trials in three major complementary therapies (acupuncture, herbal medicine, homeopathy). This article is dealing with herbal medicine. 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 pre-tested form and summarized descriptively.

**Results:** From a total of 79 potentially relevant reviews pre-selected in the screening process 58 met the inclusion criteria. Thirty 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 practised by specialist herbalists who combine herbs and use unconventional diagnosis.

Introduction

In this second part of our series on systematic reviews in complementary therapies we report our findings on herbal medicines. 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
A detailed description of the methods used in this review of reviews is given in the first part of this series [6]. For searches in Medline 50 single plant names and the 'exploded' term 'medicinal plants' were combined with the standard search strategy for systematic reviews. As a specific intervention-related inclusion criterion we required that reports reviewed 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. Disease-oriented reviews including a variety of interventions were included only if they reviewed at least 4 herbal medicine trials.

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 preventive or therapeutic use [89], two 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 five reviews dealing with dementia and cerebral insufficiency (total number of trials included about 50) all drew positive conclusions [15–17]. 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, one 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 nine 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 randomised 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 two reviews. For saw palmetto there is good evidence for efficacy over placebo while for the other three the data are inconclusive (see table 3).
Table 1: Systematic reviews of clinical trials of ginkgo biloba extracts

| Author Year | Indication           | Intervention       | Comparisons       | Studies | Features 1/2/3/4/5 | Results                                                                 | Author’s Conclusion                                                                 |
|-------------|----------------------|--------------------|-------------------|---------|---------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Pittler 2000 | intermittent claudication | ginkgo placebo     | 8 RCT             | y/y/y/y | Increase of pain-free walking distance over placebo after 12 or 24 weeks 34 m (95%CI 26–43 m) | Evidence for a modest benefit of uncertain clinical relevance                       |
| Moher 2000  | intermittent claudication | ginkgo placebo     | 5 RCT             | y/y/y/n/y | Increase of pain-free walking distance over placebo after 24 weeks 32 m (95%CI 14–50 m) | Inconsistent results from the few available small studies do not allow firm conclusions Available evidence promising but further high quality research needed. |
| Ernst 96    | intermittent claudication | ginkgo extract EGB761 | 10 RCT/CCT         | pl/pl/n/y | Most studies low quality. Increase of walking distance compared to placebo 24 to 160 m. At least similar effectiveness compared to other drugs. |                                                                                      |
| Schneider 92 | intermittent claudication | ginkgo placebo, other treatment | 7 RCT/CCT (vs. plac.), 2 RCT/CCT (other) | ?/n/n/y | mean effect size d = 0.75 (95%CI 0.44–1.07) over placebo | Effectiveness over placebo clearly shown                                          |
| Letzel 92   | intermittent claudication | ginkgo extract EGB761 ginkgo vs. plac., pentoxifyllin vs. plac., ginkgo extract EGB761 ginkgo vs. plac., placebo | 5 RCT | ?/p/n/y | Pooled increase of walking distance: 45% over placebo for ginkgo and 57% for pentoxifyllin | Ginkgo extract EGB761 more effective than placebo and similarly effective as pentoxifyllin |
| Kleijnen 91 | intermittent claudication | ginkgo extract EGB761 ginkgo vs. plac., pentoxifyllin vs. plac., ginkgo extract EGB761 ginkgo vs. plac., placebo | 15 RCT/CCT | y/y/y/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 91    | cerebral insufficiency | ginkgo placebo     | 17RCT/CCT         | ?/p/p/p | 10 of 12 interpretable trials on cerebral insufficiency and all 4 interpretable trials on intermittent claudication with significant positive results | Effectiveness for both conditions biometrically shown                               |
| Ernst 99    | dementia              | ginkgo placebo     | 9 RCT             | y/y/y   | Results collectively suggest that ginkgo is more effective for dementia than placebo | Encouraging findings warranting large scale trials                                |
| Oken 98     | Alzheimer dementia   | ginkgo placebo     | 4 RCT             | y/y/n/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 Ginkgo extract superior to placebo |
| Hopfenmuller 94 | cerebral insufficiency | ginkgo placebo     | 10 RCT, 1 CCT     | n/n/n   | Global response (based on symptom scores): OR 1.98 (95%CI 1.39–2.57) in favour of Ginkgo |                                                                                      |
| Kleijnen 92 | cerebral insufficiency | ginkgo vs. plac.   | 40 RCT/CCT         | y/y/y/n | Many trials low quality. Virtually all trials reported positive | Ginkgo seems effective for cerebral insufficiency but further |
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 officinalis) [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).

Table 1: Systematic reviews of clinical trials of ginkgo biloba extracts (Continued)

| Year | Indication | Intervention | Comparisons | Studies | Results | Author’s Conclusion |
|------|------------|--------------|-------------|---------|---------|---------------------|
| Ernst 99 [18] | tinnitus | ginkgo vs. placebo | RCT/CCT hydergine (ginkgo), 4 5 RCT | y/y/y/3 trials favour ginkgo over hydergine placebo, 1 no difference, in one treatment (1 trial) | Results suggest that extracts of ginkgo biloba are effective in treating tinnitus |
| Evans 2000 [19] | macular degeneration | ginkgo placebo | 1 RCT | y/y/y/- | Insufficient evidence to recommend ginkgo for age-related macular degeneration |

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.

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

| Author Year | Indication | Intervention | Comparisons | Studies | Features | Results | Author’s Conclusion |
|-------------|------------|--------------|-------------|---------|----------|---------|---------------------|
| St John’s wort (Hypericum perforatum) | depression | hypericum | placebo and antidepressants | 8 RCT | p/y/p/ y/n | 4 placebo-controlled trials with positive results, in 4 trials standard antidepressant; tended to be slightly better 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, insufficient evidence re equivalence with antidepressants |
| Williams 2000 & [20,21] | depression (and other drugs) | hypericum | placebo and antidepressants | 14 RCT | y/y/n/ y/y | Treatment response: RR 1.98 (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 |
| Mulrow 98 [22] | depression | hypericum | placebo and antidepressants | 6 RCT | p/y/y/ y/y | Treatment response: RR 1.48 (95% CI 1.12–2.89) vs. placebo and 1.2 (1.0–1.4) vs. antidepressants | Data suggest that hypericum is superior to placebo, insufficient evidence re equivalence with antidepressants |
| Kim 99 [23] | depression | hypericum | placebo and antidepressants | 1 RCT | y/y/ | Treatment response: RR 1.98 (95% CI 1.03–1.92) vs. placebo and 0.98 (0.67–1.28) vs. antidepressants | Data suggest that hypericum is superior to placebo, insufficient evidence re equivalence with antidepressants |

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 review on all pharmacologic treatments for the respective condition RCT = randomized controlled trials, CCT = non-randomized controlled trials, CS = cohort studies, UCS = uncontrolled studies; OR = odds ratio, RR = rate ratio
Stevinson depression hypericum placebo and antidepressants 6 RCT y/y/y/ Only trials published after Linde 96; trials show effects better than placebo/similar to antidepressants Data confirm findings of earlier trials, but still insuff. evidence to assess equivalence with antidepressants Hypericum more effective than placebo. Inadequate evidence to assess equivalence with antidepressants

Linde 98 & depression hypericum placebo and antidepressants 27 RCT y/y/y/ Treatment response: RR 2.47 Linde 98 & depression hypericum placebo and antidepressants 27 RCT y/y/y/ Treatment response: RR 2.47

96 [25,26] antidepressants y/y (95% CI 1.16–3.61) vs. placebo and 1.01 (0.87–1.16) vs. antidepressants

Volz 97 depression hypericum placebo and 15 RCT p/p/n/ Most placebo-controlled trials A therapy with hypericum of mild and moderate depression can be attempted. Further studies needed

[27] antidepressants RCT/ CCT n/n positive; similarly effective as (not adequately dosed) antidepressants

Ernst 95 depression hypericum placebo and 11 RCT y/y/y/ Most of 8 placebo-controlled Hypericum is superior to placebo and seems equally effective as standard medication

Volz 2000 mild to moderate depression fluoxetine 17+9 CCT n/y/y/ y/n No direct comparison of hypericum and fluoxetine available. Mean depression score (HAM-D) reduction in hypericum trials 53%, in fluoxetine trials 55%

Friede 98 anxiety in depression hypericum placebo, amitriptyline 8 RCT ?/y/y/ Trials collectively show reduction of anxiety symptoms over placebo. Only 1 trial vs amitriptyline Hypericum is effective for depressed patients with anxiety

Table 2: Systematic reviews of clinical trials of hypericum and garlic preparations (Continued)

| Author          | Clinical Condition | Treatment | Placebo | Number of Trials | Outcome | Notes |
|-----------------|--------------------|-----------|---------|------------------|---------|-------|
| Stevinson       | hypercholesterolemia | garlic | placebo | 13 RCT           | y/y/y/ | Pooled total cholesterol 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. Meta-analysis suggests positive effects but reviewers are sceptic (low quality; own replication negative). |
| Lawrence        | cardiovasc. risk factors | garlic | mainly placebo; no other treatment | 45 RCT | 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. |
| Neil 96         | cholesterol lowering | garlic | placebo | 16 RCT           | y/p/y/ | Pooled cholesterol reduction over placebo 0.65 (95% CI 0.53–0.76) mmol/l. |
| Silagy 94       | cholesterol lowering | garlic | placebo | 5 RCT            | y/y/y/ | Pooled cholesterol reduction over placebo 0.59 (95% CI 0.44–0.74) mmol/l. |
| Silagy 94       | cholesterol lowering | dried garlic | placebo, other | 8 RCT | y/p/y/ | Pooled reduction over placebo: |
|                  |                    |          |         |                  |         |       |
Table 2: Systematic reviews of clinical trials of hypericum and garlic preparations (Continued)

| Author/Surname | Year | Indication | Intervention | Comparisons | Studies | Features | Results | Author’s Conclusion |
|----------------|------|------------|--------------|-------------|---------|----------|---------|---------------------|
| Kleijnen/1991  | 91   | cardiovasc. risk factors | garlic supplements | placebo | 18 RCT/CCT | y/p/y/y/n | SBP 7.7 (95% Cl 4.3–11.0), DBP 5.0 (2.9–7.1) mm Hg | Further research needed |
| Kleijnen/1989  | 89   | cardiovasc. garlic & | unclear | | 10 RCT, 8 CCT | y/p/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/1997   | 97   | lower limb athero-scler. | garlic | placebo | 1 RCT | y/y/y/ | Walking distance not significantly different between groups | Insufficient evidence |

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

| Author/Surname | Year | Indication | Intervention | Comparisons | Studies | Features | Results | Author’s Conclusion |
|----------------|------|------------|--------------|-------------|---------|----------|---------|---------------------|
| **Echinacea (Echinacea purpurea, angustifolia and pallida)** | | | | | | | | |
| Barrett        | 99   | upper resp. infections (incl. combinations) | echinacea | 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       | 99   | common (incl. combinations) | echinacea | placebo, no | 16 RCT | y/y/y | Minor effects in prevention and treatment, promising effects in early treatment. Heterogenous preparations | Echinacea extract can be efficacious for the common cold, but evidence insufficient for recommendations |
| Melchart       | 94   | immuno-stimulation (incl. combinations) | echinacea | placebo, no | 18 RCT, 8 CCT | y/y/y | Most studies low quality. Most studies show immunostimulating effects | Echinacea extracts can be efficacious immunostimulators, but evidence insufficient for recommendations |
| [42,43]        |      |            |              |             |         |          |         |                |
| **Cranberries (Vaccinium macrocarpon)** | | | | | | | | |
| Jepson         | 98   | urinary tract inf. (prevent) | 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         | 98   | urinary tract inf. (treatm.) | cranberries | O RCT | y/y/- | No trials meeting the inclusion criteria | No evidence available |
| **Mistletoe (Viscum album)** | | | | | | | | |
| Kleijnen       | 98   | cancer | mistletoe | placebo, no | 11 | y/y/y/y | Most studies low quality. Most | Insufficient evidence to recommend |
Table 3: Systematic reviews of clinical trials of herbal medicines (at least 2 reviews per herb) (Continued)

|    | Treatment | N/NT | RCT/CCT | Outcome | Notes |
|----|-----------|------|---------|---------|-------|
| 94 | [46]      |      |         | Studies show longer survival with mistletoe but not the best trial |       |
| Kiene 89 | cancer | mistletoe | no treatment, none | 2 RCT, 33 CCT, 11 other studies | y/n/n/ Available evidence supports positive effects of mistletoe |
| [47,48] | | | | | |

**Peppermint (Mentha piperita)**

|     | Treatment | N/NT | RCT/CCT | Outcome | Notes |
|-----|-----------|------|---------|---------|-------|
| Jailwala | irritable bowel | peppermint oil, placebo | 1. 3 RCT | y/y/y/ Chinese herbal therapy trial rated as positive, one of three | In both cases efficacy not clearly established |
| 2000 | | | 2. 1 RCT | | |
| [49] | syndr. | Chinese herbal therapy peppermint oil, placebo | | | |
| Pittler 98 | irritable bowel syndr. | peppermint oil, placebo, other treatment | 8 RCT | y/y/y/y | The role of peppermint oil for IBS has not been established beyond reasonable doubt |
| [50] | | | | | |

**Saw palmetto (Serenoa repens)**

|     | Treatment | N/NT | RCT/CCT | Outcome | Notes |
|-----|-----------|------|---------|---------|-------|
| Boyle 2000 | ben. | Permixon®, placebo | 11 RCTS, 2 UCS | 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 |
| [51] | prostate | | | | |
| Wilt 2000 &98 | hyperplasia ben. | saw palmetto, placebo, other treatment | 14 RCT (plac.), | 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. |
| [52,53] | prostate | | | | |

Legend see Table 1
Table 4: Systematic reviews of clinical trials of herbal medicines

| Author Year | Indication | Intervention       | Comparisons | Studies | Features 1/2/3/4/5 | Results                                      | Author’s Conclusion                  |
|-------------|------------|--------------------|-------------|---------|---------------------|---------------------------------------------|---------------------------------------|
| Vogler 99 [54] | various    | aloe placebo, other & no treatment | 6 RCT, 4 CCT | y/y/y | Positive results for genital herpes, psoriasis, hyper-lipidemia, diabetes; contradictory for wound healing | Promising results, but overall evidence insufficient |
| Pittler 98 [55] | cholesterol lowering | artichoke leaf extract placebo | 1 RCT | y/y/y | Effects over placebo only in the subgroup of participants with serum cholesterol > 210 mg/dl | More trials needed |
| Morse 89 [56] | atopic     | evening placebo    | 9          | n/n    | Epogam significantly better than placebo for most outcomes | No conclusion drawn |
| Vogler 98 [57] | migraine   | feverfew placebo   | 6 RCT/ CCT  | y/y/y | Majority of trials favor feverfew | Effectiveness has not been established beyond reasonable doubt |
| Ernst 2000 [58] | nausea and vomiting | ginger root placebo, metoclopramide | 2 of 3 trials on postoperative nausea positive (best negative), trials on seasickness, morning sickness and chemotherapy-induced nausea positive | to draw firm conclusions |
| Vogler 99 [59] | various    | ginseng root extract placebo, other treatment (1 trial) | 16 RCT | y/p/y | Contradictory results re. physical performance (7 trials), psychological function (5), immunomodulation (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 98 [60] | venous     | horse placebo, other treatment | 13 RCT | y/y/y | Significant effects over placebo and similar effects compared to other treatments (confirmation, long-term results, combination) | horse chestnut seeds seem to be effective; further trials needed |
| Pittler 2000 [61] | anxiety    | kava placebo       | 7 RCT | y/y/y | All trials suggest superiority | Available data suggest that kava is a treatment option for anxiety. Further studies needed |
| Lawrence 2000 [62] | liver      | milk thistle placebo, other & no treatment | 33 RCT, 1 CCT | y/y/y | Variety of conditions studied, studies often poor quality. | Efficacy is not established. Possible benefit shown most frequently for aminotransferases. The data suggest that the |
| Ernst 99 [63] | musculoskeletal pain | Phytodoler® populus, fraxinus, solidago rye grass placebo, other treatments | 10 RCT | y/p/y | Mixed and inconsistent findings Placebo-controlled trials show superiority over placebo and similar effects as NSAIDs | Combination is effective in the symptomatic treatment of musculoskeletal pain Available evidence suggests that |
| MacDonald | benign prostate | placebo, other | 4 RCT | y/y/y | Signif. improvement over | | |
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, diarrhoea, 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 (E. 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 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].

In conclusion, the systematic reviews collected for this analysis are a good tool to get an overview of the available evidence from clinical trials in the area of herbal medicine. However, applying the findings to patients care is problematic for those who are not experts in herbal medicine. In this case it might be better to directly search the literature for clinical trials of the respective product.

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

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References
1. Vickers A, Zollman CE: A B C of complementary medicine: herbal medicine BMJ 1999, 319:1050-1053
2. Schwabe U: Arzneimittel der besonderen Therapierichtungen (Naturheilmittel) In Arzneiverordnungs-Report 1998. Edited by Schwabe U, Paffrath D. Berlin: Springer, 1999:621-656
3. Brevooort P: The booming US botanical market. A new overview HerbaIGram 1998, 44:33-51
4. Barnes J: Phytotherapy: consumer and pharmacist perspectives In: Herbal medicine – a concise overview for professionals. Edited by Ernst E. Oxford: Butterworth Heinemann, 2000:19-33
5. Bodeker GC: Editorial J Altem Complement Med 1996, 3:323-326
6. Linde K, Vickers A, Hondras M, et al: Systematic reviews of complementary therapies – an annotated bibliography. Part I: acupuncture BMC Complementary and Alternative Medicine. 2001, 1:3
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 Claudiciation intermittens Fortschr Med 1996, 114:85-87
10. Schneider B: Ginkgo-biloba-Extrakt bei peripheren arteriellen Verschlusskrankheiten. Meta Analyse von kontrollierten klinischen Studien Arzneim-Forsch /Drug Res 1992, 42(1):428-436
11. Letzel H, Schoop W: Ginkgo-biloba-Extrakt EGB 761 und Pentoxifyllin bei Claudiciation intermittens. Sekundäranalyse zur klinischen Wirksamkeit VASA 1992, 21:403-410
12. Kleijnen J, Knipschild P: Ginkgo biloba für intermittierendes Claudicatio and cerebral insufficiency In: Kleijnen J. Food supplements and their efficacy. Maastricht: Rijksuniversiteit Limburg, 1991:83-94
13. Weiss G, Kallischm G: Ginkgo-biloba-Extrakt (EGB 761) – Meta-Analyse von Studien zum Nachweis der therapeutischen Wirksamkeit bei Hirnleistungssorgungen bzw. peripherer arterieller Verschlusskrankheit Muench med Wschr 1991, 101:138-142
14. Ernst E, Pittler MH: Ginkgo biloba for dementia: a systematic review of double-blind, placebo- controlled trials Clin Drug In vest 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. Hopfenmuller W: Nachweis der therapeutischen Wirksamkeit eines Ginkgo biloba-Spezialextraktes – Meta-Analyse von 11 klinischen Studien mit Patienten mit Hirnleistungssorgungen im Alter Arzneim-Forsch /Drug Res 1994, 44(II):1005-1013
17. Kleijnen J, Knipschild P: Ginkgo biloba for cerebral insufficiency Br J din Pharmacol 1992, 34:352-358
18. Ernst E, Stevinson C: Ginkgo biloba for tinnitus: a review Clin Otolaryngol 1999, 24:164-167
71. Ernst E, Chrubasik S: Phyto-anti-inflammatories: a systematic review of randomized, placebo-controlled, double-blind trials. J Altern Complement Med 2000, 6:13-27
72. Budeiri D, Li Wan Po A, Dorman JC: Is Evening Primrose Oil of value in the treatment of premenstrual syndrome? Controlled 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: an herbal remedy for depression? Canadian Family Physician 1997, 43:1735-1736
75. Giles J, 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? Intern J Clin Pharmacol Ther 1999, 37:111-119
77. Kleijnen J, ter Riet G, Knipschild P: 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. Weilmayr T, Ernst E: Die therapeutische Wirksamkeit von Crataegus. Fortschr Med 1996, 114:27-29
81. Wettstein A: Does evening primrose oil contain gamma-linolenic acid? A systematic review. Phytomed 1999, 6:93-101
82. Wong AHC, Smith M, Doan 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 1, 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, Tramèr 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? Phytomed 1997, 4:79-83
90. Joy CB, Mumby-Croft R, Joy LA: Polysaturated fatty acids (fish or evening primrose oil) for schizophrenia (Cochrane Review). In: The Cochrane Library, Issue 2, 2000. Oxford: Update Software.
91. Steenov C, 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 Safety 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

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