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Research article

Systematic reviews of complementary therapies – an annotated bibliography. Part 2: Herbal medicine

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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 preventative 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 dealed 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 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, 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 variaton 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
Ginkgo (*Ginkgo biloba*)							
Pittler 2000 [7]	intermittent claudication	ginkgo	placebo	8 RCT	y/y/y/ y/y	Increase of pain-free walking distance over placebo after 12or 24 weeks 34 m (95%CI 26–43 m)	Evidence for a modest benefit of uncertain clinical relevance
Moher 2000 [8]	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
Ernst 96 [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 92 [10]	intermittent claudication	ginkgo	placebo, other treatment	7 RCT/CCT (vs. plac.), 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 92 [11]	intermitent claudication	ginkgo extract EGb 761	ginkgo vs. plac., pentoxifyllin vs. plac.	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 91 [12]	intermittent claudication	ginkgo	ginkgo vs. plac., pentoxifyllin vs placebo	15 RCT/CCT (ginkgo), 5 RCT/CCT pentoxif.	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 91 [13]	cerebral ins., intermittent claudication	ginkgo extract EGb761	placebo	17RCT/ CCT (cerebral ins.), 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 99 [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 98 [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 94 [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%CI1.39–2.57) in favour of Ginkgo	Ginkgo extract superior to placebo
Kleijnen 92 [17]	cerebral insufficiency	ginkgo	ginkgo vs. plac.	40 RCT/ CCT	y/y/y/ n/n	Many trials low quality. Virtually all trials reported positive	Ginkgo seems effective for cerebral insufficiency but further

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

			hydergine	(ginkgo), 4		results. Evidence similar as for	high quality studies are needed
			vs. plac.	RCT/CCT (hydergine)		hydergine	
Ernst 99 [18]	tinnitus	ginkgo	placebo,	5 RCT	y/y/y/	3 trials favour ginkgo over	Results suggest that extracts of
			other		y/n	placebo, 1 no difference, in one	ginkgo biloba are effective in
			treatment (1 trial)			trial ginkgo better than another treatment	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

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

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 (*Valehana 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.

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

Author Year	Indication	Intervention	Comparisons	Studies	Features 1/2/3/ 4/5	Results	Author's 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	Data suggest that hypericum is superior to placebo, insuffcient
						standard antidepr. tended to be slightly better	evidence re equivalence with antidepressants
Williams 2000 & Mulrow 98 [21,22]	depression	hypericum (and other drugs)	placebo and antidepressants	14 RCT	y/y/n/ y/y	Treatment response: RR 1.9 (95%C11.2–2.8) 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 99 [23]	depression	hypericum	placebo and antidepressants	6 RCT	p/y/y/ y/y	Treatment response: RR 1.48 (95%C11.03–1.92) 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

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

Stevinson 99 [24]	depression	hypericum	placebo and antidepressants	6 RCT	y/y/y/ y/n	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
Linde 98 & 96 [25,26]	depression	hypericum	placebo and antidepressants	27 RCT	y/y/y/ y/y	Treatment response: RR 2.47 (95%CI1.69–3.61) vs. placebo and 1.01 (0.87–1.16) vs. antidepressants	Hypericum more effective than placebo. Inadequate evidence to assess equivalence with antidepressants
Volz 97 [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 95 [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 2000 [29]	mild to mod. 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 98 [30]	anxiety in depressed p.	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
Garlic (*Allium sativum*)							
Lawrence 2000 [31]	cardiovasc. risk factors	garlic	mainly placebo; no & 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 fibrionolytic activity	Insufficient data to draw conclusion regarding clinical cardiovascular outcomes. Garlic preparations may have small, positive, short-term effects on lipids
Stevinson 2000 [32]	hypercholesterolemia	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 hyperchol. is therefore of questionable value
Silagy 94 & Neil 96 [33,34]	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 93 [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 94	lowering	dried garlic	placebo, other	8 RCT	y/p/y/	Pooled reduction over placebo:	Garlic maybe of some clinical use

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

[36]	blood press.	(Kwai)	treatment		y/y	SBP 7.7 (95% CI 4.3–11.0), DBP 5.0 (2.9–7.1) mm Hg	in subjects with mild hypertension. Further research needed
Kleijnen 91 [37]	cardiovasc. risk factors	garlic supplements	placebo	18 RCT/ CCT	p/p/y/ y/n	Most studies with shortcomings. The majority of trials with pos. results but inconsistent effect sizes	No clear conclusion drawn
Kleijnen 89 [38]	cardiovasc. risk factors	garlic & onions	unclear	10 RCT, 8 CCT	y/p/n/ y/n	All trials with severe shortcomings. Fresh garlic with beneficial effcts, onions and commercially available supplements yielded contradictory results	Inadequate evidence to justify supplementation, further research needed
Jepson 97 [39]	lower limb athero-scler.	garlic	placebo	1 RCT	y/y/y/ y/-	Walking distance not significantly different between groups	Insufficient evidence

legend see table 1

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

Author Year	Indication	Intervention	Comparisons	Studies	Features 1/2/3/ 4/5	Results	Author's Conclusion
Echinacea (*Echinacea purpurea, angustifolia and pallida*)							
Barrett 99 [40]	upper resp. infections	echinacea (incl. combinations)	placebo	13RCT	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 [41]	common cold	echinacea (incl. combinations)	placebo, no treatment	16 RCT	y/y/y/ y/p	Minor effects in prevention and treatment, promising effects in early treatment. Heterogen. preparations	Echinacea extract can be efficacious for the common cold, but evidence insufficient for recommendations
Melchart 94 [42,43]	immuno-stimulation	echinacea (incl. combinations)	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 98 [44]	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 [45]	urinary tract inf. (treatm.)	cranberries		O RCT	y/y/-/ -/-	No trials meeting the inclusion criteria	No evidence available
Mistletoe (*Viscum album*)							
Kleijnen	cancer	mistletoe	placebo, no	11	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)*

94 [46]			treatment	RCT/ CCT	n/n	studies show longer survival with mistletoe but not the best trial	mistletoe outside of clinical trials
Kiene 89 [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 2000* [49]	irritable bowel syndr.	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 98 [50]	irritable bowel syndr.	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 IBS has not been established beyond reasonable doubt
Saw palmetto (*Serenoa repens*)							
Boyle 2000 [51]	ben. prostate hyperplasia	Permixon® (saw palmetto)	placebo, other treatment	11 RCTs, 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 2000 &98 [52,53]	ben. prostate hyperplasia	saw palmetto	placebo, other treatment	14 RCT (plac), 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

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

Table 4: Systematic reviews of clinical trials of herbal medicines *(Continued)*

2000 & Wilt 2000 [64,65]	hyperplasia	pollen extract	therapy		y/y	placebo in subjective, but not objective symptoms; no differences compared to tadenan and paraprost	Cernilton® is well tolerated and modestly improves subjective symptoms. Further studies needed
Ernst 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 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 84 [68]	breast engorgement	cabbage leaves	usual care	1 RCT	y/y/n/ y/n	fewer women stopping breast feeding among those receiving cabbage leaves	Further research desirable
Armstrong 99 [69]	atopic eczema	Chinese herbal therapy	placebo	2 RCT	y/y/n/ *y/n*	2 positive studies by the same treat analysis	Evidence encouraging but insufficient given the potential of relevant side effects
Ernst 97 [70]	hypoglyc. 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 hypoglcemic plant remedies not supported by rigorous research. Further studies required
Ernst 2000 [71]	analgetic or inflamm. 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

legend see table 1

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 particluar 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: **ABC 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,* 1999621-656
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: Herbal medicine – a concise overview for professionals. Edited by Ernst E. Oxford: Butterworth Heinemann,* 200019-33
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 1: 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 Claudicatio 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: **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. Food supplements and their efficacy. Maastricht: Rijksuniversiteit Limburg,* 199183-94
13. Weiss G, Kallischnigg G: **Gingko-biloba-Extrakt (EGb 761) – Meta-Analyse von Studien zum Nachweis der therapeutischen Wirksamkeit bei Hirnleistungsstorungen bzw. peripherer arterieller Verschlusskrankheit** *Muench med Wschr* 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. Hopfenmuller W: **Nachweis der therapeutischen Wirksamkeit eines Ginkgo biloba-Spezialextraktes – Meta-Analyse von 11 klinischen Studien mit Patienten mit Hirnleistungsstörungen im Alter** *Arzneim-Forsch /Drug Res* 1994, **44(II)**:1005-1013
17. Kleijnen J, Knipschild P: **Gingko 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

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 Int 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** *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** *Pharmacopsychiat* 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** *Comprehensive Psychiatry* 2000, **41 (suppl 1)**:133-137
30. Friede M, Wüstenberg P: **Johanniskraut zur Therapie von Angstsyndromen bei depressiven Verstimmungen** *Ztschr 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 [http://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 Roy Coll Phys* 1994, **28**:39-45
34. Neil HAW, Silagy CA, Lancaster , *et al*: **Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis** *J Roy Coll Pract London* 1996, **30**:329-334
35. Warshafsky S, Kamer RS, Sivak SL: **Effect of garlic on total serum cholesterol** *Ann Int Med* 1993, **119**:599-605
36. Silagy CA, Neil HA: **A meta-analysis of the effect of garlic on blood pressure** *J Hypertension* 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,* 199173-82
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 Arzneimittein – 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** *Herdecke: Dissertation,* 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.* [http://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** *Natural Medicine Journal* 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** *Medicine* 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 America* 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?** *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 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?** *Intern J Clin Pharmacol Ther* 1999, **37**:111-119
77. Kleijnen J, ter Riet G, Knipschild P: **Teunisbloemolie. Een overzichtvan 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** *Phytomed* 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 quantiative 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: **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 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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