Rheumatology 2001;40:779–793

Herbal medicines for the treatment of osteoarthritis: a systematic review

L. Long, K. Soeken[1] and E. Ernst

Department of Complementary Medicine, School of Postgraduate Medicine and Health Studies, University of Exeter, 25 Victoria Park Road, Exeter EX2 4NT, UK and [1]University of Maryland School of Medicine, Complementary Medicine Program, Kernan Hospital Mansion, 2200 Kernan Drive, Baltimore, MD 21207-6697, USA

Abstract

Objective. Limitations in the conventional medical management of osteoarthritis indicate a real need for safe and effective treatment of osteoarthritis patients. Herbal medicines may provide a solution to this problem. The aim of this article was to review systematically all randomized controlled trials on the effectiveness of herbal medicines in the treatment of osteoarthritis.

Methods. Computerized literature searches were carried out on five electronic databases. Trial data were extracted in a standardized, predefined manner and assessed independently.

Results. Twelve trials and two systematic reviews fulfilled the inclusion criteria. The authors found promising evidence for the effective use of some herbal preparations in the treatment of osteoarthritis. In addition, evidence suggesting that some herbal preparations reduce consumption of non-steroidal anti-inflammatory drugs was found. The reviewed herbal medicines appear relatively safe.

Conclusions. Some herbal medicines may offer a much-needed alternative for patients with osteoarthritis.

KEY WORDS: Osteoarthritis, Degenerative joint disease, Herbal medicine, Phytomedicine.

Osteoarthritis (OA) is a progressive rheumatic disease characterized by the degeneration of articular cartilage. It is the most common of all rheumatic disorders and is destined to become one of the most prevalent and costly diseases in our society [1].

Therapeutic interventions conventionally employed for OA include the use of physiotherapy and antidepressant therapies, patient education [2] and weight control. In addition, drug therapy includes non-opioid analgesics such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), topical analgesics, opioid analgesics and intra-articular steroid injection. Such treatments may prove ineffective in some patients and NSAIDS often have serious adverse effects [3, 4]. Gastrointestinal complications are frequently reported with NSAIDs, with 12 000 hospitalizations and about 2000 deaths attributed to NSAID use in the UK every year [1, 3–6]. Hence there appears to be a need for drugs with good efficacy and low toxicity in the treatment of OA. Specifically, there is a need for safe and effective drugs for patients who do not respond well to conventional medical therapy. Such patients are turning increasingly to complementary/alternative medicines (CAM).

Submitted 25 September 2000; revised version accepted 31 January 2001.

Corresponding author: L. Long.

The use of CAM by sufferers of rheumatic diseases is highly prevalent and increasing. Arthritis is the sixth most frequently cited health problem treated with CAM in the USA [7]. Individuals who use CAM regularly are more likely to have OA and severe pain [8]. Patients suffering from musculoskeletal problems are likely to be users of herbal treatments [9]. It is therefore important to determine the effectiveness and safety of herbal medicines in the treatment of OA.

The objective of this systematic review is to evaluate the existing evidence from randomized controlled trials (RCTs) of herbal medicines and plant extracts for OA that are either taken orally or applied topically.

Methods

Identification of clinical trials

Systematic literature searches were performed to identify all RCTs of herbal medicines for OA. Computer databases used were Medline, Embase, Biosis, CINAHL and the Cochrane Library (all from their respective inception to May 2000). The search terms used were 'osteoarthritis', 'osteoarthrosis', 'degenerative joint disease', 'degenerative arthritis', 'degenerative arthrosis', 'gonarthrosis' and 'coxarthrosis'. Herbal search terms used were 'botanic', 'phyto', 'herb' and all their derivatives, together with individual plant and

herb names. A manual search for additional trials was performed using the bibliographies of studies and reviews located through the electronic searches and by scanning our own files. In addition, 11 experts and 15 manufacturers in the field were contacted to provide published and unpublished material.

All potential articles (or abstracts if only available as abstracts) were read in full and, if additional information was required, authors were contacted wherever possible.

Inclusion/exclusion criteria

There were no restrictions regarding language or age group in this systematic review. Studies were limited to RCTs of patients with OA. RCTs with any type of objective and/or subjective parameters were considered. Comparative studies of one herbal treatment measured against another active drug were included, as were relevant systematic reviews. Parenterally applied herbal preparations were excluded [10]. Studies focusing exclusively on back pain and osteoarthritic conditions of the spine, including cervical spondylosis, were excluded. Animal studies were excluded, as were trials that were lacking in essential methodological detail, such as dosage descriptions [11]. Trials that did not include baseline data and clinical end-points were also excluded [12]. All articles were read by two reviewers and any disagreements were resolved through discussion.

Data extraction and quality assessment

Data relating to demographic patient information, interventions, outcomes, results, treatment duration, documentation of power calculation and inclusion/exclusion criteria and the assessment of concomitant medications and compliance were extracted by the first author into predefined tables (Tables 1 and 2) and validated by the other authors. Data relating to adverse effects were extracted into Table 3 and validated by the last author.

Methodological quality was assessed using the standard scoring system developed and validated by Jadad *et al.* [13], with items on random allocation, double-blinding and description of dropouts and withdrawals.

Results

Twelve trials and two systematic reviews fulfilled the above criteria and were included. Key data are summarized in Tables 1, 2 and 3.

Articulin-F

A crossover RCT to test the clinical effectiveness of Articulin-F, an Ayurvedic herbomineral formulation containing *Withania somnifera* root (450 mg), *Boswellia serrata* oleo-gum resin (100 mg), *Curcoma longa* rhizome (50 mg) and zinc (50 mg) in the treatment of OA was performed by Kulkarni *et al.* [14]. The study was double-blind, with a mixed sample of 42 patients attending a rheumatology out-patient clinic who showed symptoms of OA. They were randomly assigned to receive either two capsules of herbomineral formulation or identical placebo capsules 8 h after food. Each treatment was given for a period of 3 months and then (after a washout period of 2 weeks) the patients were transferred to the other treatment for a further 3 months. Treatment with the herbomineral formulation significantly improved the severity of pain ($P < 0.001$) and disability score ($P < 0.05$). Other parameters, including morning stiffness, Ritchie articular index, grip strength and joint score, showed favourable non-significant trends.

Avocado/soybean unsaponifiables

Extract of avocado and soya bean, termed avocado/soybean unsaponifiables (ASU), is made of unsaponifiable fractions of avocado oil and soya bean oil. Preclinical studies suggest that a 1:3 to 2:3 ASU mixture may be active in OA.

In 1997, Blotman *et al.* [15] conducted a 3-month double-blind, placebo-controlled, parallel-group RCT in a mixed group of out-patients suffering from either hip or knee OA. Thirty-five rheumatologists evaluated the effectiveness of ASU in reducing NSAID consumption. Patients were assigned randomly to take either one capsule of 300 mg ASU or one indistinguishable placebo capsule daily for 3 months. All patients took one of seven predefined NSAIDs during the first 45 days of the trial and were permitted to resume the same treatment, if needed, during the second half of the trial. Effectiveness was measured primarily by the proportion of patients resuming NSAID consumption and the delay before reintake. In the second half of the study (day 45 to day 90), the proportion of patients resuming NSAID therapy and the time spent off the NSAID drug each showed a significant difference in favour of the ASU treatment. Observed reductions in NSAID intake in the treatment group were supported by secondary outcome measures. Patients' overall ratings were significantly better in the experimental group ($P < 0.01$) and so were improvements in the functional index ($P < 0.01$). Changes in pain [measured on a visual analogue scale (VAS)] over time were similar in the two groups. Improvements were more evident with hip OA than knee OA.

Maheu *et al.* [16] randomly assigned a mixed sample of 164 patients diagnosed with OA of the knee or hip into two groups receiving either a daily capsule of ASU (300 mg) or a placebo capsule in a 6-month trial. After a 25-day washout period, analgesic or NSAID intake (from a predefined list) was allowed if judged necessary. Effectiveness was measured primarily according to Lequesne's functional index (LFI). Secondary outcome measures included assessment of pain and functional disability, as scored on a 100-mm VAS, and NSAID/analgesic intake. At the end of the trial, the patients' and physicians' overall assessments were scored on a 5-point verbal scale. Intergroup comparisons of changes

between baseline and month 6 values for LFI, pain (VAS), functional disability (VAS) and patient's and physician's overall assessments significantly favoured the ASU group. Improvements appeared to be better in patients with hip OA rather than knee OA. Fewer patients in the ASU group required NSAIDs ($P = 0.054$), suggesting that ASU may help to reduce NSAID consumption in patients with OA.

Capsaicin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is derived from hot chilli peppers. It is used as a topical analgesic for a variety of conditions characterized by pain. A meta-analysis of three double-blind, placebo-controlled RCTs [17–19] (192 capsaicin patients, 190 controls) for the treatment of primary OA with topically applied capsaicin has been published [20]. Trials were abstracted for response data and analysed using both a fixed effects model and a random effects model. The odds ratio (OR) of the response rate of subjects receiving topical capsaicin relative to that of the subjects on placebo was determined and used as the main outcome measure. The response rate difference (RD) was used as the response variable under the random effects model. The results in all three trials favoured capsaicin cream for improvements in pain and articular tenderness, although only one of these trials reached the usual statistically significant level ($P = 0.05$). The meta-analysis showed that capsaicin cream was better than placebo in the treatment of OA [OR = 4.36 (95% confidence interval [CI] = 2.77, 6.88); RD = 0.29 (95% CI = 0.2, 0.37)].

An additional RCT not included in this meta-analysis was located [21]. Altman *et al*. [21] performed a double-blind, parallel, vehicle-controlled, six-centre study with a mixed population of 113 patients suffering from OA of the knee, ankle, elbow, wrist or shoulder. One hundred and thirteen patients were assigned randomly to receive 0.025% capsaicin cream or vehicle cream as placebo. Cream was applied to joints four times daily for 12 weeks. At the end of 12 weeks of treatment, patients' and physicians' global (5-point scale) evaluations of pain showed that a significantly greater percentage of capsaicin-treated patients improved compared with vehicle-treated patients ($P = 0.03$), while pain severity as measured by VAS was found to be significantly decreased ($P = 0.02$). Overall, capsaicin-treated patients had significantly greater improvement in tenderness on passive range of motion (4-point scale) ($P = 0.03$) and physician palpation ($P = 0.01$) than vehicle-treated patients. A 5-point severity scale for 'today's pain' and secondary outcome measures of morning stiffness using a two-question method and a modified health assessment questionnaire showed no significant differences.

Devil's claw

Devil's claw (*Harpagophytum procumbens*) is a medicinal plant native to Africa. Its active ingredients are thought to be iridoid glycosides. Guyader [22] conducted a double-blind RCT in which 50 OA patients were given capsules containing 400 mg *Harpagophytum* extract (with an iridoid glycoside content of 1.5%) or placebo at a dosage of two capsules three times daily for 3 weeks. One month after the beginning of the treatment, the patients were assessed. Outcome was assessed with a 4-point pain intensity score based on pain at rest, on active and passive mobilization, on articular pressure, and on walking and night pain. Administration of the extract was associated with a statistically significant decrease in pain severity. Improvements were more frequent in moderate than in severe cases.

In another placebo-controlled, double-blind RCT in 89 outpatients with pain due to OA, the effectiveness of capsules containing 335 mg of powdered *Harpagophytum* with an iridoid glycoside content of 3% were assessed at a dosage of two capsules three times daily for 2 months [23]. The clinical parameters, measured on days 0, 30 and 60, were severity of pain (score) and joint mobility determined by measuring finger–floor distances. Results revealed a significant drop in pain intensity and a significant increase in spinal and coxofemoral mobility in the treated group.

Eazmov

Biswas *et al*. [24] performed a comparative RCT to determine the effectiveness of Eazmov, an Ayurvedic herbal preparation containing *Cyperus rotundus*, *Tinospora cordifolia*, *Saussurea lappa*, *Picrorrhiza kurroa* and *Zingiber officiniale*, compared with diclofenac in the treatment of a mixed sample of 60 patients with OA ($n = 31$), non-specific arthritis or rheumatoid arthritis. Patients were allocated randomly to take 1 capsule (50 mg) of either Eazmov or diclofenac three times daily after meals for 6 months. They were assessed weekly for pain severity, morning stiffness, Ritchie articular index, joint score, disability score and grip strength. The clinical efficacy of Eazmov was found to be significantly inferior to that of diclofenac regarding pain severity ($P < 0.001$) and disability scores ($P < 0.05$).

Ginger

Sixty-seven patients with OA of the hip or knee were randomized to three treatment periods of 3 weeks each in a placebo-controlled crossover study of ginger extracts and ibuprofen [25]. Either 170 mg capsules of ginger extract (Eurovita Extract 33, EV.ext-33), 400 mg ibuprofen tablets or placebo were administered three times daily. There was an initial 1-week washout period, with no washout period between the three treatments. Acetaminophen was administered as a rescue drug for pain relief during the study. VAS for pain assessment, the Lequesne index (LI) for either hip or knee, and range of motion were assessed at study entry and after each treatment period, including the initial washout period. Consumption of acetaminophen was recorded. A highly

Table 1. RCTs of herbal medicines in the treatment of OA

Reference	Jadad score	Sample size	Design	Intervention/control	Primary outcome measures	Main results
14	3	42	Double-blind, crossover, placebo-controlled	Articulin-F (an Ayurvedic herbomineral formulation)/ placebo every 8 h after food for 2 × 3 months	Severity of pain (score), morning stiffness, joint score (ARA), RI, grip strength, disability (score)	Articulin-F significantly improved pain severity and disability score
15	5	163	Double-blind, placebo-controlled, parallel-group, phase III, multicentre	ASU extract of avocado and soya (1 capsule containing 300 mg)/placebo taken daily for 3 months. Patients in both groups given a predefined NSAID during first 45 days	Daily NSAID consumption	ASU significantly reduced NSAID consumption and delayed resumption of NSAIDs after stoppage in regular NSAID users
16	4	164	Double-blind, placebo-controlled, parallel-group multicentre	ASU extract of avocado and soya (1 capsule containing 1300 mg)/ placebo taken daily for 6 months	LFI	ASU significantly improved pain and functional disability. Assessment by patients and physicians favoured ASU treatment
21	3	113	Double-blind, vehicle-controlled, parallel arm, multicentre	Capsaicin cream (0.025%)/placebo vehicle cream applied topically four times daily for 12 weeks	Physician's and patient's global 5-point pain score, pain severity (VAS and a 5-point scale), tenderness measured by palpation and passive range of motion (4-point scale)	Capsaicin significantly reduced pain
17	3	101 OA $n = 70$	Double-blind, placebo-controlled multicentre	Capsaicin cream (0.025%)/placebo vehicle cream applied four times daily for 4 weeks	Physician's and patient's global 5-point pain scores, pain severity (VAS and a 5-point scale)	Capsaicin significantly reduced pain
18	4	21 OA $n = 14$	Double-blind, placebo-controlled	Capsaicin cream (0.075%)/placebo vehicle cream applied topically four times daily for 4 weeks	Pain severity (VAS and a 5-point scale), functional capacity (modified HAQ), morning stiffness, grip strength, joint swelling, tenderness (dolorimeter)	Capsaicin significantly reduced tenderness ($P > 0.02$) and pain ($P > 0.02$) associated with OA
19	1	51	Double-blind, vehicle-controlled	Capsaicin cream (0.025%) applied to hand 4 times daily for first 3 weeks and twice daily thereafter for the remaining 6 weeks of the study	Articular tenderness and pain (VAS)	Significant reduction in articular tenderness found with active compared with vehicle treatment
22	4	50	Double-blind, placebo-controlled	Devil's claw extract (2 capsules; 1.5% iridoid glycoside content)/ placebo taken 3 times daily	4-point pain intensity score	Devil's claw significantly reduced pain
23	3	89	Double-blind, placebo-controlled	Devil's claw extract (2 capsules; 3% iridoid glycoside content)/ placebo taken 3 times daily	Severity of pain and joint mobility	Devil's claw significantly improved pain and joint mobility
24	4	60 OA $n = 31$	Double-blind, comparative parallel design	Eazmov herbal preparation (1 capsule) or diclofenac (50 mg) three times daily for 6 months	Severity of pain (score), morning stiffness, RI, joint score (ARA), disability score, grip strength	Eazmov significantly inferior to diclofenac, regarding pain severity and disability scores. Better side-effects profile for Eazmov

25	3	56	Double-blind, placebo-controlled, double-dummy, crossover	Ginger extract (1 capsule containing 170 mg)/ibuprofen (1 tablet containing 400 mg)/ placebo taken 3 times daily for 3 × 21 days	Pain (VAS)	A ranking for the three treatment periods was found for pain relief (VAS): ibuprofen > ginger extract >placebo. No significant differences between ginger extract and placebo
26	3	35	Double-blind, double-dummy, crossover	Gitadyl herbal medicine (3 tablets/day) or Ibumetin (capsules containing 400 mg) 3 times daily for 2 × 21 days	Pain at rest, pain at work and walking ability (symptom score)	Insignificant reduction of symptoms in both groups. No significant difference between groups
30	4	108 OA $n = 53$	Double-blind, comparative parallel design	Phytodolor (3 × 30 drops/day) or diclofenac (3 × 25 mg/day) for 2 weeks	Pain, swelling and function as judged by doctors/patients	Both treatments yielded the same clinical results
Unpublished, 1990[a]	3	47 OA $n = 25$	Double-blind, placebo-controlled, 4-armed, 2-centre	Double-, normal- or half-strength Phytodolor (3 × 30 drops/day) or placebo drops for 4 weeks	Pain, morning stiffness as judged by doctors/patients	Significant difference in all actively treated groups with no significant difference between them
Unpublished, 1991[b]	3	108 OA $n = 34$	Three-armed, double-blind against placebo; open against piroxicam	Phytodolor (3 × 30 drops) or placebo drops or piroxicam (20 mg per day) for 4 weeks	Pain and immobility (categorical scale)	Significant pain reduction in both actively treated groups with no significant difference between them
31	4	240 OA $n = 140$	Double-blind, comparative	Phytodolor (3 × 40 drops/day) or diclofenac (3 × 25 mg/day) for 3 weeks	Global symptom score and joint mobility	Therapeutic equivalence between the two groups
28	3	40 OA n not stated	Double-blind, placebo-controlled	Phytodolor (3 × 30 drops) or placebo for 3 weeks	Joint mobility, pain at rest and pain upon pressure (evaluation by doctor) and use of rescue medication	Significant difference in favour of active medication
29	3	30 OA n not stated	Double-blind, placebo-controlled	Phytodolor (3 × 40 drops) or placebo for 3 weeks	Requirement of rescue medication and custom-made pain score	Significantly less requirement of rescue medication in actively treated group
32	5	82 OA $n = 51$	Double-blind, placebo-controlled	Reumalex herbal preparation (2 tablets equivalent to 20–40 mg salicylic acid)/ placebo daily for 2 months	AIMS 2	Reumalex had a significant mild analgesic effect
33	3	27	Double-blind, placebo-controlled crossover	Stinging nettle leaf/white deadnettle leaf (placebo) applied topically once a day for 1 week followed by 5-week washout period	Pain (VAS) and disability (SHAQ)	Pain and disability scores significantly lower after 1 week of treatment with stinging *vs* non-stinging nettles (deadnettle)
34	4	78	Double-blind, placebo-controlled	Willow bark extract (1360 mg equivalent to 240 mg salicin)/ placebo taken daily for 2 weeks	WOMAC pain index	Willow bark had a significant moderate analgesic effect

ARA, American Rheumatism Association; AIMS2, revised and expanded version of the Arthritis Impact Measurement Scale; SHAQ, Stanford Health Assessment Questionnaire; WOMAC, Western Ontario and McMaster University Osteoarthritis Index.

[a]M. Bernhardt, B. Kiemel and U. Dormehl.

[b]M. Bernhardt, A. Keimel, G. Belucci and P. Spasojevie.

Table 2. Further methodological details of RCTs

Reference	Sex ratio (M : F)	Mean age of sample group (range) (yr)	Inclusion/ exclusion criteria stated	Concomitant medications recorded	Compliance assessed	Power calculation performed	Joint location of OA described	No. of premature withdrawals/ dropouts during trial described	Assessment of and grouping according to severity and activity/duration of OA	Diagnostic criteria
14	10 : 32	48.4 ± 2.6 (47–78)	Yes	All other medications stopped during trial	Yes	No information	No	No information	No information	Pain, morning stiffness, stiffness and/or joint swelling, disability and/or loss of function due to joint deformity, with radiological changes
15	55 : 108	62.9 ± 8.8 (45–80)	Yes	Predefined NSAIDs and restricted acetaminophen use allowed. No analgesics or slow-acting drugs, e.g. chondroitin sulphate, diacerhin, oxaceprol or glucocorticoids allowed during treatment period	Yes	Yes	Knee or hip	13	Regular painful active primary OA of at least 6 months duration with regular pain and functional impairment experienced at least 3 months before study	Primary OA of knee or hip verified according to ACR guidelines.[1] Radiographic examination of knee and hip within 1 year before the study. Patients required to have stage IB, II or III lesions according to the Kellgren–Lawrence classification[2] modified by subdivision of stage I into IA (< 25% joint space loss, minimal osteophyte) and IB (25–50% joint space loss, minimal osteophyte)
16	46 : 118	64.1 ± 7.5 (45–75)	Yes	Predefined NSAIDs, analgesics and other concomitant medications allowed and recorded. No slow-acting medications allowed	Yes	Yes	Knee or hip	20 (5 more withdrawals in 2 month post-treatment follow-up)	Regular painful active primary OA of at least 6 months duration with regular pain experienced at least 3 months before study	Primary OA of the knee verified according to the ACR clinical criteria.[3] Primary OA of the hip verified according to ACR clinical and radiographic criteria. [4]Radiographic examination of knee and hip within 6 months before the study. Patients required to have stage IB, II or III lesions according to Kellgren–Lawrence classification[2] modified by sub-division of stage I into IA (<25% joint space loss, minimal osteophyte) and IB (25– 50% joint space loss, minimal osteophyte)

21	41 : 72	63 ± 12 61 ± 12 (18–86)	Yes	No NSAIDs or narcotic analgesics permitted during study. Acetaminophen allowed with restricted use	Yes	No information	Knee, ankle, elbow, wrist or shoulder	17	Primary or post-traumatic OA. Average duration noted. At least moderate pain with motion or weight-bearing activity	Morning stiffness of <30 min, crepitus on active and passive motion of the target joint. Bony enlargement of the target joint. One or more of the following radiographic findings of the target joint: joint space narrowing, sub-chondral sclerosis, osteophytes, joint swelling, joint deformity
17	OA patients: 15 : 21	OA patients: 62 (31–74)	Exclusion criteria not mentioned	Continuation of standard oral arthritis medication allowed. Intra-articular corticosteroid injections and topical medications including corticosteroids[c] prohibited	Yes	No information	Knee	8	Moderate to very severe knee pain	Diagnosis based on physical examination and radiological changes typical of OA, accompanied by negative laboratory test results for other causes of arthritis. Severity evaluated using categorical pain scale
18	13 : 22	General sample: 61 ± 2 OA patients: 65 ± 2	Yes	NSAIDs, DMARDs and non-drug modalities of treatment (e.g. splints, physical therapy) allowed throughout study. No intra-articular steroids or topical agents allowed	No information	No information	Hand	1	Primary OA with painful involvement of the hands of at least moderate severity	Diagnosis based on classical findings on examination
19	No information	No information	No	No information	No information	No information	Hand	No information	At least moderate joint pain	All patients met 1991 ACR OA criteria
22	11 : 39	64.6 (28–86)	No	No information	Yes	No	General OA	4	Severity and duration assessed. Moderate and severe cases distinguished	No information
23	39 : 50	(55–75)	Yes	No information	No information	No information	No	No information	Minimum 2 yr articular pathology of arthritic origin. Articular pain on examination, although pain severity not assessed	No information

Table 2. *Continued*

Reference	Sex ratio (M : F)	Mean age of sample group (range) (yr)	Inclusion/ exclusion criteria stated	Concomitant medications recorded	Compliance assessed	Power calculation performed	Joint location of OA described	No. of premature withdrawals/ dropouts during trial described	Assessment of and grouping according to severity and activity/duration of OA	Diagnostic criteria
24	28 : 32	53.6 ± 3.4	Yes	All other medications stopped during trial	Yes	No	No	No information	Duration assessed	Pain, morning stiffness, stiffness and/or joint swelling, disability and/ or loss of function due to joint deformity with radiological changes
25	15 : 41	66 (24–87)	Yes	No NSAIDs/ analgesics. Acetaminophen allowed and recorded	Yes	Yes	Knee or hip	19	Minimum pain on movement (VAS). Duration and LI assessed	Clinical dysfunction and pain due to OA and radiologically verified OA (Kellgren grade I–II, $n=16$; grade III–IV, $n=40$) of the hip or knee
26	No information	57.6 ± 15.8 in Gitadyl group 55.8 ± 15.9 in Ibumetin group (>30)	Yes	Dextropropoxyphene allowed during trial	No information	No information	No	6	Clinical symptoms of mild to moderate OA for >6 months	No information
30	42.3%: 55.8%	60.2 ± 10.9	Yes	Numerous medications (but not for arthritis)	No information	No information	Knee ($n=34$), hip ($n=9$)	20	No information	No information
Unpubl.[a]	15 : 31	(31–88)	Yes	NSAIDs and 'most other medications' discontinued or not allowed	No information	No information	No information	4	No information	Clinical diagnosis
Unpubl.[b]	77 : 34	(27–71) (averages given only for subgroups)	Yes	None given	No	No information	Knee or hip	No information	No information	Clinical diagnosis
31	96 : 144	(22–75) (averages only in subgroups)	Yes	Essential medications were continued, muscle relaxation and psychotropic drugs were not allowed	No	No information	Knee	19	No information	Radiologically confirmed
28	No information	(50–80)	No	'As necessary'	No	No information	No information	2	No information	Clinical diagnosis
29	7 : 23	66.3	No information	Diclofenac as rescue medication	No information	No information	22 knee, 4 hip, 2 thumb	No information	No information	No information

32	No information	62.21 ± 12.05	Yes	All medications recorded. Only existing self-prescribed medications allowed	Yes	No	No	8	Severity and duration assessed. All had long-term low-grade OA	Clinical assessment and diagnosis by a rheumatologist, with levels of disability, joint damage, pain and wider distress also noted
33	4 : 23	60 (45–82)	Yes	Patients allowed existing medications (analgesics and NSAIDs) during trial. No steroid injections allowed 3 months before trial	Yes	Yes	Base of thumb or index finger	1	Duration assessed	Persistent pain at the base of thumb or index finger of at least 10 weeks' duration consistent with clinical diagnosis of OA
34	59 : 19	52.4 ± 7 53.5 ± 10.5	Yes	No additional analgesics, NSAIDs or systemic corticosteroids allowed during trial. Other medications recorded. Physical therapy assessed	Yes	No information	Knee or hip	5	Severity and duration assessed. Severity higher in placebo group	OA verified according to ACR guidelines[1]

DMARD, disease-modifying anti-rheumatic drug; ACR: American College of Rheumatism; ARA: American Rheumatism Association.

[a]M. Bernhardt, B. Kiemel and U. Dormehl.

[b]M. Bernhardt, A. Keimel, G. Belucci and P. Spasojevie.

[c]Patients undergoing physical therapy or using non-drug treatments allowed if no change in regimen allowed.

[1]Altman RD. Criteria for classification of clinical osteoarthritis. J Rheumatol 1991;18(Suppl. 27):10–12.

[2]Kellgen JH, Lawrence DM. Radiological assessment of osteoarthritis. Ann Rheum Dis 1957;16 : 494–502.

[3]Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K *et al*. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.

[4]Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K *et al*. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505–14.

Table 3. Adverse effects recorded in reviewed randomized controlled trials

Reference	Herbal medicine	Observed adverse effects
14	Articulin-F	Subjects treated with Articulin-F experienced nausea ($n = 2$), dermatitis ($n = 3$) and abdominal pain ($n = 3$)
15	ASU	Total no. of adverse effects: ASU 10, placebo 12. Total no. of patients experiencing adverse effects: ASU 9, placebo 10; gastric pain, ASU 4, placebo 5; nausea/vomiting, ASU 1, placebo 2; dyspepsia, ASU 1, placebo 1; diarrhoea, ASU 0, placebo 2; constipation, ASU 1, placebo 1; heartburn, ASU 2, placebo 0; herpes zoster, ASU 1, placebo 0; asthenia, ASU 0, placebo 1; flatulence, ASU 0, placebo 1
16	ASU	Total no. of adverse effects: ASU 33, placebo 25. Total no. of patients experiencing adverse effects: ASU 23 (27.4%), placebo 20 (25.6%). In the ASU group, a case of eczema, fever associated with migraine and a case of gastralgia and associated headache were thought to be adverse effects associated with ASU treatment, and these patients withdrew from the study. Other adverse reactions in the ASU group were gastric disorders (5), pyrosis (1), nausea (1), vomiting (1), febrile colitis (1), headache (2), drowsiness (2), flu syndrome (2), allergy (1), urticaria (1) and pruritus (2). A relationship with the study drug was considered certain in only 3% of these cases. Overall assessments by patient and investigator showed good tolerability of treatment, with no difference between ASU and placebo
21	Capsaicin	Mild to moderate burning or stinging at application [26 (46%) for capsaicin, 2 for placebo]. Two patients in treatment group withdrew because of adverse effects attributed to capsaicin (moderate burning at application site and severe knee pain). Other adverse experiences included headache, backache, toothache, cold and flu symptoms, dizziness, sinusitis and rhinitis and were not considered attributable to the use of capsaicin cream
17	Capsaicin	Burning (mostly mild and transient) experienced at the site of application [23 (44%) for capsaicin, 1 for placebo]. Two patients treated with capsaicin dropped out of the study after 2 weeks because of mild or moderate burning. Other adverse experiences included migraine, cramps, back pain and rhinitis and were not considered attributable to the use of capsaicin cream
18	Capsaicin	Burning of the skin locally was observed with use of capsaicin cream. Burning reduced over first week and became increasingly tolerable in all patients receiving the active drug. One patient (rheumatoid arthritis group) stopped treatment with capsaicin after 5 days because of burning. A second patient with rheumatoid arthritis only applied the drug twice daily because of local burning
19	Capsaicin	Mild burning or stinging at application sites with capsaicin cream
22	Devil's claw	Subjects treated with devil's claw experienced nausea (1), diarrhoea (1), gastralgia (1), pruritis (1) and exanthema (1). Subjects in the placebo group experienced aerophagy (1), gastralgia (2), sweating (1) and headache (1)
23	Devil's claw	No undesired effects reported
24	Eazmov	Total no. of adverse effects: Eazmov 14, diclofenac 42. Total no. of patients experiencing adverse effects: Eazmov 10 (33%), diclofenac 20 (67%); abdominal pain, Eazmov 2, diclofenac 12; asthenia, Eazmov 0, diclofenac 3; fever, Eazmov 0; diclofenac 2; headache, Eazmov 1, diclofenac 5; digestive system overall, Eazmov 11, diclofenac 16; dyspepsia, Eazmov 6, diclofenac 7; anorexia, Eazmov 2, diclofenac 1; flatulence, Eazmov 2, diclofenac 2; nausea, Eazmov 1, diclofenac 4; diarrhoea, Easmov 0, diclofenac 0; vomiting, Eazmov 0, diclofenac 2; dizziness, Easmov 0, diclofenac 2; alopecia, Eazmov 0, diclofenac 1; rash, Eazmov 0, diclofenac 1
25	Ginger extract	In the 67 patients receiving test drugs, a total of 47 adverse events were registered in 34 patients. Adverse events were gastrointestinal complaints (placebo period 8, ginger extract period 9, Ibuprofen period 14). These complaints were characterized as bad taste (5 for ginger extract period only), dyspepsia (placebo 1, ginger extract 1, Ibuprofen 7), changes in stools/intestinal trouble (placebo 6, ginger extract 1, Ibuprofen 7) or nausea (placebo 1, ginger extract 1, Ibuprofen 3). Allergic reactions were noted in 3 patients: skin allergy (placebo period), periorbital oedema (Ibuprofen period) and conjunctivitis (ginger extract period)
26	Gitadyl	Patients experienced GI problems (Gitadyl 3, Ibuprofen 6), pain and headaches (Gitadyl 4, Ibuprofen 3) and allergies (Gitadyl 1, Ibuprofen 1)
30	Phytodolor	Total no. of patients experiencing adverse effects: Phytodolor 9, diclofenac 10. Adverse effects experienced after 4 weeks of treatment with Phytodolor included gastrointestinal symptoms (2), nausea (3), diarrhoea (1), skin allergy (1), vertigo (1)
Unpublished[a]	Phytodolor	1 case of generalized pruritus experienced with double strength Phytodolor (probably related) and 1 case of constipation with normal-strength Phytodolor (probably unrelated); otherwise no adverse effects
Unpublished[b]	Phytodolor	'No case of adverse effect in Phytodolor group'
31	Phytodolor	7.4% of patients in Phytodolor group and 14.2% in diclofenac group had adverse effects. In Phytodolor group, adverse effects were gastrointestinal symptoms (10), fatigue (1), allergic reaction (8), dry mouth (1), oedema (1) and vertigo (1)
28	Phytodolor	'No adverse effects were reported'
29	Phytodolor	No information provided
32	Reumalex	Subjects in Reumalex group experienced dyspeptic symptoms (1), diarrhoea (1) and severe headaches (1). Subjects in placebo group experienced headaches and digestive upset (1), angina (1), anxiety (1) and stomach cramps (1)

Table 3. *Continued*

Reference	Herbal medicine	Observed adverse effects
33	Stinging nettle	No serious adverse effects were reported or observed. 2 patients reported the sting as unpleasant but not distressing. Stinging nettle treatment caused rashes in 2 patients, although one patient had a previous history of rashes and stinging nettle may not have been the cause
34	Willow bark extract	Total no. of adverse events: willow bark extract 17, placebo 28. Total no. of patients experiencing adverse events: willow bark 16, placebo 16; skin and appendage disorders, willow bark 6, placebo 5; gastrointestinal system disorders, willow bark 3, placebo 7; infections, willow bark extract 2, placebo 2; headache/migraine, willow bark extract 1, placebo 2; change in haemogram, willow bark 1, placebo 2; hypertriglyceridaemia, willow bark 1; placebo 1; musculoskeletal pain, willow bark extract 0, placebo 2; sleeplessness, willow bark 0, placebo 2; other adverse events, willow bark 3, placebo 5

[a]M. Bernhardt, B. Kiemel and U. Dormehl.
[b]M. Bernhardt, A. Keimel, G. Belucci and P. Spasojevie.

significant ranking of effectiveness (VAS) of the three treatment periods was found, as follows: ibuprofen > ginger extract > placebo ($P < 0.0001$). The same trend was found for acetaminophen consumption ($P < 0.01$) and LI. Significant differences in these tests between ibuprofen and ginger extract as well as ibuprofen and placebo were shown. No differences between ginger extract and placebo were observed.

Gitadyl

Gitadyl is a herbal preparation containing 110 mg feverfew, 90 mg American aspen and 60 mg milfoil. Thirty-five patients who were taking NSAIDs for mild to moderate OA underwent a 2-week washout phase before being randomized to receive Gitadyl (three tablets daily) or ibuprofen (400 mg three times daily) administered for 2×21 days in a double-blind, cross-over RCT with the double-dummy technique [26]. Patients were allowed to take dextropropoxyphene as a rescue medication for pain relief. The number of tablets taken was recorded and used to assess change in condition. The primary outcome measures of pain (when resting and working) and walking ability were assessed using a symptom score on a scale of 1–4 (none, mild, moderate, strong). A non-significant trend of symptom reduction was observed in both groups, with no significant difference between groups. Gastrointestinal complaints were more frequent in patients treated with ibuprofen.

Phytodolor

Phytodolor, a fixed herbal formulation containing alcoholic extracts of *Populus tremula*, *Fraxinus excelsior* and *Solidago virgaurea*, has been shown to be effective in various rheumatic diseases, including OA. A systematic review of all double-blind RCTs for rheumatic conditions [27] included six trials for the treatment of OA fulfilling this review's inclusion criteria [28–31; M. Bernhardt, B. Kiemel and U. Dormehl, unpublished results; M. Bernhardt, A. Keimel, G. Belucci and P. Spasojevie, unpublished results]. These trials demonstrate significant results for pain reduction [M. Bernhardt, B. Kiemel and U. Dormehl, unpublished results; M. Bernhardt, A. Keimel, G. Belucci and P. Spasojevie, unpublished results], mobility [31] and NSAID consumption [28, 29] with administration of Phytodolor. They also suggest that Phytodolor is as effective as NSAIDs but has fewer adverse effects [30, 31; M. Bernhardt, A. Keimel, G. Belucci and P. Spasojevie, unpublished results].

Reumalex

Mills *et al.* [32] conducted a double-blind RCT with patients suffering from chronic stable arthritic conditions, predominantly OA. Eighty-two patients with OA or rheumatoid arthritis, with moderate disability and pain, were randomly allocated to two groups. One group took two tablets of Reumalex (a herbal medicine containing 100 mg Pulv White Willow bark, 40 mg Pulv Guaiacum Resin BHP, 35 mg Pulv Black Cohosh BHP, 25 mg Pulv Ext Sarsparilla 4 : 1 and 17 mg Pulv Ext Poplar Bark 7 : 1) equivalent to 20–40 mg salicylic acid per day while the other took two indistinguishable placebo tablets for a 2-month period. Subjects with OA ($n = 51$) showed a statistically significant difference in pain compared with placebo as measured by the Arthritis Impact Measurement Scales (AIMS) score ($P < 0.05$). Use of a modified Ritchie score showed no intergroup difference. Mean mobility and function scores remained, on average, unchanged throughout the study. There were no differences in analgesic consumption, which was monitored as a secondary outcome measure.

Stinging nettle

Twenty-seven patients with OA pain at the base of the thumb or index finger were randomized to receive topical treatment with stinging nettle leaf (*Urtica dioica*) followed by placebo treatment using white deadnettle (*Lamium album*) leaf or vice versa in a double-blind crossover RCT [33]. White deadnettle leaf looks like a stinging nettle leaf but has no sting. Stinging nettle leaf was applied daily for 1 week to the painful area. After a 5-week washout period, the placebo treatment was

applied for a 1-week period. After 1 week of treatment with nettle sting, reductions in both pain (VAS) and disability (Stanford Health Assessment Questionnaire) were significantly larger than with placebo ($P = 0.026$ and $P = 0.0027$ respectively). No significant differences in either score were observed following the 5-week washout period. There was a non-significant decline in daily use of analgesic and anti-inflammatory drugs following 1 week of treatment with stinging nettle.

Willow bark

Schmid *et al.* [34] randomized 78 hospital in-patients suffering from OA of the knee or hip joints to receive two tablets twice daily of either willow bark extract (corresponding to 240 mg salicin per day) or placebo tablets for a 2-week period. Drug effectiveness was measured primarily by the pain dimension of the WOMAC OA index [35]. All patients also received regular physical therapy following standard procedures. A statistically significant advantage of the active treatment over placebo was observed ($P = 0.047$). Secondary outcome measures of physical function were better in the treatment group compared with placebo, although this was not statistically significant and no differences in stiffness were observed between the two groups during the study period. A significant positive effect of the active medication was confirmed by overall assessments both by the physician and by the patients ($P < 0.01$). No significant correlation was observed between the different physical therapy methods and the primary outcome measure, suggesting that the observed medication effect was not influenced by the physical therapy. No relevant differences between outcome were observed in knee and hip OA.

Discussion

The review found promising evidence in the form of RCTs for the use of some herbal preparations in reducing pain and improving mobility, function and disability in OA. While there is no compelling evidence for significant clinically relevant benefits for Eazmov

Table 4. Adverse effects listed in the literature

Herb	Adverse effects listed in reference texts
Withania somnifera (Ashwagandha)[a]	Has effects on CNS and may interact with CNS depressants and amphetamines[3]
Boswellia serrata (Salei guggul)	None known[3]
Turmeric root (*Curcumba longa* rhizome)[a]	Long-term use frequently results in gastrointestinal disturbances and may cause gastric ulcers.[4] Some concern about safety of turmeric extracts after reports of adverse thyroid changes in pigs.[5]
Capsicum	Redness and burning sensation at site of application. Rare allergy[1]
Devil's claw (*Harpagophytum procumbens*)	Mild digestive upset[1]
Ginger (*Zingiber officiniale*)[b]	Rare; limited to heartburn and digestive upset[1]
Milfoil (yarrow)	Allergic contact dermatitis, photosensitivity and uterine stimulant (with increased doses)[3]
Feverfew (*Tanacetum partherium*, *T. microphyllum*)[c]	Mouth ulceration from chewing leaves and gastrointestinal upset. Post-feverfew syndrome (including nervousness, tension, fatigue and joint ache) has been noted.[1] It has been reported to cause contact dermatitis.[5]
Poplar (American aspen, black poplar, quaking aspen, white poplar)[c,e]	Asthma, contact dermatitis (propolis product), gastrointestinal bleeding, irritation (similar to salicylates), hepatotoxic potential (related to tannin component), pruritus, renal dysfunction, tinnitus[4]
Solidago virgaurea (golden rod)[d]	None known[2]
Populus tremula (white poplar)[d]	In very rare cases, allergic reactions may occur[2]
Fraxinus excelsior (ash)[d]	None known
Guaiacum resin[e]	None known[2]
Black cohosh[e]	Rare. Limited to gastric upset. Historical evidence suggests throbbing headaches, nervous and cardiovascular depression can occur at high doses.[1] May cause vertigo, headache, prostration and gastrointestinal irritation when taken in large doses[5]
Sarsparilla[e]	Because of the saponin content, local irritations could occur[2]
Willow bark (*Salix alba, S. purpurea*, *S. fragilis* and others)[e]	Rare nausea, headache and digestive upset[1]
Stinging nettle (*Urtica dioica*)	None known

CNS, central nervous system.

[1]Boon H, Smith M. The botanical pharmacy. The pharmacology of 47 common herbs. Quarry Press, 1999.

[2]Blumenthal M *et al.*, eds. The complete German Commission E monographs. Therapeutic guide to herbal medicines. American Botanical Council, 1998.

[3]Miller LG, Murray WJ. Herbal medicinals. A clinician's guide. New York: Pharmaceutical Products Press, 1998.

[4]Fetrow CW, Avila JR. Professional handbook of complementary and alternative medicines. Springhouse (PA): Springhouse Corporation, 1999.

[5]Martindale, the extra pharmacopoeia, edn 1. London: Royal Pharmaceutical Society, 1996.

[a]Constituent of Articulin-F.

[b]Consituent of Easmov.

[c]Constituent of Gitadyl.

[d]Constituent of Phytodolor.

[e]Constituent of Reumalex.

[24], Gitadyl [26] or ginger extract [25], there is weak evidence, in the form of single RCTs, for mild to moderate relief of symptoms using Reumalex [32], willow bark [34], common stinging nettle [33] and the Ayurvedic herbal preparation Articulin-F [14]. There is promising evidence for devil's claw [22, 23] and ASU [15, 16] and moderately strong evidence for Phytodolor [27] and capsaicin cream [20, 21] for the relief of OA symptoms. ['Weak evidence' describes herbs with a single RCT with significant results; 'promising evidence' describes herbs with two trials that produced favourable outcomes; 'moderately strong evidence' describes herbs with three or more favourable trials.]

All of the individually reviewed trials were found to be of high methodological quality as assessed by the Jadad scale [13]; trials were considered to be of high quality if they attained 3 out of a maximum of 5 points. However, seven of the 12 RCTs reviewed were unreplicated studies and as such can only provide weak evidence for effectiveness. Although all 12 trials were generally found to be of good methodological quality, failure to implement or state inclusion/exclusion criteria [22], compliance [23, 26], withdrawals [14, 23, 24] and power calculation [14, 21–24, 26, 32, 34] were evident. Some RCTs did not distinguish between patients with mild and severe forms of OA [e.g. 14, 23] or differing joint location [e.g. 14, 23, 32], yet this would be important for assessing the effectiveness of herbal medicines in patients presenting with mild or moderate symptoms, as some treatments appear less effective in severe cases, e.g. devil's claw [22]. Differentiation between joint locations of OA would be important as treatments may be more effective for OA in one particular joint rather than another, e.g. hip joints tended to respond more favourably than knee joints to ASU treatment [15, 16]. Many of the studies used different diagnostic criteria for inclusion, only three trials distinguishing between primary (idiopathic) and post-traumatic (secondary) OA [15, 16, 21]. Other studies did not mention the concomitant use of NSAIDs, analgesics or other medications during trials [22, 23]. This is particularly important if adverse effects are noted which could be attributed to NSAIDs or the test medication.

Promising evidence from two RCTs showed that ASU could significantly improve hip or knee OA symptoms and reduce patients' NSAID consumption [15, 16]. ASU was found to have a delayed (by 2 months) treatment effect that resulted in improved pain and function. This suggests that ASU is an effective slow-acting drug for OA. There is growing evidence, mainly in the form of *in vitro* studies, that ASU may stimulate the deposition and repair of extracellular matrix components. Although the active ingredient(s) of ASU remain unknown, ASU has been shown to have an inhibitory effect on various interleukins [36–38], prostaglandin E_2 production [38] and collagenase synthesis [38]. ASU stimulates collagen synthesis in articular chondrocyte cultures [38] and may promote transforming growth factor β-induced matrix repair mechanisms in articular cartilage [39]. Furthermore, ASU increased the production of plasminogen activator inhibitor 1, an effect that could help in blocking the plasmin cascade that leads to metalloproteinase activation [39]. Although the clinical evidence for ASU is promising, it is noteworthy that both RCTs published to date originate from the same research group. Independent replication would seem to be a precondition before acceptance of this therapy.

Extracts of devil's claw have been shown in two RCTs to reduce pain and increase mobility significantly in patients with OA [22, 23]. However, in neither study were concomitant medications mentioned. *In vitro* experiments have shown the iridoid glycoside harpagoside to be an active component of devil's claw, while *in vivo* experiments indicate that the plant extract elicits significant antioxidant activity which may be responsible for its reported experimental and clinical anti-inflammatory action [40].

Phytodolor has been shown to relieve many OA symptoms, particularly pain, in a reasonably large number of double-blind RCTs of good methodological quality [27], as assessed by the Jadad score [13]. Two RCTs showed that Phytodolor was as clinically effective as conventional NSAIDs while two other RCTs showed a reduction in NSAID consumption with Phytodolor treatment. Caveats associated with the included trials are discussed by the author, although the question of potential publication bias for this registered commercial herbal preparation is not explored in the review. The alcoholic extracts of Phytodolor's constituents (*Populus tremula*, *Fraxinus excelsior* and *Solidago virgaurea*) are proportioned in the ratio of 3 : 1 : 1. The active ingredients of Phytodolor are salicin, salicyl alcohol, phenolcarbon acids, flavonoids, triterpensaponines and coumarin derivatives and the herbal mixture is standardized to 1 mg/ml of salicin, 0.07 mg/ml of total flavonoids and 0.14 mg/ml of isofraxidine. The mechanism of action of Phytodolor is proposed to lie in the inhibition of arachidonic acid metabolism via the cyclooxygenase and lipoxygenase pathways, leading to suppression of mediators of inflammation, such as prostaglandin E_2 [41].

Topically applied capsaicin is proposed to exert its action by stimulating a subpopulation of nociceptive pain neurones. Exposure to capsaicin brings about the depletion of substance P, neurones subsequently becoming insensitive to all other exposure, including exposure to capsaicin itself [43, 44].

The incidence of adverse effects for these herbal medicines appears to be low, and they may offer a much-needed alternative for individuals with long-term chronic OA (Tables 3 and 4). Hundreds of herbal remedies are used for treating OA, and the research literature reflects only a small percentage of them. It is recommended that all herbal treatments promoted for OA are submitted to rigorous scientific scrutiny. Future RCTs of herbs for OA should distinguish between patients with mild and severe forms of the condition so that mild to moderate benefits of herbal preparations

are not missed. In addition, differentiation or stratification according to joint location of OA is recommended so that herbal preparations potentially suitable for the particular treatment of certain joint locations of OA can be distinguished. Some of the studies reviewed included outcome measures such as grip strength, walking time and joint tenderness, which are considered unreliable measures of OA by the WHO (World Health Organization) and OARSI (Osteoarthritis Research Society International) [45, 46]. Future studies should use the recommended core of outcome measures [46].

The question arises of the clinical relevance and implications of the findings summarized in this review. It seems that herbal remedies that have been shown to be effective could be employed in order to lower or stop the consumption of NSAIDs and to reduce the incidence of adverse effects of NSAIDs. This would, at the same time, generate long-term safety data, which are urgently needed, for these herbal medicines.

It is concluded that a number of herbal medicines may be effective for the treatment of symptoms, especially pain, associated with OA. Considering the large number of people suffering from OA and the known adverse effects associated with NSAID use, this area is under-researched and would seem to merit further attention.

Acknowledgements

We thank Barker Bausell and Brian Berman, University of Maryland School of Medicine, Complementary Medicine Program, Baltimore, USA for their useful comments.

References

1. Brooks PM, March LA. New insights into osteoarthritis. Med J Aust 1995;163:367–9.
2. Weinberger MTWM, Booher P, Katz BP. Can the provision of information to patients with osteoarthritis improve functional status? A randomised controlled trial. Arthritis Rheum 1989;32:1577–83.
3. Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain 2000;85:169–82.
4. Buchanan W. Implications of NSAID therapy in elderly in-patients. J Rheumatol 1990;4:29–32.
5. Caradoc-Davies T. Non-steroidal anti-inflammatory drugs, arthritis and gastrointestinal bleeding in elderly in-patients. Age Ageing 1984;13:295–8.
6. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs. N Engl J Med 1994;331:1675–9.
7. Astin JA. Why patients use alternative medicine. J Am Med Assoc 1998;279:1548–53.
8. Rao JK, Mihaliak K, Kroenke K, Bradley J, Tierney WM, Weinberger M. Use of complementary therapies for arthritis among patients of rheumatologists. Ann Intern Med 1999;131:409–16.
9. Ernst E. Usage of complementary therapies in rheumatology: A systematic review. Clin Rheumatol 1998;17:301–5.
10. Stange R, Moser C, Goedings P, Mansmann U, Buehring M. Randomised trial with mistletoe injections for osteoarthritis of the knee in comparison to treatment with diclofenac. Forsch Komplementarmed 2000; 7:29–58.
11. Chopra A, Lavin P, Chitre D, Patwardhan B, Polisson R. A clinical study of Ayurvedic (Asian Indian) medicine in OA knees. Arthritis Rheum 1998;41(Suppl.):S198.
12. Ferraz MB, Periera RB, Iwata NM, Atra E. Tipi. A popular analgesic tea: double-blind cross-over trial in osteoarthritis. Clin Exp Rheumatol 1991;9:205–12.
13. Jadad AR, Moore RA, Carrol D *et al*. Assessing the quality of reports of randomised clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
14. Kulkarni RR, Patki PS, Jog VP, Gandage SG, Patwardhan B. Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. J Ethnopharmacol 1991;33:91–5.
15. Blotman F, Maheu E, Wulwik A, Caspard H, Lopez A. Efficacy and safety of avocado/soybean unsaponifiables in the treatment of symptomatic osteoarthritis of the knee and hip. A prospective, multicenter, three-month, randomized, double-blind, placebo-controlled trial. Rev Rhum Engl Ed 1997;64:825–34.
16. Maheu E, Mazieres B, Valat JP *et al*. Symptomatic efficacy of avocado/soybean unsaponifiables in the treatment of osteoarthritis of the knee and hip: a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial with a six-month treatment period and a two-month follow-up demonstrating a persistent effect. Arthritis Rheum 1998;41:81–91.
17. Deal CL, Schnitzer TJ, Lipstein E *et al*. Treatment of arthritis with topical capsaicin: a double-blind trial. Clin Ther 1991;13:383–93.
18. McCarthy GM, McCarty DL. Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. J Rheumatol 1992;19:604–7.
19. Schinitzer TJ, Morton C, Coker C, Flynn P. Effectiveness of reduced applications of topical capsaicin (0.025%) in osteoarthritis. Arthritis Rheum 1992;35:S132.
20. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. A meta-analysis. Eur J Clin Pharmacol 1994;46:517–22.
21. Altman RD, Aven A, Holmburg CE *et al*. Capsaicin cream 0.025% as monotherapy for osteoarthritis: A double-blind study. Semin Arthritis Rheum 1994;23(Suppl.):25–33.
22. Guyader M. Les plantes antirhumatismales. Etude historique et pharmacologique, et étude clinique du nébulisat d'*Harpagophytum procumbens* DC chez 50 patients arthrosiques suivis en service hospitalier. Paris: Université Pierre et Marie Curie, 1984, PhD thesis.
23. Lecomte A, Costa JP. *Harpagophytum* dans l'arthrose: Etudes en double insu contre placebo. 37°2 Le Magazine 1992;15:27–30.
24. Biswas NR, Biswas K, Pandey M, Pandy RM. Treatment of osteoarthritis, rheumatoid arthritis and non-specific arthritis with a herbal drug: A double-blind, active drug controlled parallel study. JK Pract 1998;5:129–32.
25. Bliddal H, Rosetzky A, Schlichting P *et al*. A randomized, placebo-controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. Osteoarthritis Cartilage 2000;8:9–12.
26. Ryttig K, Schlamowitz PV, Warnoe O, Wilstrup F. Gitadyl versus ibuprofen in patients with osteoarthrosis.

The result of a double-blind, randomized crossover study. Ugeskr Laeg 1991;153:2298–9.
27. Ernst E. The efficacy of Phytodolor® for the treatment of musculoskeletal pain—a systematic review of randomized clinical trials. Nat Med J 1999;2:14–6.
28. Huber VB. Therapie degenerativer rheumatischer Erkrankungen. Fortschr Med 1991;109:248–50.
29. Schadler W. Phytodolor N zur Behandlung aktivierter Arthrosen. Rheuma 1988;8:280–90.
30. Baumann D, Focke G, Kornosoff G. Phytodolor bei Patienten mit aktivierter Gonarthrose, Koxathrose bzw. Schulter-Arm-Syndrom. Multizentrische randomisierte Doppelblindstudie versus Diclofenac-Natrium. Darmstadt: Steigerwald GmbH. Interner Forschungsbericht, 1989.
31. Hawel R. Phytodolor vs Diclofenac bei rheumatischen Erkrankungen. Darmstadt: Steigerwald GmbH. Interner Forschungsbericht, 1991.
32. Mills SY, Jacoby RK, Chacksfield M, Willoughby M. Effect of a proprietary herbal medicine on the relief of chronic arthritic pain: a double blind study. Br J Rheumatol 1996;35:874–8.
33. Randall C, Randall H, Dobbs F, Hutton C, Sanders H. Randomized controlled trial of nettle sting for treatment of base-of-thumb pain. J R Soc Med 2000;93:305–9.
34. Schmid B, Tschirdewahn B, Kotter I *et al*. Analgesic effects of willow bark extract in osteoarthritis: results of a clinical double-blind trial. FACT: Focus Alternative Complementary Ther 1998;3:86.
35. Bellamy N, Buchanan W, Goldsmith C, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
36. Mauviel A, Daireux M, Hartmann DJ, Galera P, Loyau G, Pujol JP. Effets des insaponifiables d'avocat et de soja (PIAS) sur la production de collagene par des cultures de synoviocytes, chondrocytes articularies et fibroblasts dermiques. Rev Rhum Mal Osteoartic 1989;56:207–11.
37. Mauviel A, Loyau G, Pujol JP. Effet des insaponofiables d'avocat/soja (Piascledine) sur l'activite collagenolytique de cultures de synoviocytes rhumatoides humains et de chondrocytes articulaires de lapin traites par l'interleukine 1. Rev Rhum Mal Osteoartic 1991;58:241–5.
38. Henrotin Y, Labasse A, Zheng SX *et al*. Effects of three avocado/soybean unsaponifiable mixtures on human articular chondrocyte metabolism. Arthritis Rheum 1996; 39:S227.
39. Boumediene K, Felisaz N, Bogdanowicz P, Galera P, Guillou GB, Pujol JP. Avocado/soya unsaponifiables enhance the expression of transforming growth factor beta1 and beta2 in cultured articular chondrocytes. Arthritis Rheum 1999;42:148–56.
40. Bhattacharya A, Bhattacharya SK. Anti-oxidant activity of *Harpagophytum procumbens* (devil's claw). Br J Phytother 1999;5:68–71.
41. Chrubasik S, Junck H, Breitschwerdt H, Conradt CH, Zappe H. Effectiveness of *Harpagophytum* extract WS 1531 in the treatment of exacerbation of low back pain: a randomised placebo-controlled double-blind study. Eur J Anaesthesiol 1999;16:118–29.
42. Bach GJ, Chubasik S. Wirksamkeit eines Kombinationspraparates aus Zitterpappel, Goldrute und Esche bei rheumatishen Beschwerden. Rheumatherapie mit Phytopharmaka 1997:131.
43. Fusco BM, Giacovazzo M. Peppers and pain. The promise of capsaicin. Drugs 1997;53:909–14.
44. Baron R. Capsaicin and nociception: from basic mechanisms to novel drugs. Lancet 2000;356:785–6.
45. Guidelines for the clinical investigations of drugs used in rheumatic diseases. European Drug Guidelines, Series 5. Copenhagen: World Health Organization, Regional Office for Europe, European League Against Rheumatism 1985 March:21–4.
46. Bellamy N, Kirwan J, Boers M *et al*. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24:799–802.