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Evidence of Effectiveness of Herbal Antiinflammatory Drugs in the Treatment of Painful Osteoarthritis and Chronic Low Back Pain

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Treatment with herbal medicines is very popular in Europe. In order to get information on the evidence of effectiveness of oral herbal medicines in the treatment of pain in the joints or lower back, OVID(MEDLINE), PUBMED and COCHRANE COLLABORATION LIBRARY were searched back to 1985 for systematic reviews. The level of evidence of effectiveness was defined as *strong* – at least two confirmatory studies demonstrating a clinical relevant effect, *moderate* – one confirmatory study with a clinical relevant effect and/or multiple exploratory studies of good quality; otherwise the evidence was *insufficient* or *conflicting* in the case of inconsistent findings.

Fifteen systematic reviews were identified. The evidence of effectiveness was strong for a proprietary unsaponifiable avocado soybean fraction and *Harpagophytum* preparations containing >50 mg harpagoside in the daily dosage, moderate for ginger and a proprietary rose hip and seed powder, insufficient for *Boswellia serrata* gum resin and other herbal preparations and inconsistent for a proprietary willow bark extract.

Further rigorous studies are required to confirm the usefulness of herbal medicines in the treatment of osteoarthritic complaints and chronic low back pain in order to enable acceptance of the herbal medicines into the treatment guidelines. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: osteoarthritis; pain; devil's claw; avocado soybean; rose hip and seed; ginger; salai guggal.

INTRODUCTION

The number of studies investigating oral herbal antiinflammatory drugs in the treatment of osteoarthritis (OA) and low back pain is steadily increasing and an updated Cochrane Systematic Review on 'Herbal Therapy for Osteoarthritis' is expected soon (Little C, personal communication). Whereas in Germany, preparations from devil's claw, willow bark and nettle herb are widely used as OA medicines (Chrubasik, 2004), an avocado-soy bean fraction and a powder from devil's claw are favoured in France (Blotman *et al.*, 1997; Maheu *et al.*, 1998; Appelboom *et al.*, 2001; Chantre *et al.*, 2000), a powder from rose hip and seed is prominent in Scandinavia (Warholm *et al.*, 2003; Rein *et al.*, 2004) and an extract of cat's claw standardized on 0.75 mg pentacyclic oxindol alkaloids is used in Austria (Mur *et al.*, 2002). Preparations from ginger (Bliddal *et al.*, 2000; Altman and Marcussen, 2001; Wigler *et al.*, 2003) or salai guggal (Kimmatkar *et al.*, 2003) or the gamma linolenic acid (GLA) containing seed oils from evening primrose, borage or blackcurrant (Belch *et al.*, 1988; Leventhal *et al.*, 1993; Leventhal *et al.*, 1994; Zurier *et al.*, 1996) are less popular for the treatment of osteoarthritic pain in Europe.

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Herbal antiinflammatory medicines provide a broad spectrum mechanism of action (Table 1). They interact to various extents with the inflammatory cascade (COX-1 and/or COX-2 and/or LOX), but experimental data also indicate interaction with cytokine production, the mediators of cartilage destruction. Other mechanisms of action include elastase or hyaluronidase inhibition, antioxidative effectiveness and other still unidentified effects that may contribute to the overall analgesic and joint protective effects. The aim of this study was to assess the evidence of effectiveness of oral herbal medicines in the treatment of painful osteoarthritis and chronic low back pain.

METHODS

Computerized literature searches were carried out by the authors (OVID(MEDLINE), PUBMED and COCHRANE COLLABORATION LIBRARY back to 1985) and also manually to identify systematic reviews using the terms *Harpagophytum procumbens* ('or' devil's claw), *Salix* ('or' willow bark), *Urtica* ('or' nettle), *Rosa canina* ('or' rose hip and seed), avocado soybean, *Oenothera biennis* ('or' evening primrose), *Ribes nigrum* ('or' blackcurrant), *Borago officinalis* ('or' borage), *Zingiber officinale* ('or' ginger), *Boswellia serrata* ('or' salai guggal), *Uncaria* ('or' cat's claw) ('and' reviews 'and' human).

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Table 1. Effect mechanism suggested from *in vitro* studies

	Inhibition of				Elastase* Hyaluronidase	Antioxidative effect
	COX-1	COX-2	LOX	Cytokines		
Devil's claw[a]	no	Fiebich *et al.*, 2001; Chrubasik *et al.*, 2002a	Loew *et al.*, 2001	Fiebich *et al.*, 2001; Chrubasik *et al.*, 2002a; Huang *et al.*, 2006	*Boje *et al.*, 2003	Kaszkin *et al.*, 2004; Huang *et al.*, 2005
Willow bark	Krivoy *et al.*, 2001; Khayyal *et al.*, 2005	Fiebich and Chrubasik, 2004; Khayyal *et al.*, 2005	Wurm *et al.*, 1982; Khayyal *et al.*, 2005	Fiebich and Chrubasik, 2004; Khayyal *et al.*, 2005	Kuppsamy *et al.*, 1990; Rohnert *et al.*, 1998	Kahkonen *et al.*, 1999
Nettle herb	El Haouari *et al.*, 2006	Obertreis *et al.*, 1996a	Obertreis *et al.*, 1996a	Obertreis *et al.*, 1996b; Teucher *et al.*, 1996; Schulze-Tanzil *et al.*, 2002	ni	Ozen and Korkmaz, 2003; Kanter *et al.*, 2005; Harput *et al.*, 2005
Avocado soybean	ni	Henrotin *et al.*, 2003	ni	Mauviel *et al.*, 1991; Kut-Lasserre *et al.*, 2001; Henrotin *et al.*, 2003; Andriamanalijaona *et al.*, 2006	*Kut *et al.*, 1998	ni
Rose hip and seed	ni	ni	ni	ni	ni	ni
Ginger	Wu *et al.*, 1993; Nurtjahja-Tjendraputra *et al.*, 2003	Tjendraputra *et al.*, 2001; Frondoza *et al.*, 2004; Kim *et al.*, 2004	Kiuchi *et al.*, 1992	Frondoza *et al.*, 2004; Kim *et al.*, 2004	ni	Wang *et al.*, 2003; Kuo *et al.*, 2005
Salai guggal	no	no	Ammon *et al.*, 1991	ni	*Safayhi *et al.*, 1997	Altmann *et al.*, 2004
Cat's claw[b]	Aguilar *et al.*, 2002	Aguilar *et al.*, 2002	ni	Sandoval *et al.*, 2000; Allen-Hall *et al.*, 2007; Miller *et al.*, 2006	ni	Sandoval *et al.*, 2000; Sandoval *et al.*, 2002; Goncalves *et al.*, 2005; Pilarski *et al.*, 2006
Seed oils with GLA	Boberg *et al.*, 1985	Vang and Ziboh, 2005	Vang and Ziboh, 2005	Rothman *et al.*, 1997; DeLuca *et al.*, 1999; Furse *et al.*, 2002	ni	ni

[a] Anticonvulsive action (Mahomed and Ojewole, 2006).
[b] Interaction with 5-HT2 receptors (Jurgensen *et al.*, 2005).
ni = not investigated.

Methodological quality and level of evidence were assessed as described in a previous review (Gagnier *et al.*, 2004; Agosti *et al.*, 2006; Chrubasik *et al.*, 2006a): Quality items: A, eligibility criteria specified, B, randomization appropriate, C, treatment allocation concealed, E, similarity at baseline, F, outcome measures and control interventions explicitly described, G, co-interventions comparable, H, outcome measures relevant, I, adverse events and J, drop-outs fully described, K, sample size based on *a priori* power calculation, L, intention-to-treat analysis, N, point estimates and measures of variability, presented for the primary outcome measure, O, appropriate timing giving a Total Score (TS) of 13 with a cut off of 10 for high quality.

The level of evidence was defined as *strong* – at least two confirmatory studies demonstrating a clinical relevant effect, *moderate* – consistent findings among one confirmatory study with a clinical relevant effect and/or multiple exploratory studies with a quality score of at least 10, *insufficient* only one high quality exploratory study and/or exploratory studies of low quality, *conflicting* inconsistent findings among two confirmatory studies and/or multiple exploratory studies.

RESULTS

A total of 657 citations (293 OVID(MEDLINE), 328 PUBMED and 36 COCHRANE COLLABORATION LIBRARY) were screened and 15 systematic reviews were identified (Table 2). The details of the studies considered in the reviews with a total quality score of at least 10 and of the confirmatory study by Biegert *et al.* (2004) – not considered in the reviews) are listed on the webpage (www.uniklinik-freiburg.de/rechtsmedizin/live/forschung/phytomedicine/originalartikel.html). None of the reviews were the data pooled due to different outcome measures or endpoints or because of weaknesses of the studies. Strong evidence of effectiveness exists only for 300 mg of an avocado soybean unsaponifiable fraction (three confirmatory studies, effect size clinically relevant: Ernst, 2003) and for *Harpagophytum procumbens* preparations that contained more than 50 mg harpagoside in the daily dosage (two confirmatory studies (effect size small), two exploratory studies of high quality: Chrubasik *et al.*, 2003a). Moderate evidence of effectiveness exists for a powder from the rose hip and seed subspecies *lito* (two exploratory studies of high quality: Chrubasik *et al.*, 2006a) and ginger preparations (two confirmatory studies (effect size very small), one exploratory study of high quality: Chrubasik *et al.*, 2005a). The evidence of effectiveness was insufficient for *Boswellia serrata* gum resin (one exploratory study of low quality: Basch *et al.*, 2004), herbal mixtures and nettle herb mentioned in the global systematic reviews (Ernst and Chrubasik, 2000; Long *et al.*, 2001; Little and Parsons, 2001; Soeken, 2004; Setty and Sigal, 2005; Gagnier *et al.*, 2006). For willow bark, the evidence is conflicting (Schmid *et al.*, 2000; Chrubasik *et al.*, 2000; Biegert *et al.*, 2004) due to a recent confirmatory study with a negative result (Biegert).

DISCUSSION

The updated ACR guidelines for the treatment of osteoarthritis recommend the use of non-pharmacological treatments to reduce the consumption of those synthetic medications that are associated with adverse events, such as NSAIDs (www.rheumatology.org/). Herbal preparations are not included in these recommendations although a main advantage of OA treatment with herbal medicines is the low incidence of adverse events (ESCOP Monographs). Serious adverse events to date have not occurred for any of the herbal preparations.

At least 60% of the patients suffering from OA hip or knee pain or of non-specific low back pain treated with the aqueous *Harpagophytum* extract Doloteffin^{R} benefited to various extents from the treatment (Chrubasik *et al.*, 2002b). There was no difference in response attributable to the location of pain. Those who responded had a mean pain decrease of 80% after 2 to 3 months which was maintained over the year of extract consumption (Chrubasik *et al.*, 2005a). This was

Table 2. Number of systematic reviews investigating herbal preparations for OA or low back pain, references and evidence of effectiveness as evaluated in this review

	No	References	Evidence
Avocado soybean unsaponifiables	1	Ernst, 2003	Strong for 300 mg/day
Devil's claw	5	Chrubasik *et al.*, 2003a, 2004; Gagnier *et al.*, 2004; 2006 (see below) Braendler *et al.*, 2006; Brien *et al.*, 2006	Strong for preparations with >50 mg harpagoside in the daily dosage
Ginger	1	Chrubasik *et al.*, 2005b	Moderate for lipophilic extracts
Rose hip and seed	1	Chrubasik *et al.*, 2006a	Moderate for a subspecies *lito* powder
Willow bark	1	Gagnier *et al.*, 2006 (see below)	Conflicting for a 70% ethanol extract with 240 mg salicin/day
Salai guggal or other preparations	6	Basch *et al.*, 2004 Ernst and Chrubasik, 2000; Long *et al.*, 2001; Little and Parsons, 2001; Soeken 2004; Setty and Sigal, 2005; Gagnier *et al.*, 2006	Insufficient

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confirmed in a second surveillance study over 1 year (Chrubasik *et al.*, 2007). The effectiveness of Harpagophytum preparations that contained more than 50 mg harpagoside in the daily dosage was not inferior to NSAIDs (Chantre *et al.*, 2000; Chrubasik *et al.*, 2003b). Since there is strong evidence for *Harpagophytum* preparations as well as for the avocado soybean unsaponifiables in alleviating osteoarthritic pain, the usefulness of these preparations should not be neglected and their possible place in the treatment schedule before that of the NSAIDs should be considered.

The doses investigated in the clinical trials have been chosen empirically (see webpage), one might therefore assume that higher doses might be more effective. Two studies investigating different doses of an aqueous *Harpagophytum* extract (Chrubasik *et al.*, 1999) and an ethanol willow bark extract (Chrubasik *et al.*, 2000) indicate such a dose-dependent effect. However, for the avocado soybean unsaponifiables a ceiling effect was observed (Appelboom *et al.*, 2001). If herbal preparations are used, the standardization on marker constituents should be considered. Non-characterized herbal preparations may be ineffective (Chrubasik *et al.*, 1996a).

Animal data suggest that herbal medications may prevent the destruction of cartilage in addition to their antiinflammatory effect (Mazieres *et al.*, 1993; Khayyal and el-Ghazaly, 1998; Cake *et al.*, 2000; Chrubasik *et al.*, 2006b). Unfortunately, a study over 2 years on the structural effect of the avocado soybean fraction failed to demonstrate reduced joint space loss in patients suffering from hip arthrosis (Lequesne *et al.*, 2002). It may well be that the preventive effect of the herbal medicines requires early commencement of the treatment before anatomic lesions have occurred and more sensitive diagnostic methods to detect small cartilage changes. We disagree with the recommendation of Eisenberg and coworkers, that herbal treatment be started only after all other treatments have failed (Eisenberg *et al.*, 1998). Further studies are urgently required that prove clinical effectiveness beyond any doubt. Such studies need to consider the quality criteria defined by the International Conference of Harmonization, in particular to apply an *a priori* hypothesis with sufficient power (www.ich.org/). Otherwise herbal treatment of painful osteoarthritis or non-specific low back pain will fail to gain access into the treatment guidelines.

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Details of the randomized double-blind studies investigating the impact of herbal medicines on chronic OA or low back pain and having a quality score of at least 10.

A eligibility criteria specified, B randomization appropriate, C treatment allocation concealed, E similarity at baseline, F outcome measures and control interventions explicitly described, G co-interventions comparable, H outcome measures relevant, I adverse events and J drop-outs fully described, K sample size based on *a priori* power calculation, L intention-to-treat analysis, N point estimates and measures of variability presented for the primary outcome measure, O appropriate timing giving a Total Score (TS) of 13.

* including 500–1500 mg of dried galanga rhizomes; H harpagoside, G gingerol

§ hypothesis not proven; C control or placebo

§§ group Salix had less patients with hip arthrosis, no information on duration of disease, consumption on analgesics, state of depression etc.

	Avocado Soybean Unsaponifiables		
Source	Blotman *et al.*, 1997 *Rev Rhum Engl Ed* **64:** 825–834	Maheu *et al.*, 1998 *Arthritis Rheum* **41:** 81–91	Appelboom *et al.*, 2001 *Scand J Rheumatol* **30:** 242–247
n =	153	164	260
Drug	300 mg	300 mg	300, 600 mg
Extract	Fraction	Fraction	Fraction
Solvent			
Control	Placebo	Placebo	Placebo
Marker			
Design	Parallel	Parallel	Parallel
Duration	3 mos	6 mos	3 mos
A	hip, knee	hip, knee	hip, knee
B	yes	yes	yes
C	yes	yes	yes
E	yes	yes	yes
F	yes	yes	yes
G	yes	yes	yes
H	yes	yes	yes
I	yes	yes	yes
J	yes	yes	yes
K	yes	yes	yes
L	yes	yes	yes
N	yes	yes	yes
O	yes	yes	yes
Effect vs C	superior	superior	superior
TS	13	13	13

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	Harpagophytum procumbens			
Source	Chantre *et al.*, 2000 *Phytomedicine* **7**: 177–183	Chrubasik *et al.*, 1996b *Phytomedicine* **3**: 1–10	Chrubasik *et al.*, 1999 *Eur J Anaesthesiol* **16**: 118–129	Chrubasik *et al.*, 2003b *Rheumatology* **42**: 141–148
n =	122	118	197	88
Drug	2.6 g	4.5 g	4.5 g	4.5
Extract	Powder	1.5-2.5:1	6-9:1	1.5-2.5:1
Solvent		Water	Water	Water
Control	Diacerhein	Placebo	Placebo	Vioxx
Marker	60 mg H	50 mg H	50/100 mg H	60 mg H
Design	Parallel	Parallel	Parallel	Parallel
Duration	over 16 wks	4 wks	4 wks	6 wks
A	hip, knee	nsLBP	nsLBP	nsLBP
B	yes	yes	yes	Yes
C	yes	yes	yes	Yes
E	yes	yes	yes	Yes
F	yes	yes	yes	Yes
G	yes	yes	yes	Yes
H	yes	yes	yes	Yes
I	yes	yes	yes	Yes
J	yes	yes	yes	Yes
K	yes	(yes)§	yes	No
L	yes	no	yes	Yes
N	yes	no	yes	Yes
O	yes	yes	yes	Yes
Effect vs C	not inferior	superior	superior	not inferior
TS	13	10.5	13	12

	Rosa canina lito	
Source	Rein *et al.*, 2004 *Phytomedicine* **11**: 383–391	Warholm *et al.*, 2003 *Curr Ther Res* **64**: 21–31
n =	112	100
Drug	5 g	5 g
Extract	Powder	Powder
Solvent		
Control	Placebo	Placebo
Marker	1.5 mg galactolipid	1.5 mg galactolipid
Design	Cross-over	Parallel
Duration	over 3 months	over 4 months
A	OA multiple sites	hip, knee
B	yes	yes
C	yes	yes
E	yes	don't know
F	yes	yes
G	yes	yes
H	yes	yes
I	yes	yes
J	yes	yes
K	no	no
L	yes	yes
N	no	no
O	yes	yes
Result vs	superior	superior
TS	10	10

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	Salix species		
Source	Schmid *et al.*, 2000 *Z Rheumatol* **59:** 314–320	Chrubasik *et al.*, 2000 *Am J Med* **109:** 9–14	Biegert *et al.*, 2004 *J Rheumatol* **31:** 2121–2130
n =	78	210	127
Drug	about 1600 mg	1573 mg	1573 mg
Extract	8-14:1	8-14:1	8-14:1
Solvent	Ethanol 70%	Ethanol 70%	Ethanol 70%
Control	Placebo	Placebo	Placebo (P), Diclofenac (D)
Marker	240 mg salicin	120, 240 mg salicin	240 mg salicin
Design	parallel	parallel	Ralallel
Duration	2 wks	4 wks	6 wks
A	knee, hip	nsLBP	knee, hip
B	yes	yes	yes
C	yes	yes	yes
E	don't know	yes	don't know§§
F	yes	yes	yes
G	yes	yes	yes
H	yes	yes	yes
I	yes	yes	yes
J	yes	yes	yes
K	(yes)§	yes	yes
L	yes	yes	yes
N	no	yes	yes
O	yes	yes	yes
Result vs	superior	superior	inferior to D, similar to P
TS	11.5	13	12

	Zingiberis officinale		
Source	Bliddal *et al.*, 2000 *Osteoarthritis Cartilage* **8:** 9–12	Altman and Marcussen, 2001 *Arthritis Rheum* **44:** 2531–2538	Wigler *et al.*, 2003 *Osteoarthritis Cartilage* **11:** 783–789
n =	56	247	29
Drug	0.51 g	3-5.5 g*	1 g
Extract	20:1	10:1	not defined
Solvent	Acetone	Acetone	CO_2
Control	Placebo, Ibuprofen	Placebo	Placebo
Marker	not declared	not declared	40 mg G
Design	Cross-over	Parallel	Cross-over
Duration	3 wks	6 wks	3 mos
A	hip, knee	knee	Knee
B	yes	yes	Yes
C	yes	yes	Yes
E	yes	don't know	Yes
F	yes	yes	Yes
G	yes	yes	Yes
H	yes	yes	Yes
I	yes	yes	Yes
J	yes	yes	Yes
K	yes	yes	No
L	yes	yes	Yes
N	no	yes	Yes
O	yes	yes	Yes
Result vs	superior, not inferior	superior	Superior
TS	12	12	12

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