REVIEW ARTICLE

Evidence of Effectiveness of Herbal Medicinal Products in the Treatment of Arthritis
Part 1: Osteoarthritis

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Herbal medicinal products (HMPs) are used in a variety of oral and topical forms for the treatment of osteoarthritis. The aim of this study was to update a previous systematic review published in 2000. We searched electronic databases (MEDLINE, EMBASE, CISCOM, AMED, CINAHL, Cochrane registers) to June 2007, unrestricted by date or language, and included randomized controlled trials that compared HMPs with inert (placebo) or active controls in patients with osteoarthritis. Five reviewers contributed to data extraction. Dis-agreements were discussed and resolved by consensus with reference to Cochrane guidelines and advice from the Cochrane Collaboration.

Thirty-five studies (30 studies identified for this review update, and 5 studies included in the original review) evaluating the effectiveness of 22 HMPs were included. However, due to differing HMPs, interventions, comparators, and outcome measures, meta-analysis was restricted to data from studies of three HMPs: topical capsaicin, avocado-soybean unsaponifiables, and the Chinese herbal mixture SKI306X showed benefit in the alleviation of osteoarthritic pain.

Several studies investigating products from devil's claw, and a powder from rose hip and seed, reported favorable effects on osteoarthritic pain, whereas two studies of a willow bark extract returned disparate results. Three studies of Phytodolor N[R] were of limited use because doses and measures were inconsistent among trials. The remaining Single studies for each HMP provided moderate evidence of effectiveness. No serious side effects were reported with any herbal Intervention.

Despite some evidence, the effectiveness of none of the HMPs is proven beyond doubt. The obvious potential benefits of HMPs in the treatment of Osteoarthritis are reduced reliance on synthetic medications with the associated risks of harmful adverse events, but further clinical trials are necessary before HMPs can be adopted in osteoarthritis treatment guidelines. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: Herbal medicine; Osteoarthritis; Clinical trials; effectiveness; Cochrane Review

INTRODUCTION

The American College of Rheumatology (ACR) has published recommendations for the medical management of Osteoarthritis (OA; Altman *et al,* 2000). Management goals include control of pain and improvement in f unction and health-related quality of life, with avoidance, if possible, of toxic effects of therapy. Implied in these goals is that non-pharmacologic modalities should be considered as first interventions or together with first-line drug therapies. Herbal medicinal products (HMPs) are not among the options recommended, although they are used in a variety of oral and topical forms for the treatment of OA (Herman *et al,* 2004).

Patients' reasons for using HMPs include: (1) dissatis-faction with conventional treatment; (2) desire to control own health care; (3) agreement with the philosophy and ideas of alternative therapies (Astin, 1998); and (4) avoidance of adverse side effects of conventional therapies (Ernst *et al,* 1995).

The mechanism of action of the HMPs is broader than that of the non-steroidal anti-inflammatory drugs (NSAIDs) and/or analgesics in current use for painful Osteoarthritis. Although the exact mechanisms of action have not yet been elucidated, there is no doubt that all plant materials act via several pathways (some not yet identified), including Inhibition of cyclooxygenäse (COX) and/or lipoxygenäse (LOX), inhibition of cytokine release, inhibition of elastase or hyaluronidase, as well as antioxidative activity (Chrubasik *et al,* 2007; further details in Table 1). Capsaicin has a different mode of action; it alters synthesis, storage, transport, and release of substance P (Buck and Burks, 1986) and

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

	Inhibition of				
	COX-1	COX-2	LOX	Cytokines	Elastase" Hyaluronidase
Avocado soybean *Persea americana Glycine max*	not investigated	Henrotin *et al.*, 1998; 2003; Au *et al.*, 2007 Gabay *et al.*, 2007	not investigated	Mauviel *et al.*,1991 Boumediene *et al.*, 1999 Kut-Lasserre *et al.*, 2001 Henrotin *et al.*,1998; 2003; 2006; Altinel *et al.*, 2007 Andriamanalijaona *et al.*, 2006; Au *et al.*, 2007 Gabay *et al.*, 2007	Kut *et al.*, 1998
Cat's claw** *Uncaria* species	Aguilar *et al.*, 2002	Aguilar *et al.*, 2002	not investigated	Sandoval *et al.*, 2000; 2002 Allen-Hall *et al.*, 2007 Aguilar *et al.*, 2002 Miller *et al.*, 2006	not investigated
Devil's claw* *Harpagophytum procumbens*	**no activity** Fiebich *et al.*, 2001 Whitehouse 1983	Fiebich *et al.*, 2001 Chrubasik *et al.*, 2002b Kundu *et al.*, 2005 Na *et al.*, 2004 Huang *et al.*, 2006 Abdelouahab *et al.*, 2008	Loew *et al.*, 2001 Günther *et al.*, 2006	Fiebich *et al.*, 2001 Chrubasik *et al.*, 2002b Huang *et al.*, 2006 Chrubasik *et al.*, 2006	"Boje *et al.*, 2003
Ginger *Zingiber officinalis*	Wu *et al.*, 1993 Nurtjahja- Tjendraputra *et al.*,2003 Kiuchi *et al.*,1992	Tjendraputra *et al.*, 2001 Frondoza *et al.*, 2004 Kim *et al.*, 2004 Lantz *et al.*, 2007	Kiuchi *et al.*,1992	Frondoza *et al.*, 2004 Kim *et al.*, 2004 Lantz *et al.*, 2007	"Tsukahara *et al.*, 2006
Nettle herb *Urtica dioica*	El Haouari *et al.*, 2006 Obertreis *et al.*, 1996(a)	not investigated	Obertreis *et al.*, 1996(a)	Obertreis *et al.*, 1996(b) Teucher *et al.*, 1996 Riehemann *et al.*, 1999 Klingelhöfer *et al.*, 1999 Schulze-Tanzil *et al.*, 2002	"Melzig *et al.*, 2001
Rose hip and seed *Rosa canina*	Jäger *et al.*, 2007 Wenzig *et al.*, 2007	Jäger *et al.*, 2007 Wenzig *et al.*, 2007	**no activity** Wenzig *et al.*, 2007	not investigated	"Rennert *et al.*, 2002
Phytodolor[R] **Herbal mixture**		Schaser *et al.*, 2006 Bonaterra *et al.*, 2007	Meyer *et al.*, 1995	Schaser *et al.*, 2006 Bonaterra *et al.*, 2007	"Kruedener *et al.*, 1996 "Melzig *et al.*, 1999
SKI 306X Herbal mixture	not investigated	Kim *et al.*, 2005a	Kim *et al.*, 2005a	Kim *et al.*, 2005a Choi *et al.*, 2002	not investigated
Salai guggal *Boswellia serrata*	Siemoneit *et al.*, 2007	**no activity** Ammon *et al.*,1993 Siemoneit *et al.*, 2007	Ammon *et al.*, 1991; 1993 Poeckel *et al.*, 2006 Wildfeuer *et al.*, 1998	Roy *et al.*, 2005; 2006 Takada *et al.*, 2006 Gayathri *et al.*, 2007 Chevrier *et al.*, 2005	Safayhi *et al.*, 1997
Curcuma longa	Chainani-Wu, 2003	Chainani-Wu, 2003	Chainani-Wu, 2003	Chainani-Wu, 2003	Chainani-Wu, 2003
Willow bark *Salix* species	Khayyal *et al.*, 2005	Fiebich & 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
Arnica *Arnica montana*	not investigated	not investigated	Tornhamre *et al.*, 2001	Lyss *et al.*, 1997; 1999 Klaas *et al.*, 2002	"Siedle *et al.*, 2002; 2003
Comfrey *Symphytum officinale*	not investigated	not investigated	not investigated	not investigated	not investigated

* anticonvulsive action (Mahomed and Ojewole, 2006); ** interaction with 5-HT2 receptors (Jürgensen *et al.*, 2005).
"elastase if not marked hyaluronidase, collagenase.

Antioxidative Effect	Inhibition of Cytpokines				
	Interleukin-1ß	TNF-α	NF-κB	MMPs	Others
Kim et al., 2000 Au et al., 2007	Mauviel et al., 1991 Henrotin et al., 2003 Andriamanalijaona et al., 2006 Au et al., 2007	Au et al., 2007	Gabay et al., 2007	Henrotin et al., 1998 Gabay et al., 2007	Henrotin et al., 1998; 2003 2006; Altinel et al., 2007 Boumediene et al., 1999 Andriamanalijaona et al., 2006
Sandoval et al., 2000 Sandoval et al., 2002 Goncalves et al., 2005 Pilarski 2006	Allen-Hall et al., 2007	Sandoval et al., 2000 Sandoval et al., 2002 Allen-Hall et al., 2007	Aguilar et al., 2002	not investigated	Miller et al., 2006 not investigated
Kaszkin et al., 2004 Huang et al., 2006	Chrubasik et al., 2002b	Fiebich et al., 2001 Chrubasik et al., 2002b	Huang et al., 2006	not investigated	not investigated
Wang et al., 2003 Kuo et al., 2005 Asnani et al., 2007 Cao et al. 1993 Zhou and Xu, 1992	not investigated	Frondoza et al.,2004 Lantz et al., 2007	Frondoza et al., 2004 Kim 2004	not investigated	not investigated
Ozen et al., 2003 Kanter et al., 2005 Harput et al., 2005	Obertreis et al., 1996(b) Teucher et al., 1996	Obertreis et al., 1996(b) Teucher et al., 1996	Riehemann et al., 1999	Schulze-Tanzil et al., 2002	Riehemann et al., 1999 Klingelhoefer et al., 1999
Wenzig et al., 2007 Daels-Rakotoarison et al., 2002	not investigated	not investigated	not investigated	not investigated	not investigated
Strehl et al., 1995 Meyer et al., 1995 Hartwich et al., 2006 Rohnert et al., 1998a,b	Schaser et al., 2006	not investigated	not investigated	not investigated	not investigated Gayathri et al., 2007 **pro-inflammatory** Khajuria et al., 2008 Chevrier et al., 2005
Kim et al., 2005	not investigated	Kim et al., 2005	not investigated	Kim et al., 2005	Choi et al., 2002
pro-oxidative Altman et al., 2004 Glaser et al., 1999 **anti-oxidative** Gayathri et al., 2007	Gayathri et al., 2007	Roy et al., 2006	Takada et al., 2006	Roy et al., 2006	Roy et al., 2005, Gayathri et al., 2007, **pro-inflammatory,** Khajuria et al., 2008, Chevrier et al., 2005
Chainani-Wu, 2003	not investigated	Chainani-Wu, 2003	Bengmark, 2006	not investigated	Chainani-Wu, 2003
Kahkonen et al., 1999 Rohnert et al., 1998a,b Khayyal et al., 2005	Fiebich & Chrubasik, 2004 Khayyal et al., 2005	Khayyal et al., 2005	not investigated	not investigated	Khayyal et al., 2005
not investigated	Klaas et al., 2002	Klaas et al., 2002	Lyss et al., 1997 Klaas et al., 2002	not investigated	not investigated
not investigated	not investigated	not investigated	not investigated	not investigated	not investigated

thus, transmission of pain, stimulates vanilloid receptors (Dedov and Roufogalis,2000), and also destroys reversibly the fine nerve endings (Nolano *et al*, 1999) as well as inhibiting LOX (Flynn *et al*, 1986).

Interaction with cytokine release and collagen synthesis suggests that HMPs may interact with cartilage destruction. Avocado-soybean unsaponifiables (ASU) significantly prevented the occurrence of bruised cartilage lesions in a postcontusive model of OA in rabbits (Mazieres *et al*, 1993). Rabbits with unilateral transection of the anterior cruciate ligament and removal of the medial meniscus of the right knee (to induce traumatic OA), and fed with the *Harpagophytum* extract FB9195 over six months, excreted significantly less collagen cross-links (markers of bone and cartilage turnover; Hadzhiyski *et al*, 2006) than did control rabbits. Also, gene expression of tissue inhibitor of metalloproteinases-2 (TIMP-2) was significantly increased in cartilage of these *Harpagophytum*-treated rabbits (Chrubasik *et al*, 2006). At a dose of 200 mg/kg SKI306K reduced OA-like histological changes induced by injecting collagenase into the right-knee joint of mature rabbits. In contrast, diclofenac had no effect at 10 mg/kg (Choi *et al*, 2002).

The aim of this review was to update an existing systematic review on the effectiveness of HPMs in the treatment of OA (Little *et al*, 2000) by adding data from relevant randomized controlled trials published in the period from January 2000 to June 2007.

METHODS

All randomized controlled (placebo or active control) parallel and crossover trials examining the effects of HMPs for treating OA were included if patients were diagnosed with OA according to the ACR criteria (Altman *et al*, 1986; 1990; 1991). Studies with samples defined according to vague descriptions (e.g., 'joint pain') were not considered. Studies with participant samples defined according to incomplete or partial ACR criteria were included, and notes provided to identify possible weaknesses in sample selection.

Any form of herbal intervention compared with an inert (placebo) or active control, via any route of administration, was included. Herbal therapy used in conjunction with other treatments or combined with a non-herbal substance were also included if the effect of the non-herbal intervention was: (1) consistent among all groups, and (2) quantifiable. Herbal intervention included any plant preparation (whole, powder, extract, standardized mixture) but excluded homeopathy, aromatherapy, or any preparation of synthetic origin.

Primary outcomes included: changes in assessed clinical measures of effectiveness (e.g., WOMAC, Lequesne index); changes in self-reported measures of effectiveness (e.g., pain, use of medication); and any adverse reaction (AE). Secondary outcomes included general well-being or satisfaction indicators.

We searched the following electronic databases (from 1966): Cochrane Musculoskeletal Group Register; Cochrane Complementary Medicine Field Register; Cochrane Controlled Trials Register (CCTR); MEDLINE; EMBASE; CISCOM; AMED; CINAHL;

Dissertation Abstracts; BIDS IST Thesaurus and free text searches were performed across each database to combine the terms arthritis and herbal medicine. The general structure of the search strategy was arthritis (or Synonyms) and herb (or Synonyms). No methodological filter was applied and the search was not limited by language.

The following keywords were applied as search terms: arthritis, rheumatoid arthritis, reactive arthritis, adjuvant arthritis, infective arthritis, Osteoarthritis, gouty arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, periarthritis. Free text search terms included arthrit* and also combined the terms hip, knee, joint, musculoskeletal and pain, inflammation, movement, stiffness, medicine herbal, medicines herbal, herbal medicine, drugs Chinese herbal, plants medicinal. Free text search terms included herb* or plant*. On completion of the primary search, a secondary search combined the terms arthritis (or synonym) and each named herb. All titles and abstracts identified from electronic databases and other searches were independently examined by two investigators (CL, MC). A full manuscript was retrieved for each record that had the possibility of meeting the review criteria. Three reviewers (CL, MC, SC) independently assessed eligibility of retrieved studies for review according to the inclusion criteria. Five reviewers (MC, SC, AB, JG, TP) contributed to data extraction. Data were extracted from each eligible study by two reviewers acting independently. Where a study was defined as a crossover trial, data were extracted only up to the point of crossover in order that these data could be compared with those derived from parallel trials.

Two review authors (MC, SC) independently assessed the risk of bias of each included trial, against key criteria: random sequence generation; allocation concealment; blinding of participants, personnel and outcomes; incomplete outcome data; selective outcome reporting; and other sources of bias, in accordance with methods recommended by the Cochrane Collabo-ration (Higgins and Green, 2008). Each of these criteria was explicitly judged using: A = yes (low risk of bias); B = no (high risk of bias); C = unclear (either lack of Information or uncertainty over the potential for bias). Potential disagreements were discussed and resolved by referring to the original protocol and, if necessary, arbitration by member(s) of the Cochrane Steering Group.

Descriptive results are reported for all included studies. Studies with the same outcome measures and comparators were included in the meta-analyses. For dichotomous outcomes, odds ratios or relative risks were calculated. For continuous outcomes, a mean difference (MD) was calculated and confidence intervals (CI) reported at 95%. Chi-square and I^2 tests of heterogeneity were conducted and fixed or random effects models were chosen appropriately. Threshold values (p and I^2) for heterogeneity were not determined *a priori;* rather heterogeneity was reported using both chi-squared and I^2 values, with I^2 of 30-60% considered to represent moderate heterogeneity, and I^2 of more than 60% as substantial heterogeneity. This categorical Classification was consistent with the chi-square analyses if $p = 0.10$ was accepted as the arbiter of significance. Reasons for heterogeneity were explored by reviewing

study designs and results. I^2 values of 80% or greater were considered to represent unacceptable heterogeneity indicating that the studies could not be rationally pooled.

Main results of the review are presented in summary of findings tables, including an overall grading of the evidence using the GRADE approach (Schunemann, 2008a), and a summary of the available data on the main outcomes, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schunemann,2008b). Quality of evidence for each herbal intervention was classified as High, Moderate, Low, or Very Low as an indication of confidence in the results of studies and meta-analyses. For example, high-quality evidence is robust and further studies are very unlikely to change our confidence in the estimate of effect; conversely, low-quality evidence is open to question and further research is very likely to have an influence on our confidence in the estimate of effect and may change the estimate.

RESULTS

From approximately 2500 citations, a total of 30 new studies were identified for inclusion in the updated review, including six studies published between 1988 and 1997 that had been overlooked in the previous review (Schadler, 1988; Bernhardt *et al*, 1991; Huber, 1991; McCarthy and McCarthy, 1992; Altman *et al*, 1994; Schmelz *et al*, 1997; Bliddal *et al*, 2000; Leban *et al*, 2000; McCleane, 2000; Randall *et al*, 2000; Schmid *et al*, 2000; Schnitzer *et al*, 1994; Altman and Marcussen, 2001; Appelboom *et al*, 2001; Frerick *et al*, 2001; Jung *et al*, 2001; 2004; Piscoya *et al*, 2001; Badria *et al*, 2002; Biller, 2002; Lequesne *et al*, 2002; Kimmatkar *et al*, 2003; Warholm *et al*, 2003; Wigler *et al*, 2003; Biegen *et al*, 2004; Rein *et al*, 2004; Teekachunhatean *et al*, 2004; Winther *et al*, 2005; Grube *et al*, 2007; Widrig *et al*, 2007). New studies were added to the five studies included in the original review (Deal *et al*, 1991; Ferraz *et al*, 1991; Mills *et al*, 1996;Blotman *et al.*, 1997; Maheu *et al*, 1998). Thirteen studies are open to question because: (1) participants self-identified as having OA and a formal diagnosis might not have been established at baseline (Schadler, 1988; Huber, 1991; Schmelz *et al*, 1997; Randall *et al*, 2000; Badria *et al*, 2002; Grube *et al*, 2007); or (2) the criteria by which OA was established are inconsistent with ACR or European League Against Rheumatmism (EULAR) requirements (Deal *et al*, 1991; Ferraz *et al*, 1991; McCleane, 2000; Jung *et al*, 2001; Kimmatkar *et al*, 2003; Warholm *et al*, 2003; Rein *et al*, 2004). Two of the studies included participants with either rheumatoid arthritis or OA (Deal *etal*, 1991; Mills *et al*, 1996) but, in both cases, separate data for the OA subgroups were presented. One study appeared to have partly been reported twice (Rein *et al*, 2004; Winther *et al*, 2005), and the latter publication was excluded initially, but after discussion with the authoring group, was retained in the review and data extracted. The authors argued that one ethics committee approved the studies in a Single application, but that the studies were clinically and scientifically independent, using differing outcome measures. Our enquiries to the relevant ethics committee received no reply.

Reasons for excluding studies were: (1) not a randomized controlled trial; (2) discussion paper; (3) full study details not available; (4) unable to identify the herbal components of the intervention; (5) case series; (6) review paper; (7) inappropriate Statistical analysis; or (8) duplicate publication. A sub-analysis of one study (Rein *et al*, 2004) was identified in another publication (Winther *et al*, 2004), but was excluded from this review to avoid repetition of data. In the original review, one study was classified as pending assessment subject to full translation of the texts (Loew, 1996). In this update, language was no barrier to inclusion, and this study was excluded for other reasons.

Twenty six of the 35 studies were of parallel design (Bernhardt *et aZ.*,1991; Deal *et al*, 1991; Huber, 1991; McCarthy and McCarthy, 1992; Altman *et al*, 1994; Mills *et al*, 1996; Blotman *et al*, 1997; Schmelz *et al*, 1997; Maheu *et al*, 1998; Leban *et al*, 2000; McCleane, 2000; Schmid *et al*, 2000; Schnitzer *et al*, 1994; Altman and Marcussen , 2001; Appelboom *et al*, 2001; Frerick *et al*, 2001; Jung *et al*, 2001; 2004; Piscoya *et al*, 2001; Biller, 2002; Lequesne *et al*, 2002; Warholm *et al*, 2003; Biegert *et al*, 2004; Teekachunhatean *et al*, 2004; Grube *et al*, 2007; Widrig *et al*, 2007), and eight studies used a crossover design (Schadler, 1988; Ferraz *et al*, 1991; Bliddal *et al*, 2000; Randall *et al*, 2000; Kimmatkar *et al*, 2003; Wigler *et al*, 2003; Rein *et al*, 2004; Winther *et al*, 2005). One study was described as a crossover trial, but the methodology and reported results indicated that this study was conducted as a parallel trial (Badria *et al*, 2002), and in this review, this study is classified as a parallel design.

The 35 studies evaluated the effectiveness of 22 HMPs (Table 2). Six of these were not fully characterized so that the study could not be repeated (Ferraz *et al*, 1991; Altman and Marcussen, 2001; Piscoya *et al*, 2001; Badria *et al*, 2002; Teekachunhatean *et al*, 2004; Widrig *et al*, 2007). Oral mono-preparations were pre-pared from rose hip and seed, devil's claw root, willow bark, ginger root, *Petiveria alliacea* (tipi) herb, cat's claw root, and the gum resine of *boswellia serrata*. Topical HMPs included capsaicin and preparations from stinging nettle leaf, arnica herb and comfrey root. Oral HMP mixtures included patented Piascledine 300[R], Phytodolor N[R], Duhuo Jisheng Wan (DJW), Reumalex[R], a combination of extracts of two ginger species and a combination of a *boswellia carteri* and a *curcuma longa* extract (Table 2).

Only six studies adequately met all six validity criteria and thus were at minimal risk of bias (Maheu *et al*, 1998; Schmid *et al*, 2000; Altman and Marcussen, 2001; Lequesne *et al*, 2002; Wigler *et al*, 2003; Biegert *et al*, 2004). Ten studies were described as randomized but the method of randomization was not reported, or was reported in insufficient detail to allow replication of the method (Deal *et al*, 1991; Bliddal *et al*, 2000; Leban *et al*, 2000; Randall *et al*, 2000; Frerick *et al*, 2001; Piscoya *et al*, 2001;Biller, 2002;Teekachunhatean *et al*, 2004; Grube *et al*, 2007; Widrig *et al*, 2007). One study was not randomized (Huber, 1991). This study, along with seven others, was described as double-blind, but methods of blinding were not reported

Table 2. Details of the herbal medicinal products used for the treatment of osteoarthritis (OA) in randomized controlled double-blind studies

SM study medication, $ethanolic extract stated in the thesis (University of Tübingen), **Information provided by manufacturer but not reported in paper, *Harpagoside content estimated indirectly and approximately from iridoid glycoside (IG) content in daily dose of raw material, otherwise taken from Sporer and Chrubasik (1999) and Salus and Sporer (unpublished).
GLA gammalinolenic acid, $50 g/100 g gel, marker details from Bioforce AG/Schweiz

| Plant | | Brand | Preparation | Drug/Extract ratio | mg/day | Marker | | References |
Name	Part					Constituent	mg/day	
Harpagophytum procumbens	root	Arthrotabs	aqueous extract	1.5–2.5:1	2400	harpagoside	30	Schmelz
		Flexiloges	ethanolic (60%) extract	4.5–5.5:1	960	harpagoside	<30	Frerick
		Flexiloges	ethanolic (60%) extract	4.5–5.5:1	960	harpagoside	<30	Biller
		Harpadol	cryoground powder		2610	harpagoside	60	Leban
Populus tremula	bark, leaf	Phytodolor	fresh plant ethanolic (45,6%) extract	3:1:1	5–8 ml	salicin	4.8–8	Schadler
Fraxinus excelsior	bark					salicyl alcohol	0.48–0.8	Bernhardt
Solidago virgaurea	herb					isofraxidin	0.67–1.1	Huber
						total flavonoids	0.34–0.56	
Salix pupurea + daphnoides	bark	SM	ethanolic (70%) extract	10–20:1	1360	salicin	240	Schmid
Salix daphnoides		SM (Assplant = Assalix)	ethanolic (70%) extract	8–14:1	1573	salicin	240	Biegert
Rosa canina	rose hip and seed	Litozin	powder		5000	galactolipid	1.5	Warholm Rein
Zingiber	root	Eurovita 33	acetone extract**	20:1**	510	not stated		Bliddal
		Zintona EC	CO2 extract	not stated	1000	gingerol	40	Wigler
Zingiber officinale + Alpinia officinale		EXT 77	acetone extract$$	20:1**	not stated	not stated		Altman 2002
		daily dose 900 mg	not stated	not stated	not stated	not stated		
Persea gratissima (P)	oil	Piascledine 300	unsaponifiable fraction 1/3 P;2/3 G		300	not stated		Blotmann
Glycine max (G)					600			Maheu
					300			Appleboom
					600			Lequesne
					300			
Boswellia serrata	gum resine	CapWokvel	extract, solvent not stated	not stated	999	boswellic acid	40%	Kimmatkar
						organic acids	65%	
Boswellia carteri +	gum resine	SM	extract, solvent not stated	not stated	not stated	boswellic acid	37.5%	Badria
Curcuma longa	root	daily dose 1500 mg	extract, solvent not stated	not stated	not stated	not stated		

Species	Part	Product	Extraction form	Ratio	Dose	Active compound	Concentration	Author
Uncaria guianensis	bark							Piscoya
			freeze-dried aqueous extract	not stated	100	not stated		
Urtica dioica (local)	leaf	SM		not stated				Randall
Capsicum (local)	fruit	Zostrix		0.025%	4x	capsaicin	0.025%	Deal
	fruit	Arlacel 165		0.075%	4x	capsaicin	0.075%	McCarthy
	fruit	Zostrix		0.025%	4x	capsaicin	0.025%	Altman 1994
	fruit	Zostrix		0.025%	4x – 2x	capsaicin	0.025%	McCleane
	fruit							Schnitzer
Clematis mandshurica	root	SKI306X	ethanol 30% extracts	7:1	50–150	oleanolid acid	4%	Jung 2001
Prunella vulgaris	flower	1:1:2	thereafter	7:1	50–150	rosmarinic + ursolic acids	0.2 + 0.5%	Jung 2004
Trichosanthes kirilowii	root	SKI306X	butanol extraction	7:1	100–300	acids: hydroxybenzoic	0.03%	
Clematis mandshurica	root		ethanol 30% extracts	7:1	150	hydroxymethoxybenzoic	0.03%	
Prunella vulgaris	flower		thereafter	7:1	150	trans-cinnamic	0.05%	
Trichosanthes kirilowii	root		butanol extraction	7:1	300	see above		
Salix alba	cortex	Rheumalex	powder		200	salicin	40–80 mg	Mills
Guaiacum officinale	resin		powder		80			
Cimicifuga racemosa	root		powder		70			
Smilax officinale?	root		extract, solvent not stated	4:1	50			
Populus tremulus?	cortex		extract, solvent not stated	7:1	34			
Symphytum officinale	radix	Kytta Salbe f	ethanolic (60%) extract	2:1	3 × 6 cm	allantoin	0.2–0.5%	Grube
Arnica montana	herb	A. Vogel Arnica Gel	tincture, 50% ethanol$	20:1	3 × 4 cm	not stated		Widrich
Chinese Mixture[footnote]	footnote	Duhuo Jisheng Wan	powder		3 × 3 g	not stated		Teekachunhatean
Petiveria alliacea	herb	SM	aqueous extract	9 g/600 ml	600 ml	not stated		Ferraz

[footnote] 7.75% each of: radix angelicae pubescentiis, radix gentianae macrophyllae, cortex eucommiae, radix achyranthis bidentatae, radix angelicae sinensis, herba taxilli, radix rehmanniae preparata, rhizoma chuanxiong, cortex cinnamomi, radix ledebouriellae.
5% each of: radix paeoniae alba, radix codonopis, radix glycyrrhizae, poria.
2.5% herba asari.

(Schadler, 1988; Ferraz et al, 1991; Mills et al, 1996; Schmelz et al, 1997; Appelboom et al, 2001; Jung et al, 2001; Badria et al, 2002). All five studies of topical capsaicin were down-graded despite reporting a complete description of the double-blinding method, because we considered that placebo validity and blinding may be compromised by b Urning side effect of this topical intervention (Deal et al, 1991; McCarthy and McCarthy, 1992; Altman et al, 1994; McCleane, 2000; Schnitzer et al, 1994).

Allocation concealment was assessed according to the Cochrane format, as described in the methods (Higgins and Green, 2008). Allocation concealment was well described and considered adequate in 11 studies (Bernhardt et al, 1991; Altman and Marcussen, 2001; Bliddal et al, 2000; Schmid et al, 2000; Biller, 2002; Lequesne et al, 2002; Kimmatkar et al, 2003; Wigler et al, 2003; Biegert et al, 2004; Rein et al, 2004; Widrig et al, 2007), and could not be clearly determined in any other study, although it is emphasized that failure to conceal allocation could not be determined either.

Topical capsaicin

Five studies (n = 456) compared topical capsaicin for the control of OA hand pain with placebo. Although in all studies, the placebo vehicle Creams were prepared and packaged to appear indistinguishable from the active agent, blinding and placebo validity may have been compromised by a local burning Sensation that may occur as a side effect with topical capsaicin application. In one study, burning at the site of application was noted by 44% of participants treated with capsaicin and by one treated with placebo (Deal et al, 1991). In four studies, 0.025% wv capsaicin cream was applied four times daily (Deal et al, 1991; Altman et al, 1994; McCleane, 2000; Schnitzer et al, 1994). One of these studies included two additional parallel group comparisons (to glyceryl trinitrate, and a combination of capsaicin and glyceryl trinitrate). A further study compared a higher dose (0.075% wv) capsaicin cream to placebo (McCarthy and McCarthy, 1992).

Since all studies investigating 0.025 %ww capsaicin cream used a 100 mm visual analogue scale (VAS 0-100) for pain assessments, these data were pooled in sub-groups according to the length of intervention, either three or four weeks, and whether results were reported as absolute scores or percentage change in VAS.

Absolute VAS pain scores alter three weeks of intervention were in favor of capsaicin (two studies, 122 participants; MD -6.81, CI -14.58 to 0.96; McCleane, 2000; Schnitzer et al, 1994). Results alter four weeks of intervention were similar (two studies, 179 participants; MD -8.26, CI -14.88 to -1.65; Altman et al, 1994; McCleane, 2000). When these subgroups were combined, the results are consistent; MD -7.65, CI -12.69 to -2.61.

Some investigators reported pain improvement in terms of VAS percentage changes. Results consistently favored capsaicin over placebo: alter three weeks MD -18.50%, CI -40.95 to 3.95 (Schnitzer et al, 1994), and after four weeks MD -13.90, CI -32.39 to 4.59 (Deal et al, 1991). Similar results were achieved when pain was assessed on a categorical pain scale: MD -0.35, CI -0.80 to 0.10 after four weeks (Deal et al, 1991) or when physician's global evaluation was considered (scored

1-3, with 3 representing complete resolution of Symptoms): MD 0.39, CI -0.10 to 0.88 after four weeks (Deal et al, 1991).

Although the results of these studies are similar and consistently in favor of topical capsaicin for the relief of OA pain, the evidence of effectiveness was considered as moderate. Although sample size and consistent results over several studies might satisfy a higher grading of evidence quality, allocation concealment was unclear in each of the studies, and blinding is problematic in studies of topical agents. We considered that the quality of these studies may have been somewhat compromised by the possibility that participants may be able to differentiate the active intervention from the placebo of the basis of a burning side effect and dampened our Classification of the evidence accordingly. There is moderate level evidence that four-times-daily use of topical capsaicin (0.025 %wv) cream over three or four weeks significantly reduces OA pain.

Avocado-soybean unsaponifiables (ASU)

The original review concluded that the evidence for ASU in the treatment of OA was convincing (Blotman et al, 1997; Maheu et al, 1998). A further study supported this conclusion (Appelboom et al, 2001). Another study of the ASU over two years did, however, not reveal any differences between groups, neither in the primary outcome measure of joint width, nor in clinical parameters including pain, function, NSAID consumption (Lequesne et al, 2002). All four studies compared a daily dose of 300 mg ASU to placebo, and one study included an additional group that received 600 mg ASU daily (Appelboom et al, 2001). A total of 609 participants with OA completed these trials, and in one study sub-group of people with OA of the hip and OA of the knee were identified and analyzed independently (Maheu et al, 1998). Pooling of results for NSAID consumption measured as diclofenac equivalents, pain (VAS 0-100 mm), and Lequesne functional index indicated that these studies were highly heterogeneous, returning I^2 of approximately 80% for each meta-analyses of each of these outcome measures. Although the longer trial returned results that conflicted with the shorter trials, it was designed to investi-gate structural joint changes as the primary outcome, and clinical outcomes were of secondary importance (Lequesne et al, 2002). The investigators reported that they were surprised by the lack of symptomatic improvements among participants in the ASU group, and were unable to explain why this trial was markedly different to those of other well designed trials of ASU in people with OA (Lequesne et al, 2002). Rather than present a Single meta-analysis, we have sub-grouped these studies according to the dose of ASU used and the length of the intervention period.

Pain (VAS 0-100). In two studies (326 participants), pain scores were pooled using a fixed effects model, MD was -10.79, CI -14.91 to -6.66 after three months of 300 mg ASU daily intake (Blotman et al, 1997; Appelboom et al, 2001). Results from the one study (156 participants) that included a 600 mg daily dose are consistent in favor of ASU (MD -14.20, CI -20.82 to -7.58; Appelboom et al, 2001). Results after six months of treatment with a 300 mg daily dose of ASU also favor ASU (MD -10.40, CI -17.20 to -3.60; Maheu et al, 1998), but after 12 months, results indicate no superior

performance than placebo (MD 1.00, CI -6.58 to 8.58; Lequesne *et al*, 2002). Results also differ somewhat according to region. Maheu *et al.* (1998) reported greater improvement amongst participants with OA of the hip (MD -13.80, CI -25.22 to -2.38) compared with those with OA of the knee (MD -7.10, CI -14.45 to 0.25).

Physical function. Lequesne algofunctional index was used as a measure of overall physical function in all studies (Blotman *et al*, 1997; Maheu *et al*, 1998; Appelboom *et al*, 2001; Lequesne *et al*, 2002). Again, results differed according to the length of intervention. After three months, use of either 300 mg or 600 mg ASU daily was favored (300 mg: MD -1.78, CI -2.49 to -1.06; 600 mg: MD -1.30, CI -2.38 to -0.22) as was treatment with the 300 mg dose after six months: MD -2.10, CI -3.21 to -0.99. But no difference was seen compared to placebo after 12 months of treatment with the 300 mg ASU dose: MD 0.10, CI -0.78 to 0.98. In one study, also functional disability (VAS 0-1000 mm) was assessed and had improved after six months in the ASU 300 mg group: (MD -13.20, CI -20.00 to -6.40; Maheu *et al*, 1998).

Despite multiple studies with adequate sample sizes, the evidence that three or six months of daily use of 300 mg of ASU affords statistically significant improvements in pain was graded as moderate because allocation concealment was unreported (unclear) in each of the studies showing these improvements. In all other ways, these studies were well designed, and the consistent results across three studies are convincing. Improvements may not be sustained in the longer term.

Consumption of NSAIDs. Use of NSAIDs was measured in some way in each of the studies, and results on this outcome were consistent within each study with those of self-reported pain. In studies with outcomes at 3 and 12 months, mean daily NSAID use was expressed as diclofenac equivalents (Dreizer *et al*, 1997). After three months of ASU therapy, regardless of dose, ASU consumption was favored (300 mg: MWD -28.17, CI -39.24 to -17.10; 600 mg: MD -28.50, CI -48.50 to -8.95), but after 12 months of treatment with 300 mg ASU per day, there was no difference between the ASU and placebo groups (MD 0.00 CI -11.82, to 11.82). Two studies also measured NSAID use as the number of days on which NSAIDs were taken over three months (Blotman *et al*, 1997; Appelboom *et al*, 2001). Pooled results favored ASU treatment: MD -5.72, CI -8.31 to -3.12. An alternate measure of NSAID use is the number of participants who resumed NSAID use by a given time. In two studies, these dichotomous data were collected after 60 days of ASU treatment, and when pooled returned a risk ratio (RR) of 0.77, CI 0.56 to 1.04, in favor of ASU (Blotman *et al*, 1997; Maheu *et al*, 1998).

AEs. The number of participants who reported AEs was reported per group in each study. In two studies, more placebo patients reported AEs (Blotman *et al*, 1997; Lequesne *et al*, 2002), and in the other two studies, more participants in the 300 mg ASU groups reported AEs (Maheu *etal*, 1998; Appelboom *et al*, 2001). When these data are meta-analyzed for the 300 mg ASU dose there was a negligible difference in the odds of a participant in either placebo or intervention group reporting an AE (OR 1.04, CI 0.73 to 1.48). These studies together constitute high-level evidence that participants taking 300 mg of ASU daily experience no greater odds of AEs than do participants taking a placebo preparation.

HMPs from devil's claw

Three studies compared extracts of *Harpagophytum procumbens* (devil's claw) to placebo in trials completed by 174 participants (Schmelz *et al*, 1997; Frerick *et al*, 2001; Biller, 2002). One study (92 participants) compared freeze-ground crude plant material to the weak NSAID diacerhein (Leban *et al*, 2000).

In the studies using an ethanolic extract of *Harpagophytum,* no improvement in WOMAC pain scores were found (Frerick*et al,* 2001; Biller, 2002). These authors provided post-hoc definitions of improvement that favored the intervention. 'Responders' to treatment were defined as participants whose WOMAC pain scores did not increase by more than 20% either with (Frerick *etal,* 2001) or without (Biller, 2002) additional rescue medication (up to 4000 mg ibuprofen) in weeks 17 to 20 of the study. These definitions of response are inconsistent with ACR criteria for response, and data derived from these measures have not been reproduced in this review.

In contrast, aqueous extract of *Harpagophytum* showed favorable effects on OA pain measured using a 0-4 categorical rating scale, but these data are also insufficiently reported (Schmelz *et al*, 1997). *Harpagophytum procumbens* powder was equally effective as diacerhein in reducing pain as measured using a 100 mm VAS (Leban *et al*, 2000). This study constitutes moderate evidence that four months daily use of 2610 mg *Harpagophytum procumbens* powder is not significantly different from 100 mg diacerhein, producing comparable improvements in pain. In this same study, participants in the *Harpagophytum* group used fewer NSAIDS (diclofenac) and analgesics (acetominophen/ caffeine) at all time points (30,60 and 120 days) than did participants in the diacerhein group. Due to differences in protocols and outcome measures, these studies were not suitable for data pooling.

Rose hip and seed powder

Three studies (291 participants) compared daily doses of 5 g of a rosehip and seed powder (Rosae caninae psuedofructus cum fructibus) to placebo and reported reductions in OA pain. Two studies used a standardized 5-point scale (0-4, 0 = no relief, 4 = almost total relief) for self-reported pain (Warholm *et al*, 2003; Rein *et al*, 2004) but the periods of intervention differed (three months, Rein *et al*, 2004; four months, Warholm *et al*, 2003), and data reporting in one study was insufficient to allow these data to be included in a meta-analysis (Warholm *et al*, 2003). The third study used the WOMAC instrument to gather self-reported measures of pain, stiffness, and physical function (Winther *et al*, 2005) . Each of these studies alone offers moderate evidence that daily consumption of 5 g of *rosa canina lito* powder produces improvement in OA pain superior to placebo, but differing outcome measures prevented meta-analyses of these data that would provide more robust evidence

Willow bark extract

Two studies (236 participants) of willow bark preparations returned differing results (Schmid *et al,* 2000; Biegert *et ai,* 2004). One study compared *Salix daphnoides* bark extract equivalent to 240 mg salicin to placebo and active (100 mg diclofenac) controls in parallel groups over six weeks to determine that although slightly more effective than placebo, willow bark was less effective than diclofenac in reducing OA pain assessed on the WOMAC pain scale (Biegert *et al,* 2004). In this study, similar numbers and severity of AEs were reported for both, the active and the control group. Another study compared the same daily dose of *Salix purpurea x daphnoides* bark extract to placebo and reported improvements in WOMAC pain scores after two weeks of intervention (Schmid *et al,* 2000).

Data from these studies were not suitable for meta-analyses because neither authors reported measures of variance (Standard deviations) for mean scores at the 14-day time point.

SKI306X

Two studies compared the Chinese herbal preparation SKI306X to placebo (Jung *et al,* 2001) or diclofenac (Jung *et al,* 2004). The earlier study (139 participants) was undertaken to determine the dose and safety profile of the intervention. The latter study (249 participants) was conducted to determine clinical efficacy. In the earlier study, daily doses of 300 mg, 400 mg, 600 mg were compared with placebo, and outcomes measured using a VAS and the Lesquesne index. Meta-analyses of these results (pooling doses) demonstrated consistent effects in favor of SKI306X for reducing pain (MD -17.36, CI -22.57 to -12.15) and improving physical function (MD -2.73, CI -3.71 to -1.74). Effect sizes for these outcomes did not show a consistent linear relationship to dose. There is moderate evidence that, regardless of dose, four weeks' daily use of SKI306X may produce statistically significant improvements in pain and physical function superior to placebo.

The number of AEs was reported per group, and more participants receiving 400 mg SKI306X reported AEs than did participants of any other group. When each of the intervention groups was compared with the placebo group, odds ratios differed between comparisons and were not consistent in direction (200 mg: OR 0.95, CI 0.23 to 3.83; 400 mg: OR 1.27, CI 0.33 to 4.95, 600 mg: OR 0.54, CI 0.11 to 2.59). When these data were meta-analyzed, there was a negligible difference in the odds of a participant in either placebo or SKI306X group reporting an AE (OR 0.90, CI 0.40 to 2.04).

In a follow up study, daily dose of 600 mg SKI306X was compared with 100 mg diclofenac. Results favored diclofenac for pain (VAS 0-100 mm; (MD 1.31, CI -2.78 to 5.40)) and physical function (Lequesne's algo-functional index; MD 0.77, CI 0.10 to 1.44). Statistically significant changes in these measures were seen within both groups over time. Between-group differences in physical function were statistically significant (p = 0.02), but differences in self-reported pain were not (p = 0.53). This study constitutes moderate evidence that daily use of 600 mg of SKI306X over four weeks produces improvements in pain that are not statistically significantly different from 100 mg diclofenac.

Phytodolor N[R]

Three studies compared Phytodolor NR to placebo or active control (piroxicam) in 176 participants. They reported in favor of Phytodolor NR for less additional use of NSAIDs (diclofenac) and improvement in range of motion as measured by finger-to-ground distance in lumbar flexion (Schadler, 1988; Bernhardt *et al,* 1991; Huber, 1991). Finger-to-ground distance is one of the methods used to quantify the Schober test (lumbar spine flexion in Standing), and is a measure of physical function more commonly used in the assessment of people with low back pain rather than OA. It is probably a meaningful measure of physical function in participants with OA of the lumbar spine, but none of these studies were limited to participants with spinal OA. These studies could be viewed with some skepticism because they were undertaken by the manufacturer (Steigerwald Pharmaceuticals). One of these studies was a crossover design with intervention periods of seven days' duration, and used a dose of Phytodolor NR 33% greater than that used in the two other studies (Schadler, 1988). The other two studies were of parallel design, one of three weeks' duration with measures at weekly intervals (Huber, 1991), and the other of four weeks' duration with measures at baseline, weeks 1, 2, and 4 (Bernhardt *et al,* 1991). Because doses of Phytodolor NR and some of the measures differed among trials, and because most of the data from these studies were reported as composite statistics (Chi Squares, *p* values), data could not be pooled for meta-analyses.

For one study, group means and mean changes from baseline can be calculated from frequency tables reported in the paper (Bernhardt *et al,* 1991). Standard deviations could not be calculated from the data provided.

Ginger extract

Data from three studies of ginger could not be pooled because three different ginger preparations were employed (Bliddal *et al,* 2000; Altman and Marcussen, 2001; Wigler *et al,* 2003).
A standardized extract of two species of ginger, *Zingiber officinale* and *Alpina galanga,* (EVEXT 77) was compared with placebo in 261 people with OA of the knee (Altman and Marcussen, 2001), and improvements in all components of the WOMAC score were reported in favor of the ginger group over placebo. These improvements were statistically significant for the WOMAC stiffness score (MD -8.30, CI -15.09 to -1.51, p = 0.02) and the WOMAC total score (MD -6.20, CI -12.24 to -0.16, p = 0.04), but not for the other domains of the WOMAC score. Also, significant improvement in favor of ginger were reported in pain (100 mm VAS) after Walking 50 feet (MD -9.60, CI -16.81 to -2.39, p = 0.009) and patient global assessment (MD 0.30, CI 0.06 to 0.54, p = 0.01). Generic measures of function and well-being (SF-36 physical and mental component

summary scores) showed no improvements among the ginger group over placebo.

A crossover trial of Zintona EC, a standardized ginger extract containing *Zingiber officinale,* with placebo reported in favor of the intervention on measures of pain on movement and handicap using the 100 mm VAS for these domains from the Hebrew version of the WOMAC (Wigler *et al,* 2003). The first arm of the crossover included 24 participants; one participant in the ginger group reported an AE (heartburn).

Another study compared a 510 mg daily dose of standardized extract of Chinese ginger (EVEXT 33) with 1200 mg ibuprofen and both tablet and capsule place-bos in a crossover trial in 67 participants (56 completed). Results reported in favor of ibuprofen for measures of pain (100 mm VAS), Lequesne algofunctional index, and use of NSAIDS (Bliddal *et al,* 2000). Data reporting in this study was insufficient to allow extraction for re-analysis.

The following Single studies constitute, at best, moderate evidence of effectiveness.

Boswellia-curcuma mixture

Although the authors described this study as a crossover trial, their reporting of the research method is consistent with a two-group parallel trial of a *Boswellia-curcuma* mixture compared with placebo over three months in patients suffering from OA (Badria *et al,* 2002). Minutes of pain-free Walking time were recorded in each group after one, two and three months of intervention. At each time point, the placebo group reported a shorter mean pain-free Walking time than the herbal mixture group; at two and three months, the differences were statistically significant (one month: MD 2.5, CI -.07 to 5.07, p = 0.06; two months: MD 4.00, CI 1.31 to 6.69, p = 0.004; three months: MD 3.5, CI 0.65 to 6.35, p = 0.02), but none of these measures were adjusted for baseline scores. For measures of pain on passive movement and pain on active movement, group means and mean changes from baseline were calculated from frequency tables reported in the paper (Badria *et al,* 2002). No measures of data spread were reported, and Standard deviations could not be calculated from the data provided.

Boswellia serrata gum resine extract

Boswellia serrata was compared with placebo in 30 participants with OA in a crossover trial of two periods of eight weeks intervention separated by a three-week wash-out period (Kimmatkar *et al,* 2003). In this review data have been extracted for the first arm of the trial only and may be considered as an eight-week parallel group trial. Pain, loss of movement, and swelling were rated using a 0-3 scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), and statistically significant improvements in favor of the *Boswellia serrata* group were reported on all measures over eight weeks of intervention (pain: MD -2.45, CI -2.85 to -2.23, p < 0.01; loss of movement: MD -2.16, CI -2.56 to -1.76, p < 0.01; swelling: MD -1.30, CI not estimable). Improvements are maintained when scores at eight weeks are adjusted for baseline differences (pain: MD -2.14, CI -2.53 to -1.75, p < 0.01; loss of movement: MD -2.00, CI -2.41 to -1.59, p < 0.01; swelling: MD -1.30, CI -1.99 to -0.61, p < 0.01).

Cat's claw extract

In a four-week, parallel group trial of an *Uncaria guia-nensis* extract compared with placebo (Piscoya *et al,* 2001), participants using the extract reported a statistically significant reduction in pain with activity within the first week of treatment (p < 0.01). The same pattern of improvements was seen in physicians' and patients' global assessments of disease activity. These improvements were maintained throughout the four-week trial, but data from these measures are not reported in sufficient detail to allow re-analysis. In contrast, reductions in night pain (MD -1.11, CI -2.64 to 0.42) and pain at rest (MD -0.52, CI -2.02 to 0.98) were not significant different although changes on these measures favored cat's claw over placebo.

Arnica tincture

Three-times-daily topical use of a gel containing *Arnica montana* extract was compared with a gel containing ibuprofen among 204 people (174 participants per protocol). Patients suffered from OA of the hands and were treated over three weeks (Widrig *et al,* 2007). Hand pain (assessed on a 100 mm VAS), hand function, 28 tender joint count, and duration and intensity of morning stiffness were not significantly different between groups, either as final end-point measures, or as change from baseline scores. Mean cumulative doses of rescue medication (acetominophen) differed only 25 mg (MD 25, CI 1066.47 to 1016.47) over the three weeks of intervention. The number of participants reporting AEs was similarly consistent between the two groups (OR 1.75 CI 0.70 to 4.37, p = 0.23). These results suggest that short-term topical use *oi Arnica* gel affords similar effects to those of ibuprofen gel. No comparison of arnica gel to placebo was identified in this systematic review of literature.

Comfrey extract

In a large (n = 220) parallel group trial, three-times-daily topical use of an ointment containing comfrey root (Symphyti offic. radix) extract was compared with placebo over three weeks. Grube *et al* (2007) found that treatment with comfrey root extract resulted in statistically significant improvements on 100 mm VAS measures of total pain, pain at rest, and pain on movement, and on WOMAC scores of pain, stiffness, physical function and overall score. Data from this study could not be extracted for further analysis because the trial authors reported neither absolute scores nor measures of data spread (Standard deviations, confidence intervals) for any outcomes. Mean within-group changes from baseline in pain at rest, pain on movement.

Reumalex[R]

A self-regulated dose ('two tablets at a time') of the herbal mixture Reumalex[R] was compared with placebo over two months of treatment. Both, patients with RA and patients with OA were recruited for this study, and separate data for the OA subgroup were provided for the primary outcomes of AIMS 2 pain score and modified Ritchie index (Mills *et ai*, 1996). At the end of the treatment period, mean reduction in AIMS 2 pain score was greater in the Reumalex[R] group (MD -0.89, CI -1.73 to -0.05). When this measure was repeated using a baseline pain score that had been averaged over the two months prior to the study, the Reumalex group showed a greater improvement (MD -1.04, CI -1.95 to -0.13). Statistically significant differences in the modified Ritchie index were identified between the Reumalex[R] group and the placebo group, but these differences were not preserved when data for the OA sub-group were considered separately (MD -0.59, CI -2.90 to 1.72).

Diary recordings of analgesic use for the whole group showed a small increase in use for those taking Reumalex[R] compared with a small decrease among those taking placebo. Separate data for this outcome among the OA subgroup were not presented. Four participants withdrew from each of the placebo and intervention groups due to side effects, and a further five (Reumalex[R] n = 2, placebo n = 3) complained of exacerbation of Symptoms, but it is unclear how many of these participants were patients with OA.

Tipi tea

Overall, the study of tipi tea (Ferraz *et al.,* 1991) was inadequately reported, although it should be noted that the study was published only in the form of a letter. Attempts to obtain a report of the study in greater detail were not successful. Data reported in this study were not adequate for re-analysis. Participants receiving tipi tea and those receiving placebo tea showed some improvement, although no significant differences were found between the two groups. The study was small (n = 20, crossover design) and provided little detail with regard to inclusion criteria. Pain scales against which outcomes were quantified were not disclosed. Three participants of the placebo group and two of the tipi tea group, reported mild AEs. Two participants failed to complete the trial, but reasons for their withdrawal were not stated.

Stinging nettle leaf

Seven days of topical application of stinging nettle leaf was compared with placebo (white deadnettle) for base of thumb pain (Randall *et at,* 2000). This study was of limited use because the diagnosis of OA, although likely, was not established at baseline. This study was a crossover trial, with two Single weeks of intervention, each preceded by five weeks of wash-out. Randall *et al* (2000) reported that after one week of treatment with stinging nettle compared to placebo statistically significant improvements in pain (VAS 0-100 mm; p = 0.026) and disability (Stanford Health Assessment Questionnaire disability index (HAQ-DI); p = 0.003) were achieved. Data were insufficient to allow extraction for re-analysis.

Duhuo Jisheng Wan (DJW)

The Chinese herbal mixture, DJW, was compared with active control (diclofenac 75 mg) in a randomized, double-blind, two-group parallel trial over five weeks, comprising lone week run-in, and four weeks of intervention. Two hundred participants suffering from OA entered the study, and 188 completed according to protocol, reporting parameters of pain and stiffness using a battery of 100 mm visual analogue scales, and physical function using the Lequesne index. Time to climb 10 steps was recorded in seconds. Significant improvements in pain, stiffness and physical were seen in both groups over the course of the trial, but differences between groups were not significant. This study provides moderate evidence that DJW is equally effective as diclofenac for improving OA complaints. Time from baseline to improvement was longer in participants using DJW than in participants using diclofenac. AE profiles of both groups were similar. DJW is a large dose (9 g, administered as 18 capsules per day) which may be a barrier to long-term clinical compliance.

Results summary tables and details of the calculations are presented on the webpage www. uniklinik-freiburg.de/rechtsmedizin/live/forschung/ phytomedicine/originalartikel.html. No serious adverse effects were reported with any herbal intervention.

DISCUSSION

Several of the studies included in this review were poorly described, and incomplete reporting may have led to those studies being undervalued. In particular, we made strict judgements of methodological quality on the basis of reporting (Higgins and Green, 2008), but not all reviewers agreed that this approach was the most suitable. In 1990, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 2004) was established to bring together regulatory authorities in Europe, Japan and the United States and experts from the pharmaceutical industry to determine scientific and technical aspects of product registration. In these countries, ICH guidelines are implemented in the law, and Human Research Ethics Committees would not approve a clinical trial protocol not in accordance with the ICH good clinical practice Consolidated guidelines (ICH 2004). In particular, one reviewer (SC) argued that for studies conducted in countries that have implemented the ICH guidelines into the law, we could assume that randomization and blinding and masking of outcome assessment and allocation concealment were adequately conducted even if it the study was simply reported as 'randomized and double-blind'. In order to be consistent in our treatment of all studies included in this review, we based our judgements on information reported in the manuscripts, but we acknowledge that systemic regulation of clinical trials is likely to improve the quality of study design. For example, we recognized that properly constituted Human Research Ethics Committees would only approve study protocols with adequate explanation of inclusion and exclusion criteria, reliable and valid outcome measures, and

appropriate planned Statistical analyses. The increasingly common requirements to register clinical trial protocols and provide evidence of ethics committee approval prior to Publishing study reports in reputable medical journals is also helping to increase transparency. To allow full and accurate assessment of future studies, we recommend that authors conform to the Consolidated Standards of Reporting Trials (CONSORT; Begg *et al*, 1996; Moher *et al*, 2001).

Seven studies in this review were of confirmatory design, meaning that they were fully powered studies planned to further investigate trends to effectiveness demonstrated in earlier studies (Blotman *et al*, 1997; Maheu *et al*, 1998; Leban *et al*, 2000; Appelboom *et al*, 2001; Lequesne *et al*, 2002; Biegert *et al*, 2004; Widrig *et al*, 2007). Several studies, although well designed, were probably underpowered and the lack of evidence of effect may be due to Type II error. Trends to effectiveness may be suggested from underpowered studies if improvements can be calculated and reported as effect sizes (Andersen and Stoove, 1998; Stoov6 and Andersen, 2003). Even small effect sizes may represent clinically meaningful improvements, particularly if these small effects represent improvements in a common condition with a substantial population burden of disease (e.g., OA).

Benefits derived from HMPs are influenced by the extraction and preparation of the plant material and the quantity of active principle in the final product. *Harpagophytum* ethanolic extract is incompletely extracted and contains approximately 30 mg harpagoside in the daily dosage (Sporer and Chrubasik, 1999). In contrast, equivalent doses of aqueous extract contain approximately 60 mg harpagoside per daily dose (Sporer and Chrubasik, 1999). A dose-dependent effect has been demonstrated for *Harpagophytum* and *Salix* extracts (Chrubasik *et al*, 1999; 2000). It seems likely, that extract doses with small doses of harpagoside are probably ineffective in alleviating OA pain, possibly explain-ing why two of the four *Harpagophytum* studies returned equivocal results.

It is not accurate to assume that larger doses of HMPs will always return larger benefits. A ceiling effect was observed for some products: 600 mg ASU daily returned no greater benefits that a 300 mg dose (Appelboom *et al*, 2001), and an 600 mg or 400 mg dose of SKI306X was not better than a 200 mg dose (Jung *et al*, 2001).

Although convincing evidence is available for avocado/soybean unsaponifiables, a confirmatory study over two years failed to demonstrate effectiveness except in a subgroup of people with less severe OA. Studies fail for a variety of reasons (Cameron, 2007), and although venturing into conjecture, we consider that groups may have differed at baseline according to some parameter that was not measured but may have influenced the primary outcome measures, For example, baseline data in the Lequesne study did not include details of the quantity of NSAIDs consumed or use of Opioids for pain. Neither was anything reported about the depression State of the participants which may also have influenced pain measures. Joint space loss was significantly reduced in patients with mild OA, possibly indicating that early use of ASU may act preventively, but this Suggestion needs to be confirmed in follow-up study.

OA of the knee, hip and spine is a degenerative disease affecting the joint cartilage and the underlying subchondral cartilage. Progressive loss of articular cartilage, appositional new bone formation in the subchondral trabeculae and formation of new cartilage and bone at the joint margins result in pain, stiffness, limitation of function and diminished quality of life (Sangha, 2000). Although there is no clear explanation for differences in effect among pain locations, some investigators have reported that pain from hip OA responds better to treatment with a HMP than does OA pain in other regions (Maheu *et al*, 1998; Chrubasik *et al*, 2002a), suggesting that site of joint disease may influence pain outcomes. We suggest that future researchers consider recruiting participants with particular joint involvement or stratifying results according to site of disease.

The net benefit of an intervention may be defined as the magnitude of benefit minus the magnitude of harm (ICH, 2004). Benefit and harm are not always measurable in standardized effect size units, complicating the calculation of net effect; however, the point remains that for each of the HMPs where clinical benefit is reported, clinical harm (adverse events, toxicity) must be considered in making an overall judgement of the usefulness of the intervention. Among the non-herbal medications commonly used to treat OA, NSAIDs in particular are associated with frequent and sometimes severe side effects (Gabriel *et al*, 1991), particularly gastrointestinal complications including dyspepsia, perforations, ulcers, and bleeds (Ofman *et al*, 2002; 2003), that add considerable cost to the usual care of people with OA (Smalley *et al*, 1996).

It appears that the benefit:risk ratio of HMPs is superior than that of NSAIDs. Severe AEs appear rare with herbal medicinal use. A systematic review of adverse events is available for *Harpagophytum procumbens* in 28 clinical studies (mostly observational), reporting on 6892 patients who consumed *Harpagophytum* extract for up to one year. In none of the double-blind studies was the incidence of AEs higher during treatment with *Harpagophytum* than during placebo treatment. Minor AEs were described across 20 studies in 138 of 4274 *Harpagophytum* consumers. This corresponds to an overall AE rate of around 3% (Chrubasik *et al*, 2008). Some of the observed AEs, particularly gastrointestinal complaints and allergies, were probably related to the extract intake. Three studies on preclinical toxicity indicated very low acute toxicity (ESCOP 2003). Data on chronic toxicity including mutagenicity, carcinogenicity, teratogenicity and embryogenicity were not found (Anonymous, 2003).

All other HMPs used for the treatment of OA are less well documented, and for several herbal medicines, no toxicity studies have been completed. Willow bark extract and rose hip and seed powder contain a gastro-protective principle (Gürbüz *et al*, 2003; Glinko, 1998) which may be of advantage in light of the gastrointestinal adverse events possible among patients concomitantly using NSAIDs (Ofman *et al*, 2002). According to the ESCOP monograph, treatment with willow bark extract is not restricted, and treatment pauses or dose tapering is not recommended as is the case for many other herbal medicines (e.g., feverfew). Severe specific AEs have not yet been observed in the willow bark doses employed except in rare cases allergic skin reactions. Although willow bark has only little impact on blood clotting (Krivoy *et al*, 2001), interaction studies investigating doses systematically are needed to rule out

any skepticism. Dental extractions or Operations do not appear to be contraindicated, but robust preclinical safety data are needed. In cases of known sensitivity to salicylates, the use of willow bark preparations should be avoided since an anaphylactic reaction may occur (Boullata et ai, 2003).

Use of SKI306X appeared not to be associated with a high incidence of AEs in the clinical studies, but neither preclinical safety data nor interaction or long-term studies that demonstrate the safety of SKI306X are available. If herbal extracts are combined, the superiority of the mixture over the individual herbal extracts has to be demonstrated: in vitro, in animal experiments, and in human pharmacological studies, in order to minimize intake of ineffective fractions and the occurrence of AEs. Because these data are lacking, we recommend that herbal mixtures such as SKI306X be used with caution.

The AE quota and profile for Phytodolor NR appear to be better than for NSAIDs. Gastrointestinal com-plaints were most frequently reported (2.6%), and occasionally allergic skin reactions have occurred.

Some AEs were partly due to the alcohol content of Phytodolor NR (45.6% vol, 0.7 g per 40 drops) which poses a health risk to children, and to adults with liver disease, alcoholism, epilepsy, or brain-damage. Caution is advised during pregnancy or lactation and for drivers and individuals who operate machines, even though no impairment of consciousness or reactivity is expected to occur with 0.7 g of alcohol per dose. Studies on mutagenicity, teratogenicity and toxicity in the parent animals and their progeny gave no evidence for any toxic effects arising from the intake of the combination during pregnancy and the lactation period (Gundermann, 2001).

Although the use of plants as medicines is funda-mental to traditional healthcare Systems throughout the world, the costs of herbal interventions are rarely covered by modern public health Systems. Concerns have been raised with regard to the costs, efficacy and associated AEs of HMPs (Atherton, 1994; Ernst, 1995; 1996; 1998). Our review reveals that still today the body of evidence for the effectiveness of HMPs is insufficient.

Abdelouahab N, Heard C. 2008. Effect of the major glycosides of *Harpagophytum procumbens* (Devil's Claw) on epidermal cyclooxygenase-2 (COX-2) *in vitro. J Nat Prod* **71:** 746-749.

Aguilar JL, Rojas P, Marcelo A, Plaza A, Bauer R, Reininger E, Klaas CA, Merfort I. 2002. Anti-inflammatory activity of two different extracts of *Uncaria tomentosa* (Rubiaceae). *J Ethnopharmacol* **81:** 271-276.

Allen-Hall L, Cano P, Arnason JT, Rojas R, Lock 0, Lafrenie RM. 2007. Treatment of THP-1 cells with *Uncaria tomentosa* extracts differentially regulates the expression if IL-1ß and TNF-a. *J Ethnopharmacol* **109:** 312-317.

Altinel L, Saritas ZK, Kose KC, Pamuk K, Aksoy Y, Serteser M. 2007. Treatment with unsaponifiable extracts of avocado and soybean increases TGF-beta1 and TGF-beta2 levels in canine joint fluid. *Tohoku J Exp Med* **211:** 181-186.

Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Höchberg M, Howell D, Kaplan D, Koopman W, Longley III S, Mankin H, McShane DJ, Medsger Jr. T, Meenan R, Mikkelsen W, Moskowitz R, Murphy W, Rothschild B, Segal M, Sokoloff L, Wolfe F. 1986. The American College of Rheumatology crtieria for the Classification and reporting of Osteoarthritis of the knee. *Arthritis Rheum* **29:** 1039-1049.

Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K. 1990. The American College of Rheumatology criteria for the Classification and reporting of Osteoarthritis of the hand. *Arthritis Rheum* **33:** 1601-1610.

Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, Brown C, Cooke TD, Daniel W, Feldman D, Greenwald R, Hochberg M, Howell D, Ike R, Kapila P, Kaplan D, Koopman W, Marino C, McDonald E, McShane DJ, Medsger T, Michel B, Murphy WA, Osial T, Ramsey-Goldman R, Rothschild B, Wolfe F. 1991. The American College of Rheumatology criteria for the Classification and reporting of Osteoarthritis of the hip. *Arthritis Rheum* **134:** 505-514.

Altman R, Aven A, Holmburg E, Pfeifer LM. 1994. Capsaicin cream 0.025% as monotherapy for Osteoarthritis: A double-blind study. *Sem Arthritis Rheumatism* **23** (Supp 3): 25 -32.

Altman RD, Hochberg MC, Moskowitz RW, Schnitzer TJ. 2000. Recommendations for the medical management of Osteoarthritis of the hip and knee. *Arthritis Rheum* **43**:1905-1915.

Altman RD, Marcussen KC. 2001. Effects of a ginger extract on knee pain in patients with Osteoarthritis. *Arthritis Rheumatism* **44:** 2531-2538.

Altmann A, Poeckel D, Fischer L, Schubert-Zsilavecz M, Steinhilber D, Werz, 0. 2004. Coupling of boswellic acidinduced Ca2+ mobilisation and MAPK activation to lipid metabolism and peroxide formation in human leucocytes. *B J Pharmacol* **141:** 223-232.

Ammon HP, Mack T, Singh GB, Safayhi H. 1991. Inhibition of leukotriene B4 formation in rat peritoneal neutrophils by an ethanolic extract of the gum resin exudate of *Boswellia serrata. Planta Med* **57:** 203-207.

Ammon HP, Safayhi H, MackT, Sabieraj J. 1993. Mechanism of antiinflammatory actions of curcumine and boswellic acids. *J Ethnopharmacol* **38:** 113-119.

Andersen MB, Stoove MA. 1998. The sanctity of p > .05 obfus-cates good stuff: A comment on Kerr and Goss. *J Appl Sport Psycho!* **10**:168-173.

Andriamanalijaona R, Benateau H, Barre PE, Boumediene K, Labbe D, Compere JF, Pujol JP. 2006. Effect of interleukin-1beta on transforming growth factor-beta and bone mor-phogenetic protein-2 expression in human periodontal ligament and alveolar bone cells in culture: modulation by avocado and soybean unsaponifiables. *J Peridontologyll:* 1156-1166.

Anonymous. 2003. Harpagophyti redix. In *ESCOP Monographs.* Thieme Press Stuttgart: New York; 233-240

Appelboom T, Schuermans J, Verbruggen G, Henrotin Y, Reginster JY. 2001. Symptoms modifying effect of avocado/ soyabean unsaponifiables (ASU) in knee Osteoarthritis: A double-blind, prospective, placebo-controlled study. *Scand J Rheumatology* **30:** 242-247.

Asnani V, Verma RJ. 2007. Antioxidative effect of rhizome of *Zinziber officinale* on paraben induced lipid peroxidation: an in vitro study. *Acta Pol Pharm* **64:** 35-37.

Astin JA. 1998. Why patients use alternative medicine: Results of a national study. *JAMA* **279:** 1548-1553.

Atherton DJ. 1994. Towards the safer use of traditional reme-dies. *Br Med J* **308:** 673-674.

Au RY, Al-Talib TK, Au AY, Phan PV, Frondoza CG. 2007. Avocado soybean unsaponifiables (ASU) suppress TNF-alpha, IL-1beta, COX-2, iNOS gene expression, and Prostaglandin E(2) and nitric oxide production in articular chondrocytes and monocyte/macrophages. *Osteoarthritis Cartilage* **15:** 1249-1255.

Badria FA, El-Farahaty T, Shabana AA, Hawas SA, El-Batoty MF. 2002. Boswellia-curcumin preparation for treating knee osteoarthritis: A clinical evaluation. *Alternat Complement* Trier **8:** 341-348.

Begg C, Cho M, Eastwood S, Horeton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz KF, Simel D, Stroup DF. 1996. Improving the quality of reporting of randomized controlled trials. The CONSORT Statement. *J Am Med Ass* **276:** 637-639.

Bengmark S. 2006. Curcumin, an atoxic antioxidant and natural NFkappaB, cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases. *J Parenter Enterai Nutr* **30:** 45-51.

Bernhardt M, Keimel A, Belucci G, Spasojevic P. 1991. Double-blind, randomized, comparative study of Phytodolor N and placebo as well as an open comparison with Felden 20 Tabs involving convalescent inpatients with arthrotic joint alterations. Unpublished Pharma Report [Steigrwald Pharmaceuticals, Germany].

Biegert C, Wagner I, Ludtke R, Kotter I, Lohmuller C, Gunaydin I, Taxis K, Heide L. 2004. Efficacy and safety of willow bark extract in the treatment of Osteoarthritis and rheumatoid arthritis: Results of 2 randomized double-blind controlled trials. *J Rheumatology* **31:** 2121-2130.

Biller A. 2002. Results of two randomized controlled studies and of a post-marketing surveillance study investigating a Devil's claw extract [Ergebnisse zweier randomisierter kontrollierter Studien und einer Anwendungsbeobachtung mit Teufelskrallenextrakt]. In *Phylopharmaka VII,* Schulz V, Rietbrock N, Roots I, Loew D (eds). Steinkopf-Verlag: Darmstadt; 81-92.

Bliddal H, Rosetzsky A, Schlichting P, Weidner MS, Andersen LA, Ibfelt HH, Christensen K, Jensen ON, Barslev J. 2000. A randomized, placebo-controlled, crossover study of ginger extracts and ibuprofen in Osteoarthritis. *Osteoarthritis Cartilage* **8:** 9-12.

Blotman F, Maheu E, Wulwik A, Caspard H, Lopez A. 1997. Efficacy and safety of avocado/soybean unsaponifiables in the treatment of symptomatic Osteoarthritis of the knee and hip [Efficacite et tolerance des insaponifiables d'avocat/soja dans le traitement de la gonarthrose et de la Coxarthrose symptomatiques]. *Rev Phumatisme* **64:** 825-834.

Boje K, Lechtenberg M, Nahrstedt A. 2003. New and known iridoid- and phenylethanoid glycosides from *Harpagophytum procumbens* and their in vitro inhibition of human leukocyte elastase. *Planta Med* **69:** 820-825.

Bonaterra G, Kinscherf R, Kelber O, *Weher* D, Metz J. 2007. Anti-inflammatory effects of *Populus tremula, Fraxinus excelsior, Solidago virgaurea* extracts and their combination Phytodolor® in human monocytes. *Planta Medl3:* 842.

Boullata JI, McDonnell PJ, Oliva CD. 2003. Anaphylactic reaction to a dietary Supplement containing willow bark. *Ann Pharmacother 37:* 832-835.

Boumediene K, Felisaz N, Bogdanowicz P, Galera P, Guillou GB, Pujol JP. 1999. Avocado/soya unsaponifiables enhance the expression of transforming growth factor betal and beta2 in cultured articular chondrocytes. *Arthritis Rheum* **42:** 148-156.

Buck SH, Burks TF. 1986. The neuropharmacology of capsaicin: Review of some recent observations. *Pharmacology Rev38:* 179-226.

Cameron M. 2007. When research goes pear-shaped: Report and reflections on a failed study of exercize and manual therapies for rheumatoid arthritis. Complement. *Health Practice Rev* **12:** 63-77.

Cao ZF, Chen ZG, Guo P, Zhang SM, Lian LX, Luo L, Hu WM. 1993. Scavenging effects of ginger on Superoxide anion and hydroxyl radical. *Zhongguo Zhong Yao Za Zhi* **18:** 750-751, 764.

Chainani-Wu N. 2003. Safety and anti-inflammatory activity of curcumin: a component of tumeric *(Curcuma longa). J Alternat Complement Med* **9:** 161-168.

Chevrier MR, Ryan AE, Lee DY, Zhongze M, Wu-Yan Z, Via CS. 2005. *Boswellia carterii* extract inhibits TH1 cytokines and promotes TH2 cytokines in vitro. *Clin Diagn Lab Immunol* **12:** 75-80.

Choi JH, Kim DY, Yoon JH, Youn HY, Yi JB, Rhee Hl, Ryu KH, Jung K, Han CK, Kwak WJ, Cho YB. 2002. Effects of SKI 306X, a new herbal agent, on proteoglycan degradation in cartilage explant culture and collagenase-induced rabbit Osteoarthritis model. *Osteoarthritis Cartilage* **10:** 471-478.

Chrubasik S, Junck H, Breitschwerdt H, Conradt C, Zappe H. 1999. Effectiveness of Harpagophytum extract WS 1531 in the treatment of exacerbation of low back pain: A randomized, placebo-controlled, double-blind study. *Eur J Anaesthesiol16:* 118-129.

Chrubasik S, Eizenberg E, Balan E, Weinberger T, Luzzati R, Conradt C. 2000. Treatment of low back pain exacerbations with willow bark extract: A randomized double-blind study. *Am J Med* **109:** 9-14.

Chrubasik S, Thanner J, Künzel O, Conradt C, Black A, Pollak S. 2002a. Comparison of outcome measures during treatment with the proprietary *Harpagophytum* extract Doloteffin in patients with pain in the lower back, knee or hip. *Phytomedicine* **9:** 181-194.

Chrubasik S, Fiebich B, Black A, Pollak S. 2002b. Treating low back pain with an extract of *Harpagophytum* that inhibits cytokine release. *Eur J Anaesthesiol* **19:** 209.

Chrubasik JE, Lindhorst E, Neumann E, Gerlach U, Faller-Marquardt M, Torda T, Muller-Ladner U, Chrubasik S. 2006. Potential molecular basis of the chondroprotective effect of *Harpagophytum procumbens*. *Phytomedicine* **13:** 598-600.

Chrubasik JE, Roufogalis BD, Chrubasik, S. 2007. Evidence of effectiveness of herbal anti-inflammatory drugs in the treatment of painful Osteoarthritis including chronic low back pain. *Phytotherapy Res* **21:** 675-683.

Chrubasik JE, Roufogalis BD, Wagner H, Chrubasik S. 2008. Systematic review on the safety of *Harpagophytum* prepa-rations for osteoarthritic and low back pain. *Phytotherapy Res* **22:** 149-152.

Daels-Rakotoarison DA, Gressier B, Trotin F, Brunet C, Luyckx M, Dine T, Bailleul F, Cazin M, Cazin JC. 2002. Effects of Rosa canina fruit extract on neutrophil respiratory burst. *Phytother Res* **16:** 157-161.

Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, Albert D, Renold F. 1991. Treatment of arthritis with topical capsaicin: A double-blind trial. *Clin Ther* **13:** 383-395.

Dedov VN, Roufogalis BD. 2000. Mitochondrial calcium accumu-lation following activation of vanilloid (VR1) receptors by capsaicin in dorsal root ganglion neurons. *Neurosci* **95:** 183-188.

Dreizer R, Maheu E, Julien D. 1997. Proposal of equivalence scores for non-steroidal anti-inflammatory drugs and anal-gesics for arthritis [Abstract] [Proposition d'un score d'equivalence des anti-inflammatoires non steroidiens (AINS) et des antalgiques dans l'arthrose [Abstract]]. *Rev Rhumatisme* **51:** 818.

El Haouari M, Bnouham M, Bendahou M, Aziz M, Ziyyat A, Legssyer A, Mekhfi H. 2006. Inhibition of rat platelet aggregation by *Urtica dioica* leaves extracts. *Phytotherapy Res* **20:** 568-572.

Ernst E. 1995. Bitter pills of nature: Safety issues in complementary medicine. *Pain* **60:** 237-238. Ernst E, Willoughby M, Weihmayr TH. 1995. Nine possiblereasons for choosing complementary medicine. *Perfusion* **8:** 356-358.

Ernst E. 1996. Plants as medicine: Possible benefits and potentia! risks. *Br J Ther Rehab* **3:** 99-100.

Ernst E.1998. Over-the-counter complementary remedies used for arthritis. *Pharmaceutical J* **260:** 30-831.

Ferraz MB, Pereira RB, Iwata NM, Atra E. 1991. Tipi. A populär analgesic tea: A double-blind crossover trial in Osteoarthritis (letter). *Clin Exp Rheumatoid:* 205-212.

Fiebich BL, Heinrich M, Hiller KO, Kammerer N. 2001. Inhibition of TNF-a synthesis in LPS-stimulated primary human monocytes by *Harpagophytum* extract SteiHap 69. *Phytomedicine* **8:** 8-30.

Fiebich BL, Chrubasik S. 2004. Effects of an ethanolic salix extract on the release of selected inflammatory mediators in vitro. *Phytomedicine* **11:** 135-138.

Flynn DL, Rafferty MF, Boctor AM. 1986. Inhibition of human neutrophil 5-lipoxygenase activity by gingerdione, shogaol, capsaicin and related pungent Compounds. *Prostoglandrines Leukotrienes Med* **24:** 195-198.

Frerick H, Biller A, Schmidt U. 2001. A treatment schedule for coxarthrosis: A double-blind study with Devil's claw [Stufenschema bei Coxarthrose: Doppelblindstudie mit Teufelskralle]. *Kassenarzt* **5:** 34-41.

Frondoza CG, Sohrabi A, Polotsky A, Phan PV, Hungerford DS, Lindmark L. 2004. An in vitro Screening assay for inhibitors of proinflammatory mediators in herbal extracts using human synoviocyte cultures. In Vitro Cellular. *Developmen-tal Biol - Animal* **40:** 95-101.

Gabay 0, Gösset M, Levy A, Salvat C, Sanchez C, Pigenet A, Sautet A, Jacques C, Berenbaum F. 2008. Stress-induced signaling pathways

in hyalin chondrocytes: Inhibition by avocado-soybean unsaponifiables (ASU). *Osteoarthritis Cartilage* **16:** 373-384.

Gabriel SE, Jaakkimainen L, Bombardiere. 1991. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Int Med* **115:** 787-796.

Gayathri B, Manjula N, Vinaykumar KS, Lakshmi BS, Balakrishnan A. 2007. Pure Compound from *Boswellia* serrata extract exhibits anti-inflammatory property in human PBMCs and mouse macrophages through inhibition ofTNFa, IL-1ß, NO and MAP kinases. *Int Immunopharmacol* **7:** 473-482.

Glaser T, Winter S, Groscurth P, Safayhi H, Sailer ER, Ammon HP, Schabet M, Weller M. 1999. Boswellic acids and malignant glioma: Induction of apoptosis but no modulation of drug sensitivity. *Br J Cancer* **80:** 756-765.

Glinko A. 1998. Pharmacological properties of a standardized extract from willow bark (Cortex Salicis). Thesis: Pomera-nian Academy of Medicine, Poland.

Goncalves C, Dinis T, Batista MT. 2005. Antioxidant properties of proanthoeyanidins of *Uncaria tomentosa* bark decoction: A mechanism for anti-inflammatory activity. *Phytochemis-try* **66:** 89-98.

Grube B, Grunwald J, Krug L, Staiger C. 2007. Efficacy of a comfrey root *(Symphyti offic. radix)* extract ointment in the treatment of patients with painful Osteoarthritis of the knee: Results of a double-blind, randomized, bicenter, placebo-controlled trial. *Phytomedicine* **14:** 2-10.

Gundermann KJ. 2001. Clinical expert report. Darmstadt, Germany: Steigerwald.

Günther M, Laufer S, Schmidt PC. 2006. High anti-inflammatory activity of harpagoside-enriched extracts obtained from solvent-modified super- and suberitical carbon dioxide extractions of the roots of *Harpagophytum procumbens. Phytochem Anal* **17:** 1-7.

Gürbüz I, Ustün O, Yesilada E, Sezik E, Kutsal O. 2003. Anti-ulcerogenic activity of some plants used as folk remedy in Turkey. *J Ethnopharmacol* **88:** 93-97.

Hadzhiyski H, Lindhorst E, Raif W, Torda T, Chrubasik S. 2006. Impact of *Harpagophytum procumbens* on the urinary pyr-idinoline deoxypyridinoline ratio in experimental Osteoarthritis [Abstract]. *Focus Altern Complement Ther* **11:** 13.

Harput US, Saracoglu I, Ogihara Y. 2005. Stimulation of lympho-cyte proliferation and inhibition of nitric oxide produetion by aqueous *Urtica dioica* extract. *Phytotherapy Pes* **19:** 346-348.

Hartwich A, Germann I, Kelber O, Muller J, Weizer D, Heinle H. 2006. Das pflanzliche Rheumapräparat STW 1 hat antioxidative Effekte. Zeitschr Rheumatol **65** (Suppl 1): 528.

Henrotin YE, Labasse AH, Jaspar JM, De Groote DD, Zheng SX, Guillou GB, Reginster JY. 1998. Effects of three avocado/ soybean unsaponifiable mixtures on metalloproteinases, cytokines and Prostaglandin E2 produetion by human artic-ular chondrocytes. *Clin Pheumatol* **17:** 31-39.

Henrotin YE, Sanchez C, Deberg MA, Piccardi N, Guillou GB, Msika P, Reginster JY. 2003. Avocado/soybean unsaponifiables increase aggrecan synthesis and reduce catabolic and proinflammatory mediator produetion by human osteoarthritic chondrocytes. *J Pheumatol* **30:** 1825-1834.

Henrotin YE, Deberg MA, Crielaard JM, Piccardi N, Msika P, Sanchez C. 2006. Avocado/soybean unsaponifiables prevent the inhibitory effect of osteoarthritic subchondral osteo-blasts on aggrecan and type II collagen synthesis by chondrocytes. *J Rheumatol* **33:** 1668-1678.

Herman C, Allen P, Hunt WC, Prasad A, Brady TJ. 2004. Use of complementary therapies among primary care clinic patients with arthritis. *Prev Chron Dis* **1:** 1—15.

Higgins JPT, Green S. 2008. *Cochrane Handbook for Systema-tic Reviews of interventions Version.* Wiley-Blackwell: Chichester, UK.

Huang TH, Tran VH, Duke RK, Tan S, Chrubasik S, Roufogalis BD, Duke CC. 2006. Harpagoside suppresses lipopolysaccharide-induced iNOS and COX-2 expression through inhibition of NF-kB activation. *J Ethnopharmacol* **104:** 149-155.

Huber B. 1991. Therapy of degenerative rheumatic diseases: Use of analgesic medication with Phytodolor N [Therapie degenerativer rheumatischer Erkrankungen: Bedarf an zusätzlicher analgetischer Medikation unter Phytodolor N], *Fortschr Med* **109:** 248-250.

ICH. 2004. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Synopsis of ICH guidelines and topics. Author: Geneva, Switzerland.

Jäger AK, Eldeen IM, van Staden J. 2007. COX-1 and -2 activity of rose hip. *Phytotherapy Res* **21:** 1251-1252.

Jung YB, Roh KJ, Jung JA, Jung K, Yoo H, Cho YB, Kwak WJ, Kim DK, Kim KH, Han CK. 2001. Effect of SKI306X, a new herbal anti-arthritic agent, in patients with Osteoarthritis if the knee: A double-blind placebo controlled study. *Am J Chinese Med* **29:** 485-491.

Jürgensen S, Dalbo S, Angers P, Santos AR, Ribeiro-do-Valle RM. 2005. Involvement of 5-HT2 reeeptors in the antinociceptive effect of *Uncaria tomentosa. Pharmacol Biochem BehavBV.* 466-477.

Kahkonen MP, Hopia AI, Vuorela HJ, Rauha JP, Pihlaja K, Kujala TS, Heinonen M. 1999. Antioxidant activity of plant extracts containing phenolic Compounds. *J Agric Food Chem* **47:** 3954-3962.

Kanter M, Coskun O, Budancamanak M. 2005. Hepatoprotective effects of *Nigella sativa* L and *Urtica dioica* L on lipid per-oxidation, antioxidant enzyme Systems and liver enzymes in carbon tetrachloride-treated rats. *World J Gastroenterol* **11:** 6684-6688.

Kaszkin M, Beck KF, Koch E, Erdelmeier C, Kusch S, Pfeilschifter J, Loew D. 2004. Downregulation of iNOS expression in rat mesangial cells by special extracts of *Harpagophytum procumbens* derives from harpagoside-dependent and independent effects. *Phytomedicine* **11:** 585-595.

Khajuria A, Gupta A, Süden P, Singh S, Malik F, Singh J, Gupta BD, Suri KA, Srinivas VK, Ella K, Qazi GN. 2008. Immunomodulatory activity of biopolymeric fraction BOS 2000 from *Boswellia serrata. Phytother Res* **22:** 340-348.

Khayyal MT, El-Ghazaly MA, Abdallah DM, Okpanyi SN, Kelber O, Weizer D. 2005. Mechanisms involved in the anti-inflammatory effect of a standardized willow bark extract. *Arzneimittel-Forsch/Drug Res* 55: 677-687.

Kim OK, Murakami A, Takahashi D, Nakamura Y, Torikai K, Kim HW, Ohigashi H. 2000. An avocado constituent, persenone A, suppresses expression of inducible forms of nitric oxide synthase and cyclooxygenase in macrophages, and hydrogen peroxide generation in mouse skin. *Biosci Biotech Biochem* **64:** 2504-2507.

Kim SO, Chun KS, Kundu JK, Surh YJ. 2004. Inhibitory effects of [6]-gingerol on PMA-induced COX-2 expression and activation of NF-kappaB and p38 MAPK in mouse skin. *Biofactors* **21:** 27-31.

Kim JH, Ryu KH, Jung KW, Han CK, Kwak WJ, Cho YB. 2005. Effects of SKI306X on arachidonate metabolism and other inflammatory mediators. *Bio Pharm Bull* **28:** 1615-1620.

Kimmatkar N, Thawani V, Hingorani L, Khiyani R. 2003. Efficacy and toerability of *Boswellia serrata* extract in treatment of Osteoarthritis of knee - A randomized double blind placebo controlled trial. *Phytomedicine* **10:** 3-7.

Kiuchi F, Iwakami S, Shibuya M, Hanaoka F, Sankawa U. 1992. Inhibition of Prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. *Chem Pharm Bull* **40:** 387-391.

Klaas CA, Wagner G, Laufer S, Sosa S, Deila Loggia R, Bomme U, Pähl HL, Merfort I. 2002. Studies on the anti-inflammatory activity of phytopharmaceuticals prepared from arnica flowers. *Planta Med* **68:** 385-391.

Klingelhöfer S, Obertreis B, Quast S, Behnke B. 1999. Antirheumatic effect of IDS 23, a stinging nettle leaf extract, on in vitro expression of T helper cytokines. *J Rheumatol* **26:** 2517-2522.

Krivoy N, Pavlotzky E, Chrubasik S, Eizenberg E, Brooks G. 2001. Effect of *Salicis cortex* extract on human platelet aggregation. *Planta Med* **67:** 209-213. Kundu JK, Mossanda KS, Na HK, Surh YJ. 2005. Inhibitory effects of the extracts of *Sutherlandia frutescens* (L) R. Br. and *Harpagophytum procumbens* DC. on phorbol ester-induced COX-2 expression in mouse skin: AP-1 and CREB as potential upstream targets. *Cancer Lett* **281:** 21-**31.**

Kuo PC, Damu AG, Cherng CY, Jeng JF, Teng CM, Lee EJ, Wu TS. 2005. Isolation of a natural antioxidant, dehydrozinge-rone from *Zingiber officinale* and synthesis of its analogues for recognition of effective antioxidant and antityrosinase agents. *Arch Pharmacol Res* **28:** 518-528.

Kuppsamy UR, Khoo HE, Das NP. 1990. Structure-activity studies of flavonoids as inhibitors of hyaluronidase. *Biochem Pharmacol* 140: 397-401.

Kut C, Assoumou A, Dridi M, Bonnefoix M, Gogly B, Pellat B, Guillou GB, Godeau G. 1998. Morphometric analysis of human gingival elastic fibres degradation by human leukocyte elastase protective effect of avocado and soybean unsaponifiables (ASU). *Pathol ß/o/***46:** 571-576.

Kut-Lasserre C, Miller CC, Ejeil AL, Gogly B, Dridi M, Piccardi N, Guillou B, Pellat B, Godeau G. 2001. Effect of avocado and soybean unsaponifiables on gelatinase A (MMP-2), stromelysin 1 (MMP-3), and tissue inhibitors of matrix metalloproteinase (TIMP-1 and TIMP-2) secretion by human fibroblasts in culture. *J Periodont* **72:** 1685-1694.

Lantz RC, Chen GJ, Sarihan M, Sölyom AM, Jolad SD, Timmermann BN. 2007. The effect of extracts from ginger rhizome on inflammatory mediator produetion. *Phytomedicine* **14:** 123-128.

Leban D, Chantre P, Foumie B. 2000. *Harpogophytum procumbens* in the treatment of knee and hip Osteoarthritis: Four-month results of a prospective, multicenter, double-blind trial versus diacerhein. *Joint Bone Spine* 67: 462-467.

Lequesne M, Maheu E, Cadet C, Dreizer RL. 2002. Structural effect of avocado/soyabean unsaponifiables on joint space loss in Osteoarthritis of the hip. *Arthritis Care Res* 47: 50-58.

Little CV, Parsons T, Logan S. 2000. Herbal therapy for treating Osteoarthritis. *Cochrane Database of Systematic Reviews,* ISSUE 4. Art. No.: CD002947 DOI: 10.1002/14651858. CD002947.

Loew D, Schuster O, Mollerfeld J. 1996. Stability and biophar-maceutical quality. A postulate for bioavailability and effectiveness of *Harpagophytum procumbens* [Stabiiitat und biopharmazeutische Qualität. Voraussetzung für Bioverfügbarkeit und Wirksamkeit von *Harpagophytum procumbens]*. In *Phytopharmaka II. Forschung und klinische Anwendung,* Loew D, Rietcrock N (eds). Steinkopf-Verlag: Darmstadt; 83-93.

Loew D, Mollerfeld J, Schrodter A, Puttkammer S, Kaszkin M. 2001. Investigations on the pharmaeokinetie properties of *Harpagophytum* extracts and their effects on eicosanoid biosynthesis in vitro and ex vivo. *Clin Pharmacol Ther* **69:** 356-364.

Lyss G, Schmidt TJ, Merfort I, Pähl HL. 1997. Helenalin, an anti-inflammatory sesquiterpene lactone from *Arnica,* selectively inhibits transcription factor NF-kappaB. *Biol Chem* 378: 951-961.

Maheu E, Mazieres B, Valat J-P, Loyau G, Le Loet X, Bourgeois P, Grouin JM, Rozenberg S. 1998. Symptomatic efficacy of avocado/soybean unsaponifiables in the treatment of Osteoarthritis of the knee and hip. *Arthritis Rheum* **41:** 81-91.

Mahomed IM, Ojewole JAO. 2006. Oxytocin-like effect of *Harpagophytum procumbens* DC (pedaliaceae) secondary root aqueous extraction on rat isolated Uterus. *Africa J Trad Complement Alternat Med* 3: 82-89.

Mauviel A, Loyau G, Pujol JP. 1991. Effect of unsaponifiable extracts of avocado and soybean (Piascledine) on the collagenolytic action of cultures of human rheumatoid syn-oviocytes and rabbit articular chondrocytes treated with interleukin-1 [Effect des insaponifiables d'avocat/soja (Piascledine) sur l'activite collagenolytique de cultures des synovocytes rhumatoides humains et de chondrocytes articulaires de lapin traites par l'interleukine-1]. *Rev Rhum Mal Osteoartic* 58: 241-245.

Mazieres B, Tempesta C, Tiechard M, Vaguier G. 1993. Pathologie and biochemical effects of a lipidic avocado and soya extract on an experimental postcontusive model of OA [Abstract]. *Osteoarthritis Cartilage* 1: 46.

McCarthy GM, McCarthy DJ. 1992. Effect of topical capsaicin in the therapy of painful Osteoarthritis of the hands. *J Rheumatology* **19:** 604-607.

McCleane G. 2000. The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful Osteoarthritis: A randomized, double blind, placebo controlled study. *Eur J Pain* 4: 355-360.

Melzig MF, Löser B, Lobitz GO, Tamayo-Castillo G, Merfort I. 1999. Inhibition of granulocyte elastase activity by caffeic acid derivatives. *Pharmazie* **54:** 712.

Meyer B, Schneider W, Elstner EF. 1995. Antioxidative properties of alcoholic extracts from *Fraxinus excelsior, Populus tremula* and *Solidago virgaurea. Arzneimittel-Forsch/Drug* Res **45:** 174-176.

Miller MJ, Ahmed S, Bobrowski P, Haqqi TM. 2006. The chrondoprotective actions of a natural produet are associated with the activation of IGF-1 produetion by human chondrocytes despite the presence of IL-1ß. *BMC Complement Altern Med* **7:** 6-13.

Mills SY, Jacoby RK, Chacksfield M, Willoughby M. 1996. Effect of a proprietary herbal medicine on the relief of chronic arthritic pain: A double-blind study. *Br J Pheumatol* **35:** 874-878.

Moher D, Schulz KF, Altman DG. 2001. The CONSORT Statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *Ann Int Med* **134:** 657-662.

Na HK, Mossanda KS, Lee JY, Surh YJ. 2004. Inhibition of phorbol ester-induced COX-2 expression by some edible African plants. *Biofactors* **21:** 149-153.

Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR. 1999. Topical capsaicin in humans: Parallel loss of epidermal nerve fibers and pain Sensation. *Pain* **81:** 135-145.

Nurtjahja-Tjendraputra E, Ammit AJ, Roufogalis BD, Tran VH, Duke CC. 2003. Effective anti-platelet and COX-1 enzyme inhibitors from pungent constituents of ginger. *Thrombosis* Res **111:** 259-265.

Obertreis B, Giller K, Teucher T, Behnke B, Schmitz H. 1996a. Anti-inflammatory effect of *Urtica dioica* folia extract in comparison to caffeic malic acid [Antiphlogistische Effekte von Extractum Urticae dioicae foliorum im Vergleich zu Kaffeoyläpfelsäure]. *Arzneimittel-Forsch/Drug Res* 46: 52-56.

Obertreis B, Ruttkowski T, Teucher T, Behnke B, Schmitz H. 1996b. Ex-vivo in-vitro inhibition of lipopolysaccharide stimulated tumor necrosis factor-alpha and interleukin-1 beta secretion in human whole blood by extractum Urticae dioicae foliorum [Ex-vivo-in-vitro-Hemmung der Lipopolysaccharid-stimulierten Tumor-Nekrose-Faktor-a und Interleukin-1 ß-Sekretion in humanem Vollblut durch Extractum Urticae dioicae foliorum]. *Arzneimittel-Forsch/ Drug Res* 46: 389-394.

Ofman JJ, MacLean CH, Straus WL, Morton SC, Berger ML, Roth EA, Shekelle P. 2002. A metaanalysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. *J Rheumatology* **29:** 804-812.

Ofman JJ, Maclean CH, Straus WL, Morton SC, Berger ML, Roth EA, Shekelle PG. 2003. Meta-analysis of dyspepsia and nonsteroidal antiinflammatory drugs. *Arthritis Rheum* **49:** 508-518.

Ozen T, Korkmaz H. 2003. Modulatory effect of *Urtica dioica* L. (Urticaceae) leaf extract on biotransformation enzyme Systems, antioxidant enzymes, lactate dehydrogenase and lipid peroxidation in mice. *Phytomedicine* **10:** 405-415.

Pilarski R, Zielinski H, Ciesiolka D, Gulewicz K. 2006. Antioxidant activity of ethanolic and aqueous extracts of *Uncaria tomentosa* (Willd.) DC. *J Ethnopharmacol* **104:** 18-23.

Piscoya J, Rodriguez Z, Bustamante SA, Okuhama NN, Miller MJS, Sandoval M. 2001. Efficacy and safety of freeze-dried cat's claw in Osteoarthritis of the knee: Mechanism of action of the species *Uncaria guianensis. Inflammation Res* **50:** 442-448.

Poeckel D, Tausch L, Kather N, Jauch J, Werz O. 2006. Boswellic acids stimulate arachidonic acid release and 12-lipoxygen-ase activity in human platelets independent of Ca2+ and differentially interact with platelet-type 12-lipoxygenase. *Mol Pharmacology* **70:** 1071-1078.

Randall C, Randall H, Dobbs F, Hutton C, Sanders H. 2000. Randomized controlled trial of nettle sting for treatment of base-of-thumb pain. *J. Royal Sei Med* **93:** 305-309.

Rein E, Kharazami A, Winther K. 2004. A herbal remedy, Hyben Vital (stand, powder of a subspecies of *Rosa canina* fruits), reduces pain and improves general wellbeing in patients with Osteoarthritis - a double-blind, placebo-controlled, randomized trial. *Phytomedicine* **11:** 383-391.

Rennert B, Melzig MF. 2002. Free fatty acids inhibit the activity of *Clostridium histolyticum* collagenase and human neutrophil elastase. *Planta Med* **68:** 767-769.

Riehemann K, Behnke B, Schulze-Osthoff K. 1999. Plant extracts from stinging nettle *(Urtica dioica),* an antirheumatic remedy, inhibit the proinflammatory transcription factor NF-kappaB. *FEBS Lett* **442:** 89-94.

Rohnert U, Schneider W, Elster EF. 1998a. Superoxid-dependent and -independent nitrite formation from hydroxylamine: Inhibition by plant extracts. *Zeitschr Naturforsch* **53:** 241-249.

Rohnert U, Koske D, Schneider W, Elstner E. 1998b. Inhibition by *Salix* extracts and Phytodolor of copper-catalyzed oxida-tive destruetions. *Zeitschr Naturforsch* **53:** 233-240.

Roy S, Khanna S, Shah H, Rink C, Phillips C, Preuss H, Subbaraju GV, Trimurtulu G, Krishnaraju AV, Bagchi M, Bagchi D, Sen CK. 2005. Human genome screen to identify the genetic basis of the anti-inflammatory effects of Boswellia in micro-vascular endothelial cells. *DNA Cell Biol2A:* 244-255.

Roy S, Khanna S, Krishnaraju AV, Subbaraju GV, Yasmin T, Bagchi D, Sen CK. 2006. Regulation of vascular responses to inflammation: inducible matrix metalloproteinase-3 expression in human microvascular endothelial cells is sensitive to anti-inflammatory Boswellia. *Antioxidants Pedox Signaling* **8:** 653-660.

Safayhi H, Rall B, Sailer ER, Ammon HP. 1997. Inhibition by boswellic acids of human leukocyte elastase. *J Pharmacol Exp Ther* **281:** 460-463.

Sandoval M, Charbonnet RM, Okuhama NN, Roberts J, Krenova Z, Trentacosti AM, Miller MJ. 2000. Cat's claw inhibits TNFa produetion and seavenges free radicals: Role in cytoprotec-tion. *Free Radic Biol Med* **29:** 71-78.

Sandoval M, Okuhama NN, Zhang XJ, Condezo LA, Lao J, Angeles FM, Musah RA, Bobrowski P, Miller MJ. 2002. Anti-inflammatory and antioxidant activities of cat's claw *(Uncaria tomentosa* and *Uncaria guianensis)* are independent of their alkaloid content. *Phytomedicine* **9:** 325-337.

Sangha O. 2000. Epidemiology of rheumatic diseases. *Rheumatology* **39** (Supp 2): 3-12.

Schadler W. 1988. Phytodolor for the treatment of activated arthrosis. *Rheuma* **8:** 288-290.

Schaser J, Bonaterra GA, Kelber O, Weizer D, Kinscherf R, Metz J. 2006. Untersuchung antiinflammatorischer Effekte des Phytopharmakons Phytodolor und seiner Einzelkomponenten in einem Monozyten-Testmodell. *Perfusion* **19:** 76-77.

Schmelz H, Hämmerle HD, Springorum HW. 1997. Analgesie effect of a Devils claw extract in various chronic degenerative joint diseases [Analgetische Wirkung eines Teufelskrallenwurzel-Extraktes bei verschiedenen chronisch-degenerativen Gelenkerkrankungen]. *In Rheumatherapie mitPhytopharmaka,* Chrubasik S, Wink M (eds). Hippokrates Verlag: Stuttgart; 86-89.

Schmid B, Ludtke R, Selbmann HK, Kotter I, Tschirdewahn B, Schaffner W. 2000. Efficacy and tolerability of a standardized willow bark extract in patients with Osteoarthritis: Randomized placebo-controlled double blind clinical trial [Wirksamkeit und vertraglichkeit eines standardisierten Weidenrindenextraktes bei Arthrose-Patienten: Random-isierte, placebo-kontrollierte Doppelblindstudie]. *Zschr Rheumatologie* **59**:1-7.

Schnitzer T, Morton C, Coker S. 1994. Topical capsaicin therapy for Osteoarthritis pain: Achieving a maintenance regimen. *Seminars in Arthritis Rheum* **23** (Supp 3): 34-40.

Schulze-Tanzil G, de Souza P, Behnke B, Klingelhoefer S, Scheid A, Shakibaei M. 2002. Effects of the antirheumatic remedy Hox alpha-a new stinging nettle leaf extract-on matrix metalloproteinases in human chondrocytes in vitro. *Histol-ogy Histopath* **17:** 477-485.

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. 2008a. Chapter 11: Presenting results and 'Summary of findings tables'. In *Cochrane Handbook for Systematic Reviews of Interventions,* Higgins JPT, Green S (eds). Wiley-Blackwell: Chichester, UK.

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, Guyatt GH. 2008b. Chapter 12: Interpreting results and drawing conclusions. In *Cochrane Handbook for Systematic Reviews of interventions,* Higgins JPT, Green S (eds). Wiley-Blackwell: Chichester, UK.

Siedle B, Gustavsson L, Johansson S, Murillo R, Castro V, Bohlin L, Merfort I. 2003. The effect of sesquiterpene lactones on the release of human neutrophil elastase. *Biochem Pharmacol* **65:** 897-903.

Siemoneit U, Hofmann B, Kather N, Lamkemeyer T, Madlung J, Franke L, Schneider G, Jauch J, Poeckel D, Werz O. 2008. Identification and functional analysis of cyclooxygenase-1 as a molecular target of boswellic acids. *Biochem Pharmacol* **5:** 503-513.

Smalley WE, Griffin MR, Fought RL, Ray WA. 1996. Excess costs from gastrointestinal dizease associated with nonsteroidalanti-inflammatory drugs. *J General Internal Med* **11:** 461-469.

Sporer F, Chrubasik S. 1999. Preparations from Devil's claw *(Harpagophytum procumbens)* [Präparate aus der Teufelskralle *(Harpagophytum procumbens)]. Zschr Phytotherapie* **20:** 235-236.

Stoove MA, Andersen MB. 2003. What are we looking at, and how big is it? *Physical Therapy in Sport* **4:** 93-97.

Strehl E, Schneider W, Elstner EF. 1995. Inhibition of dihydrofo-late reduetase activity by alcoholic extacts from *Fraxinus excelsior, Populus tremula* and *Solidago virgaurea. Arneimiüel-Forsch/Drug Res* **45:** 172-173.

Takada Y, Ichikawa H, Badmaev V, Aggarwal BB. 2006. Acetyl-11-keto-beta-boswellic acid potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis by suppressing NF-kappa B and NF-kappa B-regulated gene expression. *J Immunology* **76:** 3127-3140.

Teekachunhatean S, Kunanusom P, Rojanasthien N, Sananpanich K, Pojchamarnwitputh S, Lheiochaiphunt S, Pruksakorn S. 2004. Chinese herbal reeipe versus diclofenac in symptomatic treatment of Osteoarthritis of the knee: A randomized controlled trial. *BMC Comlementary Alternative Med* **4:** 19.

Teucher T, Obertreis B, Ruttkowski T, Schmitz H. 1996. Cytokine secretion in whole blood of healthy subjects following oral administration of *Urtica dioica* L. plant extract [Zytokin-Sekretion im Vollblut gesunder Probanden nach oraler Einnahme eines *Urtica dioica* L.-Blattextraktes]. *Arzneimittel-Forsch/Drug Res* **46:** 906-910.

Tjendraputra E, Tran VH, Liu-Brennan D, Roufogalis BD, Duke CC. 2001. Effect of ginger constituents and synthetic ana-logues on cyclooxygenase-2 enzyme in intact cells. *Bioor-ganic Chem* **29:** 156-163.

Tornhamre S, Schmidt TJ, Näsman-Glaser B, Ericsson I, Lindgren JA. 2001. Inhibitory effects of helenalin and related Compounds on 5-lipoxygenase and leukotriene C4 synthase in human blood cells. *Biochem Pharmacol* **62:** 903-911.

Tsukahara K, Nakagawa H, Moriwaki S, Takema Y, Fujimura T, Imokawa G. 2006. Inhibition of ultraviolet-B-induced wrinkle formation by an elastase-inhibiting herbal extract: implication for the mechanism underlying elastase-associated wrinkles. *Int J Dermatol* **45:** 460-468.

von Kruedener S, Schneider W, Elstner EF. 1996. Effects of extracts from *Populus tremula* L., *Solidago virgaurea* L. and *Fraxinus excelsior* L. on various myeloperoxidase Systems. *Arzneimittelforsch/Drug Res* **46:** 809-814.

Wang CC, Chen LG, Lee LT, Yang LL. 2003. Effects of 6-gingerol, an antioxidantfrom ginger, on inducing apoptosis in human leukemic HL-60 cells. *In Vivo* **17:** 641-645.

Warholm O, Skaar S, Hedman E, Molmen HM, Eik L. 2003. The effects of a standardized herbal remedy made from a subtype of *Rosa canina* in patients with Osteoarthritis: A double-blind, randomized, placebo-controlled clinical trial. *Current Therapeutic Res* **64:** 21-31.

Wenzig EM, Widowitz U, Chrubasik S, Bucar F, Knauder E, Bauer R. 2007. Phytochemical and in vitro pharmacological comparison of two rose hip preparations. *Phytomedicine* **15:** 826-835.

Whitehouse LW, Znamirowska M, Paul CJ. 1983. Devil's Claw *(Harpagophytum procumbens):* no evidence for anti-inflammatory activity in the treatment of arthritic dizease. *Can Med Assoc J* **129:** 249-251.

Widrig R, Suter A, Salier R, Melzer J. 2007. Choosing between NSAID and Arnica for topical treatment of hand Osteoarthritis in a randomized, double-blind study. *Rheumatol Int* **27:** 585-591.

Wigler I, Grotto I, Caspi D, Yaron M. 2003. The effects of Zintona EC (a ginger extract) on symptomatic gonarthritis. *Osteoarthritis Cartilage* 11: 783-789.

Wildfeuer A, Neu IS, Safayhi H, Metzger G, Wehrmann M, Vogel U, Ammon HP. 1998. Effects of boswellic acids extracted from a herbal medicine on the biosynthesis of leukotrienes and the course of experimental autoimmune encephalomyelitis. *Arzneimittelforsch/Drug Res* **48:** 668-674.

Winther K, Apel K, Thamsborg G. 2005. A powder made from seeds and Shells of a rose-hip subspecies *(Rosa canina)* reduces Symptoms of knee and hip Osteoarthritis: A randomized, double-blind, placebo-controlled clinical trial. *Scand J Rheumatol* **34:** 302-308.

Winther K, Kharazmi A, Rein E. 2004. A powder made from a subspecies of rosehip *(Rosa canina)* reduces WOMAC Symptoms scores as well as cholesterol levels in patients suffering from Osteoarthritis. *Osteoarthritis Cartilage* **13** (Supp A): S93.

Wu H, Ye DJ, Zhao YZ, Wang SL. 1993. Effect of different prepra-tions of ginger on blood coagulation time in mice. *Zhong-guo Zhon Yao Za Zhi* **18:** 147-149.

Wurm G, Baumann J, Geres U. 1982. Method for inhibiting cyclooxygenase and inflammation using cherry bioflavonoids [Beeinflussung des Arachidonsäurestoffwechsels durch Flavonoide], *Dtsch Apotheker Ztg* **122:** 2062-2068.

Zhou Y, Xu R. 1992. Antioxidative effect of Chinese drugs. *Chung Kuo Chung Yao Tsa Chih* **17:** 368-369, 373.