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Devil's Claw (*Harpagophytum procumbens*) as a Treatment for Osteoarthritis: A Review of Efficacy and Safety

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ABSTRACT

Background: Osteoarthritis (OA) is a highly prevalent musculoskeletal disorder. Conventional treatment (i.e., the use of nonsteroidal anti-inflammatory drugs—NSAIDs) is associated with well-documented adverse effects. Devil's Claw (*Harpagophytum procumbens*) a traditional South African herbal remedy used for rheumatic conditions, may be a safer treatment option. To date, 14 clinical trials have assessed its efficacy/effectiveness in OA.

Aim: To address the two main questions of importance to clinicians: (1) Does Devil's Claw work for the treatment of OA, and (2) Is it safe?

Methods: A review of the literature on Devil's Claw and OA from 1966 to 2006 was performed using multiple search databases, monographs, and citation tracking. Relevant trials in all languages were identified and included. Both internal validity (i.e., adequacy of the dosage and period of treatment for this condition, reporting of randomization, rates of dropout, blinding, and statistical analysis) and external validity (i.e., inclusion/exclusion criteria, baseline characteristics of the study populations, trial setting, and the appropriateness of the outcome measures of the trials) were assessed.

Results: Fourteen studies were identified: eight observational studies; 2 comparator trials (1 open, the other randomized to assess clinical effectiveness); and 4 double-blinded, placebo-controlled, randomized controlled trials to assess efficacy. Many of the published trials lacked certain important methodological quality criteria. However, the data from the higher quality studies suggest that Devil's Claw appeared effective in the reduction of the main clinical symptom of pain. The assessment of safety is limited by the small populations generally evaluated in the clinical studies. From the current data, Devil's Claw appears to be associated with minor risk (relative to NSAIDs), but further long-term assessment is required.

Conclusions: The methodological quality of the existing clinical trials is generally poor, and although they provide some support, there are a considerable number of methodologic caveats that make further clinical investigations warranted. The clinical evidence to date cannot provide a definitive answer to the two questions posed: (1) Does it work? And (2) is it safe? A definitive high-quality trial that addresses the necessary methodologic improvements noted is needed to answer these important clinical questions.

INTRODUCTION

Both anecdotal evidence and recent studies have implicated the potential of Devil's Claw (*Harpagophytum procumbens*) for the treatment of painful, chronic arthritic-type conditions.[1] Devil's Claw is an extract obtained from the root of the *H. procumbens* plant, a member of the sesame family found in the Kalahari region in South Africa. It has been shown that this remedy has anti-inflammatory and analgesic effects[2] making it of particular use in the treatment of

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degenerative painful rheumatic conditions, including osteoarthritis (OA). In addition, Devil's Claw has been shown to have significantly fewer adverse reactions as compared to standard conventional nonsteroidal anti-inflammatory drugs (NSAIDs)[3] and may therefore be a rational alternative treatment. Currently, Devil's Claw is marketed as a food supplement for degenerative arthritic conditions. The aim of this narrative review is to assess the methodological quality of those trials assessing Devil's Claw in the treatment of OA and to consider the safety of this treatment.

ABOUT DEVIL'S CLAW

Harpagophytum procumbens [Burch.] DC ex Meissn., is the plant that is the source of the monographed "Devil's Claw Root" extract.[4–7] It is a member of the sesame family (Pedaliaceae) and is assigned to the genus *Harpagophytum*, which includes the two species *H. procumbens* DC and *H. zeyheri* Decne. The monographs state that *H. procumbens* is the starting material for the herbal drug, although previous clinical and experimental research is based on the effects of mixed extracts of *H. procumbens* and *H. zeyheri*. In principle, the same constituents are found in both the primary and the secondary roots, but only the latter are used for the herbal drug because they have been found to contain far higher concentrations of the identifiable constituents.

Phytochemistry: Main and active constituents

The characteristic constituents of both *H. procumbens* and *H. zeyheri* are the iridoid glycosides and, in good quality material, these compounds, chiefly harpagoside (HG) can account for up to 3% of all constituents. However, on the basis of current knowledge, it cannot be assumed that HG is the only active constituent in extracts of Devil's Claw root. Other iridoids that are present in extracts of Devil's Claw root are procumbide and harpagide. Phenol derivatives, such as acetoside, and flavonoids, such as kaempferol and luteolin, may also contribute to the pharmacologic effects of the extract.[8–10] The total extract has more marked activity than individual constituents, for example, HG.[11]

Anti-inflammatory and analgesic effects

Reports of both anti-inflammatory and analgesic effects of Devil's claw in animal studies are conflicting,[12] with some showing a strong effect,[2] whereas others fail to show positive effects.[13] Anti-inflammatory effects in animal studies have been demonstrated more convincingly in chronic rather than acute conditions. Conflicting evidence may in part relate to different extract qualities and different methodologic designs.[14]

Mechanism of action

A clear mechanism for anti-inflammatory action has yet to be established, although it is purported to inhibit the arachidonic, the cyclo-oxygenase, and the lipo-oxygenase pathways.[15] *In vitro* studies by Fiebich and colleagues[16] investigated the effect of Devil's Claw extract, in primary human monocytes from healthy donors, on the stimulated release of proinflammatory cytokines. They identified that both water and alcohol extracts of *Harpagophytum* inhibited the lipopolysaccharide-induced synthesis of both prostaglandin E_2 and also the proinflammatory cytokines interleukin-6, interleukin-1β, and tumor necrosis factor-α (at concentrations of more than 100 μg/mL of extract) in a dose-dependent manner. Other *in vitro* studies have shown that HG has a significant effect on thromboxane biosynthesis.[17]

However, data from animal studies investigating the purported anti-inflammatory effects of *Harpagophytum* are less clear-cut. Using the rat model of injection of carrageenan in the paw, Whitehouse and colleagues[13] found no anti-inflammatory effects when both the extract and HG were administered orally. McLeod et al.[18] also confirmed that no effects were observed when an oral dose of the extract was given in the rat adjuvant arthritis model. However, a similar study by Lanhers and colleagues[11] did show that an intraperitoneal (i.p.) injection of the plant extract was effective in the same carageenen model used by Whitehouse, but that i.p. administration of HG was not effective.[11] Finally, *in vitro* studies show an inhibitory effect on cyclo-oxygenase 1 (COX-1) pathway that is considered to be caused by HG activity.[19]

DEVIL'S CLAW FOR THE TREATMENT OF OA

There is a body of evidence indicating that Devil's Claw may be an effective treatment in OA because of its pain-relieving (the primary concern for OA sufferers) and purported anti-inflammatory actions. The monographs published in 1990, 1996, and 2003 have implicated a role for Devil's Claw in the treatment of rheumatic disorders, including the treatment of painful OA.[4–6] In addition, the clinical use of Devil's Claw in the treatment of rheumatic disorders has been considered[1,20–28] and specifically reviewed.[26–34]

The aim of this paper is to review clinical studies that have investigated the use of Devil's Claw for the treatment of OA. The scope of this paper is to consider the findings of the current status of research and to identify where future trials should be directed. Two main questions of clinical importance will be addressed: (1) Does Devil's Claw work for the treatment of osteoarthritis? And (2) Is it safe?

CLINICAL STUDIES ASSESSING DEVIL'S CLAW IN THE TREATMENT OF OA

The following databases were searched using the terms Harpagophytum and osteoarthritis and Devil's Claw and osteoarthritis: AMED (1985–2006), CINAHL (1982–2006),

EMBASE (1980–2006), MEDLINE® (1966–2006), and ISI Web of Science (1981–2006) to identify relevant trials in all languages assessing Devil's Claw in the treatment of OA. In addition, the monographs (ESCOP, 1996; 2003; BfArM, K. E. 1989/1990) as well as through citation tracking were searched.

Fourteen (14) studies were identified that investigated the use of Devil's Claw specifically for OA or related conditions. Eight (8) were observational studies[3,35–41] (reviewed in Table 1); 2 were comparative trials (see Table 2), 1 was open[42] the other was randomized to assess clinical effectiveness[43], which is reported in the literature twice[44]; and 4 were double-blinded, placebo-controlled randomized controlled trials (RCTs) to assess the efficacy[*,45–47]; these are summarized in Table 3.

Many of the published clinical trials were conducted with methodologies that lack certain important criteria for a full assessment of the clinical value of Devil's Claw. We assessed both the internal validity (i.e., whether the dosage and period of treatment were adequate for this condition, reporting of randomization, rates of dropout, blinding, and statistical analysis) and external validity (i.e., inclusion and exclusion criteria, baseline characteristics of the study populations, trial setting, and the appropriateness of the outcome measures) of these studies.

IS DEVIL'S CLAW SAFE FOR THE TREATMENT OF OA?

OA is conventionally treated using analgesics and NSAID medication. Although NSAIDs are considered effective at reducing the pain, their toxicity has also been well documented. The main side-effects of this group of medication are gastrointestinal (GI),[15] which include heartburn, nausea, dyspepsia, vomiting, abdomen pain, perforated ulcers, and GI bleeding. Serious GI complications (e.g., perforated ulcers and bleeding) require hospitalization, with 12,000 hospitalizations and approximately 2000 deaths attributed to NSAID use in the United Kingdom every year.[13] Ten percent (10%) of hospitalizations for upper GI bleeding result in death and 80% of all ulcer deaths occurred in patients using an anti-inflammatory drug.[13] Some NSAID drugs such as rofecoxib have been recently withdrawn because of their serious side-effects.[14] Other side effects such as heart failure, headaches, and nephritic syndrome have also been reported,[12] and two COX-2 selective inhibitors (rofecoxib and valdecoxib) have been withdrawn from the market because of their elevated risk for cardiovascular disease. Identifying the safety profile of Devil's Claw as a possible alternative effective treatment for OA is therefore necessary.

The safety of Devil's Claw can be determined from in part from toxicity studies performed in animal studies (although cautious extrapolation to humans is required), adverse drug reaction/adverse events reported in clinical trials, and observational studies and spontaneous reports of suspected adverse drug reactions to the Medicines and Healthcare Regulatory Agency via the Yellow card reporting system. (The Yellow Card Scheme is run by the Medicines and Healthcare Regulatory Authority and Commission on Human Medicines (CHM) to collect voluntary information from health professionals and patients on suspected adverse drug reactions on prescribed medication, herbal remedies, and over-the-counter products).

Toxicity data

A summary of data investigating the toxicity of Devil's Claw has been reported.[12] Acute and subacute toxicity data in rodents have demonstrated low toxicity of Devil's Claw extracts. Acute oral lethal dose parameters (LD_0 and LD_{50}) have been assessed and were greater than 13.5 g/kg body weight.[13] No remarkable hematologic and gross pathologic findings were found after intake of Devil's Claw for 7 days at an oral dose of 7.5 g/kg in rats, and, in addition, no hepatic effects were identified at a lower dose of 2 g/kg for 7 days.[13] However, there have been no chronic toxicity studies and no information on its long-term tolerability.

Contraindications

The use of Devil's Claw is contraindicated in patients who have gastric and duodenal ulcers because its bitter taste evokes gastric-acid secretion; the herb is also contraindicated and also in patients with gallstones. In addition, there is pharmacologic evidence that Devil's Claw has cardiac effects,[48] with significant reductions in arterial blood pressure and antiarrhythmic effects being observed in healthy rats after treatment with Devil's Claw extract with arrhythmic medication. These data suggest that excessive doses of Devil's Claw may interfere with concurrent treatment for cardiac disorders (such as heart failure and cardiac arrhythmias). There are no data on the effects of Devil's Claw during pregnancy and lactation, and therefore its use is avoided during these periods.

Reporting of adverse events in clinical trials and observational studies

The incidence of adverse event (AE) associated with Devil's Claw use in clinical trials treating OA occurs in less than 10% of the study population. The most frequently reported adverse events (Table 1) are mild even at very high doses (8100-mg extract)[35] of the medication and include mainly GI complains (e.g., diarrhea, flatulence), although other symptoms, notably headaches, tiredness, migraines, skin rashes, and temporarily increased perspiration have been reported (see review[20]). With the lack of large-scale

*Guyader M. Les plantes antirhumatismales. Étude historique et pharmacologique, et étude clinique du nébulisat d'Harpagophytum procumbens DC chez 50 patients arthrosiques suivis in service hospitalier. Université Pierre et Marie Curie, Paris, 1984:8

Table 1. Observational Studies of Devil's Claw (*Harpagophytum procumbens*) for the Treatment of Osteoarthritis

	Study design	N	*Diagnosis/inclusion criteria*	*Period of treatment*	*Daily dose extract/HG levels/and DE ratio*	*Primary outcome*	*Result*	*Dropout*	*Adverse reactions*
Bélaiche 1982[35]	Observational	>630	Primary and secondary osteoarthritis of the hip, knee, finger, and spine	3–6 months	3000 mg or 9000 mg extract/d HG = 90–270 mg/d[a] DE = 3:1	Levels of improvement as defined by pain on walking and pain on pressure on knee joint	Dependent on condition and dosage. Improvement seen in 14.9%–56.2% at patients at 3000 mg/d dose; and 13.9%–39.08% at 9000 mg/d.	*N* = 133 (21%)	Mild gastrointestinal disturbances even at highest dose
Pinget and Lecomte 1997[36]	Observational	43	Rheumatic disorders	60 days	Extract = N/A 1500 mg/drug/d HG = 60 mg/d[a] DE = NA	Symptoms and pain	Improvement in pain and symptoms	*N* = 0 (0%)	None reported
Rutten and Schafer[37]	Observational	99	Acute and chronic spinal disorders [*N* = 23] Osteoarthritis of the knee [*N* = 76]	6 weeks	960 mg extract/d plus twice weekly injection HG = NK DE = NK	Hamberg Pain Adjective	68% of patients were pain free with significant reduction in symptoms	NK	Good tolerability
Usbeck 2000[38]	Observational	1026	Degenerative disorders in the arca of the locomotor system (lumbar spine, cervical spine, knee, shoulder, and hip)	6 weeks	960 mg extract/d HG = 24 mg/d DE = NK	Concomitant medication use	83% used study medication only; 6% used NSAID and 11% manual therapies. In addition, 61% of patients showed a decrease in pain, increased mobility in 52.5%, and 80% of doctor and patient global assessment was deemed good or very good. Tolerability was rated good or very good by 96% of population.	NK	Not reported

Schendel 2001[39]	Observational	583	Gonarthrosis and coxarthrosis	8 weeks	960 mg extract/d HG = <30 mg/d DE = 4.4–5 : 1	WOMAC pain subscale	Descriptive statistics, improvement in WOMAC pain (52.5%) and stiffness scores (49.6%), 84.6% of patients global assessment = very good or good; 61.4% stopped all convent med	$N = 2$ (0.3%)	Six AE (1%) reported included dry mouth, itchiness, and gastrointestinal symptoms
Ribbat and Schakau 2001[40]	Multicenter observational	675	Arthrosis, spondylitis, and fibromyalgia	8 weeks	Extract = NK HG = NK DE = 4.4–5 : 1 4.5 g drug daily	Range of disease-specific complaints, e.g., mobility, pain, pain, morning stiffness	50% improvement in all complaints 60% patients ceased NSAIDs	NK	NK
Chrubasik et al. 2002[3]	Observational (postmarketing surveillance)	250	Nonspecific back pain or knee and hip osteoarthritis	8 weeks	Extract = NK HG = 60 mg/d DE = 1.5–2.5 : 1	WOMAC for knee and hip; Arhus for low-back pain	Improvement in pain between 50% to 70%. Secondary outcomes (global assessment of effectiveness and pain VAS) also showed improvement. Hip+knee pain improved > back pain	$N = 22$ (9%)	Mild AE in 10% of the patients, mainly gastrointestinal complaints; allergic reactions to *Harpagophytum* in 2 patients
Wegener and Lupke 2003[41]	Observational	75	Arthrosis of the hip or knee	12 weeks	Extract = 2400 mg HG = 50 mg DE = 1.5–2.5 : 1	WOMAC (global and subscales) and weekly pain VAS	22.9% improvement on total WOMAC (and similar for subscales) and weekly pain scores improved by 25.8%	Nil (0%)	Mild AE in 4 patients (5.3%). AE included dyspepsia ($N = 2$), sensation of fullness ($N = 1$) and panic attack ($N = 1$). Causality established in 2 patients (1 fullness, and 1 dyspepsia).

NK, not known; NA, not applicable; HG, harpagoside concentration; DE, drug-to-extract ratio; NSAID, nonsteroidal anti-inflammatory drug; WOMAC, Western Onario and McMaster Universities Osteoarthritis Index; VAS, visual analogue scale; AE, adverse events; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a]HG was calculated indirectly from iridoid glycoside concentration.

Table 2. Randomized Trials with Comparator Treatment Assessing Devil's Claw (*Harpagophytum procumbens*) in Osteoarthritis

	Study design	N	*Diagnosis/ inclusion criteria*	*Period of treatment*	*Daily dose extract/ HG levels and DE ratio plus comparison medication*	*Primary outcome*	*Result*	*Dropout*	*Adverse reactions*
Schruffler et al., 1980[42]	Randomized double-blind	50	Arthrosis	28 days	1200 mg extract/d HG = <30 mg/d DE = 1.5–2.5:1 Compared to standard treatment Phenylbutazone	Global assessment, pain and severity of symptoms	80% "success rate" in verum vs. 72% phenylbutazone. Also reduction in pain greater in verum (80%) vs. placebo 72%. Also increased mobility and reduction in morning stiffness in verum compared to placebo. Descriptive statistics only.	$N = 0$ (0%)	4 patients reported AE; verum group = 0 (0%), standard medication = 4. Tolerability was classified as very good, good, or satisfying in 80% taking Devil's Claw as compared to in 72% of those taking conventional treatment.
Chantre et al., 2000[43] and Leblan et al., 2000[a]	Randomized double-blind	122	Osteoarthritis of the hip and knee	4 months	Extract = N/A 2610 mg drug/d HG = 57 mg/d DE = N/A Compared to 100 mg diacerhein	VAS pain severity	Devil's Claw was at least as effective diacerhein ($p = 0.001$)	$N = 32$ (26%)	Significantly fewer AE in verum ($p = 0.042$). Most common complaints were GI tract (i.e., diarrhea, flatulence, etc.). 10 (16%) verum patients reported AE compared to 21 diacerhein-treated patients.

HG, harpagoside concentration; DE, drug-to-extract ratio; VAS, visual analogue scale; AE, adverse events; GI, gastrointestinal.
[a]HG was calculated indirectly from iridoid glycoside concentration.

Table 3. Double-Blind, Placebo-Controlled Randomized Trials of Devil's Claw (*Harpagophytum procumbens*) for Osteoarthritis

	Study design	N	*Diagnosis/ inclusion criteria*	*Period of treatment*	*Daily dose extract/HG levels/ and DE ratio*	*Primary outcome*	*Result*	*Dropout*	*Adverse reactions*
Guyader 1984 (unpublished)	Placebo controlled DB RCT	50	Osteoarthritis	3 weeks	2400 mg extract HG = <20 mg/d[a] DE = NK versus placebo	Severity of pain on Likert scale (range 0–4) in 5 conditions	Significant reduction in pain in verum group as compared to placebo. Improvement was more frequent in moderately affected OA than in severe cases.	$N = 2$ (4%)	18% AE reported; 6 patients in verum (12%) and 3 in placebo.
Lecomte and Costa 1992[46]	Placebo controlled DB RCT	89	Osteoarthritis	8 weeks	2010 mg of extract[a] HG = 60 mg/d (3%) DE = NK vs. placebo	Pain intensity on 0–10 VAS scale	Significant decrease in pain in verum group compared to placebo after day 30 ($p = 0.018$) and day 60 ($p = 0.012$). Significant improvement in mobility in verum-treated patients.	$N = 0$ (0%)	No AE reported. All liver function tests normal at study end.
Schmelz et al. 1997[47]	Placebo controlled DB RCT	100	Osteoarthritis chronic low-back pain and myalgia	30 days	2500 mg of extract HG = 30 mg/d DE = 1.5–2.5:1 vs. placebo	Severity of pain on Likert scale	DC better than placebo. Descriptive stats only. Among verum-treated patients: only 6 had strong pain and 1 medium pain compared to: placebo: 32 had strong pain and 9 had medium pain.	$N = 9$ (9%)	AE occurred in two patients (verum $n = 1$ [1%], diarrhea; placebo, $n = 1$, mild gastritis)
Frerick et al. 2001[51]	Placebo controlled DB RCT	46	OA of the hip	20 weeks	960 mg of extract/d HG = <30 mg/d DE = 4.4–5:1 versus placebo	WOMAC pain intensity	Unable to identify primary outcome. Significant improvement in total WOMAC ($p = 0.039$), and stiffness ($p = 0.026$) scores between verum and placebo between week 20 and baseline. Functional subscore showed near-significant improvement [$p = 0.087$].	$N = 7$ (16%)	An adverse reaction in only 1 patient in the verum group (2%), epigastric discomfort with suspected cholelithiasis

DB, double blind; RCT, randomized controlled trial; HG, harpagoside concentration; DE, drug-to-extract ratio; NK, not known; AE, adverse events; VAS, visual analogue scale; DC, Devil's Claw; WOMAC, Western and Ontario McMaster Universities Osteoarthritis Index.

[a]HG was calculated indirectly from iridoid glycoside concentration.

controlled trials and generally poor reporting of side effects, it is unclear whether these are adverse drug reactions or not. The frequency of adverse events reported has been shown[42,43] to be significantly lower than for conventional treatment. However, Chantre and colleagues[43] reported a high dropout rate in the Devil's Claw–treated group of the study, which was attributed to adverse drug reactions. Sixteen patients reported adverse events; 10 of these patients had AE deemed related to Devil's Claw, the most frequently reported AE being diarrhea.

Reporting of suspected adverse drug reactions to the Medicines and Healthcare Regulatory Agency

There have been no reports of serious or major adverse drug reactions. A search for suspected adverse drug reactions reported to Medicines and Healthcare Regulatory Agency, United Kingdom in June 2003 identified 7 reports for 6 individuals. They included thrombocytopenia (2 individuals), abnormal hepatic function (1), increased levels of creatinine phospokinase (1), exacerbation of asthma (1) erythematous rash (1), and urticaria (1).

Assessing the incidence of AE from clinical trials is hampered by the small populations generally evaluated in these studies. There is very scant information on the safety of Devil's Claw long-term use or at doses higher than those stipulated in the monographs. Only 1 study[35] has assessed high doses (9000 mg/day of extract) over a clinically relevant time period (3–6 months). No serious or major AEs were reported, but some mild symptoms of mostly gastrointestinal discomfort were reported. From the current data, Devil's Claw appears to be associated with minor risk (relative to NSAIDs); however, no firm conclusion regarding the herb's safety can be made. Further assessment of safety risk is needed.

REVIEW OF THE METHODOLOGICAL QUALITY OF TRIALS ASSESSING DEVIL'S CLAW IN THE TREATMENT OF OA

Assessment of internal validity

Was the dosage adequate for the condition? The specified daily drug dosages are included in the published monographs. The European monographs recommends up to 9 g drug per day or equivalent extracts three times per day (i.e., 1–3 g extract per day)[5–6] for painful arthrosis conditions with a suggested duration of treatment for 2–3 months. On this basis, all studies gave appropriate daily dosages except for a single study in which the recommended dosage was exceeded.[35] This study was conducted prior to the ESCOP Monograph of 1996.[5]

However, preparations of Devil's Claw are not standardized but vary considerably between manufacturers in terms of both the drug: extract ratio and the concentration of HG. One constituent is singled out as a marker (which is reported in clinical trials as a measure of the "quality" of the study medication, even though it is probably only one of a number of active constituents). Indeed, there are a variety of different formulations of Devil's Claw available to the general public, but as yet there is no clear evidence that one formulation is superior to another. Manufacturing processes, dose, and detailed formulation may well differ and have been noted by previous authors.[49,50] In terms of clinical trials, to enable comparison between trials, the daily dosage of Devil's claw is therefore frequently expressed in terms of both the daily drug, extract, and HG levels. Clinical trials investigating Devil's Claw in OA have used the extract given in the dose range of 960 mg to 2610 mg extract/d, although a dosage of up to 8100 mg extract/d was used by Bélaiche.[35] Levels of HG in studies of OA have ranged from less than 20 mg/d[41] to 270 mg/d.[35] Pharmacopoeial requirements state that Devil's Claw products should contain 1.2% of HG, and two recent reviews[24,34] suggest that a daily dose of 50–60 mg HG/d or more provide more reliable evidence of efficacy. According to this criteria, 6 of the 14 OA trials listed in Tables 1–3 (in which the HG dose ascertainable) gave inadequate dosage. However, without further evidence from studies that address more systematically the aspects of therapeutic dosage and the identity of the active ingredients of Devil's Claw, it is possible only to set recommended doses for individual preparations of the root extract.

Is the treatment period adequate? The recommended period of treatment with Devil's Claw for painful arthrosis is 2 to 3 months.[5] Wegener[32] concluded that Devil's Claw at a dose in the upper range of the recommended daily dose needs to be taken for at least 4 weeks. Based on this conclusion, 2 of the 14 OA studies did not treat patients for a sufficient period of time.[45,47]

Was the method of randomization described? Six (6) of the trials are reported by the authors as being designed to randomize patients into the study. All but one[46] of these studies[42–45,47] mentioned randomization in the methodology; however, only the study by Chantre et al.[43] reported the process employed to randomize patients.

Rates of dropout. The rates of dropout from all the trials are identified in Table 1. Three of the studies[37,38,40] did not report these data. Dropout rates were highest, as would be expected, in those trials with longer periods of treatment (21% dropout rate over 3–6 treatment months[35]) (26% dropout rate over 4 treatment months[43]) (16% dropout rate over 20 treatment weeks[47]). The remainder of these studies had treatment phases of 8 weeks or less, and dropout rates were acceptable (range 0%–9%). Intention to treat (ITT) analysis in the comparative and placebo-controlled trials was performed in one study only.[43] ITT analysis was not reported in the remaining studies,[42,45–47,*] probably because of the date of publication of the majority of these studies.

Blinding. The absence of methods to ensure adequate allocation concealment (to prevent selection and confounding bias, before and up to treatment allocation) and blinding will allow the possibility of bias and the resulting effect this may have on the outcome assessment. Allocation concealment was nonexistent in most of the blinded studies; only the study by Chantre et al.[43] provided some limited information that would indicate a possible adequate concealement of treatment. Six (6) of the studies were reported by the authors as being a double-blind design.[42–47,51] However, only 1—the study by Chantre et al.—provided any description of the methods used to ensure blinding.[43] We are therefore unable to conclude whether bias may be an issue when interpreting the findings from five trials.

Was the statistical analysis appropriate for the study design? The use of appropriate statistics identified *a priori* to test the null hypotheses is essential to warrant the study conclusions drawn by the authors. Descriptive statistics were appropriately reported in all the observational studies. The positive clinical improvement identified in these studies do not provide clear evidence of the effectiveness of Devil's Claw, because these effects may be resulting from factors (i.e., the natural history of the disease, regression to the mean, or placebo effects) that could not be controlled for when using this type of study design. Of the six controlled studies, Chantre et al.,[43] Lecomte and Costa,[45] and Guyader (unpublished) clearly reported and used appropriate methods of analysis and provide support for the conclusions drawn (i.e., that Devil's Claw was at least as effective as the comparator diacerhein [$p = 0.001$] and did significantly reduce pain [the primary outcome]. The remaining controlled studies reported only descriptive statistics,[42,46,47] and therefore we are unable to draw any definitive conclusions from these studies.

Assessment of external validity

Inclusion and exclusion criteria and baseline characterisitics of the study populations. There are a number of issues to be considered. (1) Patients recruited into the trials should have been formally classified as having OA; however, this was not always transparent. The classification criteria reported to confirm a diagnosis of OA is cited in only one study,[48] although other studies[41,43,45] do list the appropriate criteria for entry into the study despite not referencing a formal classification system (e.g., the American College of Rheumatology classifications[51]). (2) Patient characteristics such as age, gender, duration and severity of disease, concurrent medication, and comorbidities should be clear in trials with comparator groups to identify how homogeneous the treatment groups are because this may impact on outcomes. Of the 6 randomized trials, only two studies[43,51] clearly defined baseline characteristics of the patients. (3) A clear description of inclusion and exclusion criteria is also necessary to comment on the generalizability of the study findings. Nine (9) of the 15 studies do not report clear descriptions of patient inclusion or exclusion criteria,[35–40,42,46,*] and it is therefore impossible to generalize the findings from these studies. Three (3) studies[43,45,47] are notably restrictive in the types of patients entered into the trial (OA is a condition more common in the elderly, and therefore there is more likelihood of concurrent illness and medication). Exclusion criteria listed in these studies include the following: no secondary arthritic joints, no concurrent blood, chronic respiratory or inflammatory disorders or other significant conditions, and no ongoing medication for other conditions. The observational study by Wegener and Lupke,[41] however, was much broader in its inclusion of patients; it only excluded patients with conditions known to be contraindicated to Devil's Claw. Finally, interpreting the findings is made more complex because a number of observational studies[3,36–38,40] and 1 double-blind RCT[46] have assessed Devil's Claw with a combination of conditions (e.g., chronic low-back pain, spinal disorders, fibromyalgia, spondylitis) besides OA. Because none of these combined studies performed subanalyses, it is not possible to generalize the impact of Devil's Claw specifically to those patients with a diagnosis of OA.

Trial setting. The number of study centers in a trial provides an indication for the generalizability of the study findings, because they will provide a broader range of patients and also remove the likelihood of bias that may potentially be found in trials conducted in a single site. Three (3) studies did not report the number of settings.[37,40,47] Most studies were single-centered trials.[35,36,42–45,47,*] Five (5) studies were multicentered, four of which were observational studies (3 centers[3]; 2 centers[45]; 116 centers[39]; 13 centers[41]), and the comparative controlled study by Chantre et al.,[43] was conducted in 30 centers.

Were the outcome measures appropriate? Appropriate and validated outcome measures (both the type and the range used) are necessary to ensure that a valid conclusion about external validity can be determined. Pain and disability are the main clinical issues associated with OA of the knee. Disease-specific measures (such as Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] for the assessment of OA of the knee and hip[52]) are the most suitable measures to evaluate this. Outcome measures to assess functional status (e.g., the Lequesne functional index, an international index for evaluating severity of OA,[53] or the Health Assessment Questionnaire[54]) are also appropriate, although none of the trials in OA used these measures as a primary outcome. Four (4) studies used validated disease-specific measures[3,39,41,47] to assess improvement in relevant symptoms. One (1) study assessed concomitant medication use as the primary outcome.[38] The majority of studies, however, assessed pain severity as their primary outcome and

therefore employed either Likert or Visual Analogue Scales (VAS) (which are not validated)[35,38,40,42–44,45,46,*] or the validated Hamberg Pain Adjective.[37] In addition, other outcomes such as patient and physician global assessment have provided a useful indication of the perceived clinical effectiveness of Devil's Claw.

IS DEVIL'S CLAW EFFECTIVE IN THE TREATMENT OF OA?

Observational studies

All the observational studies demonstrated an improvement in pain symptoms (the primary outcome in the majority of these studies) after treatment with Devil's Claw. Although all the studies used appropriate doses of the drug extract and adequate treatment periods, there are a number of methodologic issues associated with these studies. These include small sample size[36,37,41]; a combination of patient groups in 5 of the 8 studies[3,36–38,40] making it difficult to identify the improvement in patients with OA; the basing of all but one study[3] at a single site; and the fact that only half of the studies used disease-specific measures.[3,39–41] Therefore, although the authors conclude that Devil's Claw has potential in the treatment of OA, the generalizability of these findings is disputable.

RCTs with a comparator treatment

Two RCIs assessed the effectiveness of Devil's Claw as compared to standard treatment.[42,43] Both studies gave appropriate doses of the extract, and subjects were treated for an adequate period of time. The study by Chantre et al.[43] was of reasonable methodological quality. On the positive side, the sample size was acceptable, the authors adequately described the randomization and blinding process and the patient population and baseline characteristics; and adequate dose was used for an appropriate duration of time, and finally had appropriate statistical analysis. A number of factors, however, were still of concern. First, although the authors did clarify the inclusion and exclusion criteria, because no formal classification system was employed it is ambiguous whether the patients were formally diagnosed with OA; there is an issue about generalizability (this was a single-center trial, and the inclusion and exclusion criteria were narrow); and finally a generic (Pain VAS) rather than disease-specific outcome was used. The authors' conclusion that Devil's Claw was as effective as the standard treatment diacerhein (and had significantly fewer adverse events) should be considered with some caution, bearing in mind the points listed above. The other trial[42] compared Devil's Claw to the conventional treatment phenylbutazone. The authors concluded that Devil's Claw was as successful as the comparator in terms of the primary outcome (global assessment) and the secondary outcomes of pain and severity of symptoms. However, the method of blinding and randomization was not described, there was no clear description of the patient population and their baseline characteristics, the sample size was small, and the statistical analysis was inadequate (only descriptively reported). Both the internal and external validity of this study was therefore poor, so no valid conclusions can be drawn. However, the study by Chantre et al. does provide, with caution, some evidence that Devil's Claw may significantly reduce pain levels while exhibiting significantly fewer adverse reactions than standard care; and supports the need for further good-quality studies to confirm this.

RCTs with placebo

Evidence of efficacy can be obtained from the four double-blind, placebo-controlled trials. The first study was conducted by Guyader[45,*] and included 50 volunteers suffering with arthrosis who were given a 3-week treatment of Devil's Claw (2400-mg extract per day). The 50 patients received 70 treatment cycles, indicating that some patients had more than one treatment. The primary outcome was the assessment of pain severity in five different conditions as scored on a 0–4 scale. The study concluded that, despite an inadequate treatment (and nonstandardized treatment) period, those receiving the extract had a significant decrease in pain severity, in comparison to the placebo treatment, as assessed 10 days after the end of treatment. No safety data were reported in this study. Certain aspects of the quality of this study were acceptable (dosage, reporting of randomization, and statistical analysis); however, the subjects were not treated for a long enough period, nor was treatment consistent between subjects, the process of blinding was not reported, and no ITT analysis was performed. Therefore, the conclusions drawn from this study cannot be warranted.

A subsequent study by Lecomte and Costa[45] identified pain using a VAS scale from 0 to 10 as the primary outcome. Eight-nine (89) subjects were randomized to receive either placebo or Devil's Claw at a total daily dose of 2010 mg per day for 2 months. Dosage and treatment period were adequate in this study. The study identified that after 30 and 60 days of treatment, those patients who received Devil's Claw had a significant reduction in pain ($p = 0.018$ after 30 days and $p = 0.012$ after 60 days of treatment) compared to placebo. The study reported no dropouts and no AE. Despite the process of blinding not being reported in this study, the overall methodologic quality is high and the conclusions are defensible.

Schmelz et al.[46] investigated the use of Devil's Claw in patients with OA, chronic low-back pain, and myalgia for 30 days of treatment. The study concluded that Devil's Claw was better than placebo based on the primary outcome (i.e., pain severity based on a Likert scale), but the conclusions drawn are not warranted. There are a number of method-

ologic concerns about this study. These include no detailed description given of the inclusion and exclusion criteria, the randomization process, the baseline data, and the dropout rates. In addition, it is disputable whether patients received an adequate period of treatment, and there are no details of the test analysis used to substantiate the conclusions drawn.

The 20-week study by Frerick and colleagues[47] aimed to test the effect of a constant daily intake of Devil's Claw (960 mg/d) in allowing a reduction of the daily intake of ibuprofen. Forty-six patients with OA of the hip were randomized to receive either Devil's Claw plus 800 mg ibuprofen a day versus placebo plus 800 mg ibuprofen per day. After 8 weeks, the ibuprofen dose was then reduced by 50% and after a further 8 weeks all ibuprofen was removed (so patients now only received Devil's Claw or placebo). The primary outcome was the pain subscale of the WOMAC questionnaire,[52] and a subject was judged to have responded when their pain score did not increase by 20% or more. No significant differences between the groups were identified with regard to the primary outcome (pain subscale) indicating that, in this study, Devil's Claw was not superior to placebo. Those in the Devil's Claw group, however, showed significant improvement in terms of the total WOMAC and stiffness subscale scores. There are some methodologic concerns about this study; these include the small sample size, the lack of description of both the randomization and blinding processes, and in addition the baseline data indicate that the two treatment groups may not have been balanced.

Summary

From the available clinical studies, it is not yet possible to conclude that Devil's Claw is effective and/or efficacious in the treatment of osteoarthritis. However, the data from the high-quality study by Lecomte and also the comparator study by Chantre et al.[43] indicate that Devil's Claw appears effective in the reduction of the main clinical symptom of pain. Definitive high-quality trials to assess both effectiveness and efficacy are needed, taking into account the methodologic improvements identified, to determine whether this remedy is beneficial for the treatment of OA.

CONCLUSION AND DIRECTIONS FOR FUTURE TRIALS

The methodologic quality of existing clinical trials is generally poor, and although they provide some support for the potential therapeutic value of Devil's Claw in the treatment of OA, there are a considerable number of methodologic caveats that make further clinical investigations warranted. The clinical evidence, therefore, cannot provide a definitive answer to the two questions posed: Does it work and is it safe? Definitive high-quality studies are now needed that assess its effectiveness and/or efficacy (phase II) and optimal dosage (phase I). In addition, further studies are required to identify the extent of the issue regarding inconsistencies in the quality of different preparations of Devil's Claw; finally, adequate safety monitoring is imperative in all future trials.

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POTENTIAL CONFLICTS OF INTEREST

Gerry McGregor, Ph.D., is an employee of Pascoes Pharmaceuticals, Gießen, Germany, which manufactures a Devil's Claw preparation.

REFERENCES

1. Ernst E, Chrubasik S; Phyto-anti-inflammatories: A systematic review of randomized, placebo-controlled, double-blind trials. Rheum Dis Clin North Am 2000;26:13–27.
2. Baghdikian B, Lanhers MC, Fleurentin J, et al. An analytical study, anti-inflammatory and analgesic effects of *Harpagophytum procumbens* and *Harpagophytum zeyheri*. Planta Med 1997;63:171–176.
3. Chrubasik S, Thanner J, Kunzel O, et al. Comparison of outcome measures during treatment with the proprietary *Harpagophytum* extract doloteffin in patients with pain in the lower back, knee or hip. Phytomedicine 2002;9:181–194.
4. Monograph: *Harpagophytum radix* (South African Devil Claw Root) [in German]. Federal Legal Gazette, 1990;43.
5. ESCOP. Monography *Harpagophyti radix.* In: ESCOP, eds. Monographs on the Medicinal Uses of Plant Drugs, Vol. 2. Exeter, UK: Centre of Complementary Health Studies, University of Exeter, 1996:101–119.
6. ESCOP. Monography *Harpagophyti radix.* In: ESCOP, eds. Monographs on the Medicinal Uses of Plant Drugs, Vol. , 2nd ed. Exeter, UK: Centre of Complementary Health Studies, University of Exeter, 2003:233–240.
7. Monograph: *Harpagophytum radix* (South African Devil Claw Root). Report No. 43 of 2.3. 1989; corrected in Report No. 164 of 1.9.90 [in German]. In: Blumenthal M, Busse WR, Goldberg A, et al., eds. The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines. Austin: American Botanical Council, Boston: Integrative Medicine Communications, 1998.
8. Wenzel P, Wegener T, Devil Claw—a herbal anti-rheumatic [in German]. Deutsche Apotheker Zeitung 1995;13:1131–1144.
9. Wegener T, Winterhoff H. Preparing the South African devil claw remedy [in German]. Deutsche Apotheker Zeitung 2001;141:5613–5621.

10. Wegener T. Degenerative diseases of the musculoskeletal system–overview of current clinical studies of Devil's Claw (*Harpagophyti radix*). [in German]. Wien Med Wochenschr 2002;152:389–392.
11. Lanhers M, Fleruentin J, Mortier F, et al. Anti-inflammatory and analgesic effects of an aqueous extract of *Harpagophytum procumbens*. Planta Med 1992;58:117–123.
12. Barnes J, Anderson LA, Phillipson JD. Herbal Medicine: A Guide for Healthcare Professionals. London: Pharmaceutical Press, 2001.
13. Whitehouse LW, Znamirowska M, Paul CP. Devil's Claw [*Harpagophytum procumbens*]: No evidence for anti-inflammatory activity in the treatment of arthritic disease. Can Med Assoc J 1983;129:249–251.
14. Chrubasik S, Conradt C, Black A. The quality of clinical trials with *Harpagophytum procumbens*. Phytomedicine 2003; 10:613–623.
15. Tippler B, Syrovets T, Loew D, Simmet T. *Harpagophytum procumbens*: Effect of extracts on the eicosanoid biosynthesis in onophor A23187–stimulated human total blood cells. In: Loew D, Rietbrock N, eds. Phytopharmaceuticals II: Research and Clinical Application [in German]. Darmstadt: Steinkopff, 1996:95–100.
16. Fiebich BL, Heinrich M, Hiller KO, Kammerer N. Inhibition of TNF-alpha synthesis in LPS-stimulated primary human monocytes by *Harpagophytum* extract SteiHap 69. Phytomedicine 2001;8:28–30.
17. Loew D, Mollerfeld J, Schrodter A, et al. Investigations on the pharmacokinetic properties of *Harpagophytum* extracts and their effects on eicosanoid biosynthesis *in vitro* and *ex vivo*. Clin Pharmacol Ther 2001;69:356–364.
18. McLeod DW, Revell P, Robinson BV. Investigations of *Harpagophytum procumbens* (Devil's Claw) in the treatment of experimental inflammation and arthritis in the rat [proceedings]. Br. J. Pharmacol 1979;66:140P–141P.
19. Loew D, Mollerfeld J, Schrodter A, et al. Investigations on the pharmacokinetic properties of *Harpagophytum* extracts and their effects on eicosanoid biosynthesis *in vitro* and *ex vivo*. Clin Pharmacol Ther 2001;69:356–364.
20. Beuchis S, Wegener T. *Harpagophyti radix* [devil claw root]: Pharmacology, toxicology and clinical aspects [in German]. Phytotherapie 2002;4:28–33.
21. Riberio V. Review: Some herbal medicines and plant extracts reduced pain and disability and improved function in osteoarthritis. Evidenced Based Nursing 2002:5:57.
22. Walker-Bone K. Natural remedies in the treatment of osteoarthritis. Drug Aging 2003;20:517–526.
23. Chrubasik S. Osteoarthritis: Pharmacology and clinical indications of selected botanicals. Pain Clinic 2004;16:1–16.
24. Chrubasik S, Conradt, Roufogalis B. Effectiveness of *Harpagophytum* extracts and clinical efficacy. [Letter]. Phytother Res 2004;18:187–198.
25. Soeken KL. Selected CAM therapies for arthritis related pain: The evidence from systematic reviews. Clin J Pain 2004;20: 13–18.
26. Setty AR, Sigal LH. Herbal medications commonly used in the practice of rheumatology: Mechanisms of action, efficacy and side effects. Semin Arthritis Rheum 2005;34:773–784.
27. Ernst E. Musculoskeletal conditions and complementary/alternative medicine. Best Practice Res Clin Rheumatol 2004; 18:539–556.
28. Chrubasik S. Devil's Claw extract as an extract of the effectiveness of herbal analgesics. Orthopade 2004;33:804–808.
29. Wegener T, Wiedenbruck R. The Devil Claw [*Harpagophytum procumbens* DC] in treatment of rheumatic illness [in German]. Ztschr Phytother 1998;19:284–294.
30. Chrubasik S, Eisenberg E. Treatment of rheumatic pain with *Kampo* medicine in Europe. Part 1. Harpagophytum procumbens. Pain Clinic 1999;11:171–264.
31. Chrubasik S, Shvartzman P. Rheumatic pain treatment with Devil's Claw [*Harpagophyti radix*] S. Coherence 01/01/1999. Online document at: www.iaam.nl/coherence/msaima/COHINDEX.HTML Accessed January 1, 1999.
32. Wegener T. Devil's Claw: From African traditional remedy to modern analgesic and anti-inflammatory. HerbalGram. J Am Botan Council 2000;50:47–54.
33. Chrubasik C, Pollack S, Black A. Effectiveness of Devil's Claw for osteoarthritis. Rheumatology 2002;41:1332A–1333A.
34. Gagnier JJ, Chrubasik S, Manheimer E. *Harpagophytum procumbens* for osteoarthritis and low back pain: A systematic review. BMC Complement Altern Med 2004;4:1–10.
35. Bélaiche P. Clinical study of 630 patients with arthritis treated with the herbal remedy *Harpagophytum procumbens* [in French]. Phytothérapy 1982;1:22–28.
36. Pinget M, Lecomte A. The effect of *Harpagophytum* Arkocaps in degenerative rheumatism [in German]. Naturheilpraxis 1997;50:267–269.
37. Rutten S, Schafer I. Einsatz der afrikanischen Teufelskralle [Allya] bei Erkrankungen des Stutz unde Bewegungsapparates. Ergebnisse einer Anwendungscbeobachtung. Acta Biol 2000;2:5–20.
38. Usbeck C. Teufelskralle: Devil claw: Treatment for chronic pain [in German]. Arzneimittel-Forum 2000;3:23–25.
39. Schendel U. Arthritis treatment: Study with Devil Claw extract [in German]. Der Kassenarzt 2001;29/30:2–5.
40. Ribbat JM, Schakau D. Treatment of chronic painful conditions [in German]. Natura Med 2001;16:23–30.
41. Wegener T, Lupke NP. Treatment of patients with arthrosis of hip or knee with an aqueous extract of Devil's Claw [*Harpagophytum procumbens* DC]. Phytother Res 2003;17:1165–1172.
42. Schruffler H. Anti-rheumatic treatment: Progress with Devil Claw tablets without the use of steroids [in German]. Die Medizin Publik 1980:1–8.
43. Chantre P, Cappelaere A, Leblan D, et al. Efficacy and tolerance of *Harpagophytum procumbens* versus diacerhein in treatment of osteoarthritis. Phytomedicine 2000;7:177–183.
44. Leblan D, Chantre P, Fournie B. *Harpagophytum procumbens* in the treatment of knee and hip osteoarthritis: Four-month results of a prospective, multicenter, double-blind trial versus diacerhein. Joint Bone Spine 2000;67:462–467.
45. Lecomte A, Costa JP. Harpagophytum dans l'arthrose. Etude en double insu contre placebo. Le Magazine 1992;37:27–30.
46. Schmelz H, Haemmerle HD, Springorum HW. Analgesic effectiveness of Devil claw root excerpt in different chronic-degenerative joint illnesses [in German]. In: Chrubasik S, Wink M, eds. Rheumatherapie mit Phytopharmaka. Stuttgart: Hippokrates, 1997:86–89.

47. Frerick H, Biller A, Schmidt U. Hip osteoarthritis: Double-blind study with Devil claw [in German]. Der Kassenarzt 2001;5:34–41.
48. Circosta C, Occhiuto F, Ragusa S, et al. A drug used in traditional medicine: *Harpagophytum procumbens* DC. II: Cardiovascular activity. J Ethnopharmacol 1984;11:259–274.
49. Chrubasik S, Sporer F, Wink M. Harpagoside concentrations vary in different exceprt of *Harpagophytum procumbens* [in German]. Forsch Komplentar-Med 1996;3:6–11.
50. Chrubasik S, Sporer F, Wink M. Zum Wirkstoffgehalt in Arzneimitteln aus *Harpagophytum procumbens*. Forsch Komplentar-Med 3:57–63.
51. Altman R, Asch E, Bloch D. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–1049.
52. Bellamy N, Buchanan W, Goldsmith C, et al. A health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip or knee. Rheumatology 1988;15: 1833–1840.
53. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–145.
54. Lequesne MG. Indices of severity and disease activity for osteoarthritis. Semin Arthritis Rheum 1991;20(Suppl 6):48–54.

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