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Effectiveness of devil's claw for osteoarthritis

Sir, The recently published systematic review on complementary therapies for osteoarthritis [1] dealt primarily with arthritis of the hip and knee. Although some studies with mixed arthritic patterns were included, studies restricted to low back pain were specifically excluded. Two randomized placebo-controlled trials were cited concerning the effeciveness of *Harpagophytum procumbens*. Both investigated the effect of pulverized plant material containing 1.5 and 3% iridoid glycosides, and were no more than exploratory; one had no statistical calculation and the other no hypothesis. A recent definitive study [2] was not considered. It was designed with 90% power to detect a small difference [10 mm on a 100-mm visual analogue score (VAS) scale, with a background standard deviation of $\sim$22 mm] between freeze-dried *Harpagophytum* and the weak non-steroidal anti-inflammatory drug (NSAID) diacerrhein for hip or knee pain. After 4 months, no statistically significant difference was found between the two treatments. The study showed that freeze-dried root tubers of *Harpagophytum* at a dose containing 60 mg harpagoside per day was as effective as, and had fewer side-effects than, diacerrhein. Table 1 summarizes the types of controlled clinical studies with various *Harpagophytum* preparations that have been published in peer-reviewed journals [2–7]. The results of these studies demonstrate that *Harpagophytum* extracts with >50 mg harpagoside per day are helpful in alleviating pain. According to the ESCOP monograph [8], up to 9 g of crude drug with not less than 1% harpagoside is recommended for painful arthrosis and tendinitis—a dose that contains up to 90 mg of harpagoside. This marker is unlikely to be the only or even the most important active principle of the drug, but may contribute to its overall clinical effect. Although the higher concentrations of harpagoside that are found in volunteers' blood soon after ingestion of a dose of extract are associated with more *in vitro* inhibition of lipoxygenase than the lower concentrations in later samples [9], no such association has yet been demonstrated for therapeutic effect (e.g. pain relief, decrease in joint swelling). Stimulated release of inflammatory mediators (prostaglandin E2, cytokines) from human monocytes is not affected by harpagoside [10] and is a more appropriate test procedure for inflammation than treatment of whole blood with a compound that increases the calcium permeability of any cell [9]. More research is needed to investigate the contribution of the iridoid glycosides to the total effect.

A recent exploratory study of a proprietary ethanol extract of *Harpagophytum* providing only 24 mg harpagoside per day (Table 1) claimed significantly better effects than placebo. On the one hand one has to note that the group who received the extract had more initial pain than the placebo group and, as we have shown in multivariable modelling, greater initial pain tends to be associated with greater improvement [11, 12]. On the other hand it is likely that the ethanol extraction selects a range of less polar but more effective substances than does aqueous extraction, so it is possible that these putative substances are present in a greater proportion to harpagoside in ethanol extracts than in aqueous extracts. More work clearly needs to be done on what the active principle (sum of active ingredients) might be. More generally, the obvious heterogeneity in the range of *Harpagophytum* products means that no generic proof of their effectiveness is possible; the effectiveness has to be tested product by product.

Table 1. Clinical studies with medicinal products from devil's claw

Syndrome	Patients (*n*)	Study design	Control treatment	Solvent	Daily dose of marker (harpagoside) (mg)	Reference
Hip, knee	122	RDB	Diacerrhein	Freeze dried	60	[2]
NSLBP	197	RDB	Placebo	Water	50, 100	[3][a]
NSLBP	118	RDB	Placebo	Water	50	[4]
NSLBP	88	RDB	Rofecoxib	Water	60	[5][b]
NSLBP	102	Open	Conventional[c]	Water	30	[6]
Inhomogeneous	63	RDB	Placebo	Ethanol 60%	24	[7]

NSLBP, non-specific low back pain; RDB, randomized double-blind; inhomogeneous, shoulder, neck, low back and muscle.
[a]Http://www.rzuser.uni-heidelberg.de/~cn6/harpago/
[b]Soon to be available online.
[c]Miscellaneous conventional treatments.

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