



# HerbClip™

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**File: ■ Devil's Claw (*Harpagophytum procumbens*)  
■ Harpagoside**

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**RE: New Knowledge of Harpagoside: Distribution, Biosynthesis/Accumulation, and Pharmacology**

Georgiev MI, Ivanovska N, Alipieva K, Dimitrova P, Verpoorte R. Harpagoside: from Kalahari Desert to pharmacy shelf. *Phytochemistry*. August 2013;92:8-15.

Devil's claw (*Harpagophytum procumbens* and *H. zeyheri*) species have been used traditionally by the Khoisan people of Africa for fever, digestive problems, diabetes, hypertension, and blood diseases. Early studies found tuber extracts effective in rheumatoid arthritis, osteoarthritis, tendonitis, kidney inflammation, and heart disease. The European Pharmacopoeia (EP) lists devil's claw for rheumatic and arthritic issues.

Devil's claw grows slowly and has limited distribution. An iridoid glycoside, harpagoside, isolated in 1962, is considered the main component of devil's claw's iridoid pool and main active compound. Iridoids are found widely in plants. Harpagoside occurs in underground and aboveground parts of plants in several families and genera, in widely varying amounts. A metabolomics study found that two of five mullein (*Verbascum* spp.) species accumulate potentially commercial amounts of harpagoside in leaves, with a leaf metabolome quite different from non- or lower-harpagoside-containing species.

Several ways to produce devil's claw and/or harpagoside products sustainably are discussed. Root callus cultures have been tried but did not produce harpagoside, a secondary metabolite. Hairy root cultures have produced clones that can grow while submerged and accumulate 0.32 mg harpagoside/g dry root mass. While less than whole plants, this illustrates the feasibility of biotechnological production. Better selection of strains and knowledge of pathways involved are needed. Other researchers report a two-step method to propagate devil's claw in vitro. Tubers were comparable to wild plants in harpagoside and harpagide (another iridoid glycoside) content.

High-speed countercurrent chromatography (HSCCC) efficiently separates harpagoside from plant extracts, producing, for example, highly purified harpagoside from scrophularia (*Scrophularia ningpoensis*) roots. Harpagoside research has stimulated new analytical methods using high-performance liquid chromatography (HPLC). HPLC analysis of devil's claw tinctures reveals that its iridoids are stable, with levels falling by less than 10% during six months of storage under controlled conditions.

Harpagoside's biosynthetic pathways are not fully elucidated, although early steps are known. Based on iridoid synthesis in Madagascar periwinkle (*Catharanthus roseus*),

hypothetical pathways are proposed, but researchers have not yet produced higher levels of harpagoside in cultures. No methods have been reported for artificial synthesis.

Effects of *Harpagophytum* extracts are well studied in vivo. Many studies have found that extracts are anti-inflammatory and analgesic in edema and inflammation induced by various agents; some report insignificant effects. This may be due to differences in extract composition. Pure harpagoside significantly reduced or inhibited paw swelling when given orally or intraperitoneally. Devil's claw's other active compounds include harpagide, 8-O-p-coumaroyl harpagide, and the phenylethanoid glycoside verbascoside. Harpagoside content is used to standardize extracts and should equal 1.2% of therapeutic products according to the EP. A review of 15 studies on *Harpagophytum* extracts concluded that at least 50 mg/d is needed in arthritis, providing pain relief to 60% of patients. Doloteffin, a standardized devil's claw product providing 60 mg/d harpagoside, was reported effective in knee osteoarthritis in trials up to 54 weeks.

In vitro, a devil's claw fraction with 88.8% harpagoside moderately inhibited nitric oxide (NO), cyclooxygenase (COX)-1, and COX-2 in human blood. At 27.0% and 8.9%, but not at 2.0%, extracts and pure harpagoside inhibited inducible NO synthase (iNOS) in vitro. Aqueous extracts inhibited NO, COX-1, COX-2, and iNOS in a fibroblast cell line. Extracts with up to 30.0% harpagoside completely inhibited 5-lipoxygenase (5-LOX). Harpagoside suppresses lipopolysaccharide (LPS)-induced COX-2 and iNOS expression induced in RAW 264.7 cells via the nuclear factor-kappa B (NF-κB) signaling pathway. Findings suggest that harpagoside can disrupt the arachidonic acid pathway. Interestingly, harpagide has COX-2-mediated pro-inflammatory effects and can antagonize harpagoside's effects. Both moderating and synergistic effects seem to occur among devil's claw's compounds.

Devil's claw extracts affect inflammatory cytokines in vitro and in vivo. A standardized *Harpagophytum* extract, WS 1531 (Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany), reduced ionophore-stimulated cysteine-leukotriene (Cys-LT) in blood and plasma from healthy volunteers more than harpagoside or harpagoside-free fractions. *Harpagophytum* fractions influence transcriptional level events, inhibiting extracellular signal-regulated protein kinase (ERK), c-Fos expression, and DNA binding of activator protein-1 (AP-1) and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB). Harpagoside and standardized extracts protect against aconitine-induced arrhythmia and reperfusion-induced ventricular arrhythmia. Harpagoside inhibited the inflammatory mediator Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES) in human epithelial cells, showing potential benefits in respiratory disorders. In vivo, it reduced dopaminergic neurodegeneration and movement disorder in a Parkinson's disease model, boosting glial cell line-derived neurotrophic factor.

A number of possible anti-inflammatory mechanisms are proposed. Systems biology studies are needed to correlate pharmacological effects with active and synergistic agents in standardized extracts of harpagoside-bearing plants and/or cultures.

—Mariann Garner-Wizard

The American Botanical Council has chosen not to reprint the original article.

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