EUROPEAN MEDICINES AGENCY
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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Harpagophytum procumbens* DC. and/or *Harpagophytum zeheyri* Decne., radix

Draft - Revision

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne., radix
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance c) Liquid extract (DER 1:1), extraction solvent ethanol 30% V/V d) Soft extract (DER 2.5-4.0:1), extraction solvent ethanol70% V/V e) Dry extract (DER 1.5-2.5:1), extraction solvent water f) Dry extract (DER 5-10:1), extraction solvent water g) Dry extract (DER 2.6-4:1), extraction solvent ethanol 30% V/V h) Dry extract (DER 1.5-2.1:1), extraction solvent ethanol 40% V/V i) Dry extract (DER 3-5:1), extraction solvent ethanol 60% V/V j) Dry extract (DER 3-6:1), extraction solvent ethanol 80% V/V k) Dry extract (DER 6-12:1), extraction solvent ethanol 90% V/V l) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 25% (V/V)

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Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne., radix
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid or solid dosage forms for oral use.
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne., radix. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

The herbal substance consists of cut and dried, tuberous secondary root of two species of Harpagophytum (*Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne.). It contains not less than 1.2 per cent of harpagoside, calculated with reference to the dried drug (F.Eur, Harpagophyti radix, monograph 01/2011:1095).

Constituents: (**Czygan, 1987; BHP,1992; Hansel *et al.*, 1993, ESCOP, 2003, Lecomte *et al*., 1992, van Haelen *et al.,* 1983, PDR, 2004; Wichtl, 2004, Bruneton, 2002**)

The characteristic constituents are iridoid glucosides (0.5-3%), principally harpagoside, extremely bitter (0.8-3.0% in *H. procumbens*, 0.7-1.7% in *H. zeyheri*), together with 8-(p-coumaroyl)-harpagide (0.03- 0.17% in *H. procumbens*, 0.61-1.84% in *H. zeyheri*) and small amount of harpagide, procumbide and their 6^1-p-coumaroyl esters. The secondary tubers contain approximately twice as much harpagoside as the primary tubers.

The phenolic glycosides acteoside (verbascoside) and isoacteoside, and sugars (about 51%), mainly the tetrasaccharide stachyose (up to 46%) with smaller amount of raffinose(a trisaccharide), sucrose and monosaccharides are also present.

The acylated phenolic glycoside 6-acetylacteoside has been found in *H. procumbens* but not in *H. zeyheri*, so can be used to distinguish between the two *Harpagophytum* species **(Mncwangi *et al*., 2012)**

Also, the ratio of 8-O-p-coumaroylharpagide to the sum of harpagoside and 8-O-p-coumaroylharpagide is a distinguishing feature between *H. procumbens* and *H. zeyheri*. In *H. procumbens* it is below 10% while it is above 31% in *H. zeyheri* **(Mncwangi *et al*., 2012).**

Other compounds (in small amounts):

- triterpenes, mainly oleanolic acid, 3β-acetyloleanolic acid and ursolic acid
- phytosterols, mainly β-sitosterol, stigmasterol and their glucosides
- aromatic acids: caffeic, cinnamic and chlorogenic acids
- flavonoids including kaempferol and luteolin
- harpagoquinone

Adulteration: Devil's claw is occasionally adulterated with harpagoside-poor primary roots or with other bitter plants such as *Elephantorrhiza* and *Acanthosicyos***(Wichtl M., 2004; Brendler *et al*., 2006).**

- Herbal preparation(s)

a) Comminuted herbal substance for tea preparation
b) Powdered herbal substance
c) Liquid extract (DER 1:1), extraction solvent ethanol 30% V/V
d) Soft extract (DER 2.5-4.0:1), extraction solvent ethanol 70% V/V
e) Dry extract (DER 1.5-2.5:1), extraction solvent water
f) Dry extract (DER 5-10:1), extraction solvent water

g) Dry extract (DER 2.6-4:1), extraction solvent ethanol 30% V/V

h) Dry extract (DER 1.5-2.1:1), extraction solvent ethanol 40% V/V

i) Dry extract (DER 3-5:1), extraction solvent ethanol 60% V/V

j) Dry extract (DER 3-6:1), extraction solvent ethanol 80% V/V

k) Dry extract (DER 6-12:1), extraction solvent ethanol 90% V/V

l) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 25% (V/V)

Definitions in the European Pharmacopoeia:

- *Harpagophyti extractum siccum,* monograph 01/2008:1871

Dry extract obtained from devil's claw root (1095)

Production: The extract is produced from the herbal drug by an appropriate procedure using either water or a hydroalcoholic solvent that is almost equivalent in strength to ethanol (95 per cent v/v).

Content: minimum 1.5 per cent m/m of harpagoside (dried extract).

Composition of aqueous dry extracts:

Boje *et al*., 2003 compared the composition of dry extract of *H. procumbens* (DER: 1.5-2.5:1; extraction solvent: water) with a dry extract of *H. zeyheri* (DER: 1.6:1; extraction solvent: water) using HPLC method. The results obtained revealed differences, especially in harpagoside and 8-p-coumaroylharpagoside content.

Table 2 Amounts of compounds from the original water extract as determined by HPLC

Fraction or compound	*Amount in* H. procumbens *[%]*	*Amount in* H. zeyheri *[%]*
Caffeic acid (10)	0.005 ± 0.0003	traces
Acteoside (6)	0.68 ± 0.02	0.89 ± 0.004
Isoacteoside (7)	2.0 ± 0.27	3.95 ± 0.124
8-PCHG (2)	0.4 ± 0.1	4.86 ± 0.008
6'-O-Acetylacteoside (8)	0.9 ± 0.04	- - -
Pagoside (5)	0.34 ± 0.01	0.75 ± 0.016
Harpagoside (1)	2.35 ± 0.02	1.53 ± 0.003
Cinnamic acid (9)	0.09 ± 0.001	0.03 ± 0.001

Boje K et al. New and Known... Planta Med 2003; 69: 820–825

Recently **(Tomassini *et al*., 2015)** isolated a new iridoid diglucoside (6'-O-glucopyranosyl-8-O-trans-coumaroylharpagide) from an aqueous extract of *Harpagophytum procumbens* secondary roots, together with six known compounds.

Stability of iridoids in the process of extraction has been investigated using NIR-FT-Raman spectroscopy for identification and quantification of harpagoside and found to be good **(Brendler *et al*., 2006).**

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

This assessment report includes all data regarding mono-preparations containing herbal substance and herbal preparations from *Harpagophyti* radix, literature regarding combination products is not part of the assessment.

1.2. Search and assessment methodology

Databases and other sources used to research available pharmaceutical, non-clinical and clinical data on devil's claw or its relevant constituents:

- Relevant articles and references retrieved from databases: PubMed, Embase and International Pharmaceutical Abstracts were searched with the search terms 'Harpagophyti radix' combined with 'human', 'clinical trial', 'randomised controlled trial' and 'review'. For updating this Assessment Report with actual information in order to revise the HMPC monograph of 2009, the database Embase has recently been searched with search term: '*Harpagophytum* 2007-'.
- Textbooks, pharmacopoeias and monographs.

Data was also provided by the EMA on behalf of interested parties.

The EudraVigilance database and VigiLyze database of the World Health Organisation's were searched in August 2015 using the term [*Harpagophytum* radix].

The abstracts of the references found were screened manually and all articles identified that could have a possible impact on the assessment report and monograph were included. This assessment report is based on the summary of the most relevant scientific literature.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
1) Comminuted herbal substance	Indication 1: Herbal medicinal product in minor pain in joints and muscles Indication 2: Herbal medicinal product in loss of appetite and digestive disorders	Herbal tea Oral use >12 years: Indication 1: 1 teaspoon in 500 ml boiling water. Extraction time: 8 hours. 3 cups daily. Not to be taken for more than 4 weeks. Indication 2: 1 teaspoon in 500 ml boiling water. Extraction time 8 hours. 1-2 cups daily. Not to be used for more than 2 weeks.	WEU, 1997, DK
	Indication 1: Symptomatic relief of digestive disorders such as dyspepsia and flatulence. Indication 2: Adjuvant treatment of degenerative diseases in the locomotor system	Herbal tea - 2.5 g/sachet >12 years: brew 2 sachets with 500 ml boiling water, let that steep overnight, and drink the next day 3 times daily in each case 1/3 of the liquid	At least since 1976, DE, WEU
	Indication 1: Symptomatic relief of digestive disorders such as dyspepsia and flatulence. Indication 2: Adjuvant treatment of degenerative diseases in the locomotor system.	Herbal tea >12 years: brew 1 tea spoon herbal tea (=4.5 g) with 500 ml boiling water, let that steep overnight, and drink the next day 3 times daily in each case 1/3 of the liquid	At least since 1976, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system.	Herbal tea >12 years:brew 1 tea spoon herbal tea (=4-5 g) with 500 ml boiling water, let that steep overnight, and drink the next day 3 times daily in each case 1/3 of the liquid	At least since 1976, DE, WEU
	For the symptomatic treatment of loss of appetite.	Herbal tea: 1.5 g herbal drug infused with water and drink during the day	At least since 1978, DE, WEU
2) Powdered herbal substance	Traditional herbal medicinal product for relief of minor articular pain	Hard capsules - 435 mg Oral use - 3 capsules daily	THMP, 2011 (Czech Republic)
	Traditional herbal medicinal product for relief of minor articular pain.	Capsules - 435 mg Oral use - 3 capsules daily	THMP, 1989,Spain
	Mild joint pain	Hard capsules - 435mg Oral use - 3 capsules daily	THMP, 2012, Belgium
	Traditional herbal medicinal product for the relief of mild articular pain, based on traditional use only	Hard capsules -435 mg Oral use - 3 capsules per day	THMP, 2009, Portugal
	Indication 1: Herbal medicinal product in minor pain in joints and muscles	Hard capsules 370 mg (corresponding to 6,5 mg harpagoside)	WEU, 1999, DK

Active substance	Indication	Pharmaceutical form	Regulatory Status
	Indication 2: Herbal medicinal product in loss of appetite and digestive disorders	Oral use Indication 1: 2 capsules 3 times daily. Not to be taken for more than 4 weeks. Indication 2: 2 capsules 3 times daily. Not to be taken for more than 2 weeks	
	Traditional herbal medicinal product for relief of minor articular pain.	Capsule - 435 mg Oral use. Adults: 1 capsule 3 times a day (up to 6 capsules daily if is necessary) Duration of use: 4 weeks.	THMP, 1981, France
3) Liquid extract (DER 1:1), extraction solvent ethanol 30% V/V	Traditional herbal medicinal product for support of digestion. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.	Oral liquid Oral use Once daily: 15 ml oral liquid (containing 1.03 g extract)	THMP, 1995 (since 1976 with more active agents), DE
4) Soft extract (DER 2.5-4.0:1), extraction solvent ethanol 70% V/V	Traditional herbal medicinal product for support of digestion. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.	Oral liquid Once daily: 10 ml (containing 240 mg extract)	THMP, 1993 (since 1976 with with more active agents), DE
5) Dry extract (1.5-2.5:1; extraction solvent: water)	Traditional herbal medicinal product for relief of minor articular pain	Film coated tablets - 600 mg Oral use - 2 capsules daily, the dose can be increased up to 2 tablet twice daily	THMP, 2013, Czech Republic
	Traditionally used in mild rheumatic ailments	Coated tablets - 600 mg Oral use Adults: 2 x daily 1-2 coated tablets, after meals, with some water. Daily dose equivalent to 2.4-4.6 g of herbal substance.	THMP, 2012, Poland
	Traditionally used in mild rheumatic complaints	Hard capsules - 250 mg Oral use Adults: 2 x daily, 1-3 capsules. If the symptoms persist longer than 4 weeks - consult the doctor.	THMP, 2012, Poland
	For relief of minor articular pain.	Film-coated tablets - 600 mg Oral use - 300 mg to 2.4 g divided in 2 to 3 doses	THMP, 2014, Slovakia

Active substance	Indication	Pharmaceutical form	Regulatory Status
	Traditional herbal medicinal product for relief of minor articular pain.	Film-coated tablet 600 mg extractum siccum (equivalent to 900-1500 mg of *H. procumbens* DC) Oral use Adults and elderly: 1 tablet 2x daily. Dosage may be increased to 2 tablets 2x daily.	THMP, 2014, Latvia
	Traditional herbal medicinal product for supportive treatment of mild back pain, neck pain, muscle pain, articular pain and rheumatic pain	Film coated tablet - 600 mg Oral use - Adults: 2 tablets daily	THMP, 2009, Austria
	Traditionally in mild rheumatic complaints	Tablets - 600 mg Oral use - Adults: 1-2 tablets 2 times daily Daily dosage: 1.2 - 2.4 g of extract	THMP, 2012, Poland
	Traditionally in mild rheumatic complaints	Film-coated tablet - 600 mg >18 years: 2 2 times daily	2010-2014, Hungary, TUR
	Adjuvant treatment of degenerative diseases in the locomotor system	Film-coated tablet - 400 mg >12 years: 2 3 times daily	1995, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system.	Film-coated tablet - 600 mg >18 years: 2 2 times daily	2002, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system.	powder - 4 g/ sachet >12 years: content of 1 sachet dissolved in water or fruit juice 2 times daily	At least since 1976, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system. Symptomatic relief of digestive disorders such as dyspepsia and flatulence.	Film-coated tablet - 375 mg Oral use >12 years: 2 3 times daily	At least since 1976, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system Symptomatic relief of digestive disorders such as dyspepsia and flatulence.	Capsule, hard - 400 mg Oral use >12 years: 2 3 times daily	At least since 1976, DE, WEU

Active substance	Indication	Pharmaceutical form	Regulatory Status
	Traditional herbal medicinal product for support of digestion. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.	Capsule, soft - 100 mg Oral use - 1 capsule, 2-3 times daily	since 1978, DE, TUR
	Traditional herbal medicinal product for relief of minor articular pain.	Tablets - 600 mg Adults: 1 or 2 tablets 2 times daily (total of 2 or 4 tablets daily) Duration of use: 4 weeks	THMP, 2015, France 2006
	Traditional herbal medicinal product for relief of minor articular pain.	Tablets - 450 mg Oral use. Adults:1 to 6 tablets, 2 to 3 times Duration of use: 4 weeks	THMP, 2006, France
6) Dry extract (DER 5-10:1), extraction solvent water	For the symptomatic relief of osteoarthritis.	Film-coated tablet Oral use. one tablet with 200 mg extract, 3 times daily or one tablet with 400 mg extract, 2 times daily	WEU, 1978, DE
7) Dry extract (3:1; water)	Traditional herbal medicinal product for relief of minor articular pain.	Tablets - 200 mg dry extract Oral use - Adults: 3 tablets daily	THMP, 2002, Spain
8)Dry extract of Harpagophyti radix (2.6-3.1:1), extraction solvent: ethanol 30% V/V	Adjuvant treatment of degenerative diseases in the locomotor system.	Capsule, hard - 400 mg or 200 mg Oral use Single dose: 2 capsules x 400 mg; 2 times daily Single dose: 2 capsules x 200 mg; 4 times daily	At least since 1976, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system.	Capsule, soft - 400 mg Oral use >12 years: 1 4 times daily	At least since 1976, DE, WEU
9)Dry extract of Harpagophyti radix (2.8-3.4:1), extraction solvent: ethanol 30% (m/m)	Traditional herbal medicinal product for support of digestion. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use	Capsule, soft - 140 mg Oral use - 1- 2 capsules, 3 times daily	At least since 1978, DE, THMP
10)Dry extract of Harpagophyti radix (3 - 4:1), extraction solvent: ethanol 30 % V/V	Traditional herbal medicinal product for relief of minor articular pain.	Capsules - 210 mg Adults: 1 to 2 capsules 2 to 3 times daily (maximum 6 capsules per day) Duration of use: 4 weeks	Since 1990, France
	For the symptomatic relief of osteoarthritis	Film coated tablet - 450 mg Oral use - One tablet, 3 times daily	Since 1976, DE, WEU

Active substance	Indication	Pharmaceutical form	Regulatory Status
11) Dry extract of Harpagophyti radix (1.5-2.0:1), extraction solvent: ethanol 40% (V/V)	Adjuvant treatment of degenerative diseases in the locomotor system.	Film-coated tablet - 300 mg Oral use >12 years: 1 or 2 3 times daily	At least since 1976, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system (rheumatic complaints).	Film-coated tablet - 300 mg Oral use >12 years: 1 2 times daily	At least since 1976, DE, TUR according to section 105 in combination with section 109a of the German Medicinal Products Act
	For the symptomatic relief of osteoarthritis	Film-coated tablet - 300 mg Oral use >12 years: 3 tablets, 3 times daily	since 1978, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system in adults.	Capsule, soft - 300 mg Oral use >18 years: 1 2 times daily	2011, DE, THMP according to Article 16a of Directive 2001/83/EC
12) Dry extract (4.4-5.0:1 ; ethanol 60% V/V)	Traditional herbal medicinal product for relief of minor articular pain.	Film coated tablet - 240 mg Oral use - Adults and adolescents: 4 tablets	THMP, 2005, Spain
	a) Traditional herbal medicinal product for relief of minor articular pain. b) Traditional herbal medicinal product used for the relief of mild digestive disorders such as bloating and flatulence and where there is loss of appetite.	Soft capsules - 225 mg Oral use. a) Adults: 4 capsules daily b) Adults: 1 capsule	THMP, 2012, Spain
	Traditional herbal medicinal product used for relief of pain and stiffness in cases of mild joint wear (osteoarthritis).	Film-coated tablet - 480 mg Oral use - Adults and elderly: 1 tablet 2 times daily	THMP, 2005, Sweden
	Traditional herbal medicinal product for supportive treatment of mild back pain, neck pain, muscle pain, articular pain and rheumatic pain	Film-coated tablet - 480 mg Oral use - Adults: 2 tablets x daily	THMP, 2012, Austria
	Articular pain, low-back pain, muscle pain	Film-coated tablet - 480 mg Oral use - Adults: 2 tablets daily	WEU, 2008, Austria

Active substance	Indication	Pharmaceutical form	Regulatory Status
	Traditional herbal medicinal product for supportive treatment of mild back pain, neck pain, muscle pain, articular pain and rheumatic pain	Film-coated tablet - 240 mg Oral use - Adults: 2 tablets daily	THMP, 2009, Austria
	Herbal medicinal product for relief of minor articular pain.	Hard Capsule - 480 mg Oral use - 1 tablet 2 times daily; not to be taken more than 4 weeks	THMP, 2009, Romania
	Adjuvant treatment of degenerative diseases in the locomotor system	Film-coated tablet - 480 mg >12 years: 1 2 times daily	1997-2002, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system.	Film-coated tablet - 240 mg >18 years: 2 2 times daily or 1 4 times daily	1998, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system.	Film-coated tablet - 480 mg >18 years: 1 2 times daily	1998-2003, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system.	Effervescent tablet - 480 mg >12 years: 1 2 times daily	1998, DE, WEU
	Adjuvant treatment of degenerative diseases in the locomotor system.	Capsule, hard - 240 mg Oral use - 1, 4 times daily	1998, DE, WEU
	To support digestion.	Capsule, soft - 225 mg Oral use >18 years: 1 1-2 times daily	2010,DE, TUR according to Article 16a of Directive 2001/83/EC
	Traditional herbal medicinal product for relief of minor articular pain.	Tablets - 480 mg Oral use - Adults:1 tablet, 2 times daily Duration of use: 4 weeks	THMP, 2005, France
13)Dry extract (DER 3-5:1), extraction solvent ethanol 60% V/V	For the symptomatic relief of osteoarthritis. For the symptomatic treatment of dyspeptic complaints such as minor gastrointestinal spasms, flatulence and repletion.	Hard capsule - 234.7 mg extract Oral use - 2 capsules, 2 times daily	WEU, 1976, DE

Active substance	Indication	Pharmaceutical form	Regulatory Status
14)Dry extract of Harpagophyti radix (4-5:1), extraction solvent: ethanol 60% (V/V)	For relief of minor articular pain.	Capsule, soft - 200 mg >18 years: 1 4 times daily or 2 2 times daily	2010,DE, TUR according to Article 16a of Directive 2001/83/EC
15) Dry extract (DER 1.5-3:1) Extraction solvent: ethanol 60 % V/V	Traditional herbal medicinal product for relief of minor articular pain.	Tablets - 480 mg Oral use Adults (over 18 years): 1 tablet max. 2 times a day. Duration of use: 4 weeks	THMP, 2014, Estonia
	Traditional herbal medicinal product for relief of minor articular pain.	Film coated tablet - 480 mg Oral use - Adults: 4 tablets daily	THMP, 2011, Spain
16)Dry extract (DER 1.5-2.2:1) corresponding to 9-15 mg harpagoside Extraction solvent: ethanol 60 % V/V	Herbal medicinal product for the relief of minor symptoms of arthrosis	Film coated tablet - Oral use >12 years: 1-2 tablets 2 times daily. Several month of use is recommended.	WEU, 2009, DK
17) Dry extract (DER 3-6:1), extraction solvent ethanol 80% V/V	Traditional herbal medicinal product for support of digestion. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.	Soft capsule - 96 mg extract Oral use - 1 capsule, 3 times daily	THMP, 1994 (since 1976 with more active agents), DE
18) Dry extract (DER 6-12:1), extraction solvent ethanol 90% V/V	Traditional herbal medicinal product for support of digestion. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.	Soft capsule - 43,2 mg extract Oral use - 1 capsule, 2 times daily	THMP, 1976, DE
19) Other extracts(not fully described)	A traditional herbal medicinal product for the relief of minor articular pain in adults	Hard Capsule 427mg of extract (equivalent to 1493 mg – 2133 mg of devil's claw root). Extraction solvent: Ethanol 60% v/v. Oral use Adults and elderly:1 capsule, 2 times daily Duration of use: 4 weeks use	THMP, 2013, Irish

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Not applicable

Information on other products marketed in the EU/EEA (where relevant)

No data available

2.1.2. Information on products on the market outside the EU/EEA

North America (Canada): Devil's claw root is regulated as a Natural Health Product (NHP) for oral use (**NHPD Compendium of Monographs, 2008**).

The approved therapeutic indications are:

- For stimulation of appetite: 0.6-1.5 g dried secondary root tubers, per day

- For relief of digestive disturbances: 0.6-4.5 g dried secondary root tubers, per day

- For the relief of joint pain associated with osteoarthritis: 0.6-7.5 g dried secondary root tubers, per day

Duration of use: For the relief of joint pain associated with osteoarthritis: Use for a minimum of 2-3 months to see beneficial effects.

In USA only *H. procumbens* is incorporated into federal legislation and is sold as food supplements. Recently, an investigation conducted by New York Botanical Garden **(Gafner, 2015)** on marketed food supplements, using the DNA barcoding revealed that all tested samples contained *H. zeyheri*, either alone (81%) or in mixture with *H. procumbens* (19%).

2.2. Information on documented medicinal use and historical data from literature

Harpagophytum procumbens belongs to the Pedaliacea family. This perennial herbaceous plant grows naturally in the Kalahari Desert and Namibian steppes region of south-west Africa. The fruit is a capsule protected by numerous curved spines which, after the splitting of the fruit, take on a claw-like appearance. The names *Harpagophytum* (from the Greek " *harpagos*" - a grappling hook) and *devil's claw* are derived from this.

The genus *Harpagophytum* includes two species (*H. procumbens* and *H. zeyheri*) with two and three subspecies, which are differentiated by three diagnostic features: fruit characters, leaf characters and geographical distribution:

Harpagophytum procumbens (BURCH.) DC. ex MEISSN.: This species exhibits 50-60 seeds per capsule. The woody fruit is strongly differentiated with two double rows of spiny appendices. The spines of each row are at least three in number, often exceeding the length of the capsule and always exceeding its width to 2-3 times. The leaves are 3-5 lobed and the flowers typically have violet lobes with a light yellow throat, but sometimes they are purely yellow or purely violet. The species comprises two subspecies, i.e. *H. procumbens* ssp. procumbens and *H. procumbens* ssp. transvaalense, which are differentiated by fruit size and the length and number of the spiny appendices, the size of the leaves, and the degree of lobation. The two subspecies occur in different regions of southern Africa.
Harpagophytum zeyheri Decne.: This species comprises smaller fruits with less seeds (20-30 seeds). The wings of the woody fruit are set in two double rows with short spiny appendices on the top. The width of the wings rarely exceeds the width of the capsule. The leaves are ovate to three lobed and

30-400 mm long. The flowers likewise exhibit violet lobes with a light yellow throat or purely violet or purely yellow.

Devil's claw secondary tuberised roots have been widely used in Southern Africa in traditional medicine for various indications. The roots were highly prized by African bushmen, Hottenotów and Bantu tribes, as a bitter tonic for indigestion. The infusion of the roots of devil's claw was also used against fever, as a means of "cleaning blood" and to relieve rheumatic pains and joint. In various African cultures small amounts of tuber *Harpagophytum* were administered to pregnant women before approaching birth in order to eliminate the pain (**Brendlee *et al*., 2006**).

In Europe, it is used for painful arthritis, tendinitis, loss of appetite and dyspeptic complaint (**Baghdikian *et al.* 1997**)

The medicinal use has been documented in well-known handbooks dating from 1976 (Zimmerman), 1983 (BHP), 1986 (Grigorescu), 1993(Hansel *et al*.; van Haelen), 2002(Evans; Bruneton; Duke), 2003 (ESCOP) up to 2004(PDR; Wichtl M.).

Zimmerman (1976) describes the following results obtained using decoctions of devil's claw root (1 teaspoonful to 2 cups of water): improvement in small intestine complaints, normalization of constipation and diarrhoea, elimination of flatulence and stimulation of appetite.

BHP(1983) mentioned following specific indication: rheumatic disease

Dosage (three times daily) dried tuber 0.10-0.25 g; liquid extract(1:1, 25% ethanol), 0.1-0.25 ml; tincture 1:5 in 25% alcohol, 0.5-1 ml

A later version of **BHP (1992)** mentioned following indications: painful, arthroses, tendinitis; dyspepsia, lack of appetite.

Dosage: unless otherwise prescribed, three times daily;

For dyspepsia or lack of appetite: dried tuber 0.5 g in decoction; tincture(1:5, 25% ethanol) 1 ml;

For other indications: dried tuber 1.5-2.5 g in decoction; liquid extract(1:1, 25% ethanol), 1-2 ml.

Grigorescu *et al*.(1986)mentioned the African traditional use of Harpagophytum tube in decoction for small intestine complaints, while in Europe is used as bitter tonic and for the treatment of degenerative painful rheumatic disorders.

Lanhers *et al.* (1992) mentioned also the external use for the treatment of sores, boils and others skin lesions, without declaring the dosage.

van Haelen, 1993 declares that the dry root is used as eupeptique, laxative, or for articular pain (250 mg, 3 times/day), while the fresh root is used in ointment for the treatment of rheumatic pain or dysmenorrheal syndrome.

According to **Hänsel *et al.* (1993)** devil's claw (comminuted or powder) can be used for stimulation of appetite, in dyspeptic disorders, and treatment of degenerative painful rheumatic disorders.

Daily dosage: for loss of appetite: 1.5 g of drug; otherwise 4.5 g of drug is used.

Preparation of infusion: use 1 teaspoonful(equivalent to 4.5 g) comminuted drug with 300 ml boiling water. Steep to 8 hours and strain; The infusion can be taken 3 times a day. Hansel *et al*., (1993) also mentions the homeopathic preparation (*Harpagophytum procumbens* hom. HAB1, prepared with ethanol 62%)

According to **PDR (2004),**devil's claw is used in dyspeptic complains, loss of appetite and rheumatism as comminuted drug for infusions and other preparations for internal use(capsules, tablets, liquid extract) and as an ointment for external use.

Preparation of infusion: use 1 teaspoonful (equivalent to 4.5 g) comminuted drug with 300 ml boiling water. Steep to 8 hours and strain;

Daily dosage: for loss of appetite: 1.5 g of drug; otherwise 4.5 g of drug is used. The infusion can be taken 3 times a day.

Wichtl M., (2004) mentions the use as anti-rheumatic and for supportive treatment of degenerative painful rheumatic disorders, preferably in the form of dry extracts and the use for loss of appetite as well as dyspepsia on the basis of the bitter properties of the iridoids.

Products: devil's claw tea(loose pack or in filter tea bags) or dry extracts preparations in capsules, tablets, effervescent tablets and powders, with a declared content of between 200 and 480 mg extract per gram of preparation

Preparation of the tea: pour 300 ml boiling water over 4.5 g of finely cut or coarsely powdered dried root. Steep to 8 hours and strain;

Examples of extracts: **product "X"** (400 mg extract/ capsule[DER 1.5-2.5:1, solvent: water], corresponding to 800 mg dried root. The daily dosage of 6 capsules (2x3) corresponds to 4.8 g of devils claw root; **Product "Y"(**480 mg extract/ capsule[DER 4.4-5.1:1, solvent: ethanol 60% v/v].

The author (Wichtl M., 2004) cites an old German monograph (BAnz no.43, published in March 2, 1989; revised in BAnz no.164, published in September 1, 1990), where the declared indications are: loss of appetite, dyspepsia, supportive therapy of degenerative disorders of the locomotor system.

Dosage (unless otherwise prescribed): Daily dosage: for loss of appetite, 1.5 g of dried root preparations of equivalent bitter value; Otherwise: 4.5 g of dried root or equivalent preparations. Mode of administration: cut dried root for tea infusions and other preparations for oral use.

Bruneton J., 2002 declares that in France are available different products used for the symptomatic treatment of minor articular pain, such as capsules containing powdered substance adjusted to 3%, capsules with 189 mg extract adjusted to 2% or cutaneous gel based on the infusion.

Duke J.A. 2002, mentioned at least 20 indications, stating with headache and finishing with tuberculosis, but the main indication is supportive therapy of degenerative disorders of the locomotor system. Dosage depends on the herbal preparation used: 1 teaspoon chopped root/ 2 cups water, sipped through day; 1 g dry root: 5 ml alcohol/ 5 ml water; 0.1-0.25 g dry tuber as tea 3x/day; 0.1-0.25 ml liquid extract (1:1 in 15% ethanol) 3 x/day; 6-12 ml liquid extract(1:2)/day; 15-30 ml tincture (1:5)/day; 0.5-1 ml root tincture(1:5 in 25% alcohol) 3x/day;

ESCOP supplement 2009 mentions as therapeutic indications: symptomatic treatment of painful osteoarthritis, relief of low back pain, loss of appetite and dyspepsia.

Posology in adults:

Painful osteoarthritis: daily dose 2-5 g of the drug or equivalent dry extract prepared with water or ethanol/water(ethanol max. 60% v/v);

Relief of low back pain: daily dose- 4.5-9 g of the drug as dry extract equivalent to 30-100 mg of harpagoside, prepared with water or ethanol/water(ethanol max. 60% v/v);

Loss of appetite or dyspeptic complaints(adults and elderly): 0.5 g of the drug in decoction, three times daily, or preparations with equivalent bitterness value; tincture(1:10, 25% ethanol), 3 ml.

Duration of administration: Treatment for at least 2-3 months is recommended in case of painful osteoarthritis. In symptoms persist consult a doctor.

French Pharmacopoeia (ed.III) included in May 1989 the monograph of *Harpagophyton* (the herbal substance consists of cut and dried, tuberous secondary root of *Harpagophytum procumbens* DC.; it contains at least 2.2 per cent of harpagoside) and in 1992 the monograph of *"Extrait d'Harpagophytum sec".*

In France (*Bulletin Officiel No.90/22 bis,* 1990) accepted the use of Harpagophytum secondary roots for oral and topical use in one indication: traditionally used for the symptomatic treatment of minor painful articular conditions.

In Germany, Commission E published in 2.3.1989 the monograph Harpagopyti radix(Suedafrikanische Teufelskrallenwurzel) with the following indications:

- Loss of appetite, dyspeptic complaints- daily dosage: 1.5 g or preparations with corresponding bitterness value; mode of administration: comminuted drug for infusions and other preparations taken orally;

- Supportive therapy for degenerative conditions of the motor system- daily dosage: 4.5 g drug or equivalent preparations

In Table 3 information is given regarding the documented medicinal use, strength and posology for the main preparations of Harpogophyti radix as found in the phytotherapeutic handbooks.

Table 3: Overview of historical data

Herbal preparation	**Documented Use / Traditional Use**	**Pharmaceutical form Strength (where relevant) Posology Duration of use**	**Reference**
A) Dry herbal substance for decoction	a) Dyspepsia, lack of appetite. b) Painful, arthroses, tendinitis;	a) 0.5 g dried tuber in decoction x 3 times daily b) 1.5-2.5 g dried tuber in decoction x 3 times daily	BHP(1992)
B) Comminuted or powdered herbal substance for infusion	a)Stimulation of appetite, in dyspeptic disorders b) Treatment of degenerative painful rheumatic disorders.	a)1.5 g daily dose/300 ml water, divided in 3 doses; b)4.5 g of drug in 300 ml boiling water; divided in 3 doses	a) Commission E(1989), Hansel, (1993), ESCOP (2003, 2009) PDR (2004) b)BHP(1992), PDR(2004), ESCOP(2003), Hansel (1993).
C) Powdered herbal substance	Articular pain	250 mg x 3 times daily	BHP (1983) van Haelen(1993)
D) Liquid extract (1:1; ethanol 25% v/v)	Traditionally used for reumatic disease	0.1-0.25 ml, 3 times daily	BHP (1983), BHP(1992)
E) Tincture (1:5), extraction solvent: ethanol 25% (V/V)	a) Traditionally used for reumatic disease b) Dyspepsia or lack of appetite	a) 0.5-1 ml, 3 times daily b)1 ml	a)BHP (1983); b)BHP(1992)

2.3. Overall conclusions on medicinal use

Based on the documentation found in the handbooks, as listed above and the actual market data received from the Competent Authorities sufficient information was found for the cut herbal substance, powdered herbal substance, liquid extract, tincture, soft extract and dry extracts to justify at least 30 years of medicinal use including at least 15 years of the EU for the herbal substance Harpagophytum radix (Table 4).

All above mentioned preparations are for oral use, have a specified strength and posology and have indications suitable to the legal requirements in the relevant route of administration.

Table 4: Overview of evidence on period of medicinal use

During the revision process data were evaluated again regarding the criteria and the time frames of WEU and traditional use. Using the newly integrated data the classification of the extracts was changed:

1. More preparations were added concerning the indication a) *Relief of low back pain*

Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 25% (V/V)

single dose: 0.5-1 ml, 3 times daily

2. More preparations were added concerning the indication b) *Symptomatic relief of digestive disorders such as dyspepsia and flatulence:*

Dry extract (DER 1.5-2.5:1), extraction solvent: water

single dose: 100 mg; 2-3 times daily

Dry extract (DER 3-6:1), extraction solvent ethanol 80% V/V

single dose: 96 mg; 3 times daily

Dry extract (DER 2.6-4:1), extraction solvent: ethanol 30% V/V

single dose: 140-280 mg, 3 times daily

Table 4: Overview of evidence on period of medicinal use (30 years for traditional use)

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Comminuted herbal substance for tea preparation	Indication 1: For the symptomatic relief of osteoarthritis Indication 2: For the symptomatic treatment of loss of appetite.	Indication 1: 4.5 g as herbal tea, divided in 3 doses Indication 2: 1.5 g as herbal tea	since 1978 (37 years)
Powdered herbal substance	Traditional herbal medicinal product for relief of minor articular pain.	435 mg x 3 times daily Duration of use: 4 weeks.	since 1981 (>34 years)
Dry extract (1.5-2.5:1; extraction solvent: water)	Indication 1: Adjuvant treatment of degenerative diseases in the locomotor system. Indication 2: Symptomatic	1. 750-800 mg, 3 times daily 2. 100 mg, 2-3 times	since 1976 (>39 years)

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	relief of digestive disorders such as dyspepsia and flatulence.	daily	since 1978 (>37 years)
Dry extract of Harpagophyti radix (2.6-3.1:1), extraction solvent: ethanol 30% (V/V)*	Adjuvant treatment of degenerative diseases in the locomotor system.	single dose: 400 mg-800 mg; 2 to 4 times daily; daily dose: 800 mg up to 1.6 g	since 1976 (>39 years)
Dry extract of Harpagophyti radix (2.8-3.4:1), extraction solvent: ethanol 30% (V/V)*	Traditional herbal medicinal product for support of digestion	140-280 mg, 3 times daily	since 1978 (> 37 years)
Dry extract of Harpagophyti radix (3-4:1), extraction solvent: ethanol 30% (m/m)*	Traditional herbal medicinal product for relief of minor articular pain.	210 mg-420 mg, 2 to 3 times daily Duration of use: 4 weeks	since 1976 (>39 years)
Dry extract of Harpagophyti radix (1.5-2.0:1), extraction solvent: ethanol 40% (V/V)	Adjuvant treatment of degenerative diseases in the locomotor system.	300-900 mg, 2 to 3 times daily	since 1978 (>37 years)
Dry extract (DER 3-5:1), extraction solvent ethanol 60% V/V	For the symptomatic relief of osteoarthritis. For the symptomatic treatment of dyspeptic complaints such as minor gastrointestinal spasms, flatulence and repletion.	480 mg, 2 times daily	since 1976 (>39 years)
Liquid extract (DER 1:1), extraction solvent ethanol 30% V/V	Traditional herbal medicinal product for support of digestion.	Daily dose: 1.03 g extract as a single dose	since 1976 (> 39 years)
Soft extract (DER 2.5-4.0:1), extraction solvent ethanol 70% V/V	Traditional herbal medicinal product for support of digestion.	Daily dose: 240 mg extract as a single dose	since 1976 (> 39 years)
Dry extract (DER 5-10:1), extraction solvent water	For the symptomatic relief of osteoarthritis.	200 mg, 3 times daily or 400 mg, 2 times daily	since 1978 (>37 years)
Dry extract (DER 3-6:1), extraction solvent ethanol 80% V/V	Traditional herbal medicinal product for support of digestion.	96 mg, 3 times daily	since 1976 (> 39 years)
Dry extract (DER 6-12:1), extraction solvent ethanol 90% V/V	Traditional herbal medicinal product for support of digestion.	43,2 mg, 2 times daily	since 1976 (> 39 years)
Tincture (1:5), extraction solvent: ethanol 25% (V/V)	Traditional herbal medicinal product for relief of minor articular pain.	0.5-1 ml, 3 times daily	BHP (1983)

* The dry extract (DER: 2.6-4:1), extraction solvent: ethanol 30% (V/V) covers dry extracts: DER: 2.8-3.4:1, extraction solvent ethanol 30% (V/V), DER: 2.6-3.1:1; extraction solvent ethanol 30% (V/V) and DER:3-4:1, extraction solvent 30% V/ V ethanol as well.

3. Non-Clinical Data

The extracts used in the trials are specified in the comments as far as possible. Unfortunately, in many publications correct specifications of solvent and drug-extract ratio (DER) are missing. No distinction between two species (*H. procumbens* and *H. zeheyri*) is done in the published literature and often is mentioned as "devil's claw preparation". In these cases no details can be given, if the extract could not be identified otherwise.

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Primary pharmacodynamics

The analgesic and anti-inflammatory activities of devil's claw root and the iridoid glucoside harpagoside have been extensively investigated.

In vitro experiments

These studies were conducted on different extracts, extract fractions or even isolated compounds and mainly investigated the anti-inflammatory activity. Their influence on the arachidonic acid pathway has been particularly closely examined, because inhibitors of COX-1/2 have emerged as important targets for treating rheumatoid arthritis.

a) Herbal preparations

The effects of devil's claw extract (no further information) on prostaglandin synthetase were examined *in vitro*. Radiolabelled arachidonic acid and prostaglandin synthetase were incubated at 37°C for 4 minutes with various concentrations of indomethacin, acetylsalicylic acid or *Harpagophytum procumbens* extract. The percentage of inhibition of the enzyme was then determined. IC50 were then calculated and amounted to 0.376 µg/ml for indomethacin and 437 µg/ml for acetylsalicylic acid. In comparison, the concentration of *Harpagophytum procumbens* causing 50% inhibition of prostaglandin synthetase was superior to 10^5 µg/ml, this suggesting that the claimed anti-inflammatory activity of *Harpagophytum procumbens* is not mediated by the inhibition of the prostaglandin synthetase (**Whitehouse *et al*. 1983**)

Other authors have investigated the effects of *Harpagophytum procumbens* dry extract (DER 5:1 extraction solvent: water) against LPS-stimulated expressions of COX-2 and iNOS (inducible nitric oxide synthase) in murine fibroblast cell line L929. The following parameters were measured: cell viability (MTT assay), COX-1, COX-2 and iNOS mRNAs expressions (RT-PCR), PGE2 and NO biosynthesis. The results obtained did not indicate any cytotoxic effect of the extract tested towards L929 cells at concentrations up to 1 mg/ml. In LPS-stimulated cells, compared to controls, the expressions of COX-1, COX-2 and iNOS mRNAs were increased, as well as PGE2 and NO synthesis. However, when the cells were incubated with LPS and *Harpagophytum procumbens* (up to 1 mg/ml), these parameters were increased compared to controls, but significantly reduced compared to LPS-stimulated cells not incubated with *Harpagophytum procumbens* . Taking into account that NO modulates the activity of COX-2 in a cGMP-independent manner and plays a critical role in the release of PGE2 by direct activation of COX-2, the results obtained in murine cell line L929 suggest that *Harpagophytum procumbens* suppresses COX-2 and iNOS mRNAs expressions, resulting in inhibition of PGE2 synthesis. This mechanism could explain its analgesic and anti-inflammatory activities (**Jang *et al.* 2003**).

The effects of different fractions of *Harpagophytum procumbens* extracts on ecosanoid biosynthesis were evaluated on human whole blood *in vitro* (**Loew *et al.*, 2001**). A crude ethanolic extract (80% w/w), extract fractions prepared by liquid/liquid extraction with solvent of increasing polarity (from heptane to water), harpagoside and two other enriched extracts were tested. These extracts were pre-incubated with human whole blood (n=5 volunteers) for 15 minutes. Then, the Ca2+ ionophore A23187 was added to stimulate the biosynthesis of Cys-LT (cysteinyl-leukotriene) and TXB2 (thromboxane B2) by blood cells. Control samples were not pre-incubated with any extracts. Cys-LT and TXB2 were measured by radioimmunoassay. The results obtained with different fractions of the extract showed that the inhibition of A23187-stimulated Cys-LT and TXB2 biosynthesis is dependent on the harpagoside content in the extracts (see table 1).

Table I. Effect of different *Harpagophytum* extracts and extract fractions on the ionophore A23187–stimulated biosynthesis of Cys-LT and TXB_2 in vitro in human whole blood

Extract and fraction	*Harpagoside content*	*Effect on Cys-LT biosynthesis*	*Effect on TXB_2 biosynthesis*
Crude aqueous ethanolic extract	2.1%	IC_{50} = 1.45 mg/mL (61.7 µmol/L)*	2.35 mg/mL = –42.7% (no IC_{50})
Heptane fraction (fraction A)	1.3%	1.0 mg/mL = –37.3% ± 7.2% (no IC_{50})	No effect up to 1.0 mg/mL
Ethyl acetate fraction (fraction B)	19.95%	IC_{50} = 0.391 mg/mL (158 µmol/L)*	1.0 mg/mL = –27.8% ± 7.9% (no IC_{50})
Butanol fraction (fraction C)	19.5%	IC_{50} = 0.565 mg/mL (223 µmol/L)*	IC_{50} = 0.203 mg/mL (80.1 µmol/L)*
Water fraction (fraction D)	0%	No effect up to 1.0 mg/mL	No effect up to 1.0 mg/mL
Harpagoside	100%	IC_{50} = 39 µmol/L	IC_{50} = 49 µmol/L
Patented special extract WS1531 (fraction F)	7.3%	IC_{50} = 0.062 mg/mL (9.2 µmol/L)*	IC_{50} = 0.373 mg/mL (55 µmol/L)*
Constituents removed from WS1531 (fraction E)	0.36%	1.0 mg/mL = 170.5% ± 14.9% (no IC_{50})	1.0 mg/mL = 128.7% ± 24.5% (no IC_{50})

Cys-LT, Cysteinyl-leukotriene; TXB_2, thromboxane B_2; IC_{50}, 50% inhibitory concentration.
*Molar IC_{50} values were calculated on the basis of the harpagoside concentration of the extracts and extract fractions.

Table 1: Effect of different *Harpagophytum* extracts and extract fractions on the ionophore A23187-stimulated biosynthesis of Cys-LT and TXB2 *in vitro* in human whole blood

This study also showed that the different extract fractions have different pharmacological properties. For example, fraction E (that contains ethanol insoluble constituents removed from WS1531 extract) stimulates the synthesis of Cys-LT and TXB2 and consequently exerts potentially a pro-inflammatory activity (**Loew *et al.*, 2001**).

Two different dry extracts (DER 2-4:1, ethanol 36 v/v; and 4.4-5.0:1, extraction solvent: ethanol 65% v/v) were evaluated at a concentration of 1 mg/ml for their effects on the production of cartilage-degrading enzymes, matrix metalloproteinases(MMPs), in primary chondrocytes obtained from human cartilage. Immunofluorescence microscopy and Western blot analysis showed that the extracts substantially decreased the production of MMPs in both untreated and interleukin 1β-stimulated chondrocytes, the effect of the more potent extract(DER 4.4-5.0:1) being more pronounced in both cases **(Schulze-Tanzil *et al.*, 2004)**

Recently, Hostanska *et al*., 2014 investigated if external metabolic activation of the devil's claw extract by rat liver S9 mix influences its activity, assessed by measuring tumour necrosis factor-α (TNF-α), interleukin (IL) IL-6 and IL-8 levels. Devil's claw extracts dose-dependently suppressed the release of TNF-α, IL-6 and IL-8 in LPS-stimulated monocytic THP-1 cells at non-cytotoxic concentrations (50-250 µg/ml). The metabolic activation did not alternate its cytotoxicity and did not diminish its inhibitory effect. This effect was improved in the case of TNF-α inhibition as reflected by their EC50 values of 116 ± 8.2 µg/ml and 49 ± 3.5 µg/ml for the extract and metabolically activated extract, respectively.

Cytokines inhibitory activity of the extract was not affected after its external metabolic activation. However, the amount of harpagoside and caffeic acid derivates was decreased. The authors concluded that other components of the extract might have contributed to its anti-inflammatory effect.

b) Herbal preparation and isolated compounds

The inhibition of TNF-α synthesis has been investigated by **Fiebich *et al.* (2001)** on *Harpagophytum procumbens* dry ethanolic extract (DER: 4.4-5.0:1 extraction solvent: 60% ethanol v/v; containing 2.9% harpagoside, purified from lipopolysaccharides of bacterial origin) and also on LPS-free harpagide and harpagoside. Human monocytes were incubated with either extract (1 to 1000 µg/ml), harpagide or harpagoside (0.01 to 10 µg/ml each) and then LPS 10 ng/ml were added in the culture medium. After 24 hours, IL-1β, IL-6, TNF-α and PGE2 concentrations were measured in the supernatants. Controls were only incubated with LPS 10 ng/ml. The results show that the LPS-stimulated excretion of TNF-α is inhibited dose-dependently when cells are pre-treated with devil's claw extract (IC50 = 100 µg/ml). Furthermore, IL-1β, IL-6, and PGE2 were decreased at devil's claw extract concentrations superior to 100 µg/ml. On the contrary, pre-treating cells with harpagide or harpagoside up to 10 µg/ml did not influence the TNF-α synthesis, compared to control. Therefore, devil's claw extract inhibits inflammatory processes by preventing the release of TNF-α from human monocytes *in vitro*. However, harpagide and harpagoside had no activity in the same pharmacological model.

Later, the same authors (**Fiebich *et al.*, 2011)** used the same *Harpagophytum procumbens* dry ethanolic extract (DER: 4.4-5.0:1 extraction solvent: 60% ethanol v/v; containing 2.9% harpagoside) in LPS-stimulated human monocytes and RAW 264.7 cells. The extract (10- 500 µg/ml) dose-dependently inhibited the release of TNF-α as well as that of interleukin (IL)-6, IL-1b and prostaglandin E2 (PGE2). The extract prevented TNF-α and IL-6 mRNA expression in human monocytes and COX-2 in RAW 264.7 cells. Furthermore, the extract inhibited LPS-stimulated AP-1-mediated gene transcription activity and binding to the AP-1 response elements. The extract had no effect on the LPS-induced binding of nuclear factor-kB in RAW 264.7 cells or on LPS-induced activation of mitogen-activated protein kinases (MAPK), p38MAPK and JNK in human monocytes. The data indicate that this extract inhibits induction of pro-inflammatory gene expression, possibly by blocking the AP-1 pathway.

Boje *et al.* (2003) performed an *in vitro* study to evaluate the inhibiting activity of *Harpagophytum procumbens* towards the elastase from human leukocytes. An dry aqueous extract of *H. procumbens* (DER:1.5-2.5:1; extraction solvent: water), dry extract *H. zeyheri* (DER: 1.6:1; extraction solvent: water) or isolated compounds(harpagoside, 6-O-acetyllacteoside, isoacteoside, acteoside, cinnamic acid) were incubated with human neutrophile elastase for 1 hour.
At the end of the enzymatic reaction, inhibition rates were calculated and corresponding IC_{50} were then determined. IC_{50} of the dry extract of H.procumbens was 540 µg/ml is about twice as active as *H. zeyheri* (IC_{50} 1012 µg/ml). The more potent active substances in this test were 6-O-acetyllacteoside and isoacteoside, with respective IC_{50} values of 47 and 286 µg/ml (70 and 286 µM). Other compounds, including harpagoside, had IC_{50} greater than 500 µg/ml (800 µM). The elastase inhibiting potency of the aqueous extract *Harpagophytum procumbens* and its main components, with IC_{50} > 50 µM, is considered mediocre.

The effects were studies on two different purified aqueous extracts, containing 8.9%(extract 1) and 27% (extract 2) of harpagoside, on interleukin 1β-induced nitric oxide (NO) formation and transcriptional regulation of iNOS(inducible nitric oxide synthase) in rat renal mesangial cells. Concentration-dependent suppression of NO formation was observed with IC_{50} values of 0.55 µg/ml (extract 1) and 0.2 µg/ml(extract 2). Both extracts also dose-dependently inhibited iNOS and mRNA as well as cytosolic and nuclear protein levels. It was shown that these effects were due to inhibition of

NF-Kβ activation. pure harpagoside was only inhibitory at concentrations between 0.3 and 1 mg/ml. A harpagoside-free extract prepared from extract 1 also markedly inhibited iNOS expression, indicating that other constituents are involved in this effect **(Kaszhin *et al.,* 2004)**

Ouitas and Heard (2009) tested the potential transcutaneous anti-inflammatory effect of the major active components of topically applied *H. procumbens* ethanolic extract (1 mg/ml; extract obtained: 75 mg root extracted with 250 ml ethanol) using *ex vivo* skin. After transcutaneous delivery, the receptor phase at 24 h contained harpagoside (0.8 µmol/ml), harpagide (25 µmol/ml), acteoside (1.8 µmol/ml) and 8-coumaroylharpagide ($3x10^{-3}$ µmol/ml). Although this solution did not have a significant effect on either 5-LOX or iNOS on application to the skin, the expression of COX-2 and PGE2 was effectively inhibited.

Gyurkovska *et al*., (2011) demonstrated *in vitro* that pure harpagoside (at concentration of 250 µg/ml) and *H. procumbens* methanolic extracts 500 µg/ml (from cell suspension cultures and hairy roots generated by A. rhizogenes-mediated transformation) inhibit COX-1/2 expression and NO production by mouse peritoneal macrophages.

c) Isolated compounds

Harpagoside reduced NO release in LPS-stimulated macrophage cells in a dose-dependent manner with and IC50 of 39.8 µM. The induction of COX-2 and iNOS mRNA and their corresponding protein expression in LPS-treated human HepG2 hepatocarcinoma cells was significantly inhibited by harpagoside at 200 µM ($p<0.05$). Macrophage cells pretreated with harpagoside (IC_{50}: 96.4 µM) exhibited dose-dependent inhibition of LPS-induced NF-kB transcriptional activity in transfected macrophage cells. Furthermore, in contrast with the findings from **Kaszhin *et al.,* (2004),** pre-treatment of LPS-treated HeG2 cells with harpagoside at 200 µM significantly blocked the translocation of NF-kB into nuclear compartiments($p<0.05$) and degradation of the inhibitory subunit IKB-α. **(Huang *et al*., 2006)**

Qi *et al.,* 2006 tested *in vitro* the inhibitory effects of isolated iridoid glycosides (6-O-a-D-galactopyranosyl harpagoside, harpagoside, harpagide, 8-O-feruloylhapagide, 8-O-(p-coumaroyl)-harpagide and 8-O-(cis-p-coumaroyl)-harpagide) against macrophages respiratory burst on the murine macrophage-like cell line RAW 264.7. The results obtained indicated that only 8-O-(p-coumaroyl)-harpagide showed marginal inhibition activity against macrophages respiratory burst (IC50value of 32.4 µM).

The hydrolysed products of the iridoid glycosides harpagide and harpagoside have significant anti-inflammatory activity when compared to the unhydrolysed compounds. A recent study shows that hydrolysed products of harpagide and harpagoside had a significant COX-2 inhibitory activity (2.5–100mM) whereas unhydrolysed harpagide and harpagoside did not. Therefore, the hydrolysis of the glycosidic bonds of harpagide and harpagoside by b-glucosidase is a prerequisite step for COX-2 inhibitory activity **(Zhang *et al*., 2011)**

In vivo experiments

Analgesic effect

The most commonly used methods for measuring peripheral analgesic activity were the various forms of the writhing tests in mice, hot-plate test and the Randall–Selitto test in rats. The same tests were performed on extracts but also on isolated compounds, therefore no distinction between studies performed on extracts and studies on isolated compounds can be done.

a) Herbal preparations and/or isolated compounds

A dry aqueous extract of *H. procumbens* and *H. zeyheri* (prepared as: 50 g root infused then macerated for 12 h with 500 ml water, then freeze-dried; containing 2.04 to 2.2% harpagoside) was tested for its analgesic activity in the writhing test. It was administered intraperitoneally to male Swiss mice at doses in the range of 100 to 1200 mg/kg (**Baghdikian *et al.* 1997**). Acetylsalicylic acid was used as a reference peripheral analgesic compound at the dose of 68 mg/kg. Control animals received 0.9% NaCl solution under the same experimental conditions. Thirty minutes after these administrations, the animals were injected a 1.2% acetic acid solution by intraperitoneal route. Each animal was then isolated and observed for 30 minutes. During this period, the number of writhings and stretchings was recorded. The percentage of protection against the acetic acid algic effect was then calculated for each group. The results indicated that *Harpagophytum procumbens* dose-dependently decreased the number of writhings and stretchings from the 400 mg/kg dose (35% protection). The maximal effect was observed at 1200 mg/kg, the percentage of protection reaching 62%. Comparatively, acetyl salicylic acid (68 mg/kg) induced a protection of 59%.

Lanhers *et al.,* (1994) investigated the effect of dry standardised aqueous extract of *H. procumbens* (DER 1:1.5; extraction solvent: water; the extract contains 1.8% harpagoside) and the effect of harpagoside. The intraperitoneally tested doses were 50, 100, 200 and 400 mg/kg (for the extract) and 5 and 10 mg/kg (for harpagoside). Acetylsalicylic acid (68 mg/kg) and morphine sulphate (1.15 mg/kg) were used as reference peripheral/central analgesic compounds. The results indicated that *Harpagophytum procumbens* dose-dependently decreased the number of writhings and stretchings from the 100 mg/kg dose (47% protection). The maximal effect was observed at 400 mg/kg, the percentage of protection reaching 78%. Harpagoside exerted a protective effect against the painful stimuli at the dose of 10 mg/kg only (10 mg harpagoside corresponding to twice the harpagoside content of 400 mg extract). The author also investigated the effect of harpagoside and extract after acid acid treatment (HCl 0.1 N (pH 1) during 3 hours at 38°C), condition that reproduced the physico-chemical conditions found in the stomach. The acid treatment abolished their analgesic activity in the writhing test.

The same authors evaluated the protection potential of the dry extract (DER 1:1.5; extraction solvent: water; the extract contains 1.8% harpagoside) and harpagoside against heat induced pain Male Swiss mice were placed in a glass flack bathing in water whose temperature was maintained at 56°C. Reaction times of mice before any treatment were recorded– time to obtain a response to heat stimuli, e.g. licking of the forepaws, jumping. Then, mice were intraperitoneally injected the extract (200 and 400 mg/kg) or harpagoside (10 mg/kg). Acetylsalicylic acid (68 mg/kg) and morphine sulphate (4.6 mg/kg) were used as reference substances. The procedure to measure time reactions was repeated after 30 minutes. Each animal was its own control. In this test, *Harpagophytum procumbens* , harpagoside and acetylsalicylic acid did not increase the reaction time of mice. On the contrary, morphine sulphate (4.6 mg/kg) exerted a significant protective effect on heat-induced pain, as the reaction time was increased by 46% 30 minutes after its administration(**Lanhers *et al.,* 1994**).

A dry aqueous extract from devil's claw root administered intraperitoneal to mice at 50-800 mg/kg 30 minutes before exposure to thermal - and chemical-induced nociceptive pain stimuli (hot-plate test and acid acetic writhing test respectively), produced significantly analgesic effects($p < 0.05$ to $p<0.001$). The highest dose of extract provided protection of 64.4 and 70.3% respectively in the two models, compared to 82.6 and 89.0% protection after diclofenac at 100 mg/kg i.v **(Mahomed *et al.,* 2004)**

In the Randall–Selitto test, the threshold of pain induced by a sub-plantar injection of 0.1 ml of 20% yeast solution in rats was measured just before, and 30 and 60 min after, a single intraperitoneal injections of a Devil's Claw extract (DER 4.4-5:1, extraction solvent 60%) at doses of 200, 400 and 800 mg/kg. **(Morgenstern and Pollex, 1998).** At 30 min post-administration of the extract the

doses of 200 and 400 mg/kg exhibited a dose-dependent increase in the pain threshold of 28.5 and 61.5% respectively; 800 mg/kg produced no further increase. The effects were superior to those of diclofenac sodium at 80 mg/kg.

The anti-nociceptive effects of an intraperitoneally administered dry extract of devil's claw (DER 4:1, ethanol 60% v/v, extract containing 1.5% of harpagoside) were studied in rats using the hot plate test after acute treatment (25 mg, 50 mg or 100 mg/kg on day 5 after injection of Freud's adjuvant) and chronic treatment (100 mg/kg on days 20 to 40 after in injection of Freud's adjuvant). Both treatments produced significant increases in withdrawal latency ($p < 0.05$ on days 6-8 and 20-40 respectively) **(Andersen *et al.,* 2004)**

Oral pre-treatment of mice with an aqueous dry extract (containing 1.9% harpagoside)at doses of 30-300 mg/kg attenuated significantly times of licking/biting both first and second phases of formalin injection in mice in the dose-dependent manner. Subcutaneous injection of naloxone (5 mg/kg, s.c.) before oral administration of devil's claw root dry extract (300 mg/kg) significantly attenuated antinociceptive effect of devil's claw root dry extract in the second phase of the formaline test($p<0.0010$, authors suggesting the involvement of an opioidergic mechanism **(Uchida *et al*., 2008)**

Other workers **(Erdoes *et al.,* 1978)** found no consistent analgesic effects in mice after oral administration of various extracts (methanolic and buthanolic extracts) and isolated compound(harpagoside) from devil's claw root at doses of 20 and 200 mg/kg.

Anti-inflammatory effect

a) Isolated compounds (harpagoside, harpagogenin)

Different animal models of inflammation were used: the carrageenan-induced mouse/rat paw oedema **(Lanhers *et al.,* 1994; Recio *et al.,* 1994);** the TPA-induced mouse ear oedema **(Recio *et al.,* 1994);** the granuloma pouch test (**Eichler and Koch 1970);** zymosan induced arthritis **(Dimitrova *et al*., 2013)**

• Carrageenan-induced mouse paw oedema **(Recio *et al.,* 1994)**

This study was designed to evaluate the anti-inflammatory activity of harpagoside (100 mg/kg) and 11 other iridoids administered orally to female Swiss mice. Control animals received the vehicle in the same conditions. Indomethacin at the dose of 7 mg/kg was used as a reference product. Each group was composed of 6 mice. One hour after these administrations, each mouse was injected a 3% w/v suspension of carrageenan in its right hind paw to induce oedema. The volumes of the injected and contra-lateral paws were measured at 1, 3 and 5 hours after the induction of inflammation. The values of the oedema volume and the oedema inhibition percentage were calculated for each group. The authors considered that harpagoside administered orally did not exert a notable protective effect in this test.

• Carrageenan-induced rat paw oedema **(Lanhers *et al.,* 1994)**

Male OFA rats were administered harpagoside by intraperitoneal route at the doses of 5 and 10 mg/kg. In the same conditions, indomethacin (2.5, 5 and 10 mg/kg) was used at a reference product and the controls received 0.9% NaCl solution. Twelve rats per harpagoside group were used, as well as 13 control rats and 10 rats per indomethacin group. Thirty minutes after these administrations, each rat received a subplantar injection of a 1% carrageenan suspension in its right back paw. The average volume of the back paws of each animal were measured before any treatment and at different time points after the injection of the carrageenan suspension (30 min, 1, 2, 3, 4, 5, 6 and 24 hours). For each group, the following data were then calculated: average volumes of the back paws before

treatment and at the different time points, and percentages of variation (percentages of oedema). In control animals, a local oedema was observed 30 minutes after the injection of the carrageenan suspension, and reached a maximal intensity after 3 or 4 hours (% of oedema = 56 to 67%). Then, the oedema progressively decreased but still remained obvious after 24 hours. The intraperitoneal pretreatment with harpagoside did not induce an inhibitory effect on carrageenan-induced oedema, contrary to indomethacin.

• TPA-induced mouse ear oedema **(Recio *et al.,* 1994)**

Application of a single dose of 12-O-tetradecanoylphorbol-13-acetate (TPA) to mouse ears induces an acute inflammatory reaction consisting of erythema, oedema and polymorphonuclear leukocyte (PMN) infiltration. TPA was applied on the right ear of mice (2 groups, 6 per group). Then, harpagoside was administered topically at the dose of 1 mg (right ear). The reference substance was indomethacin, 0.5 mg (right ear). Left ears of the animals served as controls, and were applied vehicle (EtOH) or acetone, which was used to dissolve TPA or harpagoside. After 4 hours, animals were sacrificed and the swelling induced by TPA was assessed in terms of the increase in the weight of the right ear biopsy over that of the left ear. The results indicate that harpagoside 1 mg/kg induced an inhibition of 36.2 % of the oedema, as compared to controls. This oedema inhibition percentage amounted to 87.1% with indomethacin 0.5 mg/kg. Therefore, it was concluded that harpagoside did not exert anti-inflammatory effects in this model.

• Granuloma pouch test **(Eichler** and **Koch 1970)**

In this test, an aseptic inflammation with large volumes of haemorrhage is induced. Here, croton oil (0.5 ml, 0.5%) was used as irritant in Wistar rats. Harpagoside (20 mg/kg) and harpagogenin (20 mg/kg) were tested following daily intraperitoneal administration for 12 days. Phenylbutazone (40 mg/kg) was used as a reference substance. The results indicated that harpagoside and harpagogenin induced a significant inhibition of exudate production (respective values of 33.8% and 28.9%), of granuloma weight (respective values of 29.9%,$P<0.01$; 24.5%,$P<0.01$) and of tissue granulation (respective values of 19.2% $P<0.02$; 14.6%,$P<0.01$)

• Zymosan induced arthritis **(Dimitrova *et al*., 2013)**

Harpagoside at dose of 20 mg/kg administered intraperitoneally during the first 10 day after zymosan induced arthritis in mice (induction was done by intraarticular injection of 180 µg zymosan A from Saccharomyces cerevisiae) ameliorated the development of and reduced pathological changes in joints as shown by the decreased histological score for cell infiltration in synovial cavity (3.5±0.2 in vs 2.0±0.16), cartilage loss (2.5±0.3 vs 1.8±0.5) and bone resorption (2.4±0.2 vs. 1.8±0.4).

b) Herbal preparations

Various extracts of devil's claw (mainly dry aqueous extracts) have been evaluated for their antiinflammatory activity in mice and rats. Different animal models of inflammation(acute or chronic) were used: the carrageenan-induced rat paw oedema **(Baghdikian *et al.,* 1997, Lanhers *et al.,* 1994, McLeod *et al.,* 1979, Whitehouse *et al.,* 1983, Soulimani *et al.,* 1983);** the adriamycine-induced rat paw oedema **(Jadot and Lecomte 1992);** albumin-induced rat paw oedema **(Mahomed *et al*., 2004);** the adjuvant-induced arthritis in rats **(McLeod *et al.,* 1979, Whitehouse *et al.,* 1983; Andersen *et al*., 2004),** and the granuloma pouch test **(Erdös *et al.,* 1978).**

• Carrageenan-induced rat paw oedema

Different dry extracts of *H. procumbens* were tested in this model by intraperitoneal and oral routes.

– Intraperitoneal route

A standardised dry aqueous extract of *H. procumbens* (DER 1:1.5; extraction solvent: water; the extract contains 1.8% harpagoside) was administered to rats at the following dose levels: 100, 200 and 400 mg/kg – doses expressed in terms of dried plant material. As precised in the protocol described above, a carrageenan suspension was injected thirty minutes after in the right back paw of each animal. The average back paw volume of each rat was measured before any treatment and at different time points after the injection of the inflammatory agent (up to 24 hours). The results showed that the local oedema induced by the carrageenan suspension was reduced dose-dependently by a pre-treatment by *Harpagophytum procumbens* from the dose of 100 mg/kg within 2-3 hours. The intensity of the anti-inflammatory effect was maximal 3 hours after carrageenan injection. Then, it progressively declined, but still remained significant after 24 hours. The oedema inhibition percentages were 38%, 63% and 72% at respectively 100, 200 and 400 mg/kg (3 hours). Compared to indomethacin (2.5 to 10 mg/kg), whose effect reached a maximal intensity 30 minutes after injection of the carrageenan suspension and remained steady for 5 hours, the anti-inflammatory effect of *Harpagophytum procumbens* was more transient **(Lanhers *et al.*, 1994).**

A dry aqueous extract of *H. procumbens* and *H. zeyheri* (prepared as: 50 g root infused then macerated for 12 h with 500 ml water, then freeze-dried; containing 2.04 to 2.2% harpagoside) was administered to rats at doses of 400, 800 and 1200 mg/kg – doses expressed in terms of dried plant material **(Baghdikian *et al.*, 1997).** Control animals received a 0.9% NaCl solution, and the reference substance used was indomethacin 10 mg/kg. A 1% carrageenan suspension was injected in the right back paw (subplantar route) 30 minutes after these administrations. The average volumes of each rat back paws were measured before any treatment and at different time points after the injection of the inflammatory agent (up to 24 hours). In controls, a local oedema was observed 1 hour after the injection of the carrageenan suspension, and reached a maximal intensity after 3 or 4 hours and still remained obvious after 24 hours. The carrageenan-induced oedema was dose-dependently decreased in animals pre-treated with *Harpagophytum procumbens* from 400 mg/kg. This inhibitory effect was significant 3 and 4 hours after the injection of the phlogistic agent in the 400 mg/kg group (percentages of inhibition respectively 43 and 30%); in the 800 and 1200 mg/kg groups, it was more marked and sustained (significant from 1 to 5 hours), the maximal inhibition being reached 3 hours after induction of the oedema (56 and 64% inhibition, respectively). The inhibitory effect of indomethacin was recorded as soon as 1 hour after the injection of carrageenan and reached a maximum at 3 hours (58% inhibition). Then, it remained steady for 5 hours. This effect was still significant after 24 hours.

– Oral route

Wistar rats were administered either an dry aqueous extract of *H. procumbens* (DER 2:1; extraction solvent: water) at dose of 1 g/kg, indomethacin as a reference substance (5 mg/kg), or 0.5% tragacanth. One hour after these administrations, carrageenin 0.1% was injected into the rear right foot of each animal, and volumes of both rear feet were then measured at hourly intervals. The peak reaction was observed 4 hours after the injection of the phlogistic agent. At this time point, the anti-inflammatory effect of the extract and indomethacin were evaluated taking into account the inhibition of the oedema intensity. Respective inhibition percentages were 6% and 63%. Therefore, this extract of devil's claw did not exert any anti-inflammatory effect in these conditions **(McLeod *et al.*, 1979).**

An extract of *H. procumbens* (no further information) was compared to acetylsalicylic acid (ASA) in terms of inhibition of the oedema induced in male Sprague-Dawley rats injected a 1% solution of carrageenan into the subplantar tissue of the right hind foot. The animals were pre-treated one hour before with either *H. procumbens* (20, 200, 2000, 6000 mg/kg) or ASA (200 mg/kg) by gastric gavage. Volumes of the hind feet (right and left) were measured before and 3 hours after carrageenan treatment. This study showed that *Harpagophytum* administered up to 6000 mg/kg did not reduce the

oedema consecutive to carrageenan injection (max. 20.3% inhibition, 2000 mg/kg) contrary to ASA (51.9% inhibition) **(Whitehouse *et al.,* 1983).**

– Intraperitoneal/oral/intraduodenal routes

It was suggested that devil's claw exerts an anti-inflammatory effect when administered by intraperitoneal route but not by oral route. Furthermore, this effect is abolished after treatment of the extract in conditions mimicking the physico-chemical conditions found in the stomach. Therefore, some authors conducted a study to investigate the influence of the gastric passage on the anti-inflammatory activity of *Harpagophytum procumbens* in rats **(Soulimani *et al.,* 1994).** The extracts prepared had a total glucoiridoid content 2.72%, and an harpagoside content of 0.44%. Extracts intended to be administered orally and intraduodenally were lyophilized with β-cyclodextrin in order to promote its bioavailability. The general design of the study is listed below:

- IP route: administration of the extract (100, 200 and 400 mg/kg in terms of dry material) or NaCl 0.9% (controls) followed after 30 minutes by an injection of a 1% carrageenan suspension into the back paw of each animal.

- Oral route: administration of the extract (200, 400, 800, 1600 mg/kg in terms of dry material) or water (controls) followed after 60 minutes by an injection of a 1% carrageenan suspension into the back paw of each animal.

- Intraduodenal route: ketamine anaesthesia followed by the administration of the extract (200, 400, 800, 1600 mg/kg in terms of dry material) or water (controls) and, after 60 minutes, by an injection of a 1% carrageenan suspension into the back paw of each animal.

In control animals belonging to intraperitoneal and oral groups, a local oedema appeared 1 hour after carrageenan injection; its intensity increased to reach a maximum at 3 hours. In control animals of the intraduodenal groups, the local oedema was observed 2 to 3 hours after the injection of carrageenan and reached a maximal intensity at 6-9 hours. This temporal shift was attributed to ketamine administration. In all control groups, the oedema progressively decreased in intensity but remained obvious 24 hours after its induction. Three hours after intraperitoneal administration of the extract, significant inhibition of the carrageenan-induced oedema was observed from the 100 mg/kg dose (36% inhibition of the oedema). At 400 mg/kg, the effect is maximal (67% inhibition) and was significant from 2 hours to 6 hours after oedema induction. Administered intraduodenally, the extract reduced the carrageenan-induced oedema from the dose of 200 mg/kg 6 to 9 hours after the carrageenan injection (43% inhibition). The effect was maximal at the dose of 400 mg/kg (60% inhibition). By oral route, no inhibitory effect was observed on the carrageenan-induced oedema, whatever the dose of extract administered **(Soulimani *et al.*, 1994).**

• Albumin-induced rat paw oedema

Intraperitoneal treatment with a dry aqueous extract of devil's claw(no further information) at doses of 400 and 800 mg/kg produced time-related, sustained and significant reductions in fresh egg albumin-induced acute inflammation of the rat hind paw($p<0.05$ to $p<0.001$) in comparation with a control group. Ninety minutes after albumin administration oedema inhibition due to the extract (400 and 800 mg/kg) and diclofenac (100 mg/kg i.p) was 59, 76 and 82% respectively **(Mahomed *et al*., 2004).**

• Adjuvant-induced arthritis in rats (*M. tuberculosis*; Freund adjuvant)

Female Sprague-Dawley rats were induced adjuvant arthritis by injection of *Mycobacterium tuberculosis* (0.1 ml, 1 mg/ml) into their rear right feet. Then, the following drugs were administered orally daily for 21 days: *H. procumbens* dry aqueous extract (DER 2:1; extraction solvent: water) at doses of 100 mg/kg – 1 g/kg, indomethacin (3 mg/kg, used as a reference substance), or tap water

(controls). During the administration period, the following parameters were measured: body weight and rear foot volumes. The results of the study indicated that contrary to indomethacin, *H. procumbens* administered orally did not produce a significant effect on either the primary or secondary inflammatory reaction. Moreover, when given in the high-dose group (1 g/kg), the volumes of the injected and uninjected feet were greater than controls. This unexpected effect was significant on day 7 (+16%). Therefore, the authors do not exclude the potential of *H. procumbens* to potentiate adjuvant arthritis in a manner similar to that seen with levamisole and penicillamine**(McLeod *et al.*, 1979).**

In another experiment male Sprague-Dawley rats were injected an oily suspension of *Mycobacterium butyricum* (0.05 ml, 15 mg/ml) into the right hind paw (day 0). An additional group served as a control group and was left uninfected. Oedema in the contralateral foot was monitored in each animal. On day 11, all adjuvant-pre-treated animals exhibiting a foot volume of 2 ml or more were randomly divided into 3 treatment groups and received daily until day 17, by oral route, either: water (2 ml/kg), *Harpagophytum procumbens* extract(no further information) 2 g/kg and indomethacin (3 mg/kg), as reference substance. Volumes of the feet were monitored on days 11, 15 and 17 and mean foot volumes were then calculated. The results indicate that *Harpagophytum procumbens* was ineffective in this model of inflammation after 6 days of treatment, whereas indomethacin completely alleviated the adjuvantinduced arthritis after 4 days of treatment (day 15 of the experiment) **(Whitehouse *et al*. 1983).**

Intraperitoneally administration of 100 mg/kg dry extract of devil's claw (DER 4:1, ethanol 60% v/v, extract containing 1.5% of harpagoside) to rats on days 20 to 40 after in injection of Freud's adjuvant significantly reduced paw oedema ($p < 0.05$ on days 20 to 40) **(Andersen *et al*., 2004)**

- **Granuloma pouch test**

An experiment similar to the one described above was performed with an aqueous (2.7% harpagoside) and a methanolic (3.7% harpagoside) extract of Devil's Claw administered orally at doses of 20 and 200 mg/kg. The tested extracts reduced the exhudate production by 14.29% (not significant) and 69.05% ($P<0.001$) **(Erdos *et al*., 1978).** The effect of the methanol extract was found to be similar to the effects of the NSAID drug, phenylbutazone.

c) Powdered herbal substance

- Antiinflammatory activity was evaluated in adriamycine-induced rat paw oedema.

Harpagophytum procumbens (powder in suspension in arabic gum, 3% glucoiridoids) was administered daily for 5 days to male Wistar rats by oral gavage (0, 37, 370 and 3700 mg/kg/day). Then, all animals were injected in the left hind paw (subplantar injection) 0.2 ml of a solution of adriamycine chlorhydrate (0.5 mg). The volumes of the injected paw were measured before any administration, 1 hour and 5 days after administration of the inflammatory agent. In a previous study, the authors showed that the injection of adriamycine chlorhydrate in the same conditions caused, after 1 hour, a release of serotonin and histamine. After 5 days, lipid peroxidation and free radicals were identified. In the present study, one hour after having induced inflammation, the injected paw volume was decreased in all treated groups, but the effect was maximal in the 37 mg/kg dose group (-48.07%).After 5 days, the administration of *Harpagophytum procumbens* did not inhibit the formation of free radicals, the injected paw volumes not significantly differing between control and treated animals. Therefore, it is concluded that *Harpagophytum procumbens* , after 5 days of oral administration, exerts an anti-inflammatory activity from the 37 mg/kg dosage but no anti-oxidant activity at any dose-level **(Jadot** and **Lecomte 1992)**

Mechanism of action

At least four mechanisms of action were investigated in order to explain the analgesic and anti-inflammatory activity of devil's claw. The influence on the arachidonic acid pathway, especially on the COX-2 was particularly studied and all *in vitro* experiments were already discussed.

The inhibitory potential of COX-2 was also investigated *in vivo* in ICR mice. The animals were applied a methanolic extract of *Harpagophytum procumbens* (200 and 400 µg) onto their shaven back. After 30 minutes, TPA (12-O-tetradecanoylphorbol-13-acetate, a prototype tumour inducer) was administered the same way to induce cutaneous COX-2 expression. As an underlying mechanism of COX-2 inhibition, this extract reduced TPA-stimulated catalytic activity of extra-cellular signal regulated protein kinase (ERK), which is known to regulate the activation of eukaryotic transcription factors mediating COX-2 induction. While TPA-induced activation of nuclear factor-κB remained unaffected by the extract, it inhibited TPA-induced activation of activator protein-1 (AP-1) and attenuated the expression of its key component c-Fos. Furthermore, pre-treatment with the same extract abrogated the DNA binding of cyclic AMP response element binding (CREB) protein induced by topical application of TPA (**Kundu *et al*. 2005**).

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Comparable / similar preparations to preparations of the monograph				
Dry extract of devil's claw (DER 4:1, ethanol 60% v/v, extract containing 1.5% of harpagoside)	i.p 25 mg, 50 mg or 100 mg/kg	Rats *In vivo*	Andersen *et al.,* 2004	Exhibits antinociceptive effect at all doses; 100 mg/kg had also anti-inflammatory effect (reduced paw oedema)
Dry ethanolic extract (DER 4.4-5:1, extraction solvent 60%)	i.p 200, 400 and 800 mg/kg	Rats *In vivo*	Morgenstern and Pollex, 2000.	Exhibits analgesic effect: 200 and 400 mg/kg exhibited a dose-dependent increase in the pain threshold; 800 mg/kg produced no further increase.
Dry extract of *H. procumbens*(DER: 1.5-2.5:1; extraction solvent: water), Dry extract *H. zeyheri* (DER: 1.6:1; extraction solvent: water)	no information	*In vitro* human leukocytes	Boje *et al*., 2003	Inhibition of elastase: IC_{50} of the dry extract of *H.procumbens* was 540 µg/ml is about twice as active as *H. zeyheri* (IC_{50} 1012 µg/ml).
Ethanolic dry extract (DER: 4.4-5.0:1 extraction solvent: 60% ethanol v/v; containing 2.9% harpagoside)	1-1000 µg/ml	*In vitro* Human monocytes	Fiebich *et al.,*2001	LPS-stimulated excretion of TNF-α is inhibited dose-dependently (IC50 = 100 µg/ml).
Dry aqueous extract of *H. procumbens* (DER 2:1; extraction solvent: water)	p.o 1 g/kg 21 days	Female rats *In vivo*	McLeod *et al.,* 1979	Did not exert any anti-inflammatory effect

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Isolated compounds				
Harpagoside	No information	*in vitro* on human whole blood	Loew *et al.* 2001.	IC50 = 49 µmol/L on TXB2 biosynthesis IC50 = 39 µmol/L on Cys-LT biosynthesis
Harpagide Harpagoside	0.01-10 µg/ml	*in vitro* Human monocytes	Fiebich *et al.,*2001	harpagide or harpagoside up to did not influence the TNF-α synthesis, compared to control
Harpagoside 6-O-acetyllacteoside Isoacteoside	no information	*In vitro* human leukocytes	Boje *et al.,* 2003	Inhibition of elastase: 6-O-acetyllacteoside (IC_{50}= 47 µg/ml); isoacteoside (IC_{50}= 286 µg/ml), harpagoside, (IC_{50} > 500 µg/ml)
Harpagoside	250 µg/ml	*In vitro* mouse peritoneal macrophages	Gyurkovska *et al*., 2011	Inhibit COX-1/2 expression and NO production
Harpagoside	200 µM	*In vitro* Human macrophage Human HepG2 hepatocarcinoma cells	Huang *et al*., 2006	Reduced NO release in LPS-stimulated macrophage cells in a dose-dependent manner (IC50 = 39.8 µM). The induction of COX-2 in LPS-treated human HepG2 hepatocarcinoma cells inhibited by harpagoside at 200 µM ($p<0.05$).
Isolated iridoid glycosides (6-O-a-D-galactopyranosyl harpagoside, harpagoside, harpagide, 8-O-feruloylhapagide, 8-O-(p-coumaroyl)-harpagide and 8-O-(cis-p-coumaroyl)-harpagide)	10 mM each	*In vitro* the murine macrophage-like cell line RAW 264.7.	Qi *et al.,* 2006	Only 8-O-(p-coumaroyl)-harpagide showed marginal inhibition activity against macrophages respiratory burst (IC50= 32.4 µM).
H. procumbens ethanolic extract	1mg/mL	*ex vivo* skin	Ouitas and Heard,2009	The expression of COX-2 and PGE2 was effectively inhibited
Harpagide and harpagoside and their hydrolysed products	2.5–100mM	*In vitro*	Zhang *et al.,* 2011	Hydrolysed products of harpagide and harpagoside had a significant COX-2 inhibitory activity whereas unhydrolysed harpagide and harpagoside did not.
Harpagoside	i.p 5 and 10 mg/kg	Mice *in vivo*	Lanhers *et al.,* 1994	Analgesic effect; effect was observed at 10 mg/kg
Harpagoside	p.o 100 mg/kg	Female mice *In vivo*	Recio *et al.,* 1994	No notable anti-inflammatory activity

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Harpagoside	i.p 5 and 10 mg/kg	Rats *In vivo*	Lanhers *et al.*, 1994	No anti-inflammatory activity
Harpagoside	Topically 1 mg	Mice *In vivo*	Recio *et al.*, 1994	No anti-inflammatory effects
Harpagoside Harpagogenin	i.p Harpagoside (20 mg/kg) Harpagogenin (20 mg/kg)	Rats *In vivo*	Eichler and Koch 1970	Both exhibited anti-inflammatory effect
Harpagoside	i.p 20 mg/kg	Mice *In vivo*	Dimitrova *et al.*, 2013	In zymosan induced arthritis reduced pathological changes in joints as shown by the decreased histological score for cell infiltration in synovial cavity, cartilage loss and bone resorption
Powdered herbal substance				
H. procumbens (powder suspended in arabic gum, 3% glucoiridoids)	p.o, 5 days 37, 370 and 3700 mg/kg/day	Rats *In vivo*	Jadot and Lecomte 1992	*H. procumbens*, after 5 days of administration, exerts an anti-inflammatory activity from the 37 mg/kg dosage
Other extracts				
Aqueous dry extract of *H. procumbens* and *H. zeyheri* (2.04 to 2.2% harpagoside)	i.p 100 to 1200 mg/kg	Male mice *in vivo*	Baghdikian *et al*., 1997.	Analgesic effect; the maximal effect was observed at 1200 mg/kg.
Dry extract of *H. procumbens* (DER 1:1.5; extraction solvent: water; contains 1.8% harpagoside)	i.p 50, 100, 200 and 400 mg/kg	Mice *in vivo*	Lanhers *et al.*, 1994	Exhibits analgesic effect; The maximal effect was observed at 400 mg/kg
Dry aqueous extract (contains 1.9% harpagoside)	p.o 30—300 mg/kg	Mice *In vivo*	Uchida *et al.*, 2008	Exhibits antinociceptive effect
A crude ethanolic extract (80% w/w) and extract fractions prepared with solvent of increasing polarity (from heptane to water)	0-19.5% harpagoside in the extract	*in vitro* on human whole blood	Loew *et al.* 2001	Inhibition of TXB2 and Cys-LT biosynthesis is dependent on the harpagoside content in the extracts
H. procumbens extracts	50-250 µg/ml	*In vitro* LPS-stimulated monocytic THP-1 cells	Hostanska *et al.*, 2014	Devil's claw extracts (metabolic activated or not) dose-dependently suppressed the release of TNF-α, IL-6 and IL-8.
H. procumbens ethanolic extract (75 mg root extracted with 250 ml ethanol)	1 mg/ml	*ex vivo* skin	Ouitas and Heard,2009	The expression of COX-2 and PGE2 was effectively inhibited

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Dry aqueous extract of *H. procumbens* (DER 1:1.5; extraction solvent: water; the extract contains 1.8% harpagoside)	i.p 100, 200 and 400 mg/kg	Rats *In vivo*	Lanhers *et al.,* 1994	The local oedema induced by the carrageenan suspen-sion was reduced dose-dependently by a pre-treatment with 100 mg/kg extract within 2-3 hours.
Dry aqueous extract of *H. procumbens* and *H. zeyheri* (containing 2.04 to 2.2% harpagoside)	i.p 400, 800 and 1200 mg/kg	Rats *In vivo*	Baghdikian *et al.,* 1997	The anti-inflammatory effect was dose-dependently
H.procumbens extract (no further information)	p.o 2g/kg	Rats *In vivo*	Whitehouse *et al*. 1983	Did not exert any anti-inflammatory effect
Dry extract (2.72% glucoiridoid content and 0.44% harpagoside content) + β-cyclodextrin	i.p: 100, 200 and 400 mg/kg p.o: 200, 400, 800, 1600 mg/kg Intraduodenal: 200, 400, 800, 1600 mg/kg	Rats *In vivo*	Soulimani *et al*., 1994	i.p: 100 mg/kg significantly inhibited the carrageenan-induced oedema; at 400 mg/kg, the effect is maximal. Intraduodenally, 200 mg/kg reduced while p.o no inhibitory effect was observed.

3.1.2. Secondary pharmacodynamics

Anti-oxidant activity

Herbal preparations

An ethanolic extract (53% w/v; no DER declared) of *H. procumbens* was administered to male Wistar rats by intraperitoneal route for 1, 7 or 14 days in doses of 100 and 200 mg/kg. Control animals received NaCl 0.9% in the same conditions. Selegiline 2 mg/kg was used intraperitoneally as a reference substance. At the end of the treatment period, the frontal cortex and the striatum were dissected out and the following parameters were measured: Super-oxide dismutase (SOD) activity, Catalase (CAT) activity, Glutathione peroxidase (GPX) activity, lipid peroxidation and protein estimation. In animals pre-treated at least 7 days with either *Harpagophytum procumbens* or Selegiline, the activities of SOD, CAT and GPX were dose-dependently increased, and lipid peroxidation was decreased. The authors concluded that the extract tested exerts an anti-oxidant activity at the dosages tested (Bhattacharya and Bhattacharya, 1998).

A dry aqueous extract from devil's claw root(no further data) administered intraperitoneal to mice at 50-800 mg/kg produced dose-dependent, significant reductions ($p < 0.05$ to $p< 0.001$) in the blood glucose concentrations of both fasted normal and fasted streptozotocin(STZ)-treated diabetic rats. After pre-treatment with extract at 800 mg/kg the maximal glycaemic reductions observed were 26% and 50% respectively, compared to 35 and 58% after oral pre-treatment with chlorpropamide at 250 mg/kg. The hypoglycaemic effect of the root aqueous extract became significant ($p <0.05$) 1 h following i.p. administration, reaching the peak of its hypoglycaemic effect 2–4 h after administration. The hypoglycaemic effect of the plant extract was still significant 8 h after i.p administration and the blood glucose concentrations returned to normal, baseline levels at the end of 24 h. **(Mahomed at al., 2004)**

Antimicrobial activity

Isolated diterpenes from petroleum ether devil's claw root extract ((±)-8, 11, 13-totaratriene-12, 13-diol and (±)-8, 11, 13-abietatrien-12-ol) displayed *in vitro* significant antiplasmodial activity (IC_{50}< 1 µg/mL) against both chloroquine-resistant and chloroquine-sensitive strains of *Plasmodium falciparum* **(Clarkson *et al*., 2003).**

Weckesser *et al*. (2007) reports that supercritical carbon dioxide extracts of *H. procumbens* and pure harpagoside inhibits Candida krusei (MIC=100µg/ml). However, harpagoside alone was not effective in the screening, suggesting the existence of synergy between the biologically active constituents.

Anticholinesterase activity

Isolated compounds (as verbascoside and its derivates) was found to inhibit acetylcholinesterase activity at the concentration of 100 µg/mL. Decaffeoylverbascoside showed the most potent inhibitory activity with IC_{50} value of 16.1 µM **(Bae *et al*., 2014)**

3.1.3. Safety pharmacology

Central nervous system activity

Herbal preparations

Mahomed and **Ojewole (2006)** examined the anticonvulsant activity of dry aqueous extract of *H. procumbens* (DER 28:1; extraction solvent: water against pentylenetetrazole (PTZ)-, picrotoxin (PCT)- and bicuculline (BCL)-induced seizures in mice with phenobarbitone and diazepam used as reference drugs.*Harpagophytum procumbens* extract (100–800 mg/kg) significantly delayed the onset of, and antagonised, PTZ-induced seizures, profoundly antagonised PCT induced seizures, and only partially and weakly antagonised BCL-induced seizures. The average time of onset of convulsions was delayed, while the average duration was significantly reduced. It was hypothesised that the mode of action of anticonvulsant activity was the enhancement of GABA-ergic neurotransmission and/or facilitating GABA-ergic action in the brain, but the evidence was inconclusive. However, the ability to suppress the central nervous system may be linked to its anticonvulsant activity.

Cardiovascular activity

Herbal preparations

The cardiovascular activity of *Harpagophytum procumbens* and harpagoside was evaluated in rats, and in Langendorff preparations of rabbit heart **(Circosta *et al*., 1984)**. Single doses of a dry methanolic extract (prepared as 1 part root:10 parts methanol; extract contains 2.09% total glucoiridoids/1.70% harpagoside) or harpagoside were administered either orally or intraperitoneally to conscious normotensive rats (5 per group). By i.p. route, the extract was administered from 25 to 100 mg/kg and harpagoside at 5 and 10 mg/kg. By oral route, the extract was administered from 100 to 400 mg/kg and harpagoside at 20 and 30 mg/kg. Controls received water in the same experimental conditions. Sixty minutes after these administrations (30 minutes for i.p. route), anesthetised rats were injected a pro-arythmogenic drug (either aconitine, $CaCl_2$ or epinephrine-chloroform) by i.v. route. A dose-dependent bradycardic effect was reported after *Harpagophytum procumbens* administration. At higher dose-levels (300-400 mg/kg oral and 75-100 mg i.p.), the effect became significant 30 and 15 minutes after the administration of the extract, by oral and i.p. routes respectively. It lasted up to 120 minutes. ECG records also showed P-wave changes (decreased voltage and long-lasting increased) at these higher dose-levels. Moreover, a dose-dependent reduction

of arterial blood pressure was noted. Significant responses were obtained 15 minutes after an oral dose of 400 mg/kg and i.p. doses of 50 and 100 mg/kg. This hypotensive effect lasted 75 minutes. In experiments conducted with harpagoside, the same effect on arterial blood pressure was noted by both routes of administration, and was more long-lasting compared to the extract. However, the intensity of the effect is lower, compared to the extract containing corresponding quantities of harpagoside. A protective effect of the extract against chemically-induced arrhythmias was observed from 300 mg/kg oral and 25 mg/kg i.p. doses. With harpagoside, a protective effect was reported too, but its intensity was lower than that of the extract containing corresponding quantities of harpagoside. Single doses of either the methanolic extract of *Harpagophytum procumbens* , harpagoside or harpagide, were injected in the coronary circulation of rabbit hearts – Langendorff preparations. Pro-arythmogenic drugs were added before, together with or after. The results indicate that in this model, *Harpagophytum procumbens* caused a mild positive inotropic effect at lower doses but a marked negative inotropic effect at higher dose, with a concomitant decrease in coronary flow. A mild decrease in heart rate was also reported. In the same model, the negative chronotropic and positive inotropic effects of harpagoside were comparatively higher than that of the extract. Harpagide had slight negative chronotropic and considerable negative inotropic effects. A protective effect of the extract against chemically-induced arrhythmias was observed. From this study, it is concluded that the extract of *Harpagophytum procumbens* might interfere with penetration of calcium into the myocardial cells – protection against arrhytmias induced by calcium chloride. This could explain the anti-arrhythmic effects reported in this study, in two animal models **(Circosta *et al*. 1984).**

A methanolic extract of *Harpagophytum procumbens* (prepared 1 part root :10 parts methanol; extract contains 2.09% total glucoiridoids/1.70% harpagoside) was evaluated for its protective potential against ischemic reperfusion-induced HVA in Langendorff preparations of rat heart. Isolated rat hearts were perfused by Langedorff method up to stabilisation of ECG. Then, the coronary flow was reduced to provoke an ischemic perfusion. After 30 minutes, the perfusion was brought to basal conditions. In the same time, the extract and harpagoside were added to the perfusion medium through a cannula connected to the aorta. Seven rat hearts per dose-level were used. In control hearts, polytope extrasystoles occurred 1 minute after the reperfusion. One minute later (2nd minute of reperfusion), ventricular tachycardia occurred. The treatment with *Harpagophytum procumbens* extract reduced the HVA observed in control animals from 1 mg (= 0.085 mg harpagoside) but this protective effect was improved at the dose of 2 mg. With harpagoside, a protective effect was reported too, at 0.170 mg. However, its intensity was lower than that of the extract containing corresponding quantities of harpagoside (2 mg of extract). The methanolic extract (2 mg) and harpagoside (0.170 mg) impeded the insurgence of hyperkinetic arrhythmia set off by 100 µg digitoxin, limiting this latter's toxic effects to disturbances of conduction and of the repolarisation phase. It is hypothesised by the authors that *Harpagophytum procumbens* might inhibit HVA due to a verapamil-like mechanism (calcium antagonistic effect) **(de Pasquale *et al*., 1985).**

Mahomed and **Ojewole (2004)** found that low to moderate doses of *H. procumbens* secondary tuber aqueous extract (no further data) at doses of 10–400 mg/kg produced dose-dependent hypotensive and cardiodepressant effects on the systemic arterial blood pressure and heart rate of pentobarbitone-anaesthetised rats. At doses of 10–1000 mg/ml, dose-dependent, initial slight, transient and significant contractions of isolated rat portal veins, followed by secondary, longer-lasting, significant relaxations of the cardiac muscle were noted. *Harpagophytum procumbens* decreased heart rate and arterial blood pressure in rats and exhibited a negative inotropic effect on isolated rabbit hearts. It has been suggested that it may cause QT prolongation and abnormal heart rhythms as well as influence calcium currents (verapamil-like effect).

3.1.4. Pharmacodynamic interactions

No data available

3.1.5. Conclusions

The traditional use of *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne., radix, as a (powdered) herbal drug, herbal tea, dry water or ethanolic extracts, for the relief of minor articular pain and for the relief of mild digestive disorders (loss of appetite) is well documented in a number of handbooks.

Several *in vitro* and *in vivo* studies were conducted to investigate the analgesic and anti-inflammatory activities of devil's claw (mainly on *H. procumbens*). *In vitro* studies were performed with different extracts (aqueous, methanolic or ethanolic extracts) not always well characterised therefore the relevance of these data is uncertain. For example, although a crude ethanolic extract exerted anti-inflammatory activity by inhibiting LPS-stimulated release of Cys-LT and TXB2 *in vitro*, a fraction of this extract had the opposite effect.

The same comment regarding the heterogeous type of extracts tested is applicable for the *in vivo* studies, where the results are not consistent. Only three of the extracts tested are comparable/similar to preparations of the monograph**.**

H. procumbens showed peripheral analgesic properties after intraperitoneal administration, but no studies are performed by the oral route. In various animal models of inflammation, devil's claw showed anti-inflammatory properties when administered by intraperitoneal route only. However, this activity was abolished in the same models after oral administration. The inefficacy of *H. procumbens* by oral route could result from the gastric passage of the extract. Indeed, the acid treatment of an extract, whose aims was to mimic the physico-chemical conditions found in the stomach, was reported to abolish its anti-inflammatory activity previously reported by i.p. route.

Also isolated constituents have been investigated in several *in vitro* and *in vivo* models. Isolated compounds (mainly harpagoside) were not or were slightly, effective in animal model of inflammation, whereas devil's claw extracts have shown anti-inflammatory activity in the carrageenan-induced rat paw oedema model after intraperitoneal administration. Therefore, harpagoside does not seem to be the active substance/the unique active substance involved in the antiinflammatory activity claimed for *Harpagophytum procumbens* . In the same time isolated constituents were used in unphysiological high doses to achieve effects, the clinical relevance of these investigations may be questionable.

Regarding safety pharmacology some studies conducted on a dry methanolic extract (not included in the monograph) indicated hypotensive and bradycardic effects in rats, and marked negative inotropic effect with a concomitant decrease in coronary flow was noted in isolated rabbit heart. The effects were observed also on isolated compounds(harpagoside), but their magnitude was lower than that of the extract containing corresponding quantities of harpagoside. It is concluded that *Harpagophytum procumbens* could have a verapamil-like mechanism on calcium currents. This finding was not confirmed in subsequent animal and human studies. Actually, a recently published case-report (Cuspidi *et al*., 2015) correlated subchronic use (>2 weeks) of a product containing H procumbens (no further data) with moderate systemic hypertension in a healthy postmenopausal woman.

Also the anticonvulsant activity of an aqueous extract was demonstrated in mice, but too little is known about the mode of action and the ability to suppress the central nervous system was not clinically observed.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Information about the pharmacokinetics of *Harpagophytum procumbens* is scarce, the published data are related with *in vitro* experiments conducted on isolated compounds or herbal preparations.

van Haelen (1983) conducted *in vitro* studies with harpagoside and harpagide to obtain the corresponding genin resulting form acid hydrolysis (harpagogenin). Optimal conditions were: pH 2 and 6 hours incubation in a saturated butanol-1 aqueous solution. Those conditions were chosen to mimic the physico-chemical conditions found in the stomach. The author reports that harpagogenin has not been isolated *in vivo* probably because of its high reactivity and of its high protein-binding rate.

Later**, Chubasik *et al*.,(2000)** investigated the physicochemical properties of harpagoside and its *in vitro* release from tablets and found that both pure harpagoside and harpagoside in Harpagophytum extract have an octanol-water distribution coefficient of approximately 4 which is neither dependent on temperature nor on pH. Harpagoside content decreased by about 10% in artificial gastric fluid within a period of 3 hours and remained stable in artificial intestinal fluid for a period of 6 hours.

Pharmacokinetic interactions

Wu Q *et al*., 2009 investigated the pharmacokinetics and hepatobiliary excretion of harpagoside using *in vivo* microdialysis method but also its interaction with cyclosporin A or verapamil. The harpagoside bile-to-blood distribution ratio (AUC(bile)/AUC(blood)) was 986.28+/-78.46 at i.v administration of 3 mg/kg and significantly decreased to 6.41+/-0.56 or 221.20+/-18.92 after co-administration of cyclosporin A(10 mg/kg) or verapamil(1.2 mg/kg). The results indicated that elimination of harpagoside via bile is probably regulated by P-glucoprotein (P-gp), taking into account that cyclosporin A and verapamil are P-gp inhibitors.

Also **Romiti *et al*., 2009** evaluated *in vitro* (on human kidney (HK-2) proximal tubule cell line) the effects of three Devil's Claw preparations and isolated compound, as harpagoside on the multidrug transporter P-gp. P-glycoprotein is involved in the absorption, distribution and excretion of drugs as it is present in the intestine, liver and kidney. Pgp activity and expression were tested by the calcein-AM test and by Western blotting, respectively. Three different commercial preparations, standardised on harpagoside content (2, 1.2 and 1%, respectively) inhibited P-gp activity, even if to a different extent (IC_{50} values as 285.1, 174.9 and 156.7 µg/ml), while pure harpagoside(at doses up to 200 µM) was almost ineffective. In cells cultured for three days in the presence of devil's claw preparations or pure harpagoside, a dose-dependent P-gp upregulation was found. The authors concluded that devil's claw may interact with the P-gp (influences both activity and expression of the transporter), while harpagoside modulates only its expression.

Regarding inhibitory or inductory effects on CYP *in vitro* studies suggest that *H. procumbens* may affect drugs metabolised by the CYP450 system, especially those metabolised by 2C9 and 2E1.

Budzinski *et al*., 2000 demonstrated that *in vitro* on human cytochrome P450 3A4 *H. procumbens* ethanolic extract (55% v/v ethanol) and harpagoside did not exhibit any inhibitory effects within the tested range(0.01 to 1 mg/ml).

Hilgendorf & Döppenschmidt 2003 used human liver microsomes and 8 standard subtype-specific CYP substrates to test different ethanolic extracts of Serenoa repens, Hypericum perforatum, *Harpagophytum procumbens* , Piper methysticum and Cynara scolymus. Organic solvent was removed for testing. At extract concentrations derived from dose recommendations provided by German Authorities (Commission E), differential effects of the various plants were observed. The effects ranged from strong activation of enzymatic turnover, i.e. *H. procumbens*: 272 ± 12% (p <0.001) of control for

CYP 2E1 to of most complete abolition of activity, e.g for Hypericum perforatum 3±0.7% ($p < 0.0001$) for 3A1 and 0% for 2C8. *H. procumbens* exhibited inhibitory effects on 2C19 activity(59%) as well stimulatory effects on 2E1.

Unger *et al*., 2004 revealed that devil's claw methanolic extract inhibits CYP450. Whereas the inhibitory activity of the devil's claw root extract for CYP1A2 and 2D6 was comparably low (IC_{50} >900 µg/mL), the CYP enzymes 2C8/9/19 and 3A4 were moderately inhibited with IC_{50} values in the range of 100–350 µg/mL.

Table 4. IC_{50} values (mean±SD) for the inhibition of the CYP enzymes (using the enzyme/substrate cocktail and the individual enzymes/substrates).

	Feverfew herb extract		Devil's claw root extract	
CYP	IC_{50} cocktail[a]	IC_{50} individual[a]	IC_{50} cocktail[a]	IC_{50} individual[a]
1A2	56 ± 5 µg/mL	53 ± 7 µg/mL	904 ± 28 µg/mL	997 ± 23 µg/mL
2C8	104 ± 6 µg/mL	126 ± 8 µg/mL	196 ± 13 µg/mL	254 ± 17 µg/mL
2C9	73 ± 4 µg/mL	56 ± 6 µg/mL	148 ± 12 µg/mL	121 ± 8 µg/mL
2C19	122 ± 10 µg/mL	86 ± 7 µg/mL	202 ± 8 µg/mL	155 ± 9 µg/mL
2D6	241 ± 9 µg/mL	299 ± 11 µg/mL	1038 ± 44 µg/mL	1044 ± 80 µg/mL
3A4	130 ± 5 µg/mL	148 ± 6 µg/mL	244 ± 16 µg/mL	335 ± 14 µg/Ml

[a] Mean (±SD) of triplicate determinations.

So, at least theoretically devil's claw it may have an impact on numerous pharmaceutical drugs also metabolised via these enzymes. The impact on warfarin metabolism will be discussed on **chapter 5.5.4. Drug interactions.**

Modarai *et al*., 2011 investigated the effects of 10 commercial devil's claw preparations as well as harpagoside and harpagide, of on cytochrome (CYP) P450 system. Five preparations were found to weakly inhibit CYP3A4 (IC50 124.2-327.6 µg/ml) and five were found to weakly activate X receptor PXR (EC50 10.21-169.3 µg/ml). Harpagoside and harpagide did not inhibit CYP3A4. The authors concluded that Devil's claw preparations are unlikely to have a clinically relevant effect on CYP function.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

3.3.1. Single dose toxicity

a) Herbal substance

Al Harbi *et al*., 2013 tested oral acute toxicity in mice. No alarming signs of toxicity except mild decrease in locomotive activity were observed in mice treated with 1 and 3g/kg dose of devil's claw powdered(suspended in water).

b) Herbal preparations

The acute oral LD0 and intravenous LD0 in mice of aqueous, methanolic and butanolic extracts of *Harpagophytum procumbens* were greater than 4.6 g/kg and 1.0 g/kg, respectively. A purified extract containing 85% harpagoside showed an acute oral LD0 greater than 4.6 g/kg and acute and LD50 of 395 mg/kg and 511 mg/kg, respectively (Erdös *et al*. 1978).

In another study, the LD0 and LD50 in mice of an extract of *Harpagophytum procumbens* (no further information) were superior to 13.5 g/kg. (Whitehouse *et al*. 1983)

c) Isolated compounds

The intraperitoneal LD50 of harpagoside in mice amounted to 1 g/kg, whereas the LD50 of harpagide was greater than 3.2 g/kg in the same conditions (van Haelen 1983).

3.3.2. Repeat dose toxicity

a) Herbal substance

Chronic (90 days) oral toxicity study on *H. procumbens* powdered(suspended in water) was carried out in male and female mice, treated with 100 mg/kg/day (**Al Harbi *et al*., 2013)**. All morphological, biochemical, haematological and spermatogenic changes, in addition to body weight changes and any change in vital organs were recorded. Histopathological investigation were done on vital organs. Both male and female mice in the treatment groups gained statistically significant weight which was similar and comparable to respective control groups. The water intake increased in the treatment as well as the control groups. One male animal was found to develop forelimb inflammation and snout alopecia during chronic toxicity studies. All other animals were normal and comparable to the control animals. There was no mortality of statistical significance observed in any group. Biochemical studies revealed a significant decrease in blood sugar levels and uric acid level of Devil's claw treatment groups. A slight increase in the aspartate aminotransferase (AST) levels was noticed in the treatment groups as compared to the control groups. However, haematological parameters remained comparable to the control. At the end of the treatment, the visceral condition and the vital organs of animals were found to be normal and comparable to the control. The results were substantiated by histopathological studies. The male treatment group was subjected to sperm abnormality test, but the results were negative.

b) Herbal preparations

In male Wistar rats, no significant haematological or gross pathological findings were evident following 21 days of sub-acute oral treatment with 7.5 g/kg of *Harpagophytum procumbens* extract (no further information). No hepatotoxic effects were observed with respect to liver weight or levels of microsomal protein and six liver enzymes after 7 days of oral treatment with 2 g/kg (Whitehouse *et al*. 1983).

3.3.3. Genotoxicity

No data available.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

Mahomed and **Ojewole (2009)** investigated the effect of *H. procumbens* dry aqueous extract (no further data) on longitudinal, tubular uterine horn muscle strips taken from non-pregnant and pregnant, young adult, female rats. The dry aqueous extract (10-800 µg/ml) induced concentration-related and significant ($P<0.05$) increases in the baseline tone, and caused powerful rhythmic, myogenic contractions of, oestrogen-dominated rat longitudinal uterine horn muscle strips taken from stilboesterol-pretreated, non-pregnant female rats. Relatively low to high concentrations of extract (10-800 µg/ml) also provoked concentration dependent and significant ($P<0.05$-0.001) increases in the baseline tone of, and contracted, longitudinal, tubular uterine horn muscle strips taken from female rats in the early, middle and late stages of pregnancy. Moderate to high concentrations of HPE (200-

1,000 µg/ml) always provoked powerful contractions of isolated longitudinal, tubular uterine horn muscle preparations of non-pregnant and pregnant rats. The authors concluded that *in vitro* study indicate that *H. procumbens* aqueous extract possesses spasmogenic, uterotonic action on mammalian uterine muscles.

No *in vivo* data on female animals are available.

Regarding reproductive toxicity on male mice see **Repeate dose toxicity (Al Harbi *et al*., 2013)**

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

Toxicological data on Harpagophyti radix preparations are very limited. One published study was found on the acute toxicity of herbal substance, three studies were conducted on different extracts or isolated compounds(harpagoside, harpagide) and two repeated-dose study were conducted on herbal substance and a herbal preparation (not well characterised). The results indicate that devil's claw poses a low toxicity in animals.

Due to the lack of data on genotoxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, a list entry for Harpagophity radix cannot be recommended.

3.4. Overall conclusions on non-clinical data

Results from *in vitro* and *in vivo* studies with extracts and isolated constituents, support the traditional use as relief of minor articular pain.

Specific data on pharmacokinetics and interactions are limited, especially *in vitro* effects on CYPs. *H. procumbens* may affect drugs metabolised by the CYP450 system, especially those metabolised by 2C9 and 2E1.

Non-clinical information on the safety of is scarce but suggests that methanolic extract of *H. procumbens* could have a verapamil-like mechanism on calcium currents. It is unknown if the effects observed in animals are clinically relevant due to the high doses used. Actually, clinical data suggested a possible hypertensive effect but the evidence is limited.

Some *in vitro* data suggested that devil's claw aqueous extract possesses spasmogenic, uterotonic action on mammalian uterine muscles. As there are no *in vivo* data on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. Applications for marketing authorisation of products containing harpagophyti radix preparations should include data obtained from an AMES test according to the currently valid OECD guideline 471.

4. Clinical Data

The extracts used in the trials are specified in the comments as far as possible. Unfortunately, in some publications correct specifications of solvent and drug-extract ratio (DER) are missing. In these cases no details can be given, if the extract could not be identified otherwise.

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

a) Herbal substance

No significant effects on mediators of acute inflammation (PGE2, thromboxane B2, 6-ketoprostaglandin F1α and leukotriene B4) were evident in 25 healthy volunteers after 3-week daily intake of 4 x 500 mg capsules of powdered *H. procumbens* root, containing 3% of iridoid glucosides. The subjects served as their own control and were also compared with a separate control group. It was concluded that devils claw root does not produce the biochemical effects on arachidonic acid metabolism characteristic of anti-arthritic drugs of the non-steroidal anti-inflammatory type **(Moussard *et al*., 1992)**

b) Herbal preparations

Following oral administration to 6 volunteers of 600 mg of devil's claw extract(patented special extract called WS1531, containing 25% harpagoside), the effects on biosynthesis of eicosanoids was studied *ex vivo* in samples of their blood. After stimulation with ionophore A23187 for 60 minutes the synthesis of thromboxane B2 (an indicator of COX metabolic pathway) and leukotriene C4(an indicator of the 5-lipoxygenase metabolic pathway) were measured by radio-immunoassay. Blood samples of all subjects revealed a time-dependent reversible inhibition of leukotriene C4 biosynthesis with maximum inhibition of 50% after ca. 3 hours. The biosynthesis of thromboxane B2 was not inhibited **(Loew *et al*., 2001)**.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

a) Herbal preparations

There are three studies, all described by **Loew *et al*., 2001** that investigated the kinetics of devil's claw preparation in human volunteers. In study 1, a pilot dose finding study, one volunteer ingested 400 mg of Harpagophytum extract (containing 25% harpagoside). After 14 days, the volunteer took another 600 mg, and after another14 days he took 800 mg. In study 2 6 volunteers took 600 mg of Harpagophytum extract (special extract called HF 8858, containing 25% harpagoside). In study 3, 3 volunteers received 600, 1200 and 1800 mg Harpagophytum extract called WS1531, containing 9% harpagoside as film-coated tablets. Blood was collected after 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12 and 24 hours after administration. The pharmacokinetics parameters of harpagoside are shown in table 5. The Cmax values in human blood were reached within 1.3 to 2.5 hours and the maximum value corresponds to 50.1 ng/ml, which may be the result of a considerable first-pass effect or a low oral absorption. A second peak observed after 8 hours indicated enterohepatic circulation. the elimination half-life of harpagoside was 5.6 hours.

Table II. Pharmacokinetic parameters after single oral administration of different doses of *Harpagophytum* extracts

	Dose (mg harpagoside/mg extract)					
	43.8/600 (study 1)	*100/400 (study 1)*	*108/1200 (study 3)*	*150/600 (study 2)*	*162/1800 (study 3)*	*200/800 (study 1)*
No. of human male volunteers	1	1	3	6	3	1
C_{max} (ng/mL)	15.4	16.4	8.2	32.2	27.8	50.1
t_{max} (h)	2	2.5	1.3	1.3	1.8	2.5
AUC(0-t) (ng · h/mL)	ND	65.9	17.2	157.5	160.5	225.7
AUC(0-∞) (ng · h/mL)	ND	82 .	ND	226	187.9	355.8
Terminal $t_{½}$ (h)	ND	3.7	ND	5.6	4.4	6.4
CL (L/min)	ND	20.3	ND	12.2	14.4	9.4

C_{max}, Peak concentration; t_{max}, time to reach C_{max}; AUC, area under the plasma concentration–time curve; $t_{½}$, half-life; ND, not determined.

Table 5. Pharmacokinetic parameters of harpagoside after single oral administration in humans

Baghdikian *et al*., 1999 investigated the metabolism of 3 iridoid glycosids from *Harpagophytum procumbens* by human intestinal bacteria: harpagoside, harpagide and 8-o-p-coumaroylharpagide. Those iridoids were incubated aerobically at 37°C for 24 hours with either almond β-glucosidase or a bacterial mixture from human faeces (18 strains). In these two tests, aucubinine B (a monoterpene alkaloid) was obtained from the 3 iridoids, the amount recovered being higher with human faecal bacteria than with β-glucosidase. Seventeen of the 18 bacterial strains were involved in this reaction. Furthermore, the highest formation rate was observed with harpagoside, as 12.5% harpagoside were converted to aucubinine B by human bacterial mixture.

4.2. Clinical efficacy

4.2.1. Dose response studies

There are no dose response studies available.

4.2.2. Clinical studies (case studies and clinical trials)

a) Use for the relief of mild digestive disorders

Like other bitter herbals, Harpagophytum radix is used for loss of appetite and mild digestive disorders. Several EU Member States validate such indications for Harpagophytum based on the long-standing use. Moreover, the above-mentioned properties are the oldest known in Europe for Harpagophytum; its use in articular pain is more recent. The link between bitterness of herbals (including Harpagophytum) and their use as appetite stimulating agent and to relieve digestive disorders is described in several references in literature (**Hänsel *et al*. 1993; Schilcher H 1999; Braun** and **Frohne 1987; Czygan 1987; Bisset 1994; Weiss 1991**).

Harpagophytum radix has a reported bitterness value of ca. 6000 (**Olivier *et al*., 2013**)

From experience of digestive disorders in a medical practice over a 3-year period, based on subjective assessment and on evaluation of clinical and biochemical parameters, the following results were obtained using decoctions of devil's claw root (1 teaspoonful to 2 cups of water): improvement in small intestine complaints, normalisation of constipation and diarrhoea, elimination of flatulence and stimulation of appetite (**Zimmerman, 1976)**

b) Relief of back pain

Several clinical studies involving human patients have been performed to test the pain relieving properties of *H. procumbens*, mostly in patients with lower back pain.

Controlled clinical trials

Herbal preparations

Chrubasik *et al*.1996 investigated the effectiveness of *H. procumbens* extract in treatment of acute low back pain in a four-week randomised double-blind study. Patients between 18 and 75 years of age were recruited when they had experienced at least six months of low back pain that could not be attributed to identifiable causes. 118 patients were randomised in the treatment and placebo groups. Patients in the treatment group received 800 mg Harpagophytum dry aqueous extract (DER 2.5:1) in tablets, three times daily, corresponding to harpagoside daily consumption of 50 mg. The only rescue medication allowed was tramadol. In fact, cumulative requirements for tramadol, over the last three weeks of the study period, were taken as the principal outcome measure of efficacy. Secondary end-points, were the number of pain-free patients and global assessment with the Arhus low back pain index. No difference was observed in the analgesic rescue medication sparing measurement between placebo and treatment groups. A greater number of pain-free patients were observed in the treatment group, than in placebo group but that difference did not show statistical significance. The adverse effects observed in the group treated with devil's claw were: nausea(2 patients), tachycardia(1 patient) and tussive irritation(1 patient). Overall, negative clinical results as compared to placebo were observed in this clinical study. The conclusion of the authors, was the need of further clinical trials. Future studies may also assess the effect of dose in order to obtain clinical dose-response if applicable.

Chrubasik *et al*. 1999 investigated the effectiveness of Harpagophytum aqueous dry extract WS 1531 (DER: 6-9:1) in the treatment of exacerbation of low back pain in a randomised, placebo-controlled, double-blind study. This second trial is in direct line with the previous one (**Chrubasik *et al*., 1996)**. The design of the study is identical, but two doses of Harpagophytum extract (600 and 1200 mg daily containing 50 and 100 mg of harpagoside, respectively) were assessed versus placebo. The principal outcome measure was the proportion of patients free of pain, without rescue medication (tramadol) for at least 5 days, in the fourth week. Secondary outcome measure use Arhus Index to assess pain and functional disability. Of the 197 included patients, 183 completed the trial. The number of patients free of pain in the last week of treatment (primary analysis) was small. A greater number of responders was significantly observed ($p = 0.027$) in the treatment groups (9% and 15% for 600 mg and 1200 mg respectively) than in the placebo group (5%) However, inconsistency in the direction of any dose -related effect was observed between primary and secondary analyses, in particular for the pain component. Stratification tends to indicate that only some subgroups (shorter exacerbations, less pain, no radiation) could be improved by the treatment. The suspicions of Harpagophytum-related adverse reactions were generally weak, the strongest being in 8 reports of mild gastrointestinal upset, for in each dose group, whereas only one patient in the placebo group reported any such effect. Due to the contradictory results, no clear conclusion could be drawn regarding the efficacy of Harpagophytum in the treatment of low back pain. Other points of criticism: the short duration (only 4 weeks) and the fact that the extract administered is not commercially available, which limits its external validity.

In a randomised, double-blind, placebo-controlled study, 63 patients(31 verum group and 32 placebo), between 18-62 years old, with slight to moderate muscular tension or slight muscular pain of the back, shoulder and neck received 2 x 480 mg Harpagophytum dry extract (DER 4.4-5.0:1, extraction solvent: ethanol 60% v/v) or placebo daily for 4 weeks (**Göbel *et al*. 2001)**. The efficacy of verum treatment was clear from the clinical global score and patient and physician ratings. Significant improvements were observed in muscular pain intensity (visual analogue scale) and in pressure algometer, muscle stiffness and muscular ischemia tests, but there were no differences from placebo in

antinociceptive muscular reflexes or electromyogram activity. The adverse effects observed in the verum group: 4 patients with gastrointestinal upset such as nausea, meteorism; in the placebo group: 2 patients with diarrhoea, nausea, meteorism. The study population was less homogeneous and subpopulations were not evaluated. The results of the placebo group are not in accordance with other references and therefore these results seem to be doubtful.

Chrubasik *et al*. 2003 compared in a randomised double-blind study (for 6 weeks) the effects of 2400 mg dry aqueous extract (DER 1.5-2.5:1, extract containing 60 mg of harpagoside; n=44) with those of rofecoxib(12.5 mg per day; n=44), a COX-2 selective inhibitor in the symptomatic treatment of chronic low back pain. The aim of the exploratory study was to estimate effect sizes for a number of outcome measures (number of pain-free patients, decrease in averaged daily pain score, percentage change from baseline in Arhus Low Back Pain index, requirement for rescue medication, etc.). Patients were recruited when they had experienced at least six months of low back pain that could not be attributed to identifiable causes and with current exacerbation that had lasted for at least 8 weeks. A score of 5 out of 10 on a visual analogue scale was needed. Patients were allowed to take tramadol as a rescue medication up to 400 mg per day. 88 patients were randomised in the two groups of treatment. There was no placebo group. The number of pain-free patients without taking rescue medication increased progressively during the course of treatment and more or less in both groups. No statistically significant difference was observed between the two treatments neither for pain-free patients, nor for Arhus Low Back Pain and Health Assessment Questionnaire. 14 patients in each group experienced 39 adverse effects, of which 28(13 in the Harpagophytum group) were judged to some degree attributable to the study medications. Adverse effects caused a premature termination of the study in 1/44 (2%) in the harpagophytum group vs. 6/44(14%) in the NSAID group. The reported adverse reactions were: gastrointestinal complaints(abdominal pain, diarrhoea, nausea, meteorism- 9 patients); central and peripheral nervous system (dizziness): 1 patient; circulatory collapse(2 patient); haematoma (1 patient). The interest for this clinical trial is very limited, in particular for efficacy assessment. The absence of a placebo group is questionable as for the choice of active comparator. Rofecoxib cannot be considered as a reference in the treatment of chronic low back pain. In the European Union, rofecoxib was principally indicated for symptomatic relief in osteoarthritis and rheumatoid arthritis, and for some countries in the relief of pain and the treatment of dysmenorrhoea. Furthermore the number of patients was too small to prove a definitive statistically significant equivalence between the two products. No definitive clinical conclusions can be drawn from this study.

Remaining patients from the previous study (79 of the initial 88 patients- 38 from group treated with devils claw and 35 from the group treated with rofecoxib) were invited to participate in a 1-year follow-up study (**Chrubasik *et al*. 2005)**. The aim of the study was to assess the long-term effectiveness and safety of a one-year treatment with 2400 mg dry aqueous extract of Harpagohytum (DER 1.5-2.5:1), equivalent to 60 mg harpagoside/day. All patients were treated for 54 weeks with devil's claw extract. The clinical measures to be evaluated were the Arhus Index and Health Assessment Questionnaire. The tolerability of the treatment was assessed with a verbal rating scale. Any additional analgesic treatment was allowed. A total of 30 patients dropped out before the 54 weeks of the follow-up study. Thirteen did so because of insufficient pain relief. There were no differences between the groups in terms of pain-scores, additional analgesics, the Arhus Low Back Pain index or scores from Health Questionnaire. 17 patients experienced a total of 21 adverse events during the follow-up. these included 5 gastrointestinal symptoms, 6 musculoskeletal disorders, 3 skin disorders and four other adverse events (as leucocytosis, cervical neuralgia). Adverse events caused premature termination of the study in 5 patients (6%) of harpagophytum group. As stated previously, the small number of patients and the open design of the study preclude any conclusion on the efficacy and safety of Harpagophytum extracts.

Lienert A *et al.,* 2005 published a meeting abstract of the 54th annual conference of the north German orthopaedic organisation with poor information regarding a randomised, active-controlled, mono-centric study of the Devil's claw, diclofenac and rofecoxib in the treatment of patients with unspecific lumbar pain. The study was conducted on 97 patients(median age: 53 years; range: 18.6-79.5 years) for 6 weeks. Three drug treatments (at standard recommended doses) were compared; two film-coated tablets with devil's claw ethanolic dry extract (each 240 mg, no further data) twice daily, one capsule of diclofenac (75 mg) twice daily and rofecoxib (12.5 mg) once daily. The primary efficacy criterion was the North American Spine Society (NASS) Instrument. The median reductions in mean NASS scores after 6 weeks were 20.7% for devil's claw 17.0% for diclofenac and 20.6% for rofecoxib. Parametric statistical analysis indicated equality of treatment, although in the rofecoxib group medication intake increased during the study. There were considerable differences in the number of possible causal adverse drug reactions. For devil's claw this occurred in 16% of patients which was much less than for rofecoxib (33%) and for diclofenac (56%). This study does not seem to have been published in extenso. The authors themselves conclude to an equivalent efficacy of the three treatments (ethanolic extract of devil's claw, diclofenac, rofecoxib), but small sample size and data variability make a definitive interpretation difficult. Furthermore, it is not sure whether the North American Spine Society (NASS) Instrument (German version) is valid to show change for the factor "impairment" for a study duration of six weeks.

Open Studies

Herbal preparations

In an open prospective study, 102 patients suffering from acute local non-pseudoradiating low back pain for more than 6 months received 3 x 600 mg/day of devils claw dry aqueous extract (2.5:1), equivalent to 30 mg harpagoside/day, as a mono-therapy(n=17) or combined with other therapies if needed (group J: n=51), or conventional therapy only, mainly oral NSAIDs, physical exercises or paravertebral injection(group K: n=51) **(Chrubasik *et al*., 1997)**. The number of pain-free patients after 4 and 6 weeks was comparable between the groups(group J: 16 and 20; group K: 12 and 23, respectively). After 6 weeks of therapy the Arhus low back pain index had improved in both groups by about 20%; the relative change in single components of the index(pain, invalidity and physical impairment) did not differ between the groups. The subgroup of patients(n=17) of group J receiving devil's claw extract as mono-therapy showed similar therapy outcome as group J and K

The effects of a devil's claw root dry extract(DER 4.4-5.0:1; extraction solvent: ethanol 60% v/v); 2 x 480 mg/day) in 614 patients (mean age: 60.8 years old; suffering from degenerative symptoms of musculoskeletal system (back pain, muscle pain, and tension being the most common diagnoses) were investigated in an 8-week, open, multicentre post-marketing study **(Kloker *et al*., 2003).** Biometric assessment showed improvement or disappearance of all investigated symptoms in 168 patients(27.4%), while the best results were reported for motion pain (improvement or disappearance in 82.7% of patients). The efficacy and tolerability of the treatment were rated as " very good" or " good" in 77.5% and 92.7% of cases by physicians and patients respectively. Only 3 patients (0.5%) experienced as side effects gastrointestinal disturbance(stomach pain, nausea, diarrhoea).

Schmidt *et al.,* 2005 investigated in a open prospective study the effectiveness of *Harpagophytum procumbens* in 6-weeks treatment of unspecific low back pain and compared to conventional therapy. 51 patients (male and female; mean age: 51$\pm$ 13.79 years) were included in the study and divided in 3 groups: mono-therapy group(n=17); combined therapy (n=17) and control group (n=17). Mono-therapy and combined-therapy groups received 1800 mg harpagophytum extract/day(equivalent to 30 mg harpagoside; no further data); the combined and control group were also treated with conventional therapy. The Arhus low back pain index was used for evaluation of pain and for statistical analysis a matching of pairs was performed. Efficacy of treatment was demonstrated in all groups, but

statistically significant advantages for the treatment with harpagophytum extract in comparison to conventional therapeutic interventions were not found. The range of motion did not improve in any group. Only minor adverse effects were noticed during the treatment with harpagophytum extract, related with gastrointestinal disturbance.

c) Symptomatic treatment of pain related with joint disease or osteoarthritis

Rev.1:

Only two new trials were identified (Warnock *et al.*, 2007 and Chrubasik *et al.,* 2007), both open studies that could not support an well-established indication.

Controlled clinical trials

Herbal substance

In a double-blind, placebo-controlled study on 89 ambulant volunteers with articular pains of rheumatic origin, the efficacy and tolerability of capsules containing 335 mg of powdered devil's claw root (3.0% iridoid glycoside) was assessed at a dosage of 3x2 capsules daily for 2 months. Clinical parameters measured on days 0,30 and 60, severity of pain (on a scale 0-10) and joint mobility determined by finger-floor distance during anteflexion of the trunk, revealed a significant drop in the intensity of pain($p < 0.005$) and a significant increase in spinal and coxofemural mobility ($p<0.05$) in the verum group (n=45) after 30 and 60 days. Neither side-effects nor negative changes in biological parameters(including blood tests) were observed during the 2- months period. **(Lecomte & Costa, 1992)**

A four months clinical trial, published two times in different journals but in similar terms, assessed the efficacy of Harpagophytum in the symptomatic treatment of osteoarthritis **(Leblan *et al*. 2000; Chantre *et al*., 2000).** This was a double-blind, randomised, parallel group, multicentre trial. Patients were recruited with radiologically proven osteoarthritis of the knee or the hip; the clinical criteria of the activity of the disease was a spontaneous pain of at least 50 mm on a 100 mm Visual Analogue Scale (VAS). The Lequesne Index was also used to assess activity. The clinical study compared the efficacy of Harpagophytum capsules (435 mg of powder root/capsule) at daily dosage of 3 x 2 capsules, providing a total of 2610 mg of root containing 57 mg of harpagoside (n=62) to another active medication, diacerrhein (100 mg/day; n=60), considered as a symptomatic slow acting drug for osteoarthritis. There was no placebo group. Rescue medications allowed were acetaminophen associated with caffeine and, if response was inadequate, diclofenac. Primary efficacy endpoint was defined by the level of spontaneous pain using VAS. Primary analysis was to demonstrate the non-inferiority of both treatments after 4 months of treatment. Lequesne Index, functional disability of movement assessed on a VAS, amount of taken rescue medication were used as secondary efficacy endpoints. Overall 122 patients were randomised and 92 patients completed the trial in accordance with the protocol. No differences were found between both treatment in terms of pain relief and algo-functional parameters. A significant smaller number of Harpagophytum patients experienced one or more adverse events, as compared to the diacerhein patients. Most adverse effects were gastrointestinal complaints. Diarrhea was the most common adverse event, with 26% in the diacerhein group and 8.1% in the Haragophytum group.

	Harpagophytum	*Diacerhein*
Diarrhea	5 (8.1%)	16 (26.7%)
Abdominal pain	2 (3.2%)	5 (8.3%)
Vomiting	2 (3.2%)	2 (3.3%)
Constipation	1 (1.6%)	–
Flatulence	3 (4.8%)	–
Dyspepsia	3 (4.8%)	3 (4.8%)

The downsides of the study are: small numbers of patients evaluated per referral center (30 centers for 124 patients); lack of transparency in the criteria used to incorporate patients into the study; the absence of a placebo group; the used of diacerrhein which is not a reference drug in the treatment of osteoarthritis.

Herbal preparations

In a controlled pilot study (**Schmelz** and **Hammerie, 1997**) 100 patients suffering from various rheumatic pain syndromes(activated arthrosis, chronic low back pain, mon-articular rheumatic conditions) received randomly either Harpagophytum root extract (DER 2:1; extraction solvent: ethanol 40 % v/v; n=50) or placebo(n=50). After 30 days of treatment with 2 tablets/day(2460 mg dry extract/day), the number of patients complaining of moderate pain was 6 in the verum group and 32 in the placebo group. Only one of the verum patients suffered still severe pain, in contrast to 9 patients of the placebo group. By the end of the study, the greatest therapeutic improvement was achived in the verum subgroup suffering from low back pain. Adverse effects occurred in 2 patients(verum: n=1, diarrhoea; placebo n=1, mild gastritis). The weakness of the study are: different indications assessed with a small number of patients per group, the lack of statistical interpretation and the assessment of symptoms by patients in a completely subjective way. The authors interpret the outcome of the study as a hint for a possible antiphlogistic and analgesic activity which should be confirmed by further studies.

Patients suffering from osteoarthritis of the hip participated in a 20-week, double-blind, placebo controlled study as two randomised groups. Patients in one group(n=24) were treated with 2 tablets per day, each containing 480 mg dry ethanolic devil's claw root extract (DER 4.4-5.0:1;extraction solvent: ethanol 60% v/v); those in the second group (n=22) received placebo tablets. Both groups also received identical, stepwise-reducing daily doses of ibuprofen: 2 x 400 mg for the first 8 weeks, 1 x 400 mg for a further 8 weeks and none in the last 4 weeks of the study. Efficacy was evaluated from osteoarthritis scores reported by the patients, using the Western Ontario and McMaster Universities Arthrosis Index (WOMAC) which consists of 24 questions grouped into three subscores for pain, stiffness and physical function; the responses are scored with the 10-point Likert scale or a 10 cm Visual Analogue Scale (VAS). The WOMAC score decreased from 5.01 to 3.61 in the *Harpagophytum* group and from 4.39 to 3.31 in the placebo group. An increase in pain score by a maximum of 20% in the period without ibuprofen (which was regarded as a clinically relevant response) was fulfilled by 70.8% of patients of the Harpagophytum group, but by only 40.9% of patients in the placebo group(p=0.04). Compared to 36% in the placebo group, 52% of patients in the devil's claw group were able to complete the study without using rescue therapy in the ibuprofen- free period. This paper gives some suggestions on a possible mild therapeutic effect of Harpagophytum in coxarthrosis patients, however the low number of patients (22 to 24 per group) and the study design in which Harpagophytum was given just as an add-on therapy to decreasing doses of ibuprofen precludes further conclusions on the proof of clinical efficacy **(Frerick *et al.*, 2001)**

Open studies

Herbal substance

Pinget and **Lecomte (1997)** assessed in an open uncontrolled study 43 patients with degenerative rheumatism the efficacy of capsules containing 250 mg of powdered devil's claw root at a dosage of 3x2 capsules daily for 60 days. Clinical parameters measured on days 8,15,30 and 60 were severity of pain and joint mobility. Results revealed a significant drop in the intensity of pain($p < 0.005$) and a significant increase in joint mobility. Just 2 patients reported side-effects (less than 5%) as nausea and meteorism, but none conduced to drop-out.

Herbal preparations

Engel (2000) conducted an open study to assess the clinical effectiveness and safety of Harpagophythum extract called "LI 174"[1] (DER 4.4-5:1, extraction solvent 60% v/v); 480 mg extract twice/day, on a period of 6 weeks in 1026 patients (67.6% female; 31.8% male; age range: 17-92 years). Patients with degenerative disease of the musculoskeletal system were recruited. Rescue medications (analgesics) and physical therapies were allowed. Pain and mobility improvement were observed during the overall period of the study. This study could only be supportive for safety due to its open design and absence of control group.

In an open prospective study **Müller *et al*. 2000** assessed the clinical effectiveness of capsule containing 400 mg dry *Harpagophythum* extract (DER: 2:1[2]; extraction solvent: water), 3 capsules daily, on a period of 4 weeks. 553 patients with non acute diseases of the musculoskeletal system were enrolled. An average improvement of symptoms was reported to be 45% but only minor anti-oedematous and anti-inflammatory effects were found. The ratio of adverse events was reported to be 0.9% and 5 patients suffered from severe adverse effects (abdominal symptoms). This open study with no control group is insufficient to prove the efficacy of Harpagophytum extract.

Szczepanski *et al*., (2000) treated daily for 6 weeks 25 rheumatoid arthritis patients and 20 osteoarthritis patients with 6 x 410 mg devil's claw root dry extract (DER 1.5-2.5:1; extraction solvent: ethanol 30% v/v) For the first 2 weeks the extract was added to NSAIDs as a combined therapy, and for the next 4 weeks only devil's claw root extract was administered. There were no significant changes in pain intensity or duration of morning stiffness during the period of treatment with devil's claw alone. Again no placebo group was incorporated and the study population was rather small.

In a drug monitoring study, 675 patients (mean age: 58.1 years) with painful osteoarthritis, spondylarhropathies of fibromyalgic complaints were treated daily for 8 weeks with 2 x 480 mg Harpagophytum dry extract (4.4-5.0:1, extraction solvent: ethanol 60% v/v) **(Ribbat** and **Schakau, 2001).** The main outcome criteria were the Clinical Global Impressions (CGI)score and reduction in a symptom severity score(from 0= no pain to 3= strong pain). The extent of use of non-steroidal anti-inflammatory drugs(NSAIDs) or corticosteroids as co-medication for the underlying disease was assessed as a secondary parameter. Marked therapeutic effects were observed during the study period, the mean time to onset of action being 13 days. Due to the chronicity and phasic pattern of the disease, treatment with devil's claw root extract was continued after the monitoring phase in 79% of patients. Efficacy assessed by CGI scores was rated good or very good in 82% if cases. the symptom score for painful motion decreased by 53% from 2.23(indicating moderate pain) to 1.04(indicating slight pain) after 8 weeks of treatment. Over the same period, previously prescribed co-medication was successfully reduced or even discontinued in 60.3% of the 464 patients taking NSAIDs and 56% of the 50 patients taking cortocosteroids. A clear improvement on quality of life was evident so far as the

[1] the DER is according to Gobel *et al*., 2001 that used the same LI 174 extract
[2] DER is according to the trade name of the product used

devil's claw root extract was rated better than their previous antirheumatic treatment by 62.4% of patients in terms of efficacy. Five patients stopped the treatment because of adverse events. This open study is insufficient to prove the efficacy of Harpagophytum extract due to heterogeneous study population, the absence of a control group and to the subjective estimation of the degree of the pain and of the efficacy by the patients and the physicians.

An observational study with 583 patients was conducted with patients suffering from arthrosis of the knee or the hip **(Schendel, 2001).** A daily dose of 2 x 480 mg of Harpagophytum dry extract (DER 4.4-5.0:1; extraction solvent: ethanol 60% v/v) was tested over a period of 8 weeks. The aim of the study was to examine whether Non-steroidal anti rheumatics (NSAR) can be replaced by Harpagophytum extract. Therefore patients were told that they will be able to /and should reduce or even discontinue the intake of NSAR. At the end of the study 27.9% of the patients had reduced their daily intake of NSAR while 61.4% of the patients had discontinued the treatment with NSAR. An improvement of 52.5% in the intensity of pain and an improvement of 49.68% in the rigidity was reported. Six cases of adverse events were reported. No severe adverse events occurred. This study is not conclusive due to its open design and the absence of a control group.

In a 12-week open study, multicentre drug surveillance, 75 patients (24 male and 51 female; mean age: 64 years old) suffering from osteoarthritis of the hip and/or knee were treated with 2400 mg of devil's claw root dry aqueous extract (DER 1.5-2.5:1), providing 50 mg/day of harpagoside**(Wegener** and **Lüpke 2003)**. To standardise the assessment of treatment effects, the Western Ontario and McMaster Universities (WOMAC) Arthrosis Index(10 point scale) as well as the 10 cm Visual Analogue Pain Scale (VAS) were used. Improvement of 22.2-23.8% were observed in WOMAC subscores for pain, stiffness and physical function and in the WOMAC index. Subjective VAS pain scores for actual, average, worst and total pain decreased by 22.6-25.8%. The physicians reported improvements in typical clinical findings, for example, 45% for pain on palpitation, 35% for limitation of mobility and 25% for joint crepitus. Only two cases of possible adverse reactions were reported in 3 patients (dyspeptic complaints; n=2 and sensation of fullness; n=1). Unfortunately no placebo group was incorporated in the study. This, together with the rather small study group, makes the study less reliable**.**

Warnock *et al*., 2007 assessed the effectiveness, safety and tolerability of devils claw in the treatment of Arthritis and other rheumatic conditions AORC, in an open study of 8 weeks. 259 patients took for 8 weeks 2x 480 mg dry devil's claw root extract (DER 1.5-3:1, extraction solvent: 60% ethanol v/v). Effectiveness was assessed by numeric rating scales, the Western Ontario and McMasters Universities Osteoarthritis (WOMAC) Index and the Algofunctional Hand Osteoarthritis Index. Tolerance was measured by a numeric rating scale and safety by self-reporting, blood analysis and liver function tests. Quality of life was measured by SF-12 questionnaire. Global assessments of pain, stiffness and function were performed on data available for 207 patients. Global mean scores for pain, stiffness and function were significantly reduced from baseline to week 4 and week 8 ($p < 0.0001$). Mean scores for pain in the hand, wrist, elbow, shoulder, hip, knee and back were significantly reduced from baseline to week 8 ($p < 0.05$). These mean scores for pain (except for right elbow) were also significantly reduced from baseline to week 4 ($p < 0.01$). Mean scores for pain in soft tissues were reduced from baseline (6.0 ±1.0) to week 8 (3.7 ±3.1). Quality of life measurements (SF-12) were significantly increased from baseline and 60% patients either reduced or stopped concomitant pain medication. A total of 49 drug-related adverse events were reported for 44 patients (17.0%) in the safety population. These adverse events were considered to have only a possible/probable relationship to the study medication. No serious adverse events were reported, and all were mild to moderate in severity and were in the majority gastrointestinal complaints. This study is not conclusive due to its open design and the absence of a control group.

Chrubasik *et al*., 2007 conducted an open study in 114 patients with non-specific low back pain or osteoarthritic pain in the knee or hip to examine various effects of treatment with dry aqueous extract of Harpagophytum (DER 1.5-2.5:1). All patients received 6 tablets x 400 mg= 2400 mg dry aqueous extract of *H. procumbens*, providing a daily dose of 60 mg harpagoside for up to 54 weeks. This is equivalent to 4.5 g of crude drug per day. Patients were allowed to supplement Harpagophytum with other analgesics as necessary. Initially, and at each subsequent visit, the assessments consisted of a series of established and non-validated measures. Of the 15 patients that dropped out, 9 did so because of insufficient pain relief. About a third of the 114 patients used additional analgesic medications. 49 patients experienced a total of 79 adverse events, 13 of them (all minor abdominal complaints) were deemed to be related to devil's claw. The authors declared that as there was no placebo control group, the documented improvements cannot be attributed confidently to the designated treatment with the dry extract.

Review

The reliability and quality of some of the clinical trials already presented and discussed have been investigated in detail by different research groups (Chrubasik *et al*., 2003; Gagnier *et al*., 2004; Brien *et al*., 2006; Brendler *et al*., 2006; Gagnier *et al*., 2007; Gagnier *et al*., 2010). A summary of their conclusions and are presented below:

Chrubasik *et al*., 2003

Objectives: to examine systematically the quality of the clinical trials investigating the effectiveness of Harpagophytum products. Results: the uncontrolled trials, though providing useful preliminary estimates of the possible effect of treating various conditions, could not separate the effects of the Harpagophytum product from whatever placebo effect might have been exerted in the circumstances of the study. Of the 8 randomised double blinded controlled comparisons with placebo, 6 were marred by lack of transparency, one could not provide definitive evidence from its pre-selected principal outcome measure and one provided good quality evidence of a dose dependent superiority of effect over placebo, though this was a product that is not generally available for clinical practice. One of the ramdomised controlled comparisons with comparator (Doloteffin versus rofecoxib) was intended only as a pilot and studied too few patients for definitive conclusions, whereas the other did provide good evidence that the powder is not importantly less effective than the weak NSAID diacerhein. Conclusions: Evidence of effectiveness of Harpagophytum products is not transferrable from product to product. the results of some studies suggest some effectiveness for some products, but for more of the clinically available products is the quality of evidence totally satisfactory. It is better so far with products that contain at least 50 mg of harpagoside in the daily dosage than with products (which happen to be of ethanolic extraction) that contain less.

Gagnier *et al*., 2004

Objectives: to determine the effectiveness of *Harpagophytum procumbens* preparations in the treatment of various forms of musculoskeletal pain. Results. Twelve trials were included with six investigating osteoarthritis (two were identical trials), four low back pain, and three mixed-pain conditions. Conclusions: There is limited evidence for an ethanolic Harpagophytum extract containing less than <30 mg harpagoside per day in the treatment of knee and hip osteoarthritis. There is moderate evidence of effectiveness for (1) the use of a Harpagophytum powder at 60 mg harpagoside in the treatment of osteoarthritis of the spine, hip and knee; (2) the use of an aqueous Harpagophytum extract at a daily dose of 100 mg harpagoside in the treatment of acute exacerbations of chronic non-specific low back pain; and (3) the use of an aqueous extract of *Harpagophytum procumbens* at 60 mg harpagoside being non-inferior to 12.5 mg rofecoxib per day for chronic non-specific low-back pain (NSLBP) in the short term. Strong evidence exists for the use of an aqueous

Harpagophytum extract at a daily dose equivalent of 50 mg harpagoside in the treatment of acute exacerbations of chronic NSLBP.

Brien *et al*., 2006

Objectives: To address the two main questions of importance to clinicians: (1) Does Devil's Claw work for the treatment of Osteoarthritis (OA), and (2) Is it safe?; Results: Fourteen studies were identified: eight observational studies; 2 comparator trials (1 open, the other randomised to assess clinical effectiveness); and 4 double-blinded, placebo-controlled, randomised 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.

Brendler *et al*., 2006

Conducted an evidence-based systematic review that included scientific literature, expert opinion, folkloric precedent and history. The authors concluded that there are four potential indications with different evidence grade: degenerative joint disease/osteoarthritis (Evidence grade: B); low back pain (Evidence grade: B);appetite stimulation (Evidence grade: C) and digestive tonic (Evidence grade: C); B grade represents good scientific evidence, while C grade indicates unclear or conflicting evidence.

Regarding indication in the treatment of low back pain (evidence grade: B) the authors concluded that there are several controlled human trials but the majority are small with methodological weakness. Many have been reported by the same authors. In addition, the results are limited by the known phenomenon of a large placebo effect in the treatment of this condition. Therefore, although the results can be considered promising early evidence of efficacy, additional well-designed trials are warranted before a firm conclusion can be reached.

Regarding the use in short-term management of pain related to degenerative joint disease or osteoarthritis (evidence grade: B) the authors declare that devils claw may be equally effective as drug therapies(such as NSAIs). However, many of the available studies have been small or methodologically limited, and additional trials are necessary to determine the efficacy and long-term safety of devils claw(beyond 8-12 weeks).

Gagnier *et al*. 2007

Objectives. To determine the effectiveness of herbal medicine compared with placebo, no intervention, or "standard/accepted/conventional treatments" for nonspecific low back pain. Results. Ten trials were included in this review. Two high-quality trials utilising *Harpagophytum procumbens* (Devil's claw) found strong evidence for short-term improvements in pain and rescue medication for daily doses standardised to 50 mg or 100 mg harpagoside with another high-quality trial demonstrating relative equivalence to 12.5 mg per day of rofecoxib. Two moderate-quality trials utilising Salix alba (White willow bark) found moderate evidence for short-term improvements in pain and rescue medication for daily doses standardised to 120 mg or 240 mg salicin with an additional trial demonstrating relative equivalence to 12.5 mg per day of rofecoxib. Three low-quality trials using Capsicum frutescens (Cayenne) using various topical preparations found moderate evidence for favourable results against

placebo and one trial found equivalence to a homeopathic ointment. Conclusions. *Harpagophytum procumbens* , Salix alba, and Capsicum frutescens seem to reduce pain more than placebo. Additional trials testing these herbal medicines against standard treatments will clarify their equivalence in terms of efficacy.

Gagnier 2010

Objectives. The objective of this paper is to review and summarise the evidence surrounding natural health products for chronic non-specific low back pain. Results: The author included two systematic reviews and 2 additional randomised controlled trials published subsequently to these reviews. The author found strong evidence for 50 mg harpagoside per dose of an aqueous extract of *Harpagophytum procumbens* per day reduces pain more than placebo. The author found moderate evidence for 100 mg harpagoside per dose of an aqueous extract of *Harpagophytum procumbens* compared to placebo, for an extract of willow bark yielding 120 mg salicin per day compared with placebo, for 240 mg of salicin per day in reducing pain to a greater extent than placebo, for 240 mg of salicin per day as equivalent to 120 mg salicin, for no differences in pain and function between a 60 mg daily harpagoside dose of an aqueous extract of *Harpagophytum procumbens* and 12.5 mg rofecoxib per day, for no difference in pain and overall improvement between Spiroflor SRL homeopathic gel (SRL) and Cremor Capsici Compositus FNA, the capsici oleoresin gel, for intramuscular B12 when compared with placebo.

Assessor comments: in all reviews the differences between extracts are only based on extraction solvent but did not took into account the differences between DER values, therefore the general term of "aqueous extract" used in the reviews cannot be attributed to a designated preparation. In the same time until now is unclear if harpagoside is responsible or not for analgesic effect, therefore the content in harpagoside is not relevant for the efficacy of the preparations. "The strong evidence" declared by Chrubasik et al., 2003 and Gagnier et al., 2004 is related with Chrubasik et al. 1999 study. The weaknesses of the study were already addressed, therefore clinical improvements cannot be attributed confidently to the designated treatment with the dry extract. Further studies are needed.

Table 6: Clinical studies on humans

Type	Study	Test Product(s	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
A. Relief of back pain							
A.1. Aqueous dry extract							
Chrubasik *et al*., 1996	Randomised placebo double-blind study	Placebo Verum: 800 mg extract (DER 2.5:1)/day, corresponding to 50 mg harpagoside Orally 3 times daily Duration: 4 weeks	118 patients (18-75 years) Verum (n=54) Placebo(n=55) 5 drop-out	At least 6 months of low back pain	Principal outcome: efficacy Secondary end-points: number of pain-free patients and global assessment with the Arhus low back pain index.	Student's t-test	No difference between placebo and verum
Chrubasik *et al*., 1999	Randomised, placebo-controlled, double-blind study	Placebo Verum: 600 mg or 1200 mg extract (DER 6-9:1)/day, corresponding to 50 or 100 mg harpagoside Orally Duration: 4 weeks	197 patients Placebo(n=66) Verum 600 mg (n=65) Verum 1200 mg (n= 66) 14 drop-out	At least 6 months of low back pain	Principal outcomes: the proportion of patients free of pain, without rescue medication Secondary outcomes: Arhus Index to assess pain and functional disability.	Student's t-test	More responders observed in both verum groups than in the placebo group.
Chrubasik *et al*., 2003	Randomised double-blind positive control	Verum: 2400 mg dry aqueous extract (DER 1.5-2.5:1, extract containing 60 mg of harpagoside) Control: 12.5 mg rofecoxib/day Orally Duration: 6 weeks	88 patients Verum(n=44) Control (n=44) Drop-out: 1 verum; 8 control	Chronic low back pain(for more than 6 weeks)	Outcome measures: number of pain-free patients, decrease in averaged daily pain score, percentage change in Arhus Low Back Pain index, requirement for rescue medication	Student's t-test	No difference between control and verum .
Chrubasik *et al*., 2005	1-year follow-up study	Verum: 2400 mg extract of Harpagohytum (DER 1.5-2.5:1), equivalent to 60 mg harpagoside/day. Orally Duration: 54 weeks	79 patients (38 from the devil's claw group (n=38) and 35 from the group treated with rofecoxib) Drop-out: 30 patients	Follow-up study	The clinical outcome: Arhus Index and Health Assessment Questionnaire. The tolerability of the treatment was assessed with a verbal rating scale.	Student's t-test	No differences between the groups
Chrubasik *et al*., 1997.	Open prospective study	Group J: 3 x 600 mg/day dry aqueous extract (2.5:1), equivalent to 30 mg harpagoside/day, as a mono-therapy (n=17) or combined with other therapies Group K: conventional therapy	102 patients Group J(n= 51) Group K(n=51)	Acute local non-pseudoradiating low back pain for more than 6 months	Primary outcomes: the number of pain-free patients, Arhus low back pain index	None	No differences between the groups

Type	Study	Test Product(s	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		(oral NSAIDs, physical exercises, paravertebral injection) Orally Duration: 6 weeks					
A.2. Ethanolic dry extracts							
Göbel *et al*., 2001	Randomised, double-blind, placebo-controlled study	Placebo Verum : 2 x 480 mg Harpagophytum-extract (DER 4.4-5.0:1, extraction solvent: ethanol 60% v/v) Orally, twice/daily Duration: 4 weeks	63 patients (18-62 years old) Verum (n=31) Placebo(n=32)	Slight to moderate muscular tension or slight muscular pain of the back, shoulder and neck	The efficacy assessed by clinical global score	Student's t-test	Verum treatment was superior to placebo
Kloker *et al*., 2003.	Open post-marketing study	2 x 480 mg/day Harpagophytum dry extract(DER 4.4-5.0:1; extraction solvent: ethanol 60% vv Orally Duration: 8 weeks	614 patients (mean age: 60.8 years old)	Suffering from degenerative symptoms of musculoskeletal system	Efficacy and tolerability	None	Improvement in 27.4% of patients; the best results were reported for motion pain (improvement in 82.7% of patients).
A.3. Other extracts(not defined)							
Lienert *et al*., 2005	Randomised, active-controlled, mono-centric study	Group 1: 2 x 240 mg devil's claw ethanolic dry extract (no further data) twice daily Group 2: 75 mg diclofenac, twice daily Group 3: 12.5 mg rofecoxib, once daily. Duration: 6 weeks	97patients(18.6-79.5 years)	Unspecific lumbar pain	The primary efficacy criterion was the North American Spine Society (NASS) Instrument.	None	Equivalent efficacy of the three treatments
Schmidt *et al*., 2005	Open study	CG (control group) MT (monotherapy group) and CT (combined-therapy group): 1800 mg harpagophytum extract/day(equivalent to 30 mg harpagoside; no further data); CT and CG- were also used conventional therapy Duration: 6 weeks	51 patients (male and female; mean age: 51+ 13.79 years) MT (n=17) CT(n=17) CG (n=17)	Unspecific low back pain	The Arhus low back pain index was used for evaluation of pain.	Matching of pairs	No differences

Type	Study	Test Product(s	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
B. Symptomatic treatment of pain related to degenerative joint disease or osteoarthritis							
B.1.Herbal substance							
Lecomte & Costa, 1992	Double-blind, placebo-controlled study	Placebo Verum capsule with 335 mg of powdered devil's claw root (3.0% iridoid glycoside) 3x2 capsules daily Duration: 2 months	89 volunteers Verum (n=45) Placebo(n=44)	Articular pains of rheumatic origin	Clinical parameters measured on days 0.30 and 60, severity of pain (on a scale 0-10) and joint mobility determined by finger-floor distance during anteflexion of the trunk.	Student's t-test	A significant drop in the intensity of pain and a significant increase in spinal and coxofemural mobility in the verum group after 30 and 60 days.
Lecomte & Costa, 1992	Double-blind, placebo-controlled study	Placebo Verum capsule with 335 mg of powdered devil's claw root (3.0% iridoid glycoside) 3x2 capsules daily Duration: 2 months	89 volunteers Verum (n=45) Placebo(n=44)	Articular pains of rheumatic origin	Clinical parameters measured on days 0,30 and 60, severity of pain (on a scale 0-10) and joint mobility determined by finger-floor distance during anteflexion of the trunk.	Student's t-test	A significant drop in the intensity of pain and a significant increase in spinal and coxofemural mobility in the verum group after 30 and 60 days.
Leblan *et al*., 2000; Chantre *et al*., 2000	Double-blind, randomised, Parallel group, multicentre trial	Harpagophytum capsules (435 mg of powder root/capsule) 3 x 2 capsules/daily =2610 mg of root containing 57 mg of harpagoside Diacerrhein: 100 mg/day Duration: 4 months	122 patients Harpagophytum group(n=62) Diacerrhein group (n=60) drop-out: 30 patients	Osteoarthritis	Primary endpoint: pain score and visual analog scale.		Harpagophytum was less effective than diacerrhein
Pinget and Lecomte (1997)	Open study	Capsules with 250 mg of powdered devil's claw root 3x2 capsules daily Orally Duration: 60 days.	43 patients	Degenerative rheumatism	Severity of pain and joint mobility (on days 8,15,30 and 60)	Student's t-test	A significant drop in the intensity of pain and a significant increase in joint mobility.
B.2. Dry ethanolic extracts							
Schmelz and Hammerie, 1997	Placebo controlled study	Placebo Tablets with Harpagophytum root extract(DER 2:1; extraction solvent: ethanol 40 % v/v) 2460 mg/day Duration: 30 days	100 patients Harpagophytum (n=50) Placebo(n=50).	Rheumatic pain syndromes (activated arthrosis, chronic low back pain, mon-articular rheumatic conditions)	Severity of pain	None	After 30 days: 6 patients with moderate pain (verum) vs 32 (placebo) 1 verum patient still suffered severe pain, v.s 9 (placebo); The greatest improvement - in the verum subgroup with low back pain.

Type	Study	Test Product(s	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Frerick *et al*., 2001	Double-blind, placebo controlled study	Placebo Verum: 2 tablets per day, each containing 480 mg dry ethanolic devil's claw root extract(DER 4.4-5.0:1;extraction solvent: ethanol 60% V/V); Both groups received stepwise-reducing daily doses of ibuprofen: 2 x 400 mg for the first 8 weeks, 1 x 400 mg for a further 8 weeks and none in the last 4 weeks Duration: 20 weeks	44 patients Verum (n=24) Placebo (n=22)	Osteoarthritis of the hip	Western Ontario and McMaster Universities Arthrosis Index (WOMAC) score	Student's t-test	Verum treatment reduced dosage of ibuprofen.
Engel (2000)	Open study	Harpagophythum extract (DER 4.4-5:1, extraction solvent 60% v/v); 480 mg extract twice/day, Duration: 6 weeks	1026 patients (67.6% female; 31.8% male; age range: 17-92 years).	Degenerative disease of the musculoskeletal system	Pain and mobility improvement were observed during the overall period of the study.	None	Supportive
Szczepanski *et al*., ,2000	Open study	6 x 410 mg devil's claw root dry extract (DER 1.5-2.5:1; extraction solvent: ethanol 30% v/v) For the first 2 weeks the extract was added to NSAIDs as a combined therapy, and for the next 4 weeks only devil's claw root extract was administered. Duration: 6 weeks	45 patients	Rheumatoid arthritis and osteoarthritis	Primary outcome: pain intensity, duration of morning stiffness	None	No change
Ribbat and Schakau, 2001	Open study	2 x 480 mg Harpagophytum dry extract (4.4-5.0:1, extraction solvent: ethanol 60% v/v) Duration: 8 weeks	675 patients (mean age: 58.1 years)	Osteoarthritis, spondylarhropathies of fibromyalgic complaints	The main outcome: CGI score and reduction in a symptom severity score Secondary parameter: the use of NSAIDs or corticosteroids as co-medication.	descriptive statistics	Supportive
Schendel, 2001	Observational study	A daily dose of 2 x 480 mg of Harpagophytum dry extract (DER 4.4-5.0:1; extraction solvent: ethanol 60% v/v Duration: 6 weeks	583 patients	Arthrosis of the knee or the hip	Replacement of Non-steroidal anti rheumatics (NSAR) by Harpagophytum extract.	descriptive statistics	Supportive

Type	Study	Test Product(s	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Warnock *et al*., 2007	Open study	Daily 2x 480 mg dry devil's claw root extract (DER 1.5-3:1, extraction solvent: 60% ethanol v/v). Duration: 8 weeks	259 patients Drop-out: 50 patients	Arthritis and other rheumatic conditions	WOMAC Index and the Algofunctional Hand Osteoarthritis Index..	Student's t-test	Supportive
B.3. Aqueous dry extract							
Müller *et al*., 2000	Open study	Capsule with 400 mg dry Harpagophythum extract (DER: 2:1; extraction solvent: water), 3 capsules daily Orally Duration: 4 weeks.	553 patients	Patients with non acute diseases of the musculoskeletal system	Improvement of symptoms, anti-oedematous and anti-inflammatory effects	None	Supportive
Wegener and Lüpke 2003	Open study, multicentre drug surveillance	2400 mg of devil's claw root dry aqueous extract (1.5-2.5:1), providing 50 mg/day of harpagoside Duration: 12 weeks.	75 patients (24 male and 51 female; mean age: 64 years old)	Osteoarthritis of the hip and/or knee	WOMAC Index and VAS	Student's t-test	Improvements in typical clinical findings.
Chrubasik *et al*., 2007	Open study	Tablet with 400 mg dry aqueous extract of Harpagophytum (DER 1.5-2.5:1). 6 tablets/day (daily dose of 60 mg harpagoside) Duration: 54 weeks.	114 patients Drop-out: 15 patients	Non-specific low back pain or osteoarthritic pain in the knee or hip	Overall improvements and analgesic requirements	MANOVA	Supportive

4.3. Clinical studies in special populations (e.g. elderly and children)

No data available

4.4. Overall conclusions on clinical pharmacology and efficacy

Like other bitter herbals, devil's claw is traditionally used for loss of appetite and mild digestive disorders. The link between bitterness of harpagophytum radix (that contains iridoides) and its use as appetite stimulating agent and to relieve digestive disorders is described in several references (Hänse *et al*., 1993; Schilcher H 1999; Braun and Frohne 1987; Czygan 1987; Bisset 1994; Weiss 1991). Several EU Member States approved such indications for Harpagophytum radix based on the long-standing use. The duration of use proposed (2 weeks) is in accordance with other HMPC monographs with the same indication (e.g. Centauri herba, Marrubii herba).

There are several trials that evaluated the use of devils claw for the treatment of low back pain. However the majority are small with methodological weakness. Many have been reported by the same authors. In addition, the results are limited by the known large placebo effect in the treatment of this condition, therefore the evidence of efficacy in not sufficient for a well-establish use indication.

The efficacy of harpagophytum radix has been evaluated also in the short-term management of pain related to degenerative joint disease or osteoarthritis. There were many differences in the products studied (aqueous or ethanolic extracts, different DERs, sometimes powdered root), study designs (mainly open studies) and methodology and the dosage administered that was reported either in milligrams of harpagoside or in milligrams of herbal substance or herbal preparation. Taking into account all these differences comparison of the results between products is rather difficult and it is not possible to assess correctly the impact of devil's claw on those patients.

Also the reviews that investigated the reliability and quality of some of the clinical trials suggested that no clear conclusion on efficacy can be drawn and further studies are needed, especially on long-term efficacy and safety.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

Table 7: Clinical safety data from the clinical trials

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
Chrubasik *et al.*, 1996	randomised double-blind study	placebo verum: 800 mg extract (DER 2.5:1)/day, corresponding to 50 mg harpagoside orally 3 times daily Duration: 4 weeks	118 patients (18-75 years) Verum (n=54) Placebo(n=55) 5 drop-out	at least 6 months of low back pain	Verum: nausea(2 patients), tachycardia(1 patient), tussive irritation(1 patient).	No difference was observed between placebo and verum groups.
Chrubasik *et al.*, 1999	randomised, placebo-controlled, double-blind study	placebo verum: 600 mg or 1200 mg extract (DER 6-9:1)/day, corresponding to 50 or 100 mg harpagoside orally Duration: 4 weeks	197 patients Placebo(n=66) Verum 600 mg (n=65) Verum 1200 mg (n= 66) 14 drop-out	at least 6 months of low back pain	Verum: 8 reported mild gastrointestinal upset, Placebo: one patient	A greater number of responders in the treatment groups (9% and 15% for 600 mg and 1200 mg respectively) than in the placebo group.
Chrubasik *et al.*, 2003	randomised double-blind positive control	Verum: 2400 mg dry aqueous extract (DER 1.5-2.5:1, extract containing 60 mg of harpagoside) Control: 12.5 mg rofecoxib /day Duration: 6 weeks	88 patients Verum(n=44) Control (n=44) Drop-out: 1 verum; 8 control	chronic low back pain(for more than 6 weeks)	The reported adverse reactions were: gastrointestinal complaints(abdominal pain, diarrhoea, nausea, meteorism- 9 patients); central and peripheral nervous system (dizziness): 1 patient; circulatory collapse(2 patient); haematoma (1 patient)	No difference was observed between control and verum groups.
Chrubasik *et al.*, 2005	1-year follow-up study	Verum: extract of Harpagohytum (DER 1.5-2.5:1), 2400 mg, equivalent to 60 mg harpagoside/day. Duration: 54 weeks	79 patients (38 from group treated with devils claw and 35 from the group treated with rofecoxib) Drop-out: 30 patients	Follow-up study	17 patients experienced a total of 21 adverse events during the follow-up: 5 gastrointestinal symptoms, 6 musculoskeletal disorders, 3 skin disorders and 4 other adverse events (as leucocytosis, cervical neuralgia).	No differences between the groups
Göbel *et al.*, 2001	In a randomised, double-blind, placebo-controlled study	Verum : 2 x 480 mg Harpagophytum-Extrakt LI 174 (DER 4.4-5.0:1, extraction solvent: ethanol 60% v/v) Orally, twice/daily Duration: 4 weeks	63 patients (18-62 years old) Verum (n=31) Placebo(n=32)	slight to moderate muscular tension or slight muscular pain of the back, shoulder and neck	Verum: 4 patients with gastrointestinal upset such as nausea, meteorism Placebo: 2 patients with diarrhoea, nausea, meteorism.	The efficacy of verum treatment was clear from the clinical global score and patient and physician ratings. Significant improvements were

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
						observed in muscular pain intensity (visual analogue scale) and in pressure algometer, muscle stiffness and muscular ischemia tests.
Kloker *et al.*, 2003.	open, multicentre post-marketing study	devil's claw root dry extract(DER 4.4-5.0:1; extraction solvent: ethanol 60% v/) 2 x 480 mg/day Orally Duration: 8 weeks	614 patients (mean age: 60.8 years old)	Suffering from degenerative symptoms of musculoskeletal system	3 patients (0.5%) experienced as side effects gastrointestinal disturbance(stomach pain, nausea, diarrhoea).	Biometric assessment showed improvement in 27.4% of patients, while the best results were reported for motion pain (improvement in 82.7% of patients).
Lecomte & Costa, 1992	double-blind, placebo-controlled study	Placebo Verum capsules containing 335 mg of powdered devil's claw root (3.0% iridoid glycoside) 3x2 capsules daily Duration: 2 months	89 volunteers Verum (n=45) Placebo(n=44)	articular pains of rheumatic origin	None	A significant drop in the intensity of pain and a significant increase in spinal and coxofemural mobility in the verum group after 30 and 60 days.
Leblan *et al.*, 2000; Chantre *et al.*, 2000	double-blind, randomised, parallel group, multicentre trial	Harpagophytum capsules (435 mg of powder root/capsule) 3 x 2 capsules/daily=2610 mg of root containing 57 mg of harpagoside diacerrhein: 100 mg/day Duration: 4 months	122 patients Harpagophytum group(n=62) diacerrhein group (n=60) drop-out: 30 patients	osteoarthritis	Diacerhein group: 16 patients-diarrhea; 5-abdominal pain; 2-vomiting; 3-dyspepsia Harpagophytum group: 5 patients-diarrhea; 2-abdominal pain; 2-vomiting; 3-flatulance; 1-constipation; 3-dyspepsia	Harpagophytum was less effective than diacerrhein
Pinget and Lecomte (1997)	open uncontrolled study	Capsules with 250 mg of powdered devil's claw root 3x2 capsules daily Orally Duration: 60 days.	43 patients	degenerative rheumatism	2 patients reported nausea and meteorism	A significant drop in the intensity of pain and a significant increase in joint mobility.
Schmelz and Hammerie,	Placebo controlled study	Placebo Tablets with Harpagophytum root extract(DER 2:1;	100 patients verum(n=50) Placebo(n=50).	rheumatic pain syndromes (activated	verum: n=1, diarrhoea; placebo:n=1, mild gastritis	After 30 days: 6 patients with moderate pain (verum) vs 32 (placebo)

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
1997		extraction solvent: ethanol 40 % v/v) 2460 mg/day Duration: 30 days		arthrosis, chronic low back pain, mon-articular rheumatic conditions)		1 verum patient still suffered severe pain, v.s 9 (placebo); The greatest improvement - in the verum subgroup with low back pain.
Schendel, 2001	observational study	A daily dose of 2 x 480 mg of Harpagophytum dry extract (DER 4.4-5.0:1; extraction solvent: ethanol 60% v/v) Duration: 6 weeks	583 patients	Arthrosis of the knee or the hip	None	Supportive
Warnock *et al*., 2007	Open study	Daily 2x 480 mg dry devil's claw root extract (DER 1.5-3:1, extraction solvent: 60% ethanol v/v). Duration: 8 weeks	259 patients Drop-out: 50 patients	Arthritis and other rheumatic conditions	49 drug-related adverse events (majority gastrointestinal complaints) were reported for 44 patients (17.0%)	Supportive
Müller *et al*., 2000	open study	capsule containing 400 mg dry Harpagophythum extract (DER: 2:1; extraction solvent: water), 3 capsules daily Orally Duration: 4 weeks.	553 patients	Patients with non acute diseases of the musculoskeletal system	5 patients suffered from severe adverse effects (abdominal symptoms)	Supportive
Wegener and Lüpke 2003	open study, multicentre drug surveillance	2400 mg of devil's claw root dry aqueous extract (1.5-2.5:1), providing 50 mg/day of harpagoside Duration: 12 weeks.	75 patients (24 male and 51 female; mean age: 64 years old)	osteoarthritis of the hip and/or knee	3 patients reported: dyspeptic complaints (n=2) and sensation of fullness (n=1).	Improvements in typical clinical findings.
Chrubasik *et al*., 2007	Open study	Tablet with 400 mg dry aqueous extract of Harpagophytum (DER 1.5-2.5:1). 6 tablets/day (daily dose of 60 mg harpagoside) Duration: 54 weeks.	114 patients Drop-out: 15 patients	Non-specific low back pain or osteoarthritic pain in the knee or hip	49 patients experienced a total of 79 adverse events, 13 of them (all minor abdominal complaints) were related to devil's claw.	Supportive

Review

Vlachojannis *et al*. (2008) reviewed the safety of *Harpagophytum* preparations used for osteoarthritic and lower back pain in humans. Studies dating back to 1985 were included and of the 28 clinical trials assessed, 20 stated minor adverse events. Over periods of up to 1 year, 6892 patients used these products in double blind (n=615) or observational (n=6277) trials. In none of the double-blind studies was the incidence of adverse events during treatment with Harpagophytum higher than that during placebo treatment. Minor adverse events (AE) were described in 20 studies (n= 4274) in a total of 138 patients. This corresponds to an overall adverse event rate of around 3%. Some of the AEs (e.g. gastrointestinal complaints and allergies) were probably related to *Harpagophytum*. A few reports of acute toxicity were found but there were no reports on chronic toxicity. The authors concluded that since the dosage used in most of the studies is at the lower limit and since long-term treatment with Harpagophytum products is advisable, more safety data are urgently needed.

Table 1. Studies with *Harpagophytum* products in chronological order, with some characteristics of the products used in the clinical trials (see foot note), internal validity (IV), study duration (weeks) and number of adverse events (Aes, ns not stated)

No	1st Author	Date	Brand	g/day[a]	Solvent	mg H/day[b]	A	B	C	D	IV	Weeks	Aes of n[c]
1	Schruffler	1980	Salus	2.5	Water	<30			x		fair	4	0 of 25
2	Grahame	1981	Salus	2.5	Water	<30	x				poor	5	1 of 13
3	Belaiche	1982	Extract B	9–27	Water	>90–270[b]	x				poor	up to 26	ns of 616
4	Guyadier	1984	Extract G	?	45% Ethanol	<20[b]				x	poor	3	6 of 50
5	Pinget	1990	Arkophytum	2	none	60[b]	x				poor	8.5	2 of 43
6	Lecomte	1992	Arkophytum	2	none	60[b]				x	fair	8.5	0 of 45
7	Chrubasik	1996b	Doloteffin	4.5	Water	50				x	good	4	4 of 59
8	Chrubasik	1997	Jucurba	4.5	Water	30		x			poor	6	5 of 51
9	Schmelz	1997	Arthrotabs	4.5	Water	30				x	fair	4	ns of 50
10	Chrubasik	1999	WS1531	4.5; 9	Water	50, 100				x	good	4	35 of 131
11	Schwarz	1999	Arthrotabs	4.5	Water	30	x				poor	6	12 of 2053
12	Szczepanski	2000	Pagosid	4.5	30% Ethanol	about 30	x				poor	6	11 of 51
13	Rütten	2000	Allya	4.5	60% Ethanol	<30	x				poor	6	ns of 99
14	Usbeck	2000	Rivoltan	4.5	60% Ethanol	<30	x				poor	4	ns 1026 of
15	Chantre	2000	Harpadol	4.5	none	57				x	good	17	10 of 62
16	Frerick	2001	Flexiloges	4.5	60% Ethanol	<30				x	poor	20	8 of 24
17	Gobel	2001	Rivoltan	4.5	60% Ethanol	<30				x	fair	4	4 of 31
18	Laudahn	2001	Rivoltan	4.5	60% Ethanol	<30	x				poor	8	3 of 130
19	Schendel	2001	Flexiloges	4.5	60% Ethanol	<30	x				poor	8	3 of 583
20	Ribbat	2001	Sogoon	4.5	60% Ethanol	<30	x				poor	8	3 of 675
21	Biller	2002	Flexiloges	4.5	60% Ethanol	<30				x	poor	20	ns of 39
22	Chrubasik	2002b	Doloteffin	4.5	Water	60	x				good	8	40 of 250
23	Chrubasik	2003b	Doloteffin	4.5	Water	60				x	good	6	14 of 44
24	Kloker	2003	Cefatec	4.5	60% Ethanol	<30	x				poor	8	3 of 614
25	Wegener	2003	Doloteffin	4.5	Water	60	x				poor	12	1 of 75
26	Lienert	2004	Allya	4.5	60% Ethanol	<30			x		fair	6	ca. 5 of 30
27	Chrubasik	2005	Doloteffin	4.5	Water	60	x				good	54	3 of 73
28	Chrubasik	2007	Doloteffin	4.5	Water	60	x				good	54	13 of 114

[a] Daily dose based on g raw material/day; IV, internal validity according to Chrubasik *et al.* (2003a).
Study category: A observational or interventional with no comparison except over time, B open, non-randomized comparison with conventional treatment, C randomized controlled with no or inadequate concealment of treatment allocation, D randomized controlled trial with good concealment of allocation (blinding).
[b] Harpagoside content estimated indirectly and approximately from iridoid glycoside (IG) content in daily dose of raw material, otherwise taken from Chrubasik *et al.* (1996a), Sporer and Chrubasik (1999), Chantre *et al.* (2000), Sporer unpublished data, Salushaus GmbH unpublished data.
[c] n total number of patients studied.

5.2. Patient exposure

Summarising the efficacy studies 4618 patients received devil's claw root preparations.

Aside from market presence and data from studies, there are some indirect data concerning patient exposure.

According to CITES 2012 there are some data regarding direct exports from Namibia to EU in the period of 2005-2012:

Table 1: Direct exports of *Harpagophytum* from Namibia, 2005-2012. All trade was imported by the EU-28 only.

Term (Unit)	Purpose	Source	2005	2006	2007	2008	2009	2010	2011	2012	Total
dried plants (kg)	T	W		28788.8		10290.6	17492	62303	21200	13933.6	154008
leaves (kg)	T	W								9216	9216
medicine (kg)	-	-							57000	24.9	57024.9
powder (kg)	T	W				6004.5					6004.5
roots (kg)	T	W	51060	65716	56683	131661	36893	36347	50325	120256	548941
	-	-						3000		187000	190000
roots	-	-								58000	58000
Total			51060	94504.8	56683	147956.1	54385	101650	128525	388430.5	1023194.4

Source: CITES Trade Database, UNEP-WCMC, Cambridge, UK, downloaded on 14/10/2014

The same document mentioned that imports of *Harpagophytum* roots from Namibia increased by more than 6-fold between 2011 and 2012, primarily due to an increase in reported imports by Germany and Poland, although Italy and Spain also reported imports in 2012. Germany was the main EU importer of *Harpagophytum* spp. over the period.

If patients with known intolerance to *Harpagophytum radix* are excluded, a traditional use is possible if administration follows the instructions as specified in the monograph.

5.3. Adverse events, serious adverse events and deaths

Clinical trials- see section 5.1.

Pharmacovigilance database:

In the VigiLyze database of the World Health Organisation's Uppsala Monitoring Centre for the period up to August 2015, there were some spontaneous reports of suspected adverse drug reactions associated with the single-ingredient *Harpagophytum procumbens* . The adverse reactions declared included gastrointestinal reactions, CNS disorders and allergic skin reactions. Just one case of tachycardia and cardiac failure was correlated with devils claw used(as single medication)

Case reports:

Cuspidi *et al*., (2015) correlated subchronic use (>2 weeks) of 2 capsules/day(each containing 250 mg H procumbens-no further data) with moderate systemic hypertension in a healthy postmenopausal woman.

Market overview:

Adverse events were also mentioned from some Member States. Federal Institute for Drugs and Medical devices (BfArM) reported the following adverse reactions: GI-tract: rare: nausea, vomiting, diarrhoea, flatulence; Nervous system: rare: headache, vertigo; Immune system: very rare: Hypersensitivity reactions such as anaphylactic shock, rash, hives, facial oedema.

Literature:

ESCOP 2002: mild gastro-intestinal disturbances (e.g diarrhoea, nausea, stomach upset) may occur in sensitive individuals especially at higher dosage levels.

Hypersensitivity reactions of the skin were reported **(PDR., 2004).** ESCOP monograph (ESCOP, 2009) also mentioned 3 cases of allergic skin reactions (prurit and skin etching) that have been attributed to treatment with devils claw root extracts.
On the basis of the available data the frequency is not assessable. So the frequency is not known.

5.4. Laboratory findings

According to Federal Institute for Drugs and Medical devices (BfArM) very rare was observed the rise in blood sugar level. This was confirmed only by one case of hyperglycemia reported in the VigiLyze database.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

No data available.

5.5.2. Contraindications

Harpagophyti radix is contraindicated in case of gastric or duodenal ulcer **(Blumenthal *et al*., 2000; ESCOP 2009, BHP 1992).** This is due to the drug stimulation of gastric juice secretion **(PDR, 2004)**.

As with other drugs containing bitter substances, patients with gastric ulcer should consult their doctor before use. In accordance with other HMPC monographs with bitter principles(e.g Centaurii herba) patients with active gastric or duodenal ulcer will be included on section 4.3 Contraindication.

5.5.3. Special Warnings and precautions for use

Due to lack of adequate data the use in children and adolescents under 18 years of age is not recommended.

For ethanol containing products the appropriate labelling for ethanol, taken from the guideline on excipients, must be included.

Patients with gallstones should consult a physician prior to use the devil's claw **(WHO, 2004)**

5.5.4. Drug interactions and other forms of interaction

There is limited evidence regarding interactions with other drugs.

Even that theoretically, based on preclinical studies, devil's claw may reduce blood pressure and interacts with antihypertensive drugs, clinical evidence suggests a contrary effect (hypertensive) (**Cuspidi *et al*., 2015**). Too little is known to be able to make any clinical recommendations (**Stockle's, 2009**).

Regarding interaction with warfarin and related drugs, *in vitro* studies suggested that devil's claw may inhibit CYP 450, especially isoenzyme CYP2C9 (**see Pharmacokinetics**). Although the metabolism of warfarin is complex, CYP2C9 plays a significant role, therefore it is possible that devil's claw could interfere with the metabolism of warfarin. Clinical evidence is limited to one case report that describes the development of purpura in a patient following the concurrent use of devil's claw and warfarin **(Stockle's, 2009).** The report was assessed as ‘possible’ on Naranjo’s scale suggested that the herb

might inhibit the platelet aggregation and increase the effect of warfarin resulting in abnormal bleeding **(Patel *et al*., 2008).**

5.5.5. Fertility, pregnancy and lactation

No data available. In accordance with general medical practice, the product should not be used during pregnancy or lactation.

5.5.6. Overdose

No toxic effects have been documented.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

Approximately 4618 patients received devil's claw root preparations in the controlled clinical trials (including human pharmacological studies) listed above. *Harpagophytum* root preparations were generally well tolerated. The most commonly documented side effects, when all clinical studies, VigiLyze database, spontaneous reports and information from the Member States are taken into consideration, are mild gastrointestinal complaints (nausea, abdominal pain, diarrhoea), CNS disorders (dizziness, headache) and allergic skin reactions. These reactions should be listed as undesirable effects in section 4.8 of the monograph. The frequencies are not known.

Harpagophyti radix is contraindicated in case of gastric or duodenal ulcer due to the drugs stimulation of gastric juice secretion.

There is limited evidence regarding interactions with other drugs.

Devil's claw preparation could interfere with the metabolism of warfarin, taking into account that *in vitro* studies suggested that devil's claw may inhibit CYP 450, especially isoenzyme CYP2C9 but clinical evidence is limited and has not been conclusively demonstrated.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Harpagophytum radix preparations cannot be recommended for oral use in children and adolescents under 18 years of age due to lack of adequate safety data.

6. Overall conclusions

Products containing *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne., radix have been registered as traditional herbal medicinal products or well-established use in some Member States. The medicinal use of devil's claw has been documented in several medicinal handbooks throughout a period of at least 30 years, including at least 15 years within the EU. Therefore,

Harpagophyti radix fulfils the requirements of Directive 2004/24 EC as basis for classification as a traditional herbal medicinal product.

The pharmacological activity is attributed to the whole extract; however emphasis is put on the group of iridoid glycosides ('bitters') with main components harpagoside, 8-(p-coumaroyl)-harpagide, harpagide, procumbide and their coumaroyl-esters. Typical analytical marker is harpagoside (Ph Eur).

The available clinical data is considered insufficient to support the well-established use for this herb. The traditional use indications and duration of use included in the monograph are:

Indication 1) Traditional herbal medicinal product for relief of minor articular pain.
Duration of use: 4 weeks.

Indication 2) Traditional herbal medicinal product used for the relief of mild digestive disorders such as bloating and flatulence and where there is loss of appetite.
Duration of use: 2 weeks

Harpagophyti radix is traditionally used in the following pharmaceutical forms and posology:

a) Herbal tea

Indication 1) single dose: 1.5 g comminuted herbal substance; daily dose: 4.5 g comminuted dried root in 500 ml of boiling water as herbal tea, divided in 3 doses

Indication 2) single dose: 0.5 g comminuted herbal substance; daily dose: 1.5 g comminuted dried root in 250 ml[3] boiling water as herbal tea, divided in 3 doses

b) Powdered herbal substance

Indication 1) single dose: 435 mg, 3 times daily; daily dose: 1.35 g

c) Liquid extract (DER 1:1), extraction solvent ethanol 30% V/V

Indication 1)

Daily dose: 1.03 g extract as single dose

d) Soft extract (DER 2.5-4.0:1), extraction solvent ethanol 70% V/V

Indication 1) and 2) daily dose: 240 mg extract as single dose

e) Dry extract (DER 1.5-2.5:1), extraction solvent water

Indication 1) single dose: 750-800 mg, 3 times daily

Indication 2) single dose: 100 mg; 2-3 times daily

f) Dry extract (DER 5-10:1), extraction solvent water

Indication 1) single dose: 200-400 mg, 2 to 3 times daily; daily dose: 600-800 mg

g) Dry extract (DER 2.6-4:1), extraction solvent ethanol 30% V/V

Indication 1) single dose: 400 mg-800 mg; 2 to 4 times daily; daily dose: 800 mg up to 1.6 g

Indication 2) single dose: 140-280 mg, 3 times daily

h) Dry extract (DER 1.5-2.1:1), extraction solvent ethanol 40% V/V

Indication 1) single dose: 300-900 mg; 2 to 3 times daily

[3] the quantity of water is according to general practice to prepare a tea

i) Dry extract (DER 3-5:1), extraction solvent ethanol 60 % V/V

Indication 1) and 2) single dose: 480 mg, 2 times daily

j) Dry extract (DER 3-6:1), extraction solvent ethanol 80 % V/V

Indication 2) single dose: 100 mg; 3 times daily

k) Dry extract (DER 6-12:1), extraction solvent ethanol 90 % V/V

Indication 1) single dose: 45 mg; 2 times daily

l) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 25 % (V/V)

Indication 1) single dose: 0.5-1 ml; 3 times daily.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended. No data on fertility is available.

Harpagophytum radix preparations cannot be recommended for oral use in children and adolescents under 18 years of age due to lack of adequate safety data.

The traditional use of the herbal substance and its preparations of *Harpagophyti radix* have a positive benefit risk ratio due to minimal risks.
Due to the lack of data on genotoxicity, carcinogenicity, reproductive and developmental toxicity, a list entry for Harpagophytum radix cannot be recommended.

Annex

List of references