EUROMED Herbal Extract

Devil´s Claw Extract

For The Treatment Of
Joint Ailments

EUROMED

Introduction

EUROMED is a company specialized in botanical extracts and active ingredients to be used as phytomedicines within the pharmaceutical field. EUROMED devotes itself to the development and production of these therapeutically active raw materials.

For that purposes the botanical raw materials are subjected to strict selection and controls, and the products are manufactured following production methods developed by the EUROMED company, which include controls to assure a standard quality according to the latest knowledge of the state of art in different fields: R&D, analysis, processes and facilities, therapeutical usage on a scientific basis.

EUROMED assures the quality of their products with a background of broad phytochemical know-how.

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1. Devil's Claw Extract General Information

1.1 Description

All natural

Devil's claw extract is a standardized herbal extract from *Harpagophytum procumbens* secondary roots *(*Fam. *Pedaliaceae*).

Herbal antirheumatic

Devil's claw extract is a herbal preventive and therapeutic agent for painful arthritis (osteoarthritis) and tendinitis. Treatment results in relief of pain and improves functionality and mobility.

EUROMED devil's claw extract gives most patients relief from symptoms within the first few weeks of treatment.

Devil's claw extract does not interact with other drugs.

1.2 Indications

Arthritis and tendinitis

The devil's claw extract manufactured by EUROMED is used in the treatment of painful arthritis and tendinitis.

1.3 Extract Specifications

Harpagophytum preparations usually contain about 200 to 400 mg devil's claw extract (as available from EUROMED).

1.4 Dosage and Methods of Administration

A daily oral dose of 1,200 to 4,500 mg *Harpagophytum* extract is common practice. Table 1 shows a survey of popular devil's claw preparations available on the European market.

1.5 Contraindications and Interactions

Gastric and duodenal ulcers are contraindications due to the postulated stimulation of gastric acid secretion of bitter tasting preparations. There are no known interactions with drugs usually prescribed.

1.6 Side-effects

Well tolerated

Harpagophytum extract is generally well tolerated. Mild gastro-intestinal disturbances may occur in sensitive individuals especially at higher dosages. Side effects are rare when the standardized extract is taken, however.

Tab. 1: European Herbal Preparations containing *Harpagophytum* extract.

Preparation Name	**Method of Extraction**	**Content of *Harpagophytum* Extract [mg]**	**Total Extract/day [mg]**
Arthrosetten	Ethanolic	200	1.200-1.600
Arthrotabs	Ethanolic	410	2.460
Dolo-Arthrosetten H	Ethanolic	400	1.200-1.600
Doloteffin	Aqueous	400	2.400
Harpagoforte ASmedic	Aqueous	375	2.250
Harpagophytum Arkocaps	Aqueous	500	4.500
Herbadon	Aqueous	250	1.500
Jucurba	Aqueous	300	1.800
Rheuma-Sern	Aqueous	400	1.200-1.400
Teltonal	Ethanolic	480	1.920

2 From Plant to Extract

2.1 Devil´s claw *(Harpagophytum procumbens)*: Botanical Data

Devil`s claw

The authentic plant *Harpagophytum procumbens* belonging to the family of *Pedaliaceae* comes exclusively from southern Africa, where it grows in savanna and deciduous forests [31]. The natural habitat of *Harpagophytum procumbens* is steppe-like areas of the Kalahari desert in Namibia and parts of adjacent South Africa, Botswana, Angola and Zimbabwe. It is now being cultivated as a drug plant [43, 44]. Synonyms for the English name devil´s claw are grapple and wood spider. Flowers and leaves of the plant can only be found during the short rainy season. To survive dry periods, the plant forms water-storing secondary root tubers branching out horizontally from the primary taproot. There are two similar species of *Harpagophytum (H. Procumbens* and *H. zeyheri*) which have a similar distribution and even a similar action [3, 31].

Succulent taproot

Harpagophytum is a perennial herb with several prostrate annual stems from a succulent taproot with additional tubers on lateral roots. At the beginning of the rainy season the larger nodular roots produce young shoots that lie flat on the ground, growing up to 1.5 m in length [31, 32]. Leaves are narrowly ovate to ovate, up to 65 mm long and 40 mm broad, lamina usually pinnatilobed, with 3 or 5 main lobes, sometimes polymorphic. The limbs of corollas are purple or yellowish, 25 to 40 mm in diameter. It has a characteristic large, hooked-like fruit. It has 4 rows of curved arms bearing recurved spines, the length of the longest arm exceeding the width of the capsule proper. The total diameter of fruits is up to 15 cm [31]. It name derives from the translation of the German name Teufelskralle, which means devil´s claw [51, 53].

Fig. 1: Devil´s claw (*Harpagophytum procumbens DC*) [53]

2.2 Historic use

Traditional African herbal remedy

An infusion of the tubers is used in Africa for the relief of fever and for blood diseases. It is administered to pregnant women in doses of about 0.25 g three times daily to relieve pain and in postpartum medication at lower doses. It is a general analgesic and the ointment is applied to sprains, sores, and boils. The drug has been used as a bitter tonic and as a digestive aid. Devil´s claw is dispensed as an anti-inflammatory agent and administered both orally and topically for various inflammatory conditions. The fresh tubers are applied as an ointment on women to facilitate labor [33, 57]. In general, *Harpagophytum* tubers have been used by Africans for a long time in the treatment of rheumatic diseases and gastrointestinal complaints. It was introduced into European medicine as a herbal tea for the same purposes by a German farmer in Namibia, G. H. Mehnert in the beginning of this century [53, 54].

The use of *Harpagophytum* has been well documented and recognized continuously up to the present day. This is reflected by European monographs, which recommend the use of devil's claw to relieve pain and improvement of motility in patients with arthritis and tendinits [13, 21].

2.3 Chemistry of *Harpagophytum procumbens* secondary roots

The drug devil´s claw consists of the cut, dried secondary root tubers of *Harpagophytum procumbens* DC.

Iridoid glycosides considered as active ingredients

It yields a variety of compounds, mainly iridoid glycosides (up to 3 %). The secondary tubers contain approximately twice as much harpagoside as the primary tubers [5]. Further constituents are glycosides of the flavonoids kaempferol and luteolin, chlorogenic acid and cinnamic acid, the phenylethanoid acteosid, quinone, harpagoquinone, triterpenes like ursolic and oleanic acid and derivatives, phytosterols like sitosterol and stigmasterol, and esters; sugars, mostly in form of stachyose, sucrose and monosaccharides [5, 32, 47, 50, 53, 54]. Today, the secoiridoid glycosides are supposed to contribute to the pharmacological actions and clinical efficacy [53].

The fraction of secoiridoid glycosides consists of harpagoside, procumbide, harpagide and 8-para-coumaroyl-harpagide [16, 18, 28, 30, 34, 48, 47]. Harpagoside contributes mainly to the amount of secoiridoid glycosides [18, 34, 43].

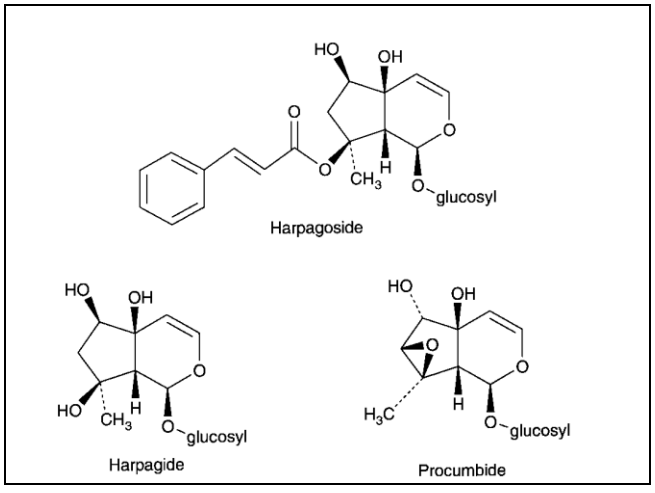

Fig. 2: Iridoid glycosides of devil´s claw [5]

2.4 Preparation of the Extract and Quality Control

Devil's claw consists of the cut, dried secondary root tubers of *Harpagophytum procumbens* DC. These tubers are obtained by wild collection in the southern parts of Africa [43, 44]. From these tubers, carefully identified and with a standard quality, EUROMED manufactures different extracts.

Permanent professional scientific botanical inspections are part of the growth of this medicinal plant [43, 44]. Devil´s claw is collected only from natural habitats, because cultivation in other environments is impossible [43, 53]. In this way the quality of EUROMED *Harpagophytum* extract is being steadily improved. Only high-quality raw plant material selected according to the strictest criteria is used. It contains not less than 1.2% of harpagoside [17, 22].

Harvested by hand

For harvesting, the soil is scooped out by hand in the area around the parts of the plant that are above ground, until the turnip shaped primary roots are revealed. From these, thin side roots branch off, at the end of which tuberous or cylindrical secondary storage roots can be found which can be up to 25 cm long and up to 6 cm thick. They may reach a depth of 2 meters. These tubers are collected, washed, sliced and dried in the sun. For continuous harvesting in the next vegetation period the holes are refilled with soil [43, 44].

Quality control of drug material

When the dried drug material arrives at EUROMED an exhaustive inspection of the raw material is carried out according to the current methods in order to guarantee the quality of the final product.

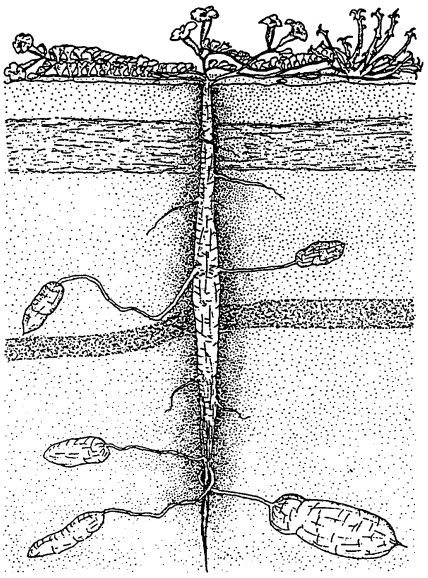

Fig. 3: Morphology of devil´s claw at natural habitats [44]

Furthermore EUROMED evaluates the possible contamination of the drug. Microbiological purity and presence of heavy metals, aflatoxins and pesticide residues are routinely examined. In doing so the company assures that the limits fixed by international standards are not exceeded.

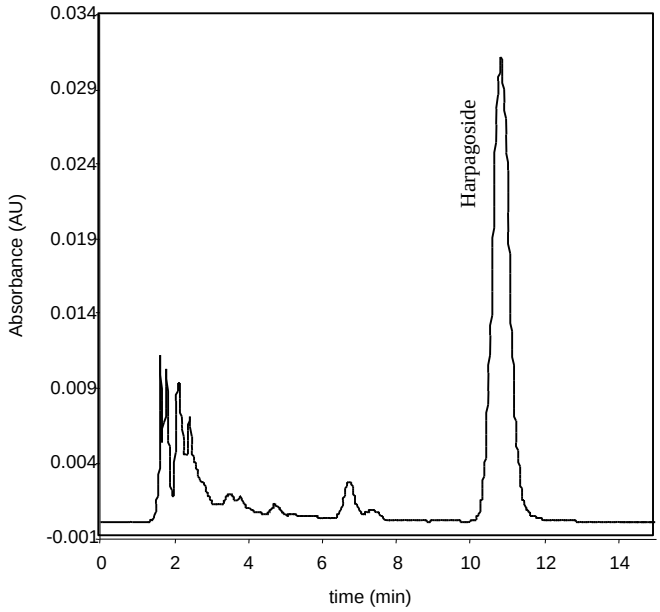

Fig. 4: HPLC-chromatogram of devil´s claw extract [43].

Standardized extraction procedure

EUROMED applies an unique extraction process to obtain the extract. This procedure meets the indications of the Commission E monograph for devil´s claw extract [13]. It provides a high yield of valuable constituents and a high-grade extract in a careful way.
The original EUROMED processes produce an ethanolic extract from the secondary tubers of *Harpagophytum procumbens*:

- **DEVIL´S CLAW DRY EXTRACT**

EXTR. HARPAGOPHYTI E RAD. SICCCUM
Fine powder, light brown color,
bitter taste and aromatic odor

The EUROMED devil's claw extract satisfies the highest quality standards. This way it is possible to meet the requirements for an effective and safe herbal medicinal product.

2.5 Standardization

Consistent batch to batch quality

The consistent batch to batch quality of the EUROMED devil's claw extract is guaranteed by a standardized production process.

Analytical specifications of devil's claw extract are:

Aspect	Fine powder, light brown color, bitter taste and aromatic odor
Identification	TLC (Ph. Fr. X ed.)
Loss on drying	Max. 5 %
Assay	Harpagoside 1.4-1.6 % (Ph. Fr. X^{ème} ed.);
Microbiology	According to Ph. Eur. 3rd ed., 5.1.4., category 3B

3 Rheumatism – Arthritis

Pain and stiffness

Arthritis or rheumatism is characterized by pain, swelling, stiffness, and redness. Arthritis is not a single disorder but the name of joint disease from a number of causes. The arthritis may involve one joint or many, and can vary in severity from a mild ache and stiffness to severe pain and, later, joint deformity. Arthritis is the number one cause of disability [24].

More than 500 rheumatic disorders

There are as many as 500 different rheumatic disorders, rheumatoid arthritis and osteoarthritis are the most common [26]. Rheumatoid arthritis is the most severe type of inflammatory joint disease. This type of arthritis is an autiimmune disorder in which the body's immune system acts against and damages joints and surrounding soft tissues. Osteoarthritis also known as degenerative arthritis or arthrosis is the most common type of arthritis. This type of arthritis results from wear and tear on the joints, develops in middle age, and most commonly troubles older people [24, 26].

3.1 Rheumatoid arthritis

Chronic progressive disease

Rheumatoid arthritis is a chronic progressive inflammatory disease involving joints and other tissues. It occurs in some 1 - 2% of adults worldwide. It is three times more common in women than in men prior to menopause; after this age the incidence is equal. Clinically, it is typified by a symmetrical, destructive, deforming polyarthritis affecting small and large peripheral joints. It is associated with a systemic disturbance and is characterized by the presence of circulating antiglobulin antibodies (also called „rheumatoid factors"). The inflammatory process, which may result in disability, usually follows a remitting course, but may be rapidly progressive [24, 26, 56].

Damage of cartilage and adjacent tissues

The pathological basis of the condition remains uncertain. It seems to be associated with T lymphocyte and macrophage activation in genetically predisposed individuals. The inappropriate chronic inflammatory response in the synovial lining damages the cartilage and adjacent tissues.

This may first become apparent as an acute episode of pain, stiffness and symmetrical swelling of a number of peripheral joints. In other cases, the patient may complain of malaise well before the joints become affected. As the disease advances, muscle atrophy and joint destruction limit movement and lead to deformities.

The management of rheumatoid arthritis is directed toward the relief of symptoms, suppression of the active disease and conservation or restoration of structure and function in the affected joints. Pain is controlled and inflammation suppressed in the first instance with acetylsalicylic acid and, when this fails, with another nonsteroidal anti-inflammatory drug (NSAID) to which a disease controlling anti-rheumatic therapy (DCART) may be added [24, 26, 56].

The following classification of antirheumatic therapies has been proposed [56]:

A. Symptom Modifying Antirheumatic Drugs (SMARD)

These improve the symptoms and clinical features of inflammatory synovitis:

- Nonsteroidal anti-inflammatory drugs (NSAID)
- Corticosteroids
- Slower acting drugs e.g., antimalarials, gold, penicillamine, antimetabolites, cytotoxic agents (Category III SMARD)

B. Disease Controlling Antirheumatic Therapy (DCART)

These change the course of rheumatoid arthritis, i.e., they both

- improve and sustain function in association with inflammatory synovitis, and
- prevent or significantly suppress the rate of progression of structural joint damage.

These changes must be sustained for a minimum period of one year; the classification must include reference to the time period for which criteria have been satisfied, e.g., two year DCART [24, 40, 56].

Physical therapy, including general and specific exercises, educational programs and psychological support are very important in preserving function and quality of life. Surgical interventions, including total joint replacement, may ameliorate severe handicap [24, 40, 56].

Adverse effects of standard therapy

NSAIDs act by inhibiting the formation of inflammatory mediators including prostaglandins. Many NSAIDs are available, and it remains impossible to predict which will be most effective in a given patient [24].

Gastrointestinal disturbances are the most frequently reported adverse effects. Inhibition of the cytoprotective effect of prostaglandins on the gastric mucosa can result in dyspepsia, peptic ulceration and hemorrhage. Disruption of the regulatory effect of prostaglandins on renal blood flow can reduce glomerular filtration, particularly in elderly subjects, and can result in acute or chronic renal failure [24, 56].

If significant symptoms and signs of inflammation persist after several weeks of intensive NSAID therapy, use of DCARTs (or Category III SMARD) should be considered. These are a diverse group of substances which include:

- aminoquinolones
- sulfasalazine
- penicillamine
- methotrexate and
- organic gold compounds.

They share the potential to suppress inflammation and slow the rate of functional and structural deterioration. Treatment should be started early in the course of the disease, before significant joint damage has occurred. However, specialist training is recommended to ensure they are used safely and to best advantage [24, 56].

3.2 Degenerative rheumatism (Osteoarthritis)

Osteoarthritis is a multifactorial age-dependent disease of synovial joints leading to a loss of articular cartilage (fibrous caps covering the articular surfaces of the bones), refashioning of the articular surfaces and osteophyte formation. It results in a progressive loss of joint movement, deformity and impairment of function.

Multifactorial chronic disease

Osteoarthritis may be localized and affect only a single joint or may be generalized and attack several joints in sequence or simultaneously. Weight-bearing and nonweight-bearing joints can be involved. Osteoarthritis of the facet joints of the spine, which is invariably associated with degenerative changes in the intervertebral discs, is termed spondylosis [11, 26, 56].

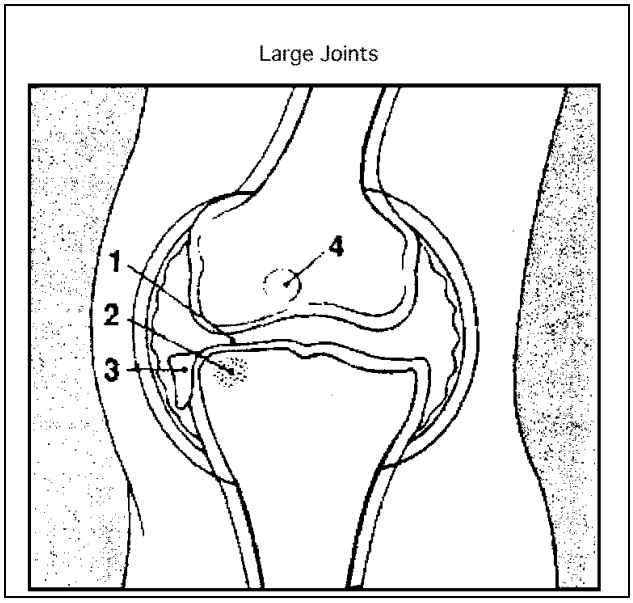

Fig. 5: Morphology of osteoarthritis.
1 defined joint space narrowing
2 subchondralsclerosis
3 osteophyte
4 cyst or pseudocyst [24]

Osteoarthritis is the most prevalent of all chronic arthropathies in every part of the world especially affecting those in middle and advancing years. There is a strong familial tendency, and several processes including inflammation, aging and abnormal joint loading are involved in its development [24].

Most important rheumatic disease

The high prevalence of osteoarthritis makes it the most important rheumatic disease in the community, both in terms of human suffering and in terms of economic impact. For the vast majority the disease is mild, remains mild and progression is not inevitable. In some cases osteoarthritis may even regress. However, many people with osteoarthritis will still advance to total joint destruction. With the development of successful joint replacement surgery, good restoration of function and gainful activity may ensue [24, 26, 56].

Characteristic: osteoarthritis of hip and knee

Characteristically, episodes of pain after physical activities occur although in the early stages, the disease is asymptomatic. There is an increasing loss of range of motion in the affected joints. For example, with osteoarthritis of the knee pain may occur in the anterior knee on climbing or descending stairs [11, 56].

There is no specific drug treatment and management is symptomatic. In osteoarthritis the patient should be encouraged to remain as physically active as possible, to reduce weight (if obese), to modify life-style by avoiding or reducing symptom-provoking activities and to relieve pain by taking analgesics and, if necessary, NSAIDS [11, 26, 56].

3.3 Lower Back Pain

Lower back pain affects up to 80% of the population

Lower back pain affects up to 80% of the population at some time during their life incurring a huge financial burden. Ninety percent of all lower back pain episodes result from excessive physical stress or overuse on the normal spinal structure and are self-limiting. Disc degeneration accounts for most of the remaining 10 %. A small but significant percentage of lower back pain is caused by specific bone pathology [9, 26, 56].

Lower back pain contributes substantially to the workload of general practice. During any 12-month period, 7 % of the adult population will consult a physician with this problem. In two separate surveys of the British general population, 38 % of adults reported a significant episode of lower back pain in one year and a third of these experienced the symptom for longer than four weeks. During the past 20 years in Britain, the prevalence of disabling lower back pain for which benefits are paid had risen exponentially [15]. These epidemiological data have been confirmed also for other countries [9].

In a large population based study the outcome of episodes of lower back pain in general practice with respect to both consultation behavior and self reported pain and disability has been examined. While 90 % of the subjects consulting a general practitioner with lower back pain ceased to consult about the symptoms within three months, most still had substantial lower back pain and related disability. Only 25% of the patients who complained about lower back pain had fully recovered 12 months later. Since most continue to have long term lower back pain and disability, effective treatment could reduce the burden of these symptoms and their social, economic, and medical impact [9, 15].

3.4 Tendinitis

Chronic tendon problems are common in orthopedic patients [1]. Relatively little is known about the etiology of these common problems and the efficacy of available treatments. It is believed that the cause of many injuries is repetitive mechanical trauma followed by an inflammatory response. Other factors, such as age related degeneration and relative avascularity in the tendon, may play an important etiologic role as well. Histopathologic studies have generally revealed degenerative lesions consistent with tendinosis and/or inflammation of the peritendinous tissues consistent with peritendinitis [1, 2].

Initial treatment should focus on patient counseling and correction of associated mechanical factors, if present. Nonsteroidal anti-inflammatory drugs can give pain relief, but there is no convincing evidence that they alter the natural history. Corticosteroid injections can be used selectively in resistant cases, but recurrences are frequent [1].

Searching for alternatives

Because of the above mentioned side effects of synthetic antirheumatic drugs, physicians and their patients look for pharmacological alternatives or additives to limit the dosage of NSAID medication and reduce adverse events. Extract of *Harpagophytum*, as available from EUROMED , is a valuable alternative and a well tolerated remedy.

4 Pharmacology

4.1 Pharmacodynamic

Anti-inflammatory and analgesic action

The anti-inflammatory, analgesic, and moreover antiarrhythmic and hypotensive effects of devil's claw, the isolated iridoid glycoside harpagoside and its aglycone harpagogenine have been extensively investigated [37, 45, 53, 54].

4.1.1 Anti-inflammatory effects

Anti-inflammatory effects have been demonstrated more convincingly in semichronic animal models than in acute animal experiments [53].

Inhibition of inflammation processes

In subacute procedures (models of formaldehyde-arthritis, Freund adjuvant-arthritis and granuloma-induced experimental arthritis), extracts of devil's claw appeared to be efficient [19, 20] although other studies have not confirmed these results [25, 55]. In the croton oil-induced granuloma pouch test in rats the reduction of inflammation produced by a 12-day intraperitoneal administration of harpagoside or its aglycone harpagogenine [19] and by oral administration of aqueous and alcoholic extracts of devil's claw [20] was similar to that of phenylbutazone.

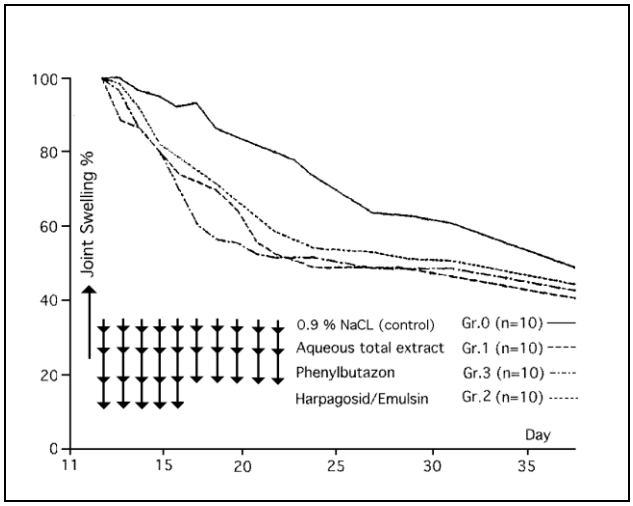

Fig. 6: Antiphlogistic activity of devil´s claw extract in the formaldehyde-induced arthritis-model in the rat: Development of the joint swelling until 38 days after formaldehyde injection at the first study-day [19]

In the formaldehyde-induced arthritis test an effect comparable to that of phenylbutazone was demonstrated with both an aqueous extract of devil's claw and with harpagogenine after a 10-day intraperitoneal administration; no effect was apparent with the glycoside harpagoside [19]. A 7-day oral treatment of devil's claw at high dose levels produced no significant effect on secondary inflammatory reaction in the rat [55]. In the carrageenan induced rat paw edema test lipophilic extracts of devil's claw administered intraperitoneally one hour before paw injection inhibited edema provocation significantly and dose-dependently (200 and 400 mg/kg body weight) [39]. The inhibition at maximal dosages (40 to 60 %) was similar to that of phenylbutazone (47 %; 80 mg/kg).

Action comparable to that of indomethacin

A 48% reduction of adriamycin-induced edema in rats was obtained after oral administration of 37 mg/kg of the powdered crude drug, containing 3.0% of iridoid glycosides [33]. Significant, dose dependent, anti-inflammatory effects in the carrageenan-induced acute edema test have been demonstrated in rats following intraperitoneal pre-treatment with devil's claw aqueous extract with a harpagoside content of 1.8% at dose levels of 100 mg/kg (38% inhibition) to 400 mg (72% inhibition). The highest dose tested (400 mg/kg) was even more effective than pre-treatment with 10 mg/kg of indomethacin (58% inhibition). Pure harpagoside was ineffective in these experiments [35].

A recent study assessed the anti-inflammatory properties of devil's claw when administered by different routes, using the carrageenan-induced edema test [46]. The activity of dry aqueous extracts, prepared from cryoground fresh plant by lyophilization was determined in rats. The results indicated that intraperitoneal pre-treatment of rats significantly reduced carrageenan-induced edema. Similarly, intraduodenal pre-treatment with extract significantly reduced edema. In contrast, when administered orally, the extracts were inefficient regardless of the dosage [46]. This is consistent with results obtained in another study [35], showing the absence of extract activity after it had been treated with hydrochloric acid, simulating acid conditions in the stomach. Since these results support the inference that gastric degradation of the active principles may occur, the use of appropriate oral preparations protected against stomach acid degradation has been suggested [35, 46].

A pretreatment with an aqueous extract of devil´s claw showed in an actual study a strong anti-inflammatory action in the carrageenan-induced rat paw edema test [3, 23]. There was observed a dose-dependency, with a maximum effect 3 to 4 hours following administration

4.1.2 Analgesic effects

A devil's claw aqueous dry extract with a harpagoside content of 1.8 % exhibited dose-dependent peripheral analgesic effects (47 % protection at 100mg/kg and 78 % protection at 400 mg/kg) in the writhing test after intraperitoneal administration into mice [35].

53 % protection at 200 mg/kg was fairly similar to the 59 % result obtained with acetylsalicylic acid at 68 mg/kg; pure harpagoside at 10 mg/kg produced 42 % protection [35]. In earlier work using the rabbit ear test, intraperitoneal administration of isolated harpagoside produced an analgesic effect comparable to that of phenylbutazone, but the glycoside hydrolyzed by emulsin and an aqueous extract of devil's claw showed no statistically significant effect [19].

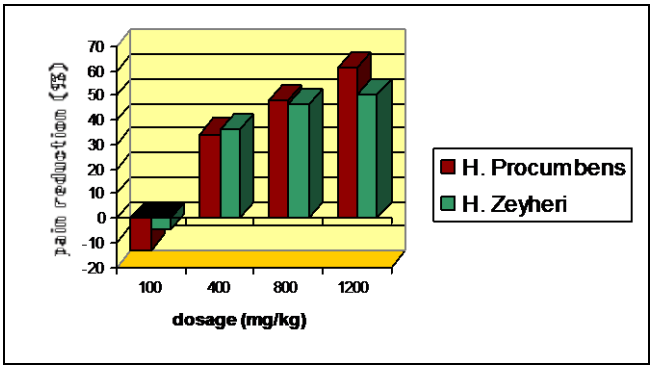

Fig. 7: Analgesic activity of devil´s claw extract (H. procumbens) compared to H. zeyheri in acetic-acid induced pain in mice [23].

In an actual situation a single pretreatment with an aqueous extract of devil´s claw significantly reduced the number of writhings and stretchings induced by an acetic acid solution in rats [3, 23]. At a dosage of 1.200 mg/kg of body weight there was observed a comparable effect to that of acetylsalicylic acid in a dosage of 68 mg/kg.

4.1.3 Further effects

Protection against arrhythmia's

Both oral and intraperitoneal treatment of rats with a dried alcoholic extract of devil's claw with a high content of harpagoside gave considerable protection against arrhythmia's induced by calcium chloride or epinephrine-chloroform [12]. An oral dose of 400 mg/kg of extract produced 50 % more effective protection against calcium chloride-induced arrhythmia than an oral dose of 100 mg/kg of lidocaine. Pure harpagoside gave much weaker protection than doses of extract containing equivalent amounts of harpagoside [12].

A crude alcoholic extract of devil's claw and, to a lesser extent, pure harpagoside showed a significant, dose-dependent, protective action against arrhythmias induced by reperfusion on isolated rat hearts [14]. The same extract showed also a protective effect against arrhythmias induced by calcium chloride and epinephrine-chloroform on isolated rabbit heart [12].

4.2 Pharmacokinetics

As for almost all herbal extracts, devil's claw extract is a complex compound. Therefore pharmacokinetic data for the total extract are not available. There are few publications available concerning the major constituent harpagoside.

Resorption of harpagoside

15 minutes after oral administration of 600 mg of devil´s claw extract containing 50 mg harpagoside, 4 ng, harpagoside per ml serum had been measured in humans after another 2 hours 15 ng was measured [7, 38]. 52 ng harpagoside per ml serum had been measured 20 minutes following an intragastral instillation in a pig of devil´s claw extract, containing 400 mg of harpagoside [6].

5 Toxicology

The toxicity of devil's claw extract (as available from EUROMED) is generally very low.

Acute Toxicity

Low acute and subacute toxicity

Aqueous and ethanolic extracts of devil's claw and the isolated compounds harpagoside and harpagide have shown very low toxicity in rodents during acute and subacute tests [20, 52, 55].

In male and female Swiss Webster mice the acute oral LD, of devil's claw was greater than 13.5 g/kg [58]. The acute intraperitoneal LD_{50} of pure constituents in mice was shown to be 1 g/kg for harpagoside and greater than 3.2 g/kg for harpagide [52].

The acute oral LD_0 and intravenous LD_0 in mice of aqueous, methanolic and butanolic extracts of devil's claw were found to be greater than 4.6 g/kg and 1.0 g/kg respectively. A purified extract containing 85 % of harpagoside showed an acute oral LD_0, greater than 4.6 g/kg and acute LD_0 and LD_{50} of 395 mg/kg and 511 mg/kg respectively [20].

Subacute Toxicity

In male Wistar rats, no significant hematological or gross pathological findings were evident following 21 days of subacute oral treatment with 7.5 g/kg of devil's claw. No hepatotoxic effects were observed with respect to liver weight or levels of microsomal protein and liver enzymes after 7 days of oral treatment with 2.0 g/kg [55].

Reproduction Toxicology

There is no data available.

Genotoxicity/Carcinogenicity

There is no data available.

6 Clinical Pharmacology

Action on arachidonic acid metabolism

No significant effects on the mediators of acute inflammation (prostaglandin E_2, thromboxane B_2, 6-ketoprostaglandin $F_{1\alpha}$, and leukotriene B_4) were evident in 25 healthy volunteers after a 3-week daily intake of 2.000 mg of powdered devil's claw containing 3 % of iridoid glycosides. The subjects served as their own control and were also compared with a separate control group. It was concluded that devil's claw does not produce the biochemical effects on arachidonic acid metabolism characteristic of anti-arthritic drugs of the nonsteroidal anti-inflammatory type [41].

Inhibition of eicosanoid-biosynthesis

Various extracts of Radix Harpagophyti as well as isolated harpagosides were investigated for eicosanoid-production in stimulated human blood [49]. Dose-dependent inhibition of leukotriene- and thromboxan-biosynthesis was measured, which was much stronger for the extracts than for the isolated harpagoside. A stronger effect was seen with the extract with a higher content of harpagoside.

The results of this study propose that some further constituents of devil´s claw total extract may contribute to the pharmacological action.

7 Proof of Clinical Effectiveness

7.1 Studies in Rheumatism

Many studies have been carried out to assess the efficacy of devil's claw in the relief of arthrosic and arthritic conditions [45, 53, 54].

6 months treatment schedule

In a large open study, 630 patients suffering from arthritis of hip, knee, fingers, and spine were treated for 6 months with devil's claw aqueous extract containing 2.5 % of iridoid glycosides at a daily dosage of 3 g to 9 g, divided into three doses [4]. Improvement was demonstrated in 42 % to 85 % of the patients, in groups according to the site of arthroses (knee 42 %, interphalanx 59 %, lumbar/cervical spine 54 %/85 %, hip 70 %). No side effects other than mild gastro-intestinal disturbances were reported, even at the highest dosage level.

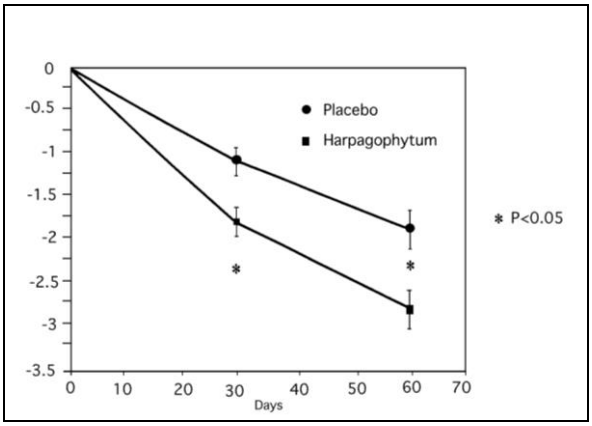

Fig. 8: Severity of pain in patients during 60 days of treatment compared to placebo [36].

Decrease of pain sensation

In a double-blind study [29], 50 patients suffering from arthritis were given 3-week courses 2.400 mg devil's claw hydroethanolic extract with an iridoid glycoside content of 1.5 %. Assessments were carried out 10 days after completion of treatment with evaluation of the severity of pain in 5 conditions on a 0 - 4 scale. Individual patients were given from one to three courses of treatment. Compared with the placebo, the extract produced a statistically significant decrease in the severity of pain. Improvements were more frequent in moderately invalidating arthritis than in the more severe cases.

In a double-blind study [36] on 89 ambulant patients with articular pains of rheumatic origin, the efficacy and tolerance of 2.000 mg of powdered devil's claw with an iridoid glycoside content of 3.0 % daily was assessed for 2 months. The clinical parameters measured on days 0, 30 and 60, severity of pain on a 0-10 scale and joint mobility determined by finger-floor distance during anteflexion of the trunk, revealed a significant drop in the intensity of pain and a significant increase in spinal and coxofemoral mobility in the treated group. Neither side effects nor changes in biological parameters (including blood tests) were observed during the 2-month study.

Pain index lowered

118 patients with chronic lower back pain were included in a 4-week randomized, placebo-controlled double-blind study with a daily dosage of 2.400 mg *Harpagophytum* extract [10]. The outcome was measured via an validated lower back pain index, including scales to measure pain sensation, mobility of the back and motility of the patient. Of the 105 patients, whom completed the study, 9 out of 51 patients of the *Harpagophytum* group and 1 out of 54 patients of the placebo group were pain free at the end of treatment. There was a median improvement of the lower back pain index of 20 % relative to the initial value in the *Harpagophytum* group compared to 8 % of placebo. This trend was related to a significant decrease in the pain index. Only minor nonspecific adverse effects occurred in the verum group.

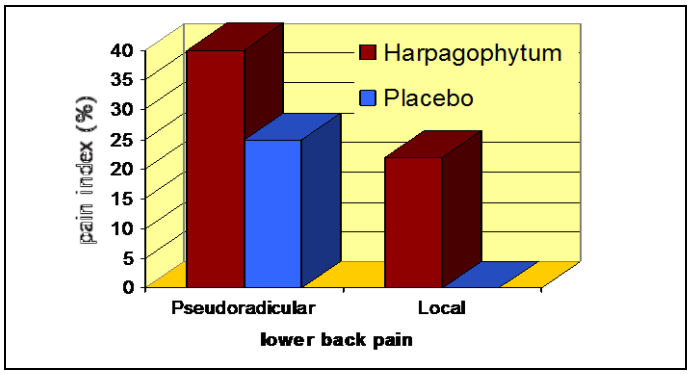

Fig. 9: Relative median change of the Arhus low back pain index in patients suffering from local and pseudoradiating low back pain after four weeks with harpagophytum extract or placebo [10].

Percentage of pain-free patients increased

In a randomized, double-blind study 197 patients suffering from chronic lower back pain local as well as pseudoradiating for at least 6 months, were treated with devil´s claw extract containing either 200 mg or 400 mg harpagoside per day or placebo for 4 weeks [8]. The outcome was measured via the lower back pain index in the study before. 182 patients completed study. The number of pain-free patients increased dose-dependently: 200 mg harpagoside: 6; 400 mg harpagoside: 10; placebo 3. No adverse events were reported.

Effective in comparison to NSAR

In a controlled study 102 patients suffering from acute local lower back pain for more than 6 months were treated with 1.800 mg devil's claw extract or with conventional treatment (NSAR) for 6 weeks [9]. The outcome was measured via the lower back pain index as in the study cited above [10]. The percentage of pain-free patients after 4 and 6 weeks of treatment was similar in both groups (devil´s claw 32 % and 29 %; NSAR-group 23 % and 45 %, respectively). After the six-week therapy the lower back pain index improved in both groups about 20 %. The relative change of the symptoms pain, invalidity and physical impairment did not differ between the groups. However, in both groups the pain index decreased significantly from week 4 to 6 of treatment. In the devil´s claw group there were reported only minor adverse events, which did not necessitate discontinuation of treatment.

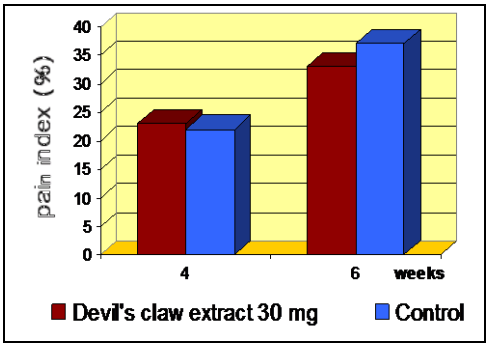

Fig. 10: Relative median change of pain index in patients suffering from local lower back pain after 4 and 6 weeks of treatment with devil´s claw extract, as mono- or co-treatment or as conventional treatment [9].

Even active in rheumatoid arthritis

43 patients with osteoarthritis and rheumatoid arthritis were enrolled in an uncontrolled study with a daily dosage of 750 mg powdered secondary tubers of *Harpagophytum* for a course of 30 days [41]. At the end of treatment there was observed a significant improvement of symptomatic, mobility and morning stiffness. Adverse events were not reported.

Periarticulary rheumatism

In a double-blind, placebo-controlled study the analgesic effect of a *Harpagophytum* extract (2.500 mg extract daily) was investigated in 100 patients with osteoarthritis, chronic lower back pain (lumbalgia) and patients with periarticulary rheumatism [42]. Following 30 days of treatment, only six patients reported strong and one patient medium pain, compared to 32 and 9 in the placebo group, respectively. Only one patient of the verum group reported diarrhea as an adverse event.

Although pharmacological experiments on rodents [35, 46] indicated that enteric coated dosage forms might be necessary for devil's claw, several clinical studies do not support this contention.

7.2 Therapeutic safety

Well tolerated

In total, about 1.500 patients were enrolled in controlled and non-controlled studies on devil's claw extract preparations for up to 6 months. No serious or major adverse events have been reported.

7.3 Summary

Reduction of pain and improvement of mobility

In conclusion, treatment devil's claw extract is an effective therapy for rheumatism, e.g. painful arthritis, lumbalgia and tendinitis. It reduces pain sensation and improves patient mobility, and therefore improves quality of life. Moreover, dosages of standard antirheumatics might be reduced.

Positively monographed

Since there are only limited herbal drugs for rheumatism available, devil's claw extract (as available from EUROMED) is of great importance for both patients and physicians. The evaluation of the Bundesgesundheitsamt/Federal Public Health Department (today: Bundesinstitut für Arzneimittel und Medizinalprodukte/Federal Institute for Drugs and Medical Devices) and of ESCOP (European Scientific Cooperative on Phytotherapy) on efficacy and safety of *Harpagophytum procumbens* secondary roots in therapy is given in positive monographs [21, 13].

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