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Treatment of osteoarthritic pain with herbal drugs

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SUMMARY

Extracts of *Harpagophytum procumbens* and *Urtica dioica* have been used to treat rheumatic pain. The pharmaceutical preparations and their apparent active principles are described. Molecular targets are cyclooxygenase and 5-lipoxygenase (*Harpagophytum*) and also cytokine release (*Urtica*). Clinical studies provide evidence for the efficacy and safety of both phytoanalgesics. These data indicate that treatment of osteoarthritic pain with *Harpagophytum* and *Urtica* extract, should be step 1 in the treatment of rheumatic pain. Less adverse effects accompany the phytoanalgesic treatment as compared to treatment with NSAIDs.

INTRODUCTION

Extracts of *Harpagophytum procumbens* and *Urtica dioica* have been employed to treat rheumatic pain (reviewed in Chrubasik and Wink 1997). In this communication , we report on pharmacological and clinical studies which clearly show that both plants contain active and effective analgesic principles.

HARPAGOPHYTI RADIX

Preparations

Harpagophytum procumbens or *H. zeyheri* grow in the steppes of South and South-West Africa. The drug consists of the cut, dried secondary roots tubers, which contain at least 2.2 % iridoid glycosides, or at least 1.0 % harpagoside. The harpagoside content of the drug varies between 1.1 and 3.6 % (n=10) (Chrubasik and Wink 1997 a). For the treatment of painful arthrosis or tendinitis, the European (ESCOP) Monograph recommends 1.5 - 3.0 g drug in decoction or equivalent aqueous or aqueous-alcoholic extracts (three times per day). This is twice the amount recommended by the German Monograph. Unfortunately, no obligation exists to declare the amount of iridoidglycosides in *Harpagophytum* preparations. Recently, an analysis of the *Harpagophytum* preparations available in Germany revealed that the mean harpagoside content of tablets varied between 0.5 and 9.3 mg, resulting in a daily consumption of 1.5 and 50 mg harpagoside (Chrubasik and Wink 1997 a). On the other hand, tea (an aqueous extract) prepared from 4.5 g or 9 g crude drug contains a mean of 90 mg or 180 mg harpagoside, respectively. Standardized extracts with up to 2 % harpagoside provide tablets, allowing a daily intake of 50 mg harpagoside. Furthermore, a special extract of *Harpagophytum procumbens* WS 1531 (drug extract ratio 6-9 : 1, harpagoside enriched, minimally 5 %) is now available. This extract has recently been employed in a dose-finding study using film-coated tablets of 200 and 400 mg extract which is equivalent to 18.4 and 37.2 mg harpagoside, respectively (allowing a intake of 50 mg and 100 mg harpagoside, respectively) (Chrubasik et al. in press). Other harpagoside-enriched extracts are under preclinical testing. In order to guarantee successful treatment, oral preparations should be standardized on harpagoside or total iridoid glycosides.

Pharmacology

Harpagoside inhibits both, cyclo-oxygenase and lipoxygenase which convert arachidonic acid into prostaglandines or leucotrienes, respectively (Tippler et al. 1996). Recent in-vitro investigations indicate that, depending on the extraction method employed, *Harpagophytum* extracts contain also at least one or more compound(s) that antagonize the effect on the both enzymes (Tippler et al. 1996).
Surprisingly, harpagoside alone seemed not to be involved in reducing the carrageenan-induced edema in rat backpaws. In this test as well as in the acid-induced writhing test in mice, intraperitoneal pretreatment with aqueous extracts of *Harpagophytum procumbens* (1.8 % harpagoside) or with lyophilizised fresh plant (administered i.p. or orally) showed a dose-dependent protection, though less pronounced than that of indomethacin or acetylsalicylate which effectively blocks cyclo-oxygenase (Baghdikian et al 1997). However, in croton oil-induced granuloma pouch test in rats, inflammation was reduced after a 12-day i.p. administration of harpagoside 20 mg/kg/day (Eichler et al. 1970) and by oral administration of aqueous and methanolic *Harpagophytum* extracts 200 mg/kg/day (Erdös et al. 1978). This effect was similar to that of phenylbutazon. A significant anti-inflammatory effect was also demonstrated in the semi-

chronic granuloma pouch test in rats (Erdös et al.. 1978). Numerous pharmacological studies were performed with non-standardised *Harpagophytum* extracts and unknown reference substances (reviewed in Chrubasik and Wink 1995). Their results are of little value. however.

Clinical studies

The clinical efficacy of *Harpagophytum* extracts was demonstrated in several studies which are discussed in the following.

a) In an open study with 630 patients suffering from arthrosis of the hip, knee, fingers and spine (Belaiche 1982), 42 % to 85 % of the patients depending on the affected organ showed improvement after 6 months of treatment with an aqueous extract containing 2.5 % of iridoid glycosides, 3 dosages with a total of 3 to 9 g powdered drug. even at the highest level. Even at the highest dosage no side-effects other than mild gastrointestinal disturbances were reported.

b) In a controlled pilot study (Schmelz and Hämmerle 1997), 100 patients suffering from various rheumatic pain syndroms received randomly either 2460 mg *Harpagophytum* extract (drug-extract ratio 2 : 1) containing 30 mg harpagoside per day or placebo. After 30 days of treatment, 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. Adverse effects occurred in two patients (verum: n=1, diarrhea; placebo n=1, mild gastritis).

c) In a double-blind study (Guyader 1984), 50 volunteers suffering from arthrosis were given 400 mg of an aqueous-ethanolic extract with an iridoid glycoside content of 1.5 % over 3 weeks. After 10 days of treatment, a statistically significant decrease in the severity of pain was deserved. Improvements were more frequent in moderate arthrosis than in the more severe cases.

d) In another double-blind study with 89 ambulant volunteers with articular pains of rheumatic origin, the efficacy of another preparation (capsules containing 335 mg of powdered drug with an iridoid glycoside content of 3 %) was assessed over two months (Lecomte 1992). The clinical parameters measured on days 0, 30 and 60, the severity of pain (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 and a significant reduction in spinal and coxofemoral mobility in the verum group. Neither side-effects nor negative changes in biological parameters (including blood tests) were observed during the 2-month period.

e) 118 patients suffering from chronic low back pain for longer than 6 months (Chrubasik et al. 1996) received randomly and double-blind either 2400 mg *Harpagophytum* extract (drug-extract ratio 2.5 : 1) containing 50 mg harpagoside per day or placebo. Prior to treatment, the groups were similar with regard to their history and biochemical data, circulatory and laboratory parameters as well as in the Arhus low back pain index and its scores for pain, invalidity and physical impairment. After 4 weeks, median Arhus low back pain index had improved by 20 % in the *Harpagophytum* group and by 8 % in the placebo group ($p < 0.059$). This significant trend of effectiveness was based on a significant decrease in the pain index ($p = 0.016$). In patients with pseudoradiating

pain into the leg(s), the median effect of *Harpagophytum* extract equalled that of the placebo. However, in patients suffering from pain not pseudoradiating into the leg(s), the pain index decrease was 25 % in the Harpagophytum group and zero in the placebo group. Nine of 54 patients receiving *Harpagophytum* extract (a total of 20 %) were completely free of pain in the 4th week of treatment compared to one patient (2 %) of the placebo group ($p = 0.008$). Only minor and nonspecific adverse effects were experienced during the *Harpagophytum* treatment.

f) Another 197 patients who suffered from low back pain - local as well as pseudoradiating -, not attributable to identifiable causes (Chrubasik et al. in press) longer than 6 months received randomly and double-blind tablets with *Harpagophytum* special extract batch 9601 containing either 200 mg or 400 mg harpagoside per day (50 or 100 mg harpagoside) or placebo, respectively. As expected, the number of pain-free patients increased dose-dependently after 4 weeks of treatment.

g) In a further controled study, 102 patients suffering from local (non-pseudoradiating) low back pain for more than 6 months were included (Chrubasik et al. 1997 b). They received either 1800 mg *Harpagophytum* extract (drug-extract ratio 2.5 : 1) with 30 mg harpagoside per day as a single or as a co-treatment, or conventional treatment (nonsteroidal anti-inflammatory drugs, physical exercises or paravertebral injections. In order to guarantee careful documentation, physicians which conducted the study investigated the patients at their consulting rooms. Patients receiving the *Harpagophytum* treatment were not favoured, but older, multimorbid and suffered longer from low back pain than patients receiving conventional treatment. The duration of local low back pain and the Arhus low back pain index did, however, not differ for the groups prior to treatment. Six weeks later, the Arhus low back pain index improved in both groups by about 20 % (n.s.). The pain index decreased significantly in the course of treatment from the 4th to the 6th week of treatment resulting in an improvement of more than 30 %. The number of pain-free patients after 4 and 6 weeks was 16 and 20 (Group *Harpagophytum*) and 12 and 23 (Group Conventional Treatment), respectively (ns). Surprisingly, the relative cost of treatment could be lowered by 2/3 when *Harpagophytum* extract were included in the low back pain treatment schedule. Only minor adverse effects that did not necessitate discontinuation of the treatment occurred during the *Harpagophytum* treatment. Despite this encouraging results, an equivalence study needs to be performed to confirm these results.

According to the European Monograph, the duration of treatment with *Harpagophyti* radix extract should not exceed 3 months. If symptoms persist, careful observation is required. Administration of *Harpagophytum* extract is contraindicated in patients suffering from gastric or duodenal ulcers; further special warnings or precautions are not required. Possible interactions with antiarrhythmic drugs cannot be excluded. In accordance with general medical practice, the extract should not be used during pregnancy and lactation without medical advice. Mild gastrointestinal disturbances may occur in sensitive individuals, especially at higher dosage levels. Toxic effects have not been reported. Preclinical safety data have confirmed a very low toxicity in rodents during acute and subacute tests.

URTICA DIOICA

Preparations

Urtica dioica grows in Europe, some parts of Asia, and in North America. Standardized exztracts are prepared from the drug (dried ariel parts of *U. dioicae*, which contains more than one active principle with antirheumatic activity, among them flavonoids, caffeoylmalic acid and an unknown cytokine release inhibiting substance. In addition, fresh material may be used, provided that ist quality complies to that of drug as outlined in the Deutsches Arzneibuch or the Pharmacopea Helvetica.

According to the ESCOP Monograph (1), the drug is indicated for adjuvant treatment of rheumatic conditions. The ESCOP Monograph recommends up to 15 g of the drug for adults , as an infusion (divided in 3 portions), whereas German Monograph recommend a maximal dose of 12 g per day.Alternatively, 0.77 g extract (7 : 1) may be used twice daily or tincture 1 : 5 (25 % ethanol) 6 - 18 ml per day or 30 - 45 ml fresh juice.

The quantity of one the active principles, caffeoylmalic acid, in *Urtica* preparations depends not only on the origin and plant parts and development stage (highest concentrations are found in the leaves) but also on the choice of the extraction solvent and extraction method (Bauer et al. 1997). Teas and preparations of fresh plants may provide more caffeoylmalic acid than other medications. Although caffeoylmalic acid is the lipoxygenase inhibiting principles in preparations from *Urtica* dioica, the clinical efficacy of *Urtica* preparations is not correlated with their caffeoylmalic acid content. Other effective ingredients must be present which need to be evaluated for standardization, in terms of optimal preparations and daily dosage.

Extract of *U. dioicae* leaves and the main phenolic ingredient caffeoylmalic acid inhibit the cyclooxygenase (IC_{50} of extract IDS-23 92 µg/ml, IC_{50} of caffeoyl malic acid 38 µg/ml). Also the 5-lipoxygenase is affected: extract IDS 23 showed a partial inhibitory effect, whereas caffeoylmalic acid inhibited the leukotriene B_4 synthesis in a dose-dependent manner (Obertreis et al. 1997). The concentrations of cytokines including tumor necrosis factor (TNF)-α and interleucin (IL)-1ß in whole blood from healthy volunteers as well as in patients suffering from osteoarthritis after lipopolysaccharid (LPS) stimulation was dose-dependently reduced by simultaneously administered *Urtica* extract IDS-23. In accordance with this, a significant decrease of LPS-stimulated cytokine release in whole blood from volunteers was demonstrated after oral intake of 1340 mg IDS extract over 21 days (Obertreis et al. 1997). In contrast, the release of interleucin-6 was stimulated by IDS-23 comparable to LPS-stimulation (Obertreis et al.1997). Phenolpropanoid derivates and flavonoids did not affect the cytokine release.*Urtica* extract prepared of a lyophylized aqueous extract in water 0.25 mg/ml, produced a 93 % inhibition of platelet activating factor-induced exocytosis of elastase from human neutrophiles. The same extract (0.2 mg/ml) showed no inhibitory activity on the biosynthesis of prostaglandins (Tunon et al. 1995). Furthermore, in the adjuvans-induced arthritis test in rats a dose-dependent reduction of the joint circumference was achieved after 25 days of treatment with IDS-23 extract. In addition, *Urtica* extract exhibits some spasmolytic activity, since it antagonized acetylcholine-induced contractions of rat ileum (Boegge et al. 1996) or a slight con-

tractions followed by relaxation in isolated smooth muscle from non-pregnant mice (Broncano et al. 1987). Application of extracts to uterine muscle from pregnant mice produced a diametrically opposed effect. The authors concluded that the extracts had adrenolytic activity, similar to the action of dihydroergotamine. Contradictory results were achieved for the central analgesic efficacy of *Urtica* extracts. However, local application to the rat tail of 0.05 ml of *Urtica* aqueous extract (100 mg lyophilized extract/ml) in the same region as subsequent application of heat in the tail flick test, produced a local anesthetic effect comparable to that of lignocaine (Lasheras et al. 1986).

Clinical studies

A post-marketing surveillance on patients suffering from osteoarthritis and rheumatoid arthritis included 8955 patients (Ramm and Hansen 1997). They received 1340 mg Urtica extract IDS-23 per day over 3 weeks. Pain at rest, during exercise and physical impairment were assessed on a verbal rating scale 0 - 4 and these improved by 55%, 45 % and 38 %, respectively. Positive effects were evident after 11 days of treatment. In about 60 % of the patients who took NSAIDs before the beginning of treatment, NSAID consumption could be reduced or even omitted. The response was higher the shorter the duration of pretreatment and the less patients had consumed NSAIDs before the beginning of the post-marketing surveillance. Adverse effects (gastrointestinal complaints, allergies, pollacuria, pruritus etc.) occurred in 1.2 % of patients.

The effectiveness of stewed Herba *Urticae* dioicae in patients suffering from acute arthritis was assessed in a pilot study (Chrubasik et al. 1996). 40 individuals took part in this open randomized study comparing the effects of a mixture with diclofenac 50 mg plus stewed Herba *Urtica* dioica with pure diclofenac 200 mg. Thirty-seven patients completed the study. Assessment was based on the decrease of the elevated acute phase protein CRP and the clinical signs of acute arthritis (physical impairment, subjective pain, pressure pain and stiffness, all assessed on a verbal rating scale 0 to 4). C-reactive protein did not correlate with the number of affected joints. After 2 weeks, median scores had improved by about 70 % relative to the initial value in both groups. Only minor adverse effects occurred during treatment. Stewed ariel parts of *U. dioica* may, thus, enhance the NSAID antirheumatic effectiveness, allowing a reduction of NSAID application.

According to the European Monograph, the duration of treatment with *Urtica* folium/herba extract is not restricted. Some contraindications are not known, special warnings or precautions are not required. However, in accordance with general medical practice, the extract should not be used during pregancy and lactation without medical advice. Undesirable effects are reported in about 1 % of patients. No toxic effects are reported. Preclinical safety data include the intraperitoneal LD_{50} of an aqueos *Urtica* extract in mice of 3.625 g/kg body weight and a study investigating an ethanolic extract equivalent to 2 g dried drug per kg which showed low toxicity in both, rats and mice after oral and intraperitoneal administration.

CONCLUSION

In conclusion, although the active principles of *Harpagophytum procumbens* and *Urtica dioica* are still not totally known, pharmacological and clinical studies clearly show their effectiveness in the treatment of rheumatic pain. Since less adverse effects accompany the phytoanalgesic treatment as compared to synthetic NSAIDs, *Harpagophytum procumbens* and *Urtica dioica* should find its place as a rational antirheumatic.

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