Anti-inflammatory phytotherapeutics: a valuable alternative to NSAID treatment in horses?

Ontstekingsremmende fytotherapeutica: een waardevol alternatief voor NSAID's bij het paard?

S. Torfs, C. Delesalle, K. Vanschandevijl, D. De Clercq, G. Van Loon, H. Nollet, P. Deprez

Department of Large Animal Internal Medicine
Faculty of Veterinary Medicine, Ghent University
Salisburylaan 133, 9820 Merelbeke, Belgium

sara.torfs@UGent.be

ABSTRACT

In equine practice, phytotherapy is meeting the increasing demand of horse owners for "natural", safe treatment methods. Long-term use of NSAIDs can cause severe adverse effects, hence the growing popularity of anti-inflammatory phytotherapeutics. At the current time, several different herbal mixes are being commercialized, which makes it difficult for horse owners and veterinarians alike to make a well-founded choice.
***Harpagophytum procumbens* (devil's claw), *Salix* spp. (willow) and *Ribes nigrum* (blackcurrant), three plants that are often used in these mixes, have been evaluated both in vitro and in vivo. Based on published studies and the evaluation of these studies, for example by the Cochrane Collaboration, there seems to be some evidence for *Harpagophytum procumbens* and *Salix* spp. having a stronger analgesic and anti-inflammatory effect than placebos in humans. In horses, however, only one limited clinical study on *Harpagophytum* has been performed up until now, while no studies were found on the use of *Salix* in horses. More research is needed before any claims concerning efficacy or safety can be made regarding the use of these plants in treating horses. It has also been claimed that *Ribes nigrum* leaves have an anti-inflammatory effect, though this has not yet been clinically proven either in humans or in horses.**
Although veterinary phytotherapy is as old as animal husbandry itself, little scientific proof can be found regarding its uses. More research is needed before phytotherapy can be advertised as a valuable and safe alternative to the more conventional treatment protocols.

SAMENVATTING

In de paardengeneeskunde is fytotherapie een antwoord op de toenemende vraag van eigenaren naar "natuurlijke", veilige behandelmethoden. Het langdurig gebruik van NSAID's kan ernstige bijwerkingen geven, vandaar de groeiende populariteit van ontstekingsremmende fytotherapeutica. Momenteel zijn er meerdere kruidenpreparaten commercieel beschikbaar maar het is moeilijk voor de paardeneigenaar en de dierenarts om hier een verantwoorde keuze uit te maken.
Harpagophytum procumbens (duivelsklauw), *Salix* spp. (wilg) en *Ribes nigrum* (zwarte bes of cassisbes), drie planten die veel gebruikt worden in de commerciële preparaten, werden zowel *in vitro* als *in vivo* geëvalueerd. Op basis van gepubliceerde studies en de beoordeling van deze studies door onder andere de Cochrane Collaboration zijn er aanwijzingen dat *Harpagophytum procumbens* en *Salix* spp. bij de mens een groter analgetisch en ontstekingsremmend effect hebben dan een placebo. Bij paarden is er echter slechts één beperkte klinische studie met *Harpagophytum* uitgevoerd, en het effect van *Salix* werd nog nooit onderzocht. Om de werkzaamheid en veiligheid van deze planten bij het paard te kunnen beoordelen, dient er meer onderzoek verricht te worden. De bladeren van *Ribes nigrum* zouden ook een ontstekingsremmende werking hebben, maar dit is momenteel noch bij de mens, noch bij het paard klinisch aangetoond.
Hoewel de veterinaire fytotherapie al even lang bestaat als de dierhouderij, is er weinig wetenschappelijk bewijs omtrent een efficiënte werking ervan. Vooraleer men de fytotherapie kan aanraden als een waardevol en veilig alternatief voor de conventionele behandelmethoden, is er duidelijk nog meer onderzoek nodig.

INTRODUCTION

Equine practitioners are often confronted with patients in need of long-term pain management, such as horses suffering from chronic arthritis or founder. In these cases, nonsteroidal anti-inflammatory drugs (NSAIDs) are the first choice of treatment, as there is no doubt about the ability of these drugs to effectively relieve pain and reduce inflammation (Moses and Bertone, 2002). The downside is that all of these drugs can provoke severe side effects, mainly in the gastrointestinal (e.g. ulceration, colitis) and renal (e.g. papillary necrosis) systems (Moses and Bertone, 2002; Laine, 2006). Recent research even suggests that long-term phenylbutazone treatment could have negative effects on healthy joints (Fradette *et al*., 2007).

Because of the increasing awareness of these side effects, many horse owners are turning towards alternative treatments, such as the herbal preparations that are being marketed as an alternative to NSAIDs. The active substances in these preparations are not synthetic, but rather botanical in origin. It is claimed that their use is not hampered by the typical NSAID-related side effects. *Harpagophytum procumbens* (devil's claw), *Salix* species (willow bark) and *Ribes nigrum* (blackcurrant) are three herbs commonly found in these products. Because of the growing popularity of these herbal alternative treatments, it is important for the equine practitioner to have some basic knowledge on the subject. It is for this reason that a critical overview of the scientific literature dealing with these analgesic phytotherapeutics is being presented in this review.

Peer reviewed articles published between 1980 and 2007 on the three herbs (*Harpagophytum*, *Salix* and *Ribes*) were collected and screened for information regarding the active substances, mechanisms of action, clinical trials, efficacy and safety. Most clinical trials, however, have been performed in humans and rodents.

Harpagophytum procumbens **or devil's claw**

Active components and mechanisms of action

This herb owes its biological and medicinal properties to a group of terpenoid secondary plant compounds known as iridoid glycosides, of which the glycoside harpagoside is the main constituent. This glycoside is predominantly found in the secondary roots of *Harpagophytum procumbens* (Lanhers *et al*., 1992; Loew *et al*., 2001). Based upon various *in vitro* studies, *Harpagophytum* seems to have a very broad-spectrum mechanism of action (Chrubasik *et al*., 2007). Loew and co-workers (2001) found that *Harpagophytum* extract and its marker substance harpagoside exert anti-inflammatory effects by interacting with eicosanoid biosynthesis. They demonstrated a close relation between serum harpagoside levels and the inhibition of leukotriene biosynthesis in human subjects. However, their study also demonstrated that harpagoside is not the only biologically active compound that has to be taken into account. Some of the tested extracts exerted a more pronounced anti-inflammatory effect than the pure harpagoside had by itself, and some *Harpagophytum* extracts were counterproductive, causing an increase in eicosanoid synthesis. The authors suggest that the extracts contain other, as yet unknown substances that also mediate important effects.

Qi and co-workers (2006) identified eleven different iridoid glycosides in a secondary root extract of *Harpagophytum procumbens*. When they studied the *in vitro* effects of these compounds on the "respiratory burst" of macrophages, it was not harpagoside, but only harpagide 8-O-(*p*-coumaroyl) that showed marginal inhibitory activity. Similarly, Kaszkin *et al*. (2004a) studied the anti-inflammatory potency of two *Harpagophytum* extracts, one containing 8.9% harpagoside and the other containing 27% harpagoside, by investigating their *in vitro* inhibitory effects on the inducible enzyme nitric oxide synthase (iNOS), which is known for its role in inflammatory processes. They found that both extracts concentration-dependently inhibited the transcription of iNOS. A similar effect was found on the production of the pro-inflammatory agent phospholipase A_2 (Kaszkin *et al*., 2004b). However, pure harpagoside was only inhibitory at concentrations far exceeding the harpagosidecontent present in the inhibitory extracts. Additionally, one harpagoside-free extract showed iNOS inhibitory activity and even anti-oxidative activity, a feature that has not been demonstrated for harpagoside until now. These findings support the hypothesis that not all biologically active substances in this medicinal herb have been identified. Huang *et al*. (2006) showed *in vitro* that harpagoside exerts its effect on iNOS by suppressing the necessary transcription factor Nuclear Factor kB. There was also an inhibition of cyclooxygenase (COX)-2 production but no influence on COX-1. Chrubasik *et al*. (2006) also demonstrated that *Harpagophytum* extract inhibits inflammatory cytokines, which are responsible for cartilage destruction. Though not all of the outcome parameters of the study were significantly influenced, they did observe a significant chondroprotective effect of *Harpagophytum* extract in an experimental joint-disease model in rabbits. *Harpagophytum* extract is also reported to have an anti-inflammatory effect on carrageenan induced paw edema in rats, but only after intra-peritoneal administration, and not after oral administration (Catelan *et al*., 2006). *Harpagophytum*-induced corticosteroid production was proposed as an explanation for this observed anti-inflammatory effect. However, this theory was overruled by the lack of effect of adrenalectomy. The ineffectiveness of oral dosing could be explained by pre-systemic degradation of the active principles in the stomach.

However, when we take all studies into consideration, the results are not univocal. Whitehouse *et al.* (1983) could not find any *in vitro* anti-inflammatory properties for *Harpagophytum* extract. At doses of over 100 times the recommended daily

dose for humans, devil's claw was completely ineffective in reducing either edema of the rat's hind paw, again induced by the pro-inflammatory agent λ-carrageenan, or in reducing adjuvant-induced arthritis. A rapid and effective reduction in edema was achieved by treatment with either indomethacin or acetylsalicylic acid. In another study, which used healthy human volunteers, no decrease in basal serum concentrations of prostaglandine (PG) E_2, PG $F_{1\alpha}$, thromboxane B_2 or leukotriene B_4 could be found after 3 weeks of oral intake of a *Harpagophytum* extract containing 3% glucoiridoids (Moussard *et al*., 1992). However, Loew *et al*. (2001) recently demonstrated a non-dose dependent decrease of the basal whole blood leukotriene level in healthy human subjects after oral administration of several doses of the *Harpagophytum* extract WS 1531, containing 9% harpagoside. No effect was seen on the thromboxane level.

A possible explanation for these contradictory results is the differences seen between studies in the composition of the *Harpagophytum* extracts tested and in analysis techniques that were used to measure the biological effects obtained. It is clear that there is some scientific evidence for anti-inflammatory activity of *Harpagophytum procumbens*, but it is also clear that not every extract is as potent. Since not all of the active substances have been identified, and since the action mechanism is only partially known, it is not possible to extrapolate test results to other (commercial) products. It is therefore necessary to clinically test every single product in order to obtain information on its effectiveness (Loew *et al*., 2001). In-depth chemical analysis of the available mixes would provide a clearer view of the trial results. Identification and quantification of active substances can be accomplished by using high performance liquid chromatography (HPLC). Clarkson *et al*. (2006) suggest two specific HPLC techniques for determining the constituents of powdered root material. Interestingly enough, although most scientific evidence is based on plant extracts, many commercial products – especially in the equine sector – consist of powdered roots.

Clinical trials

Several clinical studies involving human patients have been performed to test the pain relieving properties of *Harpagophytum procumbens*, mostly in patients with lower back pain or osteoarthritis of the knee and/or the hip joint. Again, it is difficult to compare the results of these studies with one another. There were many differences in the products studied (aqueous or ethanolic extracts, sometimes powdered root), and the dosage administered was reported either in milligrams of harpagoside or in milligrams of *Harpagophytum*.

The reliability and quality of some of these clinical trials have been investigated in detail by different research groups (Ernst and Chrubasik, 2000; Chrubasik *et al*., 2003a; Gagnier *et al*., 2004; Brien *et al*., 2006; Gagnier *et al*., 2007). The common denominator in all these reviews is the fact that clinical studies that evaluated the effect of *Harpagophytum* extracts on lower back pain gave evidence of reliability and good quality.

In 1996 Chrubasik *et al*. performed a trial in 118 patients with acute exacerbations of chronic back problems. The study took place over a 4-week period, during which half of the patients were treated with a placebo, and the other half received oral treatment with *Harpagophytum procumbens* extract. Although during the study no difference could be found between the two patient groups concerning the use of supplementary painkillers of the NSAID type, 9 out of 51 patients that received the extract were pain free at the end of the treatment, compared to only 1 out of 54 patients in the group that was given a placebo. A few years later the authors confirmed these results in another study, in which 197 patients with chronic susceptibility to back pain were treated with either a placebo or the *Harpagophytum* extract WS 1531. Patients in the group treated with the extract improved more than those in the placebo group, although the effect was not dose dependent (Chrubasik *et al*., 1999).

Both studies were reviewed by Gagnier *et al*. (2007) under the authority of The Cochrane Collaboration and within the scope of a larger project to determine the effectiveness of herbal medicine for non-specific low-back pain. The studies were deemed very valuable and scored high regarding quality. According to the study group, the combination of these two trials provides strong evidence that daily doses of an aqueous *Harpagophytum* extract are better than a placebo for obtaining short-term improvement of pain and a reduction of the use of classical pain relieving medication. Earlier on, Ernst and Chrubasik (2000) published similar conclusions based on their computerized literature searches and their evaluation of all relevant placebo-controlled, double-blind, randomized clinical trials of herbal analgesic remedies. The most important point of criticism of both Chrubasik studies is their short duration of 4 weeks and the fact that the extracts administered are not commercially available, which limits their external validity. Also, one of the trials had been performed in only one clinical referral center (Chrubasik *et al*., 2003a).

Göbel *et al*. (2001) reported a clear clinical efficacy of the *Harpagophytum* extract LI 174, marketed under the name Rivoltan®. They organized a randomized, double-blind, placebo-controlled study of 4 weeks duration of a group of 63 patients suffering from slight to moderate muscular tension or slight muscular pain in the back, shoulders and neck. This study received positive and medium ratings, respectively, in the reviews by Chrubasik *et al*. (2003a) and Gagnier *et al*. (2004). Rivoltan® was also tested in a study of 8 weeks duration, in which the preparation was administered to a group of 117 patients suffering from chronic back pain and in which significant clinical improvement was seen (Laudahn and Walper, 2001). No placebo

group was incorporated into this study, though, hence its limited value (Chrubasik *et al*., 2003a).

Another *Harpagophytum* extract, marketed under the name Doloteffin®, was compared with the COX-2 specific antagonist VIOXX® (rofecoxib) (Chrubasik *et al*., 2003b). This randomized double-blind study was done on 79 patients with lower back pain. Surprisingly, the analgesic score of the *Harpagophytum*-treated patient group was equivalent to that of the group of patients treated with the classical NSAID VIOXX®. However, the number of patients was too small to prove a definitive statistically significant equivalence between the two products (Gagnier *et al*., 2007).

Several clinical trials have been performed to evaluate the analgesic activity of *Harpagophytum* extracts in treating osteoarthritis of the knee or hip. Chrubasik *et al*. (2002) enrolled 250 patients suffering from non-specific low back pain or osteoarthritic pain in the knee or hip to check the analgesic qualities of the *Harpagophytum* extract Doloteffin®; 50 to 70% of these patients showed significant improvement by week 4, and even further improvement by week 8, when treated with this phytopharmacum. However, no placebo or NSAID control group was incorporated, which renders the results of the study less reliable (Chrubasik *et al*., 2003a). Because of the variety of clinical conditions and combinations of symptoms in the subjects, it is not possible to correctly assess the impact of devil's claw on those specific patients that had been diagnosed with osteoarthritis (Brien *et al*., 2006). Wegener and Lüpke (2003) confirmed the findings of the Chrubasik study. In a surveillance study of 12 weeks duration, conducted in 75 patients with arthrosis of the hip or knee, Doloteffin® was proven to have a clinically beneficial effect. Unfortunately, again no placebo group was incorporated. This, together with the rather small study group, makes the study less reliable (Brien *et al*., 2006).

Chantre, Leblan and co-workers performed a double-blind, randomized, multi-centre clinical study to test the efficacy of the *Harpagophytum* extract Harpadol® (Chantre *et al*., 2000; Leblan *et al*., 2000). The control group received the drug diacerhein, a so-called symptomatic slow-acting drug for osteoarthritis (SYSADOA). Unlike non-steroidal anti-inflammatory drugs, SYSADOAs do not give immediate relief, but rather act over a period of weeks to gradually reduce arthritis symptoms. In several countries they are not classified as drugs, but rather as food supplements, and their efficacy is still a source of controversy. Other examples of SYSADOAs are glucosamine sulphate, chondroitin sulphate and hyaluronic acid (Zhang *et al*., 2005). Diacerhein is known to ameliorate the course of osteoarthritis through inhibition of IL-1β synthesis (Rintelen *et al*., 2006). When Chantre and Leblan finalized their study of 4 months duration, they found that patients taking Harpadol® were using significantly less NSAIDs and analgesic drugs. They concluded that Harpadol® is comparable in efficacy and superior in safety to diacerhein. The downsides of the study are the small numbers of patients evaluated per referral center (30 centers for 124 patients) and a lack of transparency in the criteria used to incorporate patients into the study (Chrubasik *et al*., 2003a; Brien *et al*., 2006).

Szczepanski *et al*. (2000) treated 25 rheumatoid arthritis patients and 20 osteoarthritis patients with the *Harpagophytum* extract Pagosid®. For the first 2 weeks the extract was added to NSAIDs as a combined therapy, and for the next 4 weeks only Pagosid® was administered. There were no significant changes in pain perception during the period of treatment with Pagosid® alone. The authors concluded that *Harpagophytum* extract is a good alternative for NSAIDs. However, again no placebo group was incorporated and the study population was rather small.

To our knowledge, there is only one clinical study investigating the use of analgesic phytotherapeutics in horses (Montavon, 1994). Ten horses with tarsal osteoarthritis were treated with an herbal powder mix containing *Harpagophytum procumbens* and smaller quantities of *Ribes nigrum*, *Equisetum arvense* (horsetail) and *Salix alba*. The horses were treated once a day for 10 days a month during three consecutive months, getting an average daily dose of 20 grams of *Harpagophytum* powder over the entire month. The control group consisted of 10 horses that received 2 grams of phenylbutazone daily during three months. At the end of the study, the horses that were treated with the phytopharmaca showed significantly better locomotion scores in comparison to the NSAID-treated group. Moreover, the positive effects of the phytopharmaca seemed to linger on, even after cessation of the treatment. The author suggested that the anti-inflammatory properties of the herbs used are responsible for these prolonged effects. The small number of horses, the subjective visual assessment of locomotion quality and especially the lack of blinding make the results of this study unreliable.

Safety

None of the above described clinical studies mention the occurrence of significant side effects with the use of *Harpagophytum* extracts. However, most of the studies were carried out over a period of at most 8 weeks. The only study that had a longer duration was the Chantre and Leblan study, which lasted 4 months. They found the *Harpagophytum* extract to have fewer side effects than diacerhein (Chantre *et al*., 2000; Leblan *et al*., 2000). The most commonly documented side effects, when all clinical studies are taken into consideration, are mild gastrointestinal complaints and diarrhea (Chrubasik *et al*., 1999; Chantre *et al*., 2000; Leblan *et al*., 2000). In one study, rodents were treated for 21 days with a dose (7.5 g *Harpagophytum* / kg) far exceeding the dose regimen used for therapeutic treatment. No signs of toxicity were seen, but it must be added that there was also a lack of anti-inflammatory activity in this study (Whitehouse *et al*., 1983).

Conclusion

The evidence for the analgesic qualities of devil's claw is fairly limited. Most of the well-designed studies indicate that devil's claw appears to be effective in the reduction of pain in the lower back and in cases of osteoarthritis in man. At the moment, there are several *Harpagophytum* products available and both *in vitro* and *in vivo* studies indicate that the analgesic and anti-inflammatory properties differ between these products. Unfortunately, comparison of the results between products is rather difficult because of the variations in study design. In all clinical trials, the phytopharmacum has optimal effect in treatments of several weeks duration. There are no indications that the phytopharmacum is fit for treatment of acute pain. No major adverse effects were reported, but it has to be emphasized that no toxicity studies, as are required for conventional pharmaceuticals, were conducted. At the current time there is no sound scientific proof for the efficacy of *Harpagophytum* in horses. Extrapolation of the results in humans to horses is difficult, but the most likely indication for the use of *Harpagophytum* in horses might be for pain originating from (mild) degenerative joint disease, rather than for more overtly painful conditions such as chronic laminitis. More research is needed to clarify this matter.

Salix species or willow bark

Active components

The bark of willow trees (several *Salix* species, e.g. *Salix alba, Salix daphnoides*) is popular in western countries for the treatment of fever, rheumatic complaints and pain (Chrubasik *et al*., 2000; Biegert *et al*., 2004). In Canada, a number of livestock farmers are using it to treat conditions like diarrhea and mastitis (Lans *et al*., 2007). The bark of *Salix* contains variable amounts of the salicyl alcohol derivative salicin. Salicin has anti-inflammatory, antipyretic and analgesic properties similar to those of aspirin after it has been transformed into salicylic acid in the liver (Williamson, 2001). It is generally viewed as the active ingredient of *Salix alba* and therefore the salicin content is used to standardize *Salix* mixes. Besides salicin, a lot of other salicyl alcohol derivatives, flavonoids and tannins have been identified in willow bark (Kammerer *et al*., 2005) that probably contribute to the analgesic properties (Schmid *et al*., 2001a). Again, we are confronted with the issue of the heterogeneity of the herbal extracts used in clinical studies, for which reason Kammerer *et al*. (2005) proposed the application of HPLC for the analysis of herbal medicines, in order to ensure the comparability of the herbal mixes used in clinical trials.

Mechanisms of action

As previously mentioned, the medicinal properties of *Salix* extract have to be viewed as the sum of the synergistic effects of a series of constituents, including the well-known substance salacin. Fiebich and Chrubasik (2004) tested the anti-inflammatory properties of *Salix* extract by investigating the *in vitro* inhibitory effect of the bark extract on the lipopolysaccharide(LPS)-induced release of prostaglandine E_2 (PG E_2). They found evidence of a weak inhibitory effect on the production of PG E_2 and other pro-inflammatory cytokines such as tumor necrosis factor α, interleukin-1β and interleukin-6. No influence was seen on COX-1 or COX-2. Because of the known regulatory role of IL-β in the biosynthesis of matrix proteins, they suggested a possible cartilage protective activity for willow bark. Their finding that neither pure salacin nor acetylsalicylic acid exerted any effect on any of the above-mentioned pro-inflammatory cytokines is intriguing. Similar findings were reported by Giuliano and Warner (1999). This again underlines the fact that far from all the biologically active substances in this medicinal herb have yet been identified.

Unlike devil's claw, *Salix* extract seems to have a beneficial effect on both acute and chronic inflammatory processes. Khayyal *et al.* (2005) investigated the *in vivo* anti-inflammatory activity of the standardized willow bark extract STW 33-I in an acute and chronic rat inflammation model. The control animals received either pure acetylsalicylic acid, or the specific COX-2 antagonist celecoxib (Celebrex®). On a mg/kg basis, the extract STW 33-I was at least as effective as acetylsalicylic acid in reducing inflammatory exudates and in inhibiting leukocytic infiltration, as well as in preventing the rise in cytokines and prostaglandine. The extract was even more potent in reducing leukotriene production and inhibiting COX-2 response than acetylsalicylic acid. Another surprising result was the definite superiority of the extract to either acetylsalicylic acid or celecoxib in protecting the body against oxidative stress. According to Khayyal and co-workers (2005), the activity of the *Salix* extract surpassed acetylsalicylic acid on several occasions. This supports the hypothesis of the presence of synergistic components other than salicin and makes the estimation of the effective dosing in *in vivo* experiments, based on results of *in vitro* experiments, even more difficult. Wagner and Heide (2003) demonstrated an inhibitory effect of *Salix* extract on the *in vitro* production of inflammatory cytokines, in a manner consistent with Fiebich and Chrubasik (2004). However, when oral dosing was applied in human volunteers, none of these mediators were significantly inhibited. Apparently, the constituents responsible for the effect observed *in vitro* did not reach therapeutic levels in the body. Fiebich and Appel (2003) suggest that therapeutic levels are not achieved by a single dosing protocol, and propose multiple day treatment protocols instead. This hypothesis is supported by Chrubasik *et al*. (2000; 2003b), who emphasize that the beneficial effects of most phytotherapeutics gradually peak after several weeks of treatment.

Clinical studies

The analgesic efficacy of *Salix* extract on lower back pain and osteoarthritis in humans has been evaluated in several clinical trials. However, to our knowledge no trials have been performed on horses. The Chrubasik research group performed a trial of 4 weeks duration in a total of 210 patients suffering from chronic lower back pain (Chrubasik *et al*., 2000). They compared the number of pain-free patients in three study groups: one group received a low dose (120 mg) of *Salix* extract, one group received a high dose (240 mg) of *Salix* extract and a control group received a placebo. The number of pain-free patients after one week of treatment was already significantly higher in the high dose group. What was also significant is that the effect of the low dose was less pronounced and only became apparent after two weeks of treatment. This study was given a high quality score by the Gagnier review group (Gagnier *et al*., 2007). In another open, randomized, post-marketing study of 4 weeks duration, the Chrubasik research group compared the analgesic effects of the willow bark extract Assalix® to the selective COX-2 antagonist rofecoxib (VIOXX®) in a group of 228 patients with acute exacerbation of low back pain (Chrubasik *et al*., 2001). At the end of the study, there was no significant difference in effectiveness between the two treatments at the chosen dose. Surprisingly, the reported incidence of adverse effects was also similar in the two patient groups. Again, the quality of this study was positively evaluated by the Gagnier group (Gagnier *et al*., 2007). Schmid *et al*. (2001b) investigated the effect of high-dose *Salix* extract (240 mg salacin a day) on 39 patients with osteoarthritis of the knee or hip. They found that the *Salix* extract had a significant pain-relieving effect. However, although this study was placebo-controlled, the results have to be carefully interpreted because of the rather small study population.

In contrast to all the above-mentioned clinical studies, Biegert *et al*. (2004) could not find any effect of a high-dose *Salix* extract (240 mg salacin a day) when they compared its analgesic properties with diclofenac and placebo in 127 patients with osteoarthritis of the hip or knee and in 26 patients with rheumatoid arthritis. The design and outcome measures of this study were in accordance with all recommendations of the European Agency for the Evaluation of Medicinal Products (EMEA) and included all outcome measures recommended by the US Food and Drug Administration (Biegert *et al*., 2004).

Safety

The Chrubasik research group collected safety data from four different clinical studies, with a duration of 2-4 weeks and an overall total of 967 patients. The incidences of allergic skin reactions to willow bark extract, placebo and conventional treatment were 3%, 2% and 1%, respectively; the gastro-intestinal side effects were 3%, 6% and 2%, respectively, and other mild miscellaneous side effects were 2%, 4% and 4%, respectively (Chrubasik *et al*., 2003c). The occurrence of significant side effects resulting from the use of willow bark extract is minimal. Allergic reactions similar to acetylsalicylic acid allergy do seem to occur. In a Chrubasik study, one patient dropped out because of allergic symptoms (pruritus and swollen eyes), probably caused by the willow bark extract (Chrubasik *et al*., 2000). An anaphylactic reaction developed in a 25-year-old woman with asthma and a known allergy to aspirin, within 75 minutes of ingesting a dietary supplement containing willow bark extract (Boullata *et al*., 2003). The link between aspirin and willow bark allergy was also reported in a carpenter who experienced a widespread rash – similar to the rash he had previously developed with aspirin – when working with willow wood (Jennings, 2006).

Willow bark extract generally seems a safe option for treating osteoarthritic pain. However, it has to be noted that none of the clinical studies were performed over a protracted period of time (Marcus and Suarez-Almazor, 2003). Since the use of *Salix* extract is predominantly advocated for analgesic treatment of chronic degenerative joint diseases, more long-term clinical trials are needed. For example, the effect of long-term treatment on liver and kidney functioning and hematological parameters has to be evaluated. It is known that the combined use of phytotherapeutics with conventional medication sometimes leads to adverse effects (Heck *et al*., 2000). In one study (Krivoy *et al*., 2001), *Salix* extract had a significant effect on thrombocyte aggregation. Although the effect was much lower than that of a cardioprotective dose of acetylsalicylate, some issues do need to be elucidated concerning the use of *Salix* extract in patients with blood coagulation problems. It is also important to evaluate the safety of the use of *Salix* extract in patients treated with anti-coagulants such as warfarin (Krivoy *et al*., 2001).

Conclusion

It can be concluded that preparations containing willow bark extract have been tried with some success in the treatment of musculoskeletal disorders such as low back pain and osteoarthritis in humans. However, the number of clinical trials is still very limited and all positive results originated from the same research group. Therefore further studies are needed to establish the place of willow bark preparations in therapy. Nothing is known about the analgesic quality of *Salix* extract in horses, or about the safety of its use and bioavailability after oral ingestion. More research is needed before its use in horses can be advocated on the basis of scientific data.

Ribes nigrum or blackcurrant

Active components and mechanisms of action

An infusion of blackcurrant leaves (*Ribes nigrum*) is

traditionally used for the treatment of rheumatic disease. Several researchers have studied the anti-inflammatory effect of *Ribes* leaves, and the components responsible for the effect. Declume (1989) evaluated the anti-inflammatory effect of an ethanolic extract of *Ribes nigrum* on carrageenan-induced hind leg edema in rats. Both in the short-term treatment protocol in which rats received the extract only 30 minutes prior to carrageenan injection, and in the long-term treatment protocol in which rats received the extract for 21 days prior to carrageenan injection, was a dose dependent decrease seen in the development of hind leg edema. The results seen in the *Ribes* extract group were even comparable to those seen in the control group, in which the rats received the conventional anti-inflammatory drug indomethacin. Interestingly enough, none of the ten rats treated with extract for 21 days developed gastric ulceration. In the indomethacine group (n = 10), there was one case of gastric perforation (Declume, 1989).

When Tits and his co-workers (1992) analyzed *Ribes* extract by the use of HPLC, they demonstrated the presence of anti-inflammatory prodelphinidins and procyanidins. These compounds are part of the proanthocyanidines (PACs), a group of flavonoids known for their antibacterial and anti-inflammatory properties (Kontiokari *et al*., 2005). Garbacki *et al*. (2002) investigated the effect of several of these *Ribes* prodelphinidins on the production of proteoglycans, type 2 collagen and PG E_2 by human chondrocytes *in vitro*. They also evaluated the *in vitro* inhibitory potential of these prodelphinidins on COX-1 and COX-2 production in human whole blood. Although no significant results were obtained with the human whole blood experiments, human chondrocytes treated with *Ribes* extract showed significantly decreased PG E_2 and COX-2 production. When they tested the effect of PACs *in vivo* on carrageenan-induced paw edema and carrageenan-induced pleuritis in rats, they found a dose-dependent inhibitory effect on lung injury, pleural exudate formation, polymorphonuclear cell infiltration and pleural exudate levels of TNF-α, IL-1β and the acute phase protein CINC-1 (Garbacki *et al*., 2004). These researchers found evidence for different anti-inflammatory pathways for *Ribes* extract, compared to the NSAID indomethacin. It was thought that the main mechanism of the anti-inflammatory effect of proanthocyanidins probably lies in their interference with the migration of leukocytes. This was later confirmed by the same researchers, who found that PACs suppress polymorphonuclear cell infiltration during carrageenan induced pleuritis, by down-regulation of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). The research results also suggest that PACs modulate the production of vascular endothelial growth factor (VEGF). Therefore they might promote wound healing (Garbacki *et al*., 2005).

Lu and Foo (2003) and Kapasakalidis *et al.* (2006) performed a HPLC analysis on extraction residues of the berries of the blackcurrant. Both groups of researchers identified an array of polyphenols, several of which were part of the prodelphinidin group, indicating that not only the leaves but also the berries might have therapeutic potential.

Clinical studies

No clinical trials have been performed with *Ribes* extracts on humans or animals. In his *in vivo* experiment, Declume (1989) mentions a human posology of 20 ml of *Ribes* extract per day. This dose was probably chosen arbitrarily because nothing is known about the bioavailability and the metabolism of the extract. Although *Ribes nigrum* is found in several herbal mixes that are commercially available for horses, nothing is known about its analgesic properties in equids or about appropriate dosing.

CONCLUSION

Taking all the results of the above mentioned clinical trials into consideration, it seems that there is some evidence that at least two herbal products, namely *Harpagophytum* and *Salix* extract, reduce pain more than placeboes do in humans suffering from lower back pain or osteoarthritis. Concerning *Harpagophytum*, the same conclusions were made in a review by Grant *et al*. (2007). Unfortunately, almost nothing is known about the effect of these phyto-therapeutics in horses. The only study published so far did not provide reliable results. Although many commercialized herb mixes claim an analgesic effect in horses suffering from musculoskeletal diseases such as osteoarthrosis, podotrochleosis and back pain, more well-designed clinical trials in horses are needed to support these claims. Especially for the use of these phytotherapeutics in horses with laminitis, one cannot extrapolate results from human osteoarthritis studies, since chronic founder has a completely different pathogenesis than chronic degenerative joint disease.

An additional problem is the obscurity with which the producers of the herbal mixes handle their ingredient lists. Quite often the listing of the ingredients is limited to a summary of the names of the herbs included, without any indication of the quantity of each of them, or the percentages of active substances. Although nothing is known about the oral bioavailability of these products in horses, many manufacturers provide specific advice on the dosing of these mixes. However, when human dosing protocols are extrapolated to horses and subsequently compared to the composition of some of these veterinary mixes, the mixes often seem to contain subtherapeutic herbal quantities. Until now, even in human clinical trials there is no evidence of possible synergistic effects of mixed herbs, so if one wants to use herbs in horses, it would probably be better to use products based only on a single herb.

Since botanical medicines are claimed or perceived to have few side effects, they are often used on the

basis of the reasoning that “if it doesn’t do anything, then it won’t harm anything”. However, larger studies are required to ascertain the safety of these botanicals. Clearly, if a product does have a beneficial effect, then it must be influencing certain processes in the organism, and this fact implies that it can also provoke adverse effects. Although the side effects of phytotherapeutics appear to be primarily confined to mild, transient gastrointestinal complaints, some important side effects have been reported in humans. Extended safety studies should be executed, because many phytotherapeutics are used on a long-term basis. Many phytotherapeutics are marketed as a mix of several herbs, making it even more difficult to assess the safety of their use. Also, the safety of phytotherapeutics should be evaluated when they are used in combination with conventional medication, because this is often the case in practice.

In equine practice, phytotherapy is meeting the increasing demand of horse owners for "natural", gentle treatment methods. Though veterinary phytotherapy is as old as animal husbandry itself, the scientific basis for its use is insufficient. In this fast growing market, it is important for the veterinarian to adopt a critical attitude towards phytotherapeutics and to inform his clients of the lack of proof of their efficacy and safety.

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