

Pain Relief with a Proprietary Extract of Willow Bark in Rheumatology. An Open Trial.

Reinhard Saller¹, Jörg Melzer¹, Markus Felder², for the Swiss Assalix Study Group

¹ Institut für Naturheilkunde, UniversitätsSpital Zürich; ² Praxis für Rheumatologie, physikalische Medizin und Rehabilitation, Zürich, Schweiz

For approximately 2'000 years, the decoctions of the bark of the Salicaceae family have been used to treat pain, fever, and headaches. It contains salicin* which probably is the main active component 'per se', but also is a pro-drug. Salicin is stable under acidic conditions and in human saliva; β -glucuronidase activity and hydrolysis, however, convert salicin to saligenin which is further converted to salicylic acid in the liver by the cytochrome P-450 system. Peak plasma concentration of salicylic acid is found approximately three hours after oral administration of salicin. Other components are likely to contribute to the anti-inflammatory effects of the extract. Pharmacology and toxicology have been reviewed in detail elsewhere [1].

A randomised controlled trial (RCT) compared an extract of white willow to placebo in patients with chronic back pain (n=210); it reported that 39% of the patients were pain-free at a dose of 240 mg salicin vs. 21% pain free ones with 20 mg salicin and vs. 6% pain free patients with placebo [2]. Another study (n=228) compared the effects of a proprietary extract of willow bark (Assalix®, standardised to 15.2% salicin, i.e. 60 mg salicin per tablet) and a selective COX-2-inhibitor (rofecoxib, 12.5 mg) for low back pain. There was no significant difference in effectiveness between the two treatments at the doses chosen [3]. Willow bark ex-

Background: This is an observational study with a proprietary extract of willow bark (Assalix®) under conditions of daily practice in Switzerland. The scope of the study was to get a better estimate of the frequency of adverse events (and possibly identify unknown adverse reactions) and a broader picture of the efficacy. **Methods:** Any adult patient eligible for treatment with the proprietary extract of willow bark could be admitted to the trial. The study had a duration of 6–8 weeks, with an intermediate control visit after 3–4 weeks. Besides the customary demographic and anamnestic data, the variables assessed (intent to treat) were pain intensity, impairment of daily activities and global assessment of efficacy and tolerability. **Results:** 204 participating physicians treated 877 patients with different types of rheumatologic pain (Females 64.2%, age 58.76 \pm 15.69 years); 763 patients completed the study. The medical problem had persisted more than six months in 68% of the cases and 81.2% of the patients had already received another treatment. Additional anti-inflammatory drugs were co-prescribed in 39.3% of cases. The pain score at admission was 5.32 \pm 1.62 (on a scale of 0–9) and at last visit it was 2.51 \pm 2.04 (p<0.001); 'total pain relief' was reported by 14% of patients. While at admission 0.6% of the patients reported no impairment of daily activities, at last visit the proportion was 27.4%. Thirty-eight patients (4.3%) reported a total of 46 adverse events relating predominantly to digestive system (3.1%) and skin (1.6%). There were no 'serious' clinical adverse events. Adverse events were more frequent in cases receiving additional anti-inflammatory medication. **Conclusions:** The proprietary extract of willow bark (Assalix®) was well tolerated, with no unexpected adverse events identified. With the limitations inherent to the study design, it may be concluded that it was moderately effective as an analgesic in the management of dorsopathies, soft tissue disorders, inflammatory polyarthropathies and arthrosis.

Key Words: Willow bark, rheumatology, back pain, observational case series, safety, analgesia, herbal preparation

Schmerzlinderung in der Rheumatologie mit einem Weidenrinden-Spezialextrakt. Eine offene Studie.

Hintergrund: Bei der vorliegenden Studie handelt es sich um eine Anwendungsbeobachtung unter Praxisbedingungen in der Schweiz, durchgeführt mit einem Weidenrinden-Spezialextrakt (Assalix®). Ziel der Studie war es, eine bessere Einschätzung zur Häufigkeit von Nebenwirkungen (und möglicherweise die Identifizierung bisher nicht bekannter Nebenwirkungen) und zur Wirksamkeit zu erhalten. **Methoden:** In die Studie aufgenommen wurden Patienten im Erwachsenenalter, die aufgrund ihres Beschwerdebildes für eine Behandlung mit dem Extrakt geeignet waren. Die Studiendauer betrug 6–8 Wochen, wobei eine Kontrolle nach 3–4 Wochen erfolgte. Neben den üblichen demografischen und anamnestic Daten wurden die Variablen (Intent-to-treat) Schmerzintensität, Beeinträchtigung im täglichen Leben sowie globale Beurteilung von Wirksamkeit und Verträglichkeit erhoben. **Ergebnisse:** Die 204 teilnehmenden Ärzte behandelten 877 Patienten mit unterschiedlichen rheumatisch bedingten Schmerzen (Frauen 64,2%, Alter 58,76 \pm 15,69); 763 Patienten konnten die Studie abschliessen. In 68% der Fälle betrug die Dauer der Beschwerden mehr als 6 Monate und 81,2% der Patienten hatte bereits eine andere Medikation erhalten. Eine anti-inflammatorische Comedikation erfolgte bei 39,3% der Patienten. Der Schmerz-Score betrug 5,32 \pm 1,62 (auf einer Skala von 0–9) zu Studienbeginn und bei der letzten Konsultation 2,51 \pm 2,04 (p<0,001); völlige Schmerzfreiheit wurde von 14% der Patientinnen berichtet. Während zu Studienbeginn lediglich 0,6% der Patienten über keine Beeinträchtigungen in ihrem täglichen Leben berichteten, waren dies bei der Schlussvisite 27,4%. 38 Patienten (4,3%) berichteten über insgesamt 46 unerwünschte Wirkungen, die vorwiegend das Verdauungssystem (3,1%) und die Haut (1,6%) betrafen. "Ernsthafte" Nebenwirkungen wurden nicht beobachtet. Nebenwirkungen traten häufiger unter der anti-inflammatorischen Comedikation auf. **Schlussfolgerungen:** Der untersuchte Weidenrindenextrakt (Assalix®) wurde gut vertragen, unerwartete Nebenwirkungen traten keine auf. Unter Berücksichtigung des Studiendesigns kann festgestellt werden, dass der Extrakt eine moderat analgetische Wirksamkeit bei Dorsopathien, Weichteilrheuma, entzündlichen Polyarthropathien und bei Arthrose besitzt.

Schlüsselwörter: Weidenrinde, Rheumatologie, Rückenschmerzen, Anwendungsbeobachtung, Sicherheit, Analgesie, Pflanzenzubereitung

* White Willow Bark – Potentially Active Chemical Constituents: Glycosides (1.5–11%): salicylates (salicin, salicortin, populin, fragilin, tremulacin); Tannins (8–20%); Aromatic aldehydes and acids: salidroside, vanillin, syringin, salicylic acid, caffeic and ferulic acids; Salicylic alcohol (saligenin); Flavonoids.

tract also showed a moderate analgesic effect in osteoarthritis (n=78), as compared to placebo [4]. These results were not confirmed with an other proprietary extract of willow bark (n=43) in an RCT [5] against placebo (n=41) and against diclofenac (n=43). Only diclofenac was superior to placebo in this trial (WOMAC-Index, SF-36, global assessment).

The study presented herein is an open, descriptive, observational case series study with a proprietary extract of willow bark (Assalix®) under conditions of daily practice in Switzerland ("Praxiserfahrungsbericht"). The scope of such studies [6] is to obtain information about prescription modalities, acceptability, medication compliance, to get a better estimate of the frequency of adverse events (and possibly identify rare hitherto unknown adverse reactions) and to get a broader picture of the efficacy (e.g. inclusion of subgroups not studied in earlier trials).

Methods

This is an open trial with a proprietary extract of willow bark (Assalix®); the approved indications in Switzerland* are: "Rheumatic troubles such as neck pain, lower back pain and dorsalgia". The study was conducted according to ethical standards and regulatory requirements at that time in force.

Patient selection and treatment

We enrolled patients from 204 physicians in Switzerland. Any adult patient eligible for treatment with the proprietary extract of willow bark according to the approved indications could be admitted to the trial.

The study duration was 6–8 weeks, with an intermediate control visit after 3–4 weeks. Besides the customary demographic and anamnestic data including concomitant diseases and treatments, the variables recorded are shown in **table 1**. No blood chemistry, coagulation nor haematology data were recorded.

Statistics

An intention-to-treat (ITT), last observation carried forward (LOCF) approach

Tab. 1. Variables assessed in the trial

Type of data	Variables
Ordinal	<ul style="list-style-type: none"> ■ Duration of disease (< 3 months, 3–6 months, > 6 months) ■ Duration of pain episodes (continuous, recidivating prolonged episodes, short bursts) ■ Pain triggered by (pain on weight bearing, initial pain, nocturnal pain) ■ Impairment of daily activities (absent, mild, evident, important, very important) ■ Additional analgesic medication ■ Global assessments of tolerability and efficacy: <ol style="list-style-type: none"> 1. vs. previous treatment (much better, better, equal, worse, much worse than previous treatment) 2. of current treatment (very good, good, moderate, nihil)
Continuous	<ul style="list-style-type: none"> ■ Pain intensity absent – unbearable pain (scale with 10 numerical boxes)

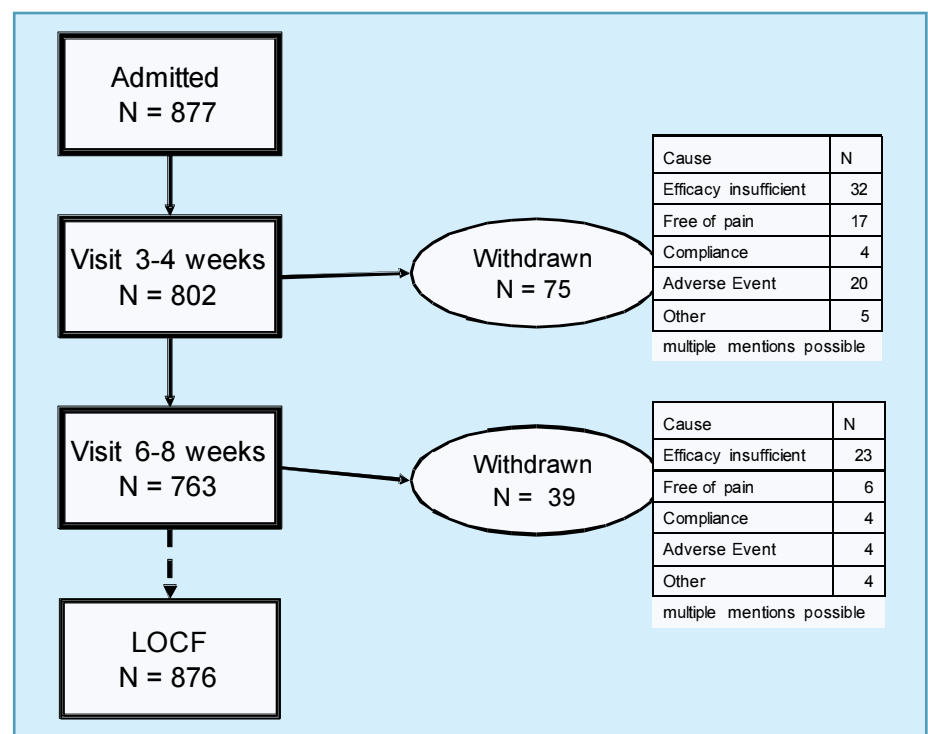


Fig. 1. Study flow.

was used in all appropriate analyses in all the cases having had at least one control visit. Missing values were replaced by the LOCF method; variables assessed only once were not replaced in the analysis. The safety population, defined as subjects who received at least one dose of the study drug and for whom post-dose data were available, were used in the analysis and evaluation of the safety variables.

Statistical analysis was performed with WinSTAT® Version 2001.1 for Excel. The continuous data are presented as means, standard deviations (SD),

and number of subjects; categorical data are presented using counts and percentages. For illustration, final data are compared with the corresponding values at baseline. Unless stated otherwise, values before vs. after treatment were compared by means of the Students-'t'-test, or the χ^2 -test for nominal or ordinal data. In the case of large or significant differences in the t-Test, a confirmatory non-parametric analysis was performed. All P values were two-

* Indications in Germany include fever, headaches, rheumatism (Rheumatoid arthritis, etc.)

Tab. 2. Rheumatologic diagnoses, grouped (ICD-10)

ICD-10	Descriptor	n	%
M05–M14	Inflammatory polyarthropathies	86	9.8
M15–M19	Arthrosis	385	44.0
M40–M54	Dorsopathies (mainly "other dorsopathies")	309	35.3
M60–M79	Soft tissue disorders	94	10.7
M80–M94	Osteopathies and chondropathies	1	0.1
	No data	2	0.2
Total		877	100.0

Tab. 3. Medications before the study and concomitant additional medications (n=number of drugs prescribed; multiple mentions possible)

	Before trial (n / %)	Additional (n / %)
NSAID	652 / 74.3	255 / 29.1
COX-2-Inh	230 / 26.2	78 / 8.9
Opioids	93 / 10.6	61 / 7
Corticosteroids	19 / 2.2	11 / 1.3
Benzodiazepines	31 / 3.5	17 / 1.9
Immunosupr.	15 / 1.7	18 / 2.1
Herbal Analg.	9 / 1	7 / 0.8
Other	47 / 5.4	23 / 2.6
No Data	6 / 0.7	1 / 0.1
Medicated	712 / 81.2	345 / 39.3
No medication	165 / 18.8	532 / 60.7
Total	877 / 100	877 / 100

Tab. 4. Mean pain score during the trial

Pain scale 0–9	Mean	SD	n
Admission	5.32	1.62	876
Week 3–4	3.15	1.87	836
Week 6–8	2.27	1.85	749
LOCF Pain	2.51	2.04	877
Difference LOCF-T0	-2.81	2.11	876

tailed, and $P < 0.05$ was considered statistically significant. No formal statistical analysis of safety data was performed.

Results

The 204 participating physicians treated 877 patients with different types of rheumatologic pain (Females 64.2%, males 35.8%, age 58.76 ± 15.69 years); 763 patients completed the study

(figure 1). The troubles had persisted more than six months in 68% of the cases and 81.2% of the patients had already received another treatment. Pain was described as 'continuous' by 46.4% of the patients while only 16.2% described pain in 'short bursts'. In most cases (76.8%) the pain was triggered by weight bearing. The diseases of the musculoskeletal system and connective tissue treated with this willow bark extract are summarized in table 2; in about two thirds of the cases the prescription was 'off-label' (Swiss approved labelling). The most common premedications and additional medications were NSAIDs and COX-2-inhibitors (co-prescribed in 39.3% of the cases; table 3).

The pain score at admission was 5.32 ± 1.62 (on a scale of 0–9) and at last visit (LOCF) it was 2.51 ± 2.04 ; that is, reduced by -2.81 ± 2.11 points (table 4, $p < 0.001$). Total analgesia was reached in 123 (14%) of the patients;

they reported 'total pain relief' for the first time after 30.01 ± 18.86 days. Also the impairment of daily activities improved markedly; while at admission only 0.6% of the patients reported no impairment, at last visit (LOCF) the proportion had increased to 27.4% (figure 2). Regarding the mean ratings of pain or the percentage reporting 'total pain relief' at the end of trial, by main category of disease, there are no notorious differences between diagnoses (table 5). However, arthrosis fared somewhat worse than the other diagnoses, a difference which becomes more evident when restricting the analysis to patients without additional medication (table 6).

Frequently, the more severe cases received an additional medication. At baseline, patients receiving additional anti-inflammatory therapy differed from those without in that they had a higher pain score (5.49 ± 1.62 vs. 5.20 ± 1.62 ; $p < 0.02$), more frequent 'severe' or 'very severe' impairment of daily activities (39.8% vs. 30.1%; $p < 0.01$), and enclosed more chronic cases (>6 months, 81.4% vs. 60.9%) and, consistently, more cases with previous treatment (96.5% vs. 71.4%). These differences in pain score and impairment of daily activities persisted at the end of the trial and the global assessment of efficacy was less favourable in patients with additional anti-inflammatory therapy ('good' or 'very good' = 56.8% vs. 75.2%; $p < 0.01$) and fewer patients had attained 'total pain relief' (5.8% vs. 19.4%; $p < 0.01$). For corrected influence of additional medication on outcomes, see below: exploratory analysis (predictors of response).

Compared with the previous treatment, 55.3% of the patients considered the proprietary extract of willow bark (Assalix®) to be "better" or "much better" regarding efficacy and 68.1% reported tolerability to have been "better" or "much better". The global assessments of the proprietary extract of willow bark were "good" or "very good" for efficacy in 65.8% of the cases and for tolerability in 92.4% of the cases (figures 3, 4).

While 62% of the patients decided to continue treatment with the proprietary extract of willow bark after the

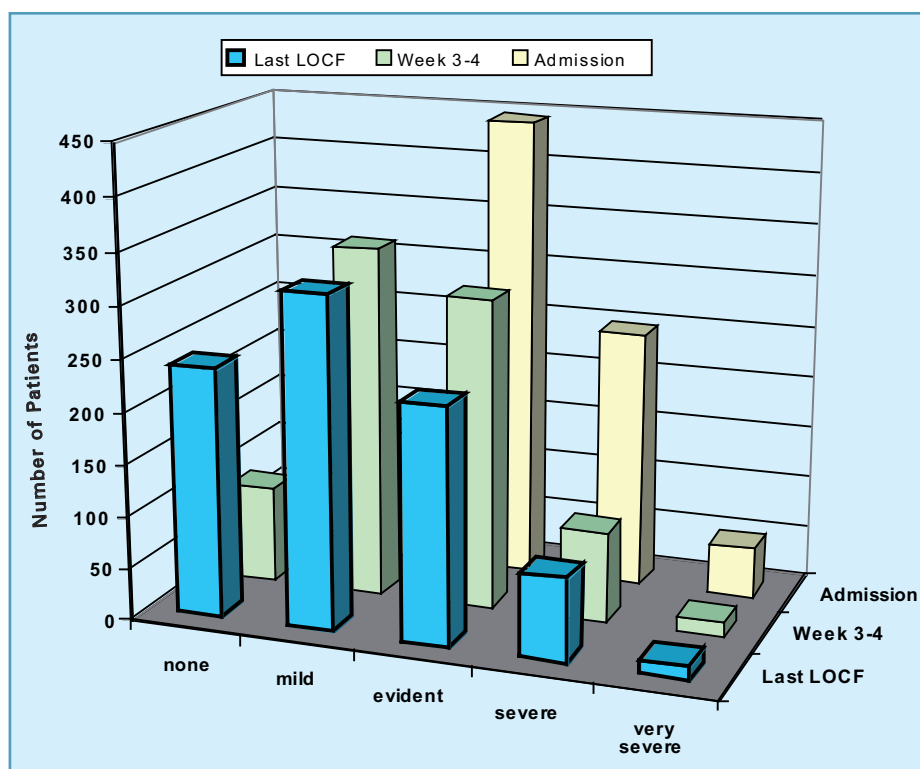


Fig. 2. Impairment of daily activities at admission, at interim and at last visit.

end of the study period, the remaining patients opted for a discontinuation, mainly because of insufficient efficacy (15.2%), absence of pain (11.3%) or poor tolerability (1.8%).

Thirty-eight (4.3%) patients reported a total of 46 adverse events relating predominantly to the digestive system (3.1%) and the skin (1.6%). Only abdominal pain (1.1%) and nonvesicular rash (1%) reached the 1% threshold. There were no 'serious' adverse events. In 30 cases treatment was discontinued, although only 5 patients reported the adverse events as being 'severe'. The investigators considered the adverse event as being 'certainly' or 'probably' treatment-related in 27 cases. No cases of cross-sensibilisation with salicylates have been reported [7]. The detailed adverse events reported during the trial, stratified by patients with or without co-medication (table 7), show that particularly abdominal pain

Tab. 5. Mean rating of pain (SD) and % of asymptomatic patients at the end of trial, by main category of disease of the musculoskeletal system

	Soft tissue disorders n = 94	Dorsopathies n = 309	Arthrosis n = 384	Inflammatory polyarthropathies n = 86
Admission	5.52 (1.63)	5.41 (1.63)	5.21 (1.58)	5.28 (1.68)
Week 3-4	3.14 (2)	3.15 (1.89)	3.07 (1.75)	3.49 (2.1)
Week 6-8	2.5 (2.07)	2.2 (1.78)	2.26 (1.79)	2.32 (1.98)
LOCF	2.67 (2.17)	2.48 (2.04)	2.48 (1.96)	2.55 (2.18)
Difference LOCF-T0	-2.85 (2.15)	-2.93 (2.09)	-2.73 (2.03)	-2.73 (2.49)
% 'total pain relief' *	19.1% (11.2, 27%)	14.6% (10.7, 18.5%)	11.5% (8.3, 14.7%)	16.3% (8.5, 24.1%)
% no impairment *	25.5% (16., 34.3%)	31.4% (26.2, 36.6%)	23.4% (19.2, 27.6%)	31.4% (21.6, 41.2%)

* = (95% CI)

Tab. 6. Patients without additional medication, mean rating of pain (SD) and % of asymptomatic patients at the end of trial, by main category of disease of the musculoskeletal system

	Soft tissue disorders n = 68	Dorsopathies n = 182	Arthrosis n = 235	Inflammatory polyarthropathies n = 49
Admission	5.49 (1.62)	5.43 (1.71)	5.12 (1.58)	5.29 (1.73)
Week 3-4	3.03 (2.05)	3.16 (1.98)	3.09 (1.73)	3.23 (1.98)
Week 6-8	2.33 (2.06)	2.19 (1.88)	2.37 (1.8)	2.16 (2.08)
LOCF	2.5 (2.15)	2.52 (2.16)	2.56 (1.94)	2.47 (2.29)
Difference LOCF-T0	2.99 (2.27)	-2.91 (2.16)	-2.56 (1.9)	-2.82 (2.69)
% 'total pain relief' *	23.5% (13.43, 33.63%)	15.9% (10.63, 21.23%)	10.2% (6.31, 14.11%)	20.4% (9.11, 31.71%)
% no impairment *	29.4% (18.61, 40.21%)	32.4% (25.62, 39.22%)	20.9% (15.65, 26.05%)	36.7% (23.23, 50.23%)

* = (95% CI)

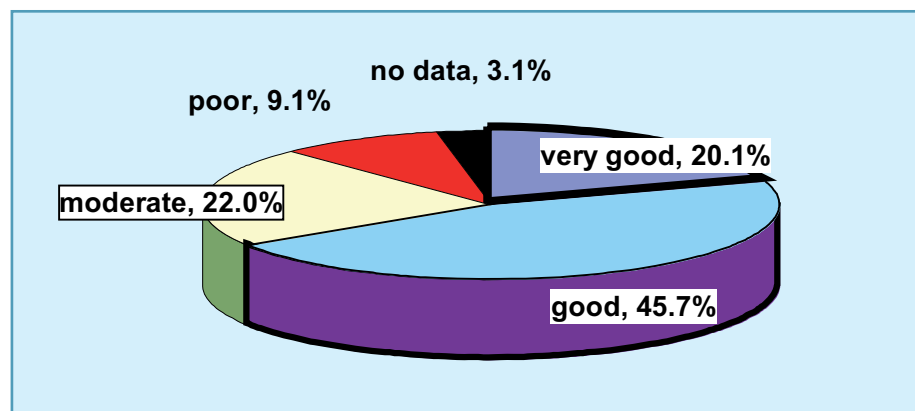


Fig. 3. Global assessment (last visit) of efficacy.

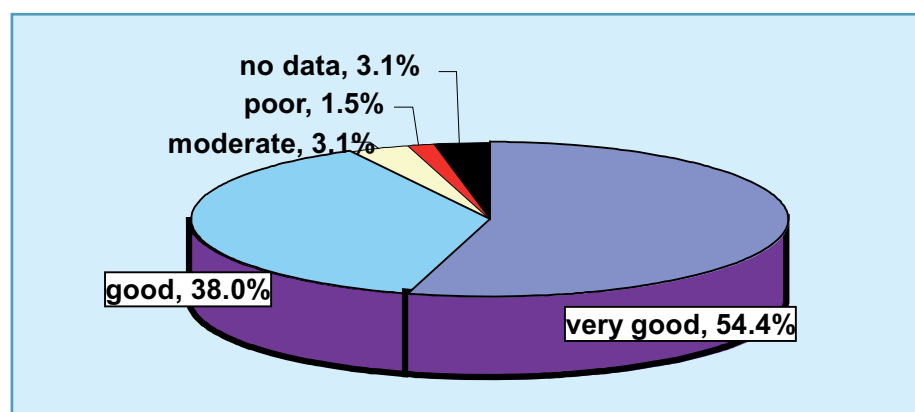


Fig. 4. Global assessment (last visit) of tolerability.

and diarrhoea were more frequent in patients with co-medication. It should be remembered that no laboratory data were recorded in this trial.

Exploratory analysis Predictors of response

Regarding the outcomes of pain reduction (Diff. LOCF – T0) and of reduction of impairment of daily activities in a stepwise regression model, it was possible to assess factors which are likely to influence these outcomes (table 8). The model included as independent variables the main diagnostic categories gender, age, duration of the disease since diagnosed, duration of the pain episodes, severity of pain (scale 0–9) and of impairment of daily activities (scale 0–4), daily dose of willow bark extract, and whether the patient had previous treatment or additional treatment. Pain reduction (Diff. LOCF – T0) and reduction of impairment of daily activities, were both favoured by

higher ratings at start, by a recent onset of the disease, by the additional administration of another analgesic or anti-inflammatory drug and by having pain in short episodes or bursts. The advantage of being younger or male was not consistent; that is, significant for one outcome but not the other.

Dose-effect relationship

Regarding the changes in pain assessments and in impairment of activities – restricted to patients in the two main diagnostic categories, without co-medication and with an initial pain-score of 5 or higher, the higher dose of 3–4 tablets daily was somewhat more effective than the lower dose. Only in patients with arthrosis did the difference between doses of mean pain reduction reach the threshold of significance: Mean pain reduction with 3–4 tablets/day –3.79 (2.1) points vs. –3.09 (2.13) score points with 1–2 tablets/day ($p=0.047$). In the case of dorsopathies, the

corresponding values were –4.15 (2.22) vs. –3.5 (2.59) score points, respectively ($p=0.128$).

Discussion

The present study with a proprietary extract of willow bark (Assalix®) confirmed the favourable tolerability of this preparation. Only 4.3% of the patients reported non-serious adverse events relating to the digestive system (3.1%), the skin (1.6%) or non-specific general symptoms (0.6%). These adverse events were more frequent in patients receiving additional anti-inflammatory medications (5.5% vs. 3.1% without co-medication). Being a descriptive, observational (case series) study, it was more likely to require statistical adjustments because of the potential for larger covariate imbalances than in randomised trials. From the point of view of efficacy, soft tissue disorders and dorsopathies fared somewhat better than arthrosis, particularly regarding ‘total pain relief’ and absence of impairment of daily activities at the end of the study. Globally, efficacy is moderate, with 14% of the patients reporting ‘total pain relief’ for the first time after one month of treatment. Nevertheless, 55.3% of the patients considered the proprietary extract of willow bark (Assalix®) to be “better” or “much better” than the previous treatment regarding efficacy. The global assessments were “good” or “very good” for efficacy in 65.8% of the cases and for tolerability in 92.4% of the cases. The global assessments correlated well with the changes in pain rating ($Rho=0.63$) and the rating of impairment of daily activities ($Rho=0.61$). The more severe cases received an additional anti-inflammatory medication which improved significantly the corrected outcomes in rating of pain and impairment of daily activities (regression analysis). Both pain reduction and improvement of daily activities were also favoured by higher ratings at start, by a recent onset of the disease and by having pain in short episodes or bursts. However, placebo effects plus disease’s natural history and regression to the mean can result

Conclusions

In this open observational study, the proprietary extract of willow bark (Assalix®) was well tolerated, without new or serious adverse events identified. With the limitations inherent to the study design, it may be concluded that it was moderately effective as an analgesic in the management of dorso-pathies (mainly “other dorso-pathies”), soft tissue disorders, inflammatory polyarthropathies, and arthrosis. A positive outcome was favoured by a recent onset of the disease, by the addition of another anti-inflammatory drug and by having pain in short episodes or bursts. An increase of the daily dose to 4 tablets is likely to be more effective than the currently recommended dose of 2 tablets per day. Adequate RCTs are needed to confirm this.

in high rates of good outcomes, which may be misattributed to specific treatment effects [8,9]. The higher dose of 3–4 tablets daily was somewhat more effective than the lower recommended dose of 1–2 tablets daily. While it would be premature to draw any conclusions from these findings in view of the limited significances and the observational nature of the trial, it may be of interest as a hypothesis for future trials with the product. For other proprietary ethanolic extracts of willow bark (Assplant® Robugen) a daily dose of up to 240 mg salicin is already recommended. The findings are in line with those of GAGNIER et al. [10] that “there is moderate evidence that a daily dose of 240 mg salicin from an extract of *Salix alba* reduces pain more than either placebo or a daily dose of 120 mg of salicin in the short term for

individuals with acute episodes of chronic non-specific low-back pain.

One of the problems of observational studies as the one presented here is the absence of a placebo control group. The true causes of improvements in pain after treatment remain unknown in the absence of independently evaluated randomized controlled trials [11]. In patients with chronic low back pain it has been shown, for example [12], that high and moderate levels of psychopathology are associated with heightened placebo analgesia (total pain relief 23.5% vs. 7.7% in patients with low psychological symptomatology).

Tab. 7. Adverse events reported during the trial, stratified by patients with or without co-medication

Term	With co-medication n = 345	No co-medication n = 488	All combined* n = 877
Abdominal pain, unspec.	6 (1.7%)	4 (0.8%)	10 (1.1%)
Rash, nonvesicular, unspec.	3 (0.9%)	5 (1%)	9 (1%)
Diarrhoea NOS	4 (1.2%)	1 (0.2%)	5 (0.6%)
Nausea	1 (0.3%)	1 (0.2%)	4 (0.5%)
Constipation, unspec.	4 (1.2%)	0 (0%)	4 (0.4%)
Urticaria, unspec.	1 (0.3%)	2 (0.4%)	3 (0.3%)
Dyspepsia	2 (0.6%)	0 (0%)	2 (0.2%)
Pruritus, NOS	0 (0%)	0 (0%)	2 (0.2%)
Other adverse events (1 diagnosis each)	3 (0.9%)	3 (0.6%)	7 (0.8%)
N adverse events (AE)	24	16	46
N Patients with AE (%)	19 (5.5%)	15 (3.1%)	38 (4.4%)

* = includes cases without data on co-medication

Tab. 8. Predictors of pain reduction and of improvement of daily activities (Diff. LOCF – T0), stepwise regression analysis

Independent variable	Dependent variable: Pain		Dependent variable: Daily activities	
	P	Pain reduction larger in cases	P	Activities improved more in cases
Duration of disease	<0.001	of recent onset	<0.001	of recent onset
Additional treatment	<0.001	with additional medication	<0.001	with additional medication
Pain at T0	<0.001	with more pain at start	<0.001	with more pain at start
Pain episodes	=0.001	with pain in short bursts	=0.001	with pain in short bursts
Pre-treated	ns	na	=0.004	with pre-treatment
Age	ns	na	=0.049	younger patients
Gender	0.039	males	ns	na

ns = not significant, na = not analysed

Acknowledgement

This study was in part supported by a grant from BIONORICA, Germany.

Conflict of interest notification

Competing interests: None declared.

References

1. März R, Kemper F. Willow bark extract – effects and effectiveness. Status of current knowledge regarding pharmacology, toxicology and clinical aspects [in German]. *Wien Med Wochenschr* 2002;152:354–359.
2. Chrubasik S, Eisenberg E, Balan E, Weinberger T, Luzzati R, Conrath C. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. *Am J Med* 2000;109(1):9–14.
3. Chrubasik S, Kunzel O, Model A, Conrath C, Black A. Treatment of low back pain with a herbal or synthetic anti-rheumatic: a randomized controlled study. *Willow bark extract for low back pain. Rheumatology (Oxford)* 2001; 40(12):1388–1393.
4. Schmid B, Ludtke R, Selbmann HK, Kotter I, Tschirdewahn B, Schaffner W. et al. Effectiveness and tolerance of standardized willow bark extract. Randomized, placebo-controlled double-blind study [in German]. *Z Rheumatol* 2000;59:314–320.
5. Biegert C. Eine randomisierte, kontrollierte klinische Studie zur Wirksamkeit und Verträglichkeit eines standardisierten Weidenrinde-extraktes in der Behandlung von Cox- und Gonarthrosen. <http://w210.ub.uni-tuebingen.de/dbt/volltexte/2003/1006/>
6. Victor N, Windeler J, Hasford J, Köpcke W, Linden M, Michaelis J, Röhmel J, Schäfer H. Empfehlungen zur Durchführung von Anwendungsbeobachtungen (Recommendations concerning the conduct of "Anwendungsbeobachtungen") der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS). [Ergebnis eines Expertengesprächs am 8. Oktober 1996].
7. Boullata JI, McDonnell PJ, Oliva CD. Anaphylactic reaction to a dietary supplement containing willow bark. *Ann Pharmacother* 2003; 37(6):832–5.
8. Ernst E, Resch KL. Education and debate: Concept of true and perceived placebo effects *BMJ* 1995;311:551–553 ,
9. Moerman DE, Jonas WB. Deconstructing the placebo effect and finding the meaning response. *Ann Intern Med* 2002;136:471–476.
10. Gagnier JJ, vanTulder M, Berman B, Bombardier C. Herbal medicine for low back pain. *The Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD004504.pub3. DOI: 10.1002/14651858.CD004504.pub3.
11. Turner JA, Deyo RA, Loeser JD, von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. *JAMA* 1994;271:1609–1614.
12. Wasan AD, Kaptchuk TJ, Davar G, Jamison RN. The association between psychopathology and placebo analgesia in patients with discogenic low back pain. *Pain Medicine* 2006;7(3):217–228.

Address for correspondence:

Reinhard Saller, MD, Professor
University of Zurich, University Hospital
Department of Internal Medicine
Institute of Complementary Medicine
Raemistrasse 100, CH-8091 Zurich
reinhard.saller@usz.ch