Treatment of Low Back Pain Exacerbations with Willow Bark Extract: A Randomized Double-Blind Study

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PURPOSE: Herbal medicines are widely used for the treatment of pain, although there is not much information on their effectiveness. This study was designed to evaluate the effectiveness of willow (*Salix*) bark extract, which is widely used in Europe, for the treatment of low back pain.

SUBJECTS AND METHODS: We enrolled 210 patients with an exacerbation of chronic low back pain who reported current pain of 5 or more (out of 10) on a visual analog scale. They were randomly assigned to receive an oral willow bark extract with either 120 mg (low dose) or 240 mg (high dose) of salicin, or placebo, with tramadol as the sole rescue medication, in a 4-week blinded trial. The principal outcome measure was the proportion of patients who were pain-free without tramadol for at least 5 days during the final week of the study.

RESULTS: The treatment and placebo groups were similar at baseline in 114 of 120 clinical features. A total of 191 patients completed the study. The numbers of pain-free patients in the last week of treatment were 27 (39%) of 65 in the group receiving high-dose extract, 15 (21%) of 67 in the group receiving low-dose extract, and 4 (6%) of 59 in the placebo group ($P < 0.001$). The response in the high-dose group was evident after only 1 week of treatment. Significantly more patients in the placebo group required tramadol ($P < 0.001$) during each week of the study. One patient suffered a severe allergic reaction, perhaps to the extract.

CONCLUSION: Willow bark extract may be a useful and safe treatment for low back pain. **Am J Med. 2000;109:9–14.**

Extracts of the bark of *Salix* (willow) species have been used for fever, mild rheumatic complaints, and pain, including mild headache. The extract is available in various forms (hydroalcoholic or aqueous extracts, dried, or as tinctures or solutions). A principal active ingredient is salicin, which is the prodrug of various salicylate derivatives (1). The European Scientific Cooperative on Phytotherapy, which summarizes the use of herbal medicines in Europe, published a monograph on willow bark in 1997 (2). The monograph recommends adult doses of various extracts that are equivalent to a maximum of 240 mg of salicin per day, but a German monograph from 1984 (Bundesanzeiger Nr. 228, December 5, 1984) recommends no more than half of that dose. The aim of this study was to compare the effectiveness and safety of the two recommended doses in alleviating exacerbations of low back pain. We used the same protocol that we had used to study the effectiveness of another plant extract (*Harpagophytum procumbens*) in the treatment of low back pain (3).

MATERIAL AND METHODS

The study was approved by the Human Ethics Committee of the Rappaport Faculty of Medicine, Technion, Haifa. We enrolled patients suffering from exacerbations of chronic low back pain with or without radiation to one or both legs. We performed a three-group, randomized, double-blind comparison of the effectiveness and adverse effects of 4 weeks of oral treatment with one of two doses of a standardized willow bark extract (120 or 240 mg salicin per day) or placebo. Patients were allowed tramadol as the only rescue medication. The prospectively chosen principal outcome measure was the proportion of patients free of pain without the use of tramadol for at least 5 days in the final week of treatment. Secondary outcomes were the proportion of patients requiring tramadol and the change from baseline in a modified version of the Arhus Low Back Pain Index (4).

The estimated minimum number of patients required in each group was 70, based on having at least 90% power to detect differences in the proportions of pain-free patients from 5% in patients receiving placebo to 15% in those receiving daily doses of willow bark extract with 120 mg salicin and to 25% in those receiving 240 mg, at an alpha of 0.05 to reject the null hypothesis of no dose-related trend, as detected with a one-tailed Cochrane-Armitage test.

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Public advertisements were used to recruit suitable patients from the Haifa area between May and November 1998. Participants were required to be between the ages of 18 and 75 years; have at least 6 months of at least intermittent low back pain that was not attributable to identifiable causes, such as disc prolapse, hip disease, spondylolisthesis, osteomalacia, or inflammatory arthritis; and have a current exacerbation of their complaint at rest and with movement that caused pain of at least 5 of 10 on a Visual Analog Scale and that was expected by the patients and their physicians to require at least 4 weeks of treatment. We excluded patients with current or recent (within 30 days) participation in any other clinical study; a serious illness; a history of drug or alcohol abuse, or requirement for psychotherapeutic agents; pregnancy, lactation, or unreliable contraceptive practice; a known allergy to any of the proposed trial medications; or difficulties with language or anticipated cooperation. An account of the study and an invitation to participate (conditional on the results of an assessment in clinic) was given to patients who met these criteria. The first 210 who gave written consent were enrolled. The patients were randomly assigned to one of the three groups by a computerized list.

At enrollment, patients completed a questionnaire about their general health, daily activity, and the characteristics of their pain. They underwent a physical examination and were asked to give a venous blood sample for screening laboratory tests. They also underwent the questioning and examination required for completing the Arhus score, which was modified for this study by the exclusion of the items relating to analgesic medications, as patients were allowed only tramadol as rescue medication. The modifications gave the score a maximum value of 120: 60 for pain, 30 for disability, and 30 for physical impairment.

The study medication contained approximately 0.153 mg of salicin per mg of extract (as quantified using high-pressure liquid chromatography) and was manufactured by Plantina GmbH Munich, Germany. Patients received coded trial medication, which consisted of pairs of identical red sugar-coated pills to be taken twice daily for 4 weeks. In the placebo group, both pills were lactose. In the low-dose (extract equivalent to 120 mg salicin per day) group, one pill contained 393.24 mg dry willow bark extract and the other lactose. In the high-dose group, both pills contained 393.24 mg dry extract. The identity of the tablets was concealed from both the patients and the investigators. Patients were allowed to supplement their trial medication with tramadol liquid (2.5 mg/mL) in doses up to 400 mg per day.

Once a week, patients were contacted by telephone to determine whether they had, or did not have, pain, as well as the doses of rescue medication on each day of the preceding week. The investigator also recorded the occurrence of adverse events by asking if the patient's well-being had been affected by the medication. Patients were encouraged to keep taking the study medication. At the end of the 4-week study period, the modified Arhus scoring was repeated.

The principal outcome measure was the proportion of patients who responded to treatment by being pain-free without tramadol for at least 5 days during the last week. The principal analysis of effectiveness was performed on an intention-to-treat basis, with patients who did not complete the study considered as nonresponders. A two-tailed Cochrane-Armitage test was applied to the null hypothesis that there was no monotonic increase in the proportion of responders with higher daily doses of willow bark. We also repeated the analysis excluding patients who did not complete the study. Categoric data were examined in contingency tables, using Fisher's exact test. Ordinal or continuously distributed data were summarized as median and quartiles, and compared with the Kruskal-Wallis or Mann-Whitney-Wilcoxon tests. A two-tailed Jonkheere-Terpstra test was used to examine for monotonic dose-related effect on the Arhus score and tramadol requirement. All analyses were performed with the Statistical Analysis System Software (SAS Institute Inc., Cary, North Carolina). Statistical significance was set at $P < 0.05$ (two-sided).

RESULTS

Equal numbers of patients were enrolled in the placebo group, the low-dose group, and the high-dose group (Table 1). The groups had similar age, height, weight, and sex, but some of their characteristics, in particular those related to pain, differed at baseline. An additional set of >100 features, including indicators of general health, professional, and employment status; physical activity; further details of the low back pain; and results of attempted treatments, is available at www.ukl.uni-freiburg.de/rechtmed/salix.html. Of these 110 features, only 6 differed statistically (at $P < 0.05$) among the three groups, including those shown in Table 1. The groups receiving willow bark extract were not favored: for example, more of the patients in the high-dose group reported low back pain that had persisted for >6 years, and they also had a greater overall Arhus low back pain score than the patients receiving placebo. The Beck scores for depression also tended to be greater in the high-dose willow bark extract group. The other characteristics of the participants were similar in the three groups. Specific causes were generally difficult to identify; the most common causes suggested by the participants' physicians were arthrosis, spondylosis, scoliosis, and disc protrusion. About 20% of all patients had a positive straight-leg raising test, and 94% had normal reflexes. About 2% had some motor impairment, and 11% had some sensory deficit. Vital signs were well matched.

Table 1. Characteristics and Features of the Pain in Participants at Enrollment

Characteristics	Placebo (n = 70)	Willow Bark Extract		*P* Value*
		Low Dose (n = 70)	High Dose (n = 70)	
	Number (Percent) or Median (25^{th}, 75^{th} Percentiles)			
Age (years)	56 (43,68)	55 (46,63)	58 (45,72)	0.28
Height (cm)	168 (160,172)	170 (160,176)	165 (160,172)	0.14
Weight (kg)	73 (67,85)	79 (68,90)	75 (63,85)	0.32
Male sex	29 (41)	35 (10)	32 (46)	0.61
Duration of low back pain ≥6 years	39 (56)	46 (66)	53 (76)	0.05
Duration of present complaints				0.65
≤7 days	11 (16)	9 (13)	6 (9)	
>7 days	10 (14)	7 (10)	10 (14)	
>90 days	49 (70)	54 (77)	54 (77)	
Radiation into leg(s)	54 (77)	53 (76)	51 (73)	0.88
Neurologic signs				
Deficits in straight leg raising	15 (21)	12 (17)	14 (20)	0.78
Motor deficit	1 (1)	2 (3)	1 (1)	1.0
Sensory deficit	5 (7)	10 (14)	7 (10)	0.42
Normal reflexes	68 (97)	64 (91)	65 (93)	0.16
Beck depression inventory	6 (2,10)	7 (5,10)	8 (5,14)	0.02
Modified Arhus low back pain score				
Total	67 (54,84)	80 (65,103)	88 (69,108)	<0.001
Pain	34 (24,44)	40 (25,56)	44 (28,57)	0.010
Invalidity	18 (14,23)	23 (17,26)	24 (17,27)	<0.001
Physical impairment index	18 (12,24)	22 (16,30)	24 (18,30)	<0.001

*The *P* values indicate a "significant" difference among the groups, presumably due to chance (see text).

The trial was completed by 191 (91%) of the 210 patients: 8 patients (7 in the placebo group and 1 in the high-dose willow bark group) dropped out because of insufficient pain relief, 4 (1 in the placebo group, 1 in the low-dose group, and 2 in the high-dose group) because of noncompliance for unspecified reasons, 2 (in the high-dose group) because they left the area unexpectedly, 2 (in the placebo group) because of gastrointestinal complaints, 1 (in the low-dose group) because of an allergic reaction, 1 (in the low-dose group) because of laboratory-confirmed anemia, and 1 (in the placebo group) who complained of adverse effects related to tramadol intake.

The principal outcome was defined as response to therapy (pain free without tramadol for at least 5 days in the fourth week of treatment). There were 4 (6%) responders in the placebo group, 15 (21%) in the low-dose group, and 27 (39%) in the high-dose group (Table 2, $P < 0.001$). Similar results were seen when drop-outs were excluded (Table 3). Of the 61 patients with neurologic deficits at baseline, 16 (26%) responded to therapy (1 of 18 in the placebo group, 7 of 22 in the low-dose group, and 8 of 21 in the high-dose group). The proportion of responders who had pain radiating into one or both legs at baseline was also greater in the treatment groups (4 [7%] of 54 in the placebo group, 13 [25%] of 53 in the low-dose group, and 21 [41%] of 51 in the high-dose group, $P < 0.001$).

A significant increase in the proportion of responders in the high-dose willow bark group was apparent after only 1 week of treatment and became progressively greater during the 4 weeks of treatment (Figure). The smaller effect seen in the low-dose group was significantly different from placebo by the second week (Tables 2 and 3). In all 4 weeks of the study, significantly more patients in the placebo group required tramadol (Tables 2 and 3). The median relative change in the overall Arhus score was significantly greater in the high-dose than in the low-dose willow bark group (Tables 2 and 3). The change in the overall Arhus score was also seen in each of its individual components (Tables 2 and 3).

Adverse reactions were scrutinized by an independent investigator. There was only one case of allergy (exanthem swollen eyes, pruritus) that could be attributed to willow bark extract (in the low-dose group). This patient's symptoms resolved 2 days after discontinuation of treatment. Two patients with short-lasting adverse events in the high-dose group (dizziness attributed to tramadol, dizziness and fatigue) later dropped out—one because of insufficient pain relief and the other for unspecified reasons. The adverse events reported by 6 patients in the placebo group were mild: in 3 cases, the patients attributed them to the tramadol (dizziness/headache, dizziness/vomiting/diarrhea, dry mouth); the remaining 3 pa-

Table 2. Comparison of the Efficacy of Willow Bark Extract (Low Dose, High Dose) with Placebo: Intention-to-Treat Analysis*

Outcomes	Placebo (n = 70)	Willow Bark Extract		*P* Value†
		Low Dose (n = 70)	High Dose (n = 70)	
	Number (Percent) or Median (25th, 75th Percentile)			
Pain free				
Week 1	2 (3)	1 (1)	6 (9)	0.10
Week 2	5 (7)	9 (13)	17 (24)	0.004
Week 3	6 (9)	10 (14)	26 (37)	<0.001
Week 4	4 (6)	15 (21)	27 (39)	<0.001
Requiring tramadol				
Week 1	45 (64)	21 (30)	16 (23)	<0.001
Week 2	35 (50)	14 (20)	6 (9)	<0.001
Week 3	35 (50)	12 (31)	7 (10)	<0.001
Week 4	33 (47)	10 (14)	3 (4)	<0.001
Percentage decline in modified Arhus score				
Total	0 (−13,5)	44 (18,60)	54 (19,90)	<0.001, 0.02
Pain	0 (−9,13)	40 (0,63)	67 (24,100)	<0.001, <0.001
Invalidity	0 (−14,23)	46 (12,78)	57 (0,89)	<0.001, 0.40
Physical Impairment	0 (−15,0)	27 (0,75)	41 (0,86)	<0.001, 0.77

* In this analysis, patients who dropped out were considered to have continued pain and to require tramadol rescue medication; Arhus scores were set to the initial values for dropouts.

† *P* value refers to the two-sided Cochrane-Armitage test for a trend for proportions, or for a two-sided Jonekheere test for a monotonic increase with dose. The second *P* value in the pair refers to the two-sided Mann-Whitney-Wilcoxon test comparing the low-dose with high-dose willow bark groups.

tients suffered from mild abdominal pain with or without diarrhea, 2 of whom discontinued the study on the first day of treatment.

DISCUSSION

It has recently been claimed that herbal medicines are not scientifically tested (5). However, a systematic review of 19 randomized placebo-controlled double-blind studies found that herbal anti-inflammatory drugs are more effective than placebo in the treatment of osteoarthritis and rheumatic pain (6). Although the mechanism of effect has not been identified in detail, all of the botanic agents that were reviewed inhibit the biosynthesis of prostaglandins and leukotrienes, and some also have antioxidant effects (6). Our study confirms previous reports (7,8) that willow bark extract (standardized to yield 240 mg of salicin) is effective in treating pain. We observed a dose-dependent analgesic effect of the willow bark extract, even although patients in the high-dose group had more severe and prolonged pain at baseline.

Willow bark extracts in Germany have to comply with the "Deutsches Arzneibuch" (1), which guarantees a salicin content greater than 1% and that the extract is free of microorganisms and heavy metals. Measurement of radioactivity is also required because of possible contamination from nuclear exposure (9); the cesium 137 radioactivity of the extract that we used was below 5 bq/kg. The European Scientific Cooperative on Phototherapy monograph places no restriction on the duration of the willow bark treatment, and has not found evidence of toxic effects, although it is recommended that the use of *Salix* preparations be avoided in patients who are sensitive to salicylates. Whereas acetylsalicylic acid may cause irreversible inhibition of platelet aggregation, blood coagulation is only slightly affected by willow bark extract with 240 mg salicin (10). In accordance with general medical practice in the use of salicylic acid derivatives, the extract should not be used during pregnancy and lactation without medical advice, as safety data are not available.

Musculoskeletal pain, including low back pain, is the most common chronic pain syndrome in industrial countries (11–15). Many therapeutic interventions for low back pain were recently assessed in a systematic review (16). Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective for the treatment of uncomplicated acute low back pain, but if the pain has persisted for longer than 3 months, there is less evidence for their efficacy. Other types of treatment for chronic low back pain (eg, epidural steroid injections, manipulation, back school, exercise, and behavioral therapy)

Table 3. Comparison of the Efficacy of Willow Bark Extract (Low Dose, High Dose) with Placebo: Drop-Outs Excluded

Outcomes	Placebo (n = 59)	Willow Bark Extract		*P* Value†
		Low Dose (n = 67)	High Dose (n = 65)	
	Number (Percent) or Median (25th, 75th Percentiles)			
Pain free				
Week 1	2 (3)	1 (1)	6 (9)	0.12
Week 2	5 (8)	9 (13)	17 (26)	0.007
Week 3	6 (10)	10 (15)	26 (40)	<0.001
Week 4	4 (7)	15 (22)	27 (42)	<0.001
Requiring tramadol				
Week 1	45 (76)	21 (31)	16 (25)	<0.001
Week 2	35 (54)	14 (21)	6 (9)	<0.001
Week 3	35 (59)	12 (18)	7 (11)	<0.001
Week 4	33 (56)	10 (15)	3 (5)	<0.001
Percentage decline in modified Arhus score				
Total	−3 (−16,11)	46 (29,62)	57 (29,92)	<0.001, 0.01
Pain	0 (−11,29)	44 (0,63)	73 (41,100)	<0.001, <0.001
Invalidity	0 (−20,31)	46 (17,79)	64 (8,90)	<0.001, 0.24
Physical Impairment	0 (−33,0)	31 (7,75)	48 (0,90)	<0.001, 0.55

* *P* value refers to the two-sided Cochrane-Armitage test for a trend for proportions, or for a two-sided Jonekheere test for a monotonic increase with dose. The second *P* value in the pair refers to the two-sided Mann-Whitney-Wilcoxon test comparing the low-dose with high-dose willow bark groups.

may help some patients (16). As most of our patients had suffered painful exacerbations lasting longer than 3 months, the response rate of about 40% with the larger dose of willow bark extract makes it a worthwhile option to consider.

Willow bark contains the prodrug salicin, which is rapidly and completely metabolized after oral administration, with salicylic acid as the main metabolite (8). The salicylate metabolites may contribute to the effects of willow bark extract (17), but cannot be responsible for all of them. Serum salicylate concentrations during treatment suggest that a daily consumption of 240 mg of salicin as extract is bioequivalent to consumption of about 50 mg of acetylsalicylate (8,18), which is a cardioprotective rather than an analgesic dose. Other ingredients of the extract may contribute to the overall analgesic effects. For example, lipoxygenase-inhibiting (19) and antioxidative (20,21) components have been identified.

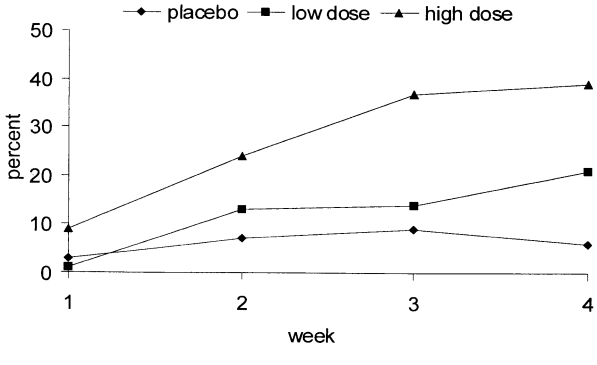

Figure. Percentage of patients who were pain free without rescue medication in weeks 1 to 4 in the placebo, and in the low-dose and high-dose willow bark groups.

Oral analgesic medications (11,22), especially NSAIDs (22), are commonly prescribed and used for the treatment of pain. However, adverse effects of NSAIDs on the gastrointestinal tract, especially bleeding and perforation, have been estimated to account for at least 7,600 deaths and 76,000 admissions to the hospital each year in the United States alone. These complications occur especially in patients at high risk because of advanced age, use of corticosteroids, previous gastrointestinal diseases, and large doses of NSAIDs (23). Coprescription of gastroprotective agents or the use of selective cyclooxygenase (COX)-2 inhibitors are effective in reducing the rates of gastrointestinal complications, but at a substantial increase in cost (24–26). The low incidence of adverse events observed in this and other studies (2,7,8) suggests willow bark extract may be an effective alternative, especially in patients who cannot tolerate NSAIDs.

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