Willow Bark: A High Potency Extract for Pain Management

Many species of Salix are used medicinally, especially Salix alba, S. daphnoides, S. purpurea and S. fragilis. Recent clinical trials indicate that a high potency willow bark extract (HPWBE) has analgesic activity but with fewer side effects than standard drug treatments. Pharmacokinetic studies have demonstrated that this activity cannot be due to salicin alone and other yet unidentified constituents and mechanisms are probably responsible.

Traditional Uses
Dioscorides in the 1st century prescribed willow bark to patients suffering from rheumatism. The antipyretic effect of willow bark was reported in detail for the first time by Edward Stone in 1763 (see below in Clinical Studies). Willow bark was traditionally used for inflammatory disorders such as rheumatism, gouty arthritis and ankylosing spondylitis. It was also considered to be a tonic, astringent bitter and an antiperiodic (antimalarial) useful for dyspepsia, chronic mucous discharges, influenza, fevers, convalescence from acute diseases, worm infestation, chronic diarrhea and dysentery, neuralgia, mild headache and passive hemorrhages. During the 18th and 19th centuries in America, willow bark was commonly recommended as a febrifuge. Native Americans also used willow bark for lumbago and as a poultice for headache. It was noted in 1876 that native South Africans had long used willow bark for treating rheumatic diseases.

Scientific Studies
Constituents
Willow bark contains salicin and salicin esters (including salicortin, 2'-O-acetylsalicortin, fragilin (2'-O-acetylsalicin) and tremulacin), other phenolic glucosides, flavonoids, polyphenols, oligomeric procyanidins and condensed tannins. The total salicin content (after hydrolysis) varies according to the species: S. daphnoides and S. fragilis (2-10%), S. purpurea (3-8.5%) and S. alba (0.5-1%). Salicin is a phenolic glucoside consisting of the aglycone saligenin (also known as salicylic alcohol) and glucose (see the diagram below).

The Differing Pharmacologies of the Salicylate Derivatives
Many articles seem to regard willow bark as a kind of herbal aspirin. But there are important differences between the salicylate compounds in willow bark and aspirin, as can be seen from the chemical diagrams below.

In terms of pharmacology, aspirin is a potent inhibitor of COX-1 and COX-2 because it causes irreversible acetylation of COX, which completely inactivates this enzyme system. Aspirin therefore has potent analgesic and anti-inflammatory activities (COX-2) but also can cause gastric damage and inhibit platelet function (COX-1).

Platelet function is affected by the inhibition of production of thromboxane A2 (a prostaglandin) by COX-1. Because aspirin irreversibly inactivates COX by acetylation and because platelets cannot make new proteins such as COX (no nucleus), the effect of aspirin persists for the life of the platelet (7 to 10 days). Even low doses of aspirin can therefore have profound blood-thinning effects.

Unlike aspirin, salicylic acid has virtually no inhibitory effect on isolated COX-1 or COX-2. However it can inhibit PG synthesis in intact cells. This means that salicylic acid or sodium salicylate will have little antiplatelet (blood thinning) effects – they lack the acetyl group. However a high dose of salicylic acid will still irritate the stomach, but this is because it is a phenol, not because of any effects on COX.

Although it has little direct effect on COX-2 once it is formed, salicylic acid could exert anti-inflammatory and analgesic activity by inhibiting COX-2 induction. Recently, it has been reported that aspirin and sodium salicylate equipotently suppress COX-2 induction at therapeutic concentrations. Also salicylates appear to have direct analgesic effects in the CNS by unknown mechanisms.

Salicin, the major salicylate compound in willow bark, effectively delivers salicylic acid into the bloodstream, but it does this in a unique way. Salicin is carried unchanged (and hence is stomach friendly) to the distal ileum or colon where gut flora remove the sugar and convert it into salicyl alcohol. The salicyl alcohol is absorbed and oxidized in the blood, tissue and liver to give salicylic acid. Salicin provides a more sustained release of salicylate than sodium salicylate itself.

To investigate the differing actions of willow bark and aspirin, 35 patients were given either willow bark extract (HPWBE delivering 240 mg of salicin per day) or placebo under double-blind conditions. Another 16 patients were given 100 mg of aspirin per day. The maximum arachidonic-acid-induced platelet aggregations were as follows:

- willow bark: 61.0 (± 21.6)%
- placebo: 78.0 (± 15.4)%
- aspirin: 12.7 (± 9.1)%

The inhibitory effect of willow bark extract on platelet aggregation was far less than aspirin and only marginally stronger than placebo (but was still statistically significant),
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> p=0.04). This means that willow bark is not a substitute for aspirin for blood thinning. However, since the mild effect was significant it should be used cautiously (under close supervision) with warfarin and NSAIDs.

The likelihood is that it is not just the salicylate compounds in HPWBE which contribute to its analgesic activity. A study involving 10 healthy volunteers found that a dose of a high potency willow bark extract (providing 240 mg/day of salicin) resulted in blood salicylate levels of around 1.4 (g/mL). In contrast, blood salicylate levels of 35 to 50 (g/mL) have been reported after taking just 500 mg of aspirin. Clearly the clinically-observed analgesic effects from willow bark (see later) must come from more than just the effects of salicyle.

Based on research on willow bark and related herbs it has been suggested that lipooxygenase and hyaluronidase inhibition and free radical scavenging effects, all from other components in willow bark, contribute to the overall analgesic effect. This means that many of the side effects, interactions and contraindications for aspirin, such as interactions with methotrexate, spironolactone and frusenide, are unlikely to apply for willow bark.

Pharmacodynamics

Clinical use of willow bark as an antipyretic and analgesic was documented from 1763-1803 and by the mid-19th century active principles were being isolated from it and herbs with similar activity: salicin from willow bark (1826-1829), salicylaldehyde from Spiraea ulmaria (meadowsweet, 1831) and methyl salicylate from wintergreen (Gaultheria spp., 1843). Salicylic acid was prepared from these isolated constituents (1835-1843) and in 1874 a factory was set up for its large scale production. The activity of salicylic acid was confirmed clinically for the treatment of rheumatic disorders in 1876. In the same year successful treatment with salicin was described for 8 patients with acute and subacute rheumatism. Unfortunately salicin was overlooked and salicylic acid remained the focus of pharmaceutical attention. As the use of salicylic acid and its salts increased, the problem of severe gastric side effects became more evident. The German pharmaceutical company Bayer began looking for a version of salicylic acid with a better side effect profile and between 1893 and 1897 Felix Hoffman developed an improved way of producing acetylsalicylic acid. He tested it on his father whose chronic arthritis improved markedly. In 1899 acetylsalicylic acid was commercially released with the name aspirin. Despite the early reports, adverse reactions to aspirin were largely ignored until the 1950s. The irony is that salicin, which is inactive until it travels past the stomach, is a much gentler substance. So too is willow bark extract.

Anti-inflammatory Activity

Saliclates have been shown to reduce prostaglandin levels in body tissues through an inhibition of cyclooxygenase in inflamed tissues (i.e. COX-2). Salicin, other constituents and willow bark extract did not inhibit prostaglandin synthesis from sheep seminal vesicles. Salicin and salicortin produced a marginal inhibition of lipooxygenase. Hexane extract of willow bark inhibited COX-1 and COX-2 by greater than 60% in an in vitro assay. However, clinical studies suggest that willow bark extract does not cause the gastrointestinal side effects of NSAIDs.

Tremulacin demonstrated anti-inflammatory activity, inhibited peritoneal leukocyte migration and writhing response in several experimental models (via injection) and inhibited leukotriene B4 biosynthesis in vitro. Salicin inhibited the spasmodic action of prostaglandin F2a on isolated rabbit non-pregnant myometrium. Tremulacin also inhibited contraction of isolated ileum induced by histamine or 5RS-A (slow-reacting substance of anaphylaxis — now defined as a group of leukotrienes) and inhibited the release of these substances from isolated tissue and cells. Metabolites of salicin and tremulacin have demonstrated anti-inflammatory activity in vitro.

Other Activity

Willow bark extract has demonstrated antioxidant activity in several in vitro systems, including the scavenging of free radicals. Unlike aspirin and sodium salicylate, salicin did not suppress lymphocyte transformation in vitro.

Pharmacokinetics

Salicin derivatives (e.g. salicortin, tremulacin) are first converted into salicin in the stomach or small intestine. Salicin is then mainly carried to the distal ileum or colon where gut flora convert it into its aglycone (salicylic alcohol). Salicylic alcohol is absorbed and oxidized in blood, tissue and liver to form salicylic acid. Salicylic acid is then converted to salicylic acid conjugates or to gentisic acid by hepatic transformation for excretion via the urine. From the excretion data it was concluded that 86% of an administered dose of salicin was absorbed. A 4-gram oral dose of salicin was rapidly metabolized, reaching a peak plasma level of salicylate in just under 2 hours. This peak plasma level was maintained for several hours. Comparison of the salicylate plasma levels obtained from both sodium salicylate and salicin demonstrated that the curve for salicin is slightly lower and flatter, indicating a greater half-life for salicin. The maximum plasma concentration of free salicylate from 4 g of salicin was 100 μg/mL, whereas 2 g of sodium salicylate yielded 150 μg/mL.

Toxicology

There is no information available on the toxicology of willow bark. The toxicity of salicylates is well documented. An overdose resulting from acute ingestion of 6.5-9.5 g of aspirin usually produces a serum salicylate level of 300 μg/mL or greater. From the pharmacokinetic study given previously, more than 50 g/day of salicin would need to be ingested in order to achieve this blood level of saliclate.

Clinical Studies

Pain Relief

The following clinical trials were conducted using a potent extract of willow bark standardized for salicin content (HPWBE). In most cases S. daphnoides and S. purpurea were prescribed, although any species of willow could be used provided the full spectrum of phytochemicals is present and sufficient salicin content is provided.

A small, randomized, double-blind, pilot study involving 21 patients indicated a clinically relevant analgesic effect from 2160 mg/day of willow bark (HPWBE), containing 240 mg/day of salicin, taken over a 2-week period. The mean reduction in the WOMAC pain score was significantly greater in the willow bark group compared to placebo (40% vs 18%). The WOMAC (Western Ontario and McMaster Universities) Osteoarthritis Index is a test questionnaire which assesses symptoms and functional disability in patients with knee and hip osteoarthritis.

A trial of double-blind, placebo-controlled design involving 78 patients tested the efficacy of a potent willow bark extract for osteoarthritis of the knee and/or hip joint. After a wash-out period of 4 days, patients received 1360 mg/day of HPWBE or placebo for 2 weeks. The active treatment corresponded to an intake of 240 mg/day of salicin, the identical-looking placebo consisted of cellulose and lactose. An analgesic effect was observed by monitoring the change in the WOMAC pain index.
The pain score of the WOMAC index was reduced by 14% from baseline values after 2 weeks' treatment with willow bark, compared to an increase of 2% in the placebo group. This difference was significant (p<0.05). Adverse effects were reported less frequently in the willow bark group than from those taking placebo. The patient diary VAS (visual analogue scales) on pain and physical function confirmed the positive result for willow bark extract and the final overall assessments (by patients and investigators) showed the superiority of willow bark extract over placebo. The analgesic effect of willow bark was mild, estimated to be 40% lower than standard NSAID treatment over the same time period (documented WOMAC pain score reduction after diclofenac treatment of 150 mg/day). However, the analgesic effect from HPWBE could increase with longer treatment times (see below).

A randomized, double-blind, three-group trial compared oral treatment with one of two doses of HPWBE or placebo (lactose) over 4 weeks. A total of 191 patients with chronic low back pain completed the study. The primary outcome measure was the proportion of patients who were pain-free, without having taken the rescue analgesic medication tramadol, for at least 5 days during the final week of the study. The numbers of pain-free patients in the last week of treatment were 39% in the high-dose group (1600 mg/day of extract containing 240 mg of salicin), 21% in the low-dose group (800 mg/day of extract containing 120 mg of salicin) and 6% in the placebo group. In addition, significantly more patients in the placebo group reported tramadol during each week of the study than those taking HPWBE (p<0.001). A dose-dependent analgesic effect was therefore observed for the HPWBE, even though patients in the high-dose group had more severe and prolonged pain at baseline. A significant response in the high dose group was evident after only one week of treatment and the smaller effect seen in the low-dose group was significantly different from placebo by the end of the second week. One patient in the low-dose group exhibited a severe allergic reaction which was attributed to willow bark extract.

A postmarketing surveillance study confirmed the efficacy of HPWBE (containing 240 mg/day of salicin for 4 weeks) in the treatment of low back pain. Forty percent of patients were pain-free at the end of the treatment period irrespective of whether or not they received additional conventional treatments.

An open, randomized, postmarketing study compared a potent HPWBE with rofecoxib (Vioxx, a selective COX-2 inhibitor) in patients with acute exacerbations of low back pain. After 4 weeks' treatment there was no difference between the two products in terms of pain, need for additional analgesics or side effects. Each group consisted of 114 patients who received either 1600 mg of HPWBE containing 240 mg/day of salicin or 12.5 mg/day of rofecoxib.

Other Conditions
On 25 April 1763 Reverend Edward Stone, an Oxfordshire clergyman, submitted a comprehensive report to the Royal Society in London indicating he had found, by clinical experience, that the bark of the willow tree was efficacious in the treatment of a variety of fevers. He described 50 cases treated for ague (fever) and intermittent disorders and stated that the results were uniformly satisfactory. He administered 20-60 grains (1.3-3.9 g) of dried, powdered bark every 4 hours to patients. Further medical reports on willow bark's antipyretic and analgesic effects emerged in Europe from 1772 to 1803.

Personal Experience and Clinical Feedback Study
The pain-relieving effects of HPWBE seem remarkable and I first approached this product with a degree of healthy scepticism. However, results in my clinic do confirm that it is an effective treatment for low back pain and arthritic pain (especially small joint arthritis).

With the support of a few colleagues I initiated a clinical feedback trial on the use of HPWBE (4 tablets/day) for arthritis and low back pain. To date, I can report on the striking results for 11 patients, given in the figure below.

Pain was rated on a scale of 1 to 10, with 10 being pain of an incapacitating nature. Background pain refers to the general level of constant pain and worst pain refers to the intensity of the worst pain episodes. Use of conventional analgesics is given as tablets per week.

The Importance of Phytoequivalence
To match the remarkable results of these clinical trials, it is necessary to match the products and doses used in the trials. Obviously similar doses of salicin need to be taken. But other components in HPWBE clearly contribute to the analgesic effect. So to achieve the same efficacy in pain management, the full phytochemical profile of any HPWBE should closely match the...
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profile of the extract used in the trials. This is a fundamental aspect of the concept known as phytoequivalence.

Clinical Summary for HPWBE

Actions: Anti-inflammatory, analgesic, antirheumatic, antipyretic.

Therapeutic Indications
- Temporary relief of acute or chronic musculoskeletal pain including low back pain, osteoarthritis, rheumatoid arthritis; other inflammatory conditions such as bursitis.
- Temporary relief of mild headache.

Dosage & Administration
ESCP recommends HPWBE containing up to 240 mg of salicin per day for adults. Clinical trial results suggest that 800-1600 mg/day of a suitably prepared HPWBE should be administered (at a dosage containing 120-240 mg/day of salicin), with a pain relieving effect observed by the end of the first week for the high dose and by the second week for the lower dose.

Suggested Combinations
Willow bark extract could be combined with other anti-inflammatory herbs such as Boswellia, celery seed, turmeric and ginger, and with St John’s wort for neuralgia and shingles.

Adverse Reactions
Salicin, being a glycoside derived from salicyl alcohol, is less irritant to the mucous membranes than actual salicylates (salicylic acid derivatives). Unlike aspirin, willow bark extract is expected to have very mild effects on platelet function. Clinicians should be aware of the possibility of Reye’s syndrome, an acute sepsis-like illness encountered exclusively in children below 15 years of age. The cause is unknown, although viral agents and drugs, especially salicylates, have been implicated.

Contraindications & Cautions
Willow bark is contraindicated in those with allergy or sensitivity to salicylates and is also contraindicated in glucose-6-phosphate dehydrogenase-deficient patients (in this condition salicylic acid causes hemolytic anemia). Use with caution during lactation as salicylates excreted in breast milk may cause rashes in babies.

Possible Interactions
Salicin does not have the same potential for interaction as aspirin because it lacks an acetyl group. Use HPWBE with due caution in patients taking warfarin and NSAIDs.

References
15. Meier B. Z Phytother 1990; 11: 50

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