Willow bark

(*Salix spp.* including *S. alba* L., *S. daphnoides* Vill., *S. purpurea* L. and *S. fragilis* L.)

Synonyms

White willow, European willow.

What is it?

The name willow bark is synonymous with the development of one of the most successful and widely used synthetic drugs, namely aspirin. The German scientist Felix Hoffman was investigating a way to reduce the gastric irritant effects of salicylic acid (originally isolated from willow bark) and produced the synthetic derivative acetylsalicylic acid in 1897. This was a serendipitous discovery because the key pharmacological properties of aspirin are largely mediated by the acetyl group he added to make the molecule. Ironically, aspirin was still active as a gastric irritant, but by a different mechanism to salicylic acid.
The stem barks from many species of willow are used medicinally, especially *Salix alba*, *S. daphnoides*, *S. purpurea* and *S. fragilis*. Recent clinical trials indicate that a high-potency standardised willow bark extract 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 also probably contribute to the observed clinical effects.

Effects

Exerts analgesic and anti-inflammatory effects by an uncertain mechanism, but unlike aspirin, is not a potent inhibitor of platelet aggregation or the enzyme cyclo-oxygenase (COX).

Traditional view

Dioscorides in the first century AD prescribed willow bark to patients suffering from rheumatism. 1 Willow bark was traditionally used for inflammatory disorders such as rheumatism, gouty arthritis and ankylosing spondylitis. 2 It was also considered to be a tonic, astringent bitter and an antiperiodic (antimalarial) useful for dyspepsia, chronic mucus discharges, influenza, fevers, convalescence from acute diseases, worm infestation, chronic diarrhoea and dysentery, neuralgia, mild headache and passive haemorrhages. 2, 3–5 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. 6 It was noted in 1876 that native South Africans had long used willow bark for treating rheumatic diseases. 7 On 25 April 1763, the Oxfordshire clergyman Reverend Edward Stone 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 noted that the results were uniformly satisfactory. Stone administered 20 to 60 grains (1.3 to 3.9 g) of dried, powdered bark every 4 h to the patients. 8 Further medical reports of the antipyretic and analgesic effects of willow bark emerged in Europe from 1772 to 1803. 7

Summary actions

Anti-inflammatory, analgesic, antirheumatic, antipyretic.

Can be used for

Indications supported by clinical trials

Temporary relief of acute or chronic musculoskeletal pain, including low back pain and osteoarthritis (good evidence).

Traditional therapeutic uses

As an antipyretic for fever management; as a treatment and preventative for headache.

Preparations

Willow bark standardised extract (WBSE) prepared from the dried root and typically containing 15% total salicin, in tablet or capsule form; dried bark as a decoction or liquid extract for internal use.

Dosage

• 800 to 1600 mg/day of WBSE containing 120 to 240 mg of salicin for anti-inflammatory and analgesic uses, as supported by clinical trial data
• 3.5 to 7 mL/day of a 1:2 liquid extract or equivalent doses (e.g. 9 to 17.5 mL/day) of a 1:5 tincture for traditional uses.

Duration of use

May be taken long term.

Summary assessment of safety

Few adverse effects from ingestion of willow bark are expected, provided the warnings and contraindications are observed. Stomach pains, nausea, headache, tiredness and allergic reaction are rarely reported as adverse reactions. Any potentiation of antiplatelet drugs is likely to be mild.

Technical data

Botany

Willow bark is a member of the Salicaceae family. *Salix alba* is a deciduous tree, up to 26 m tall, with ascending branches and a deeply fissured grey bark. The leaves are alternate, shortly petiolate, up to 11 cm long, lanceolate from a wedge-shaped base, with silky whitish appressed hairs on both sides. The flowers appear with the leaves, arranged in dense cylindrical catkins; the male ones are up to 5 cm long with two stamens, anthers yellow; the female ones are up to 4 cm; 6.5 cm in fruit. The fruit is a capsule. 9

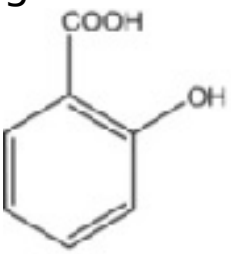
Adulteration

No adulterants have been documented. Other species of Salix low in salicin are possible substitutes.

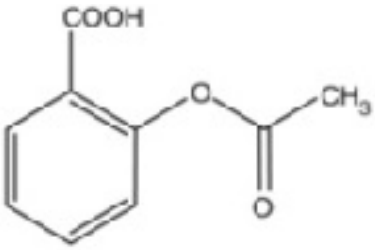
Key constituents

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. 5, 10

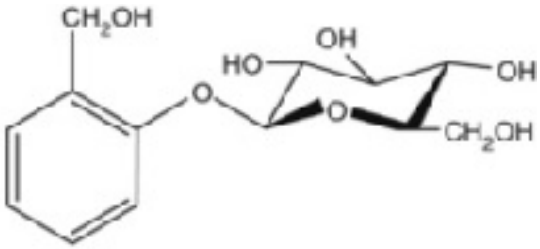
The total salicin content (after hydrolysis) varies according to the species: *S. daphnoides* and *S. fragilis* (2% to 10%), *S. purpurea* (3% to 8.5%) and *S. alba* (0.5% to 1%). 10 Salicin is a phenolic glucoside consisting of the aglycone saligenin (also known as salicyl alcohol) and glucose.



Salicylic acid



Aspirin



Salicin

Pharmacodynamics

The clinical use of willow bark as an antipyretic and analgesic was first documented from 1763 to 1803. By the mid-19th century, active principles were being isolated from this herb and others with similar activity: salicin from willow bark (1826 to 1829), salicylaldehyde from *Spiraea ulmaria* (meadowsweet, 1831) and methyl salicylate from

wintergreen (*Gaultheria spp*., 1843). Salicylic acid was prepared from these isolated constituents (1835 to 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 eight patients with acute and subacute rheumatism. Unfortunately salicin was largely overlooked and the cheaper salicylic acid remained the focus of pharmaceutical attention. As the use of salicylic acid and its salts increased, the problem of the 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. 11 In 1899 acetylsalicylic acid was commercially released with the name aspirin, apparently from the former botanical name for meadowsweet. Despite early reports, adverse reactions to aspirin were largely ignored until the 1950s. 7 The irony is that salicin, which is inactive until it travels past the stomach, is a much gentler substance on the digestive tract than either salicylic acid or aspirin.

The differing pharmacologies of the various salicylate derivatives and willow bark

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

In terms of pharmacology, aspirin is regarded as a potent inhibitor of COX-1 and COX-2 because it contains an acetyl group that causes irreversible acetylation of COX, completely inactivating this enzyme system. Aspirin therefore has analgesic and anti-inflammatory activities via this mechanism (COX-2 inhibition), but is also noted to cause gastric damage and inhibit platelet function (COX-1 inhibition). 11, 12 Specifically, platelet function is inhibited by reducing the 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 (they have no nucleus), the effect of

aspirin persists for the lifetime of the platelet (7 to 10 days). Even low doses of aspirin can therefore have profound blood-thinning effects. 12
Unlike aspirin, salicylic acid has only a weak inhibitory effect on isolated COX-1 or COX-213–15 that, despite some arguments to the contrary, 16 is unlikely to be the mechanism behind any clinically significant anti-inflammatory activity. This means that salicylic acid or sodium salicylate will have little antiplatelet (blood thinning) effects, especially since they lack the acetyl group. However, a high dose of salicylic acid can still irritate the stomach, but this is because it is a phenol, not because of any significant effects on COX-1 inhibition.
Salicin, the major salicylate compound in willow bark, appears naturally designed to minimise this gastric irritation. It effectively delivers salicylic acid into the bloodstream, but it does this in a novel 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 oxidised in the blood, tissue and liver to give salicylic acid/salicylate. Salicin provides a more sustained release of salicylate than sodium salicylate itself. 17 (For more details on the pharmacokinetics of salicin, see below and Chapter 2.)
COX-1 is constitutively expressed, whereas COX-2 is inducible by pro-inflammatory agents such as endotoxin and cytokines. Hence, although it has little direct effect on inhibiting COX-2 activity once it is formed, salicylic acid could exert anti-inflammatory and analgesic activity by inhibiting COX-2 production. It has been reported that aspirin and sodium salicylate equipotently suppress COX-2 induction at therapeutic concentrations. 11
As an elaboration of this possible inhibition of COX-2 induction, an interesting insight has been added to the aspirin and salicylate discussion by Wu. 18 It is proposed that aspirin is a less potent inhibitor of COX-2 than COX-1, and the theory that aspirin exerts its anti-inflammatory action via inhibition of COX-2 is inconsistent with experimental and clinical findings. Specifically, aspirin has a relatively short half-life in circulating blood (around 20 min) and is rapidly deacetylated to yield salicylate. Hence any long-term anti-inflammatory effect of aspirin must be derived from salicylate. Despite its low anti-COX activity, salicylate exerts a substantial anti-inflammatory effect and markedly inhibits inflammatory prostaglandin biosynthesis in intact cells and animals. 15 Based on their in vitro experiments, Wu and team have proposed that salicylate does indeed act by inhibiting the COX-2 production that would normally follow from pro-inflammatory signals to

the cell. The specific mechanism suggested is the inhibition of RSK1/2 (ribosomal S6 kinase 1/2), which is a key factor mediating COX-2 transcription. 19 Also, salicylate appears to have direct analgesic effects in the CNS by unknown mechanisms. 11

To investigate the differing actions of willow bark and aspirin on platelet function, 35 patients were given either willow bark extract (WBSE delivering 240 mg/day of salicin) or placebo under double blind conditions. Another 16 patients were given 100 mg/day of aspirin. 20 The maximum arachidonic-acid-induced platelet aggregation readings were as follows: willow bark 61.0±21.6%, placebo 78.0±15.4% and aspirin 12.7±9.1%. Hence, the inhibitory effect of willow bark extract on platelet aggregation was far less than aspirin and only marginally stronger than placebo (but was still significantly different, p=0.04). This confirms that willow bark is not a substitute for aspirin for clinically relevant antiplatelet activity. However, since the mild effect was statistically significant, WBSE should be used cautiously (under supervision) with warfarin and antiplatelet drugs.

It is likely that not just the salicylate compounds in WBSE contribute to its analgesic activity. A study involving 10 healthy volunteers found that a single dose of WBSE (providing 240 mg of salicin) resulted in blood salicylate levels of around 1.4 µg/mL. In contrast, blood salicylate levels of 35 to 50 µg/mL have been reported after taking just 500 mg of aspirin. 21 Clearly, the clinically observed analgesic effects from willow bark (see later) must come from more than just the effects of salicylate. 21

Based on research on willow bark and related herbs, it has been suggested that lipoxygenase and hyaluronidase inhibition and free radical scavenging effects, all from other components in willow bark, contribute to its overall anti-inflammatory and analgesic effects. (See below for a further discussion on this topic.) This implies that many of the side effects, interactions and contraindications for aspirin, such as interactions with methotrexate, spironolactone and furosemide, are unlikely to apply for willow bark. 22, 23

Anti-inflammatory activity

Salicin, other constituents of willow bark and willow bark extract did not inhibit prostaglandin synthesis from sheep seminal vesicles in vitro. Salicin and salicortin produced a marginal inhibition of lipoxygenase. 24 A hexane extract of willow bark inhibited COX-1 and COX-2 by greater

than 60% in an in vitro assay, 25 but the hexane extract of willow bark would represent a small fraction of its total content. Indeed, clinical studies suggest that willow bark extract does not cause the same gastrointestinal side effects as aspirin, and clinically relevant inhibition of COX-1 or COX-2 activity is considered to be unlikely, as discussed above. 26

Tremulacin demonstrated anti-inflammatory activity, inhibited peritoneal leucocyte migration and writhing response in several experimental models (via injection), and inhibited leukotriene B4 biosynthesis in vitro. 27 Salicin inhibited the spasmodic action of prostaglandin F2α on isolated rabbit non-pregnant myometrium. 28 Tremulacin also inhibited contraction of isolated ileum induced by histamine or SRS-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. 29 Metabolites of salicin and tremulacin have also demonstrated anti-inflammatory activity in vitro. 30

The effects of an ethanolic extract of willow bark were evaluated in an established in vitro assay test model using primary human monocytes. 31 IC50 values obtained for inhibition of lipopolysaccharide (LPS)-induced release of prostaglandin E2 (PGE2), reflecting COX-2-mediated release, were 47 µg/mL and 0.6 µg/mL for the willow bark extract and a rofecoxib-like research compound, respectively. However, there was no direct inhibitory effect from willow bark on COX-1 and COX-2 activity. The willow bark extract also inhibited the LPS-induced release of tumour necrosis factor-alpha, interleukin-1beta and interleukin-6, with IC50 values of 180, 33 and 86 µg/mL, respectively. Interestingly, both salicin and salicylate had no effect on any of the parameters tested.

Recently a standardised willow bark extract was examined to clarify its possible mechanism of action as an anti-inflammatory agent. 32 Various aspects were investigated in two inflammation models: the 6-day air pouch model in rats, representing the acute state, and adjuvant-induced arthritis, representing the chronic state. Parameters assessed included leucocytic infiltration, levels of cytokines and prostaglandins in blood, effects on COX-1 and/or COX-2 enzyme output and effects on free radical production. The extract was compared at two dosage levels, together with comparable anti-inflammatory doses of aspirin as a non-selective COX inhibitor and celecoxib as a selective COX-2 inhibitor. All doses were administered orally. On a mg/kg basis, the willow bark extract was at least as effective as aspirin in reducing inflammatory exudates, inhibiting leucocytic infiltration and preventing a rise in

cytokines. It was more effective than aspirin in suppressing leukotrienes and equally effective in suppressing prostaglandins. For COX-2 output (in terms of PGE2 production), willow bark was a slightly more effective inhibitor than aspirin, but much less than celecoxib. Willow bark also significantly raised reduced glutathione levels, an effect that would help limit lipid peroxidation. Based on these findings, the authors supported previous assertions that other constituents of willow bark extract, such as the polyphenols, contribute to its anti-inflammatory activity. 32 This hypothesis was supported by an investigation of five chemical fractions of a willow bark extract using in vitro and in vivo models. 33 All the studied models pointed to the contribution of complex polyphenols and flavonoids to the observed anti-inflammatory activity of the whole extract. In particular, Fraction E (containing mainly procyanidins) was considerably more active than Fraction D (which largely contained salicin) after oral dosing in the carrageenan-induced rat paw oedema model.

Other activity

Willow bark extract has demonstrated antioxidant activity in several in vitro systems, including the scavenging of free radicals. 34, 35 Unlike aspirin and sodium salicylate, salicin did not suppress lymphocyte transformation in vitro. 36

Pharmacokinetics

Salicin derivatives (e.g. salicortin, tremulacin) are first probably converted into salicin in the stomach or small intestine. Salicin is then mainly carried to the distal ileum or colon, where gut flora conversion into its aglycone (salicyl alcohol) occurs. Salicyl alcohol is absorbed and oxidised 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. 37, 38 A 4 g oral dose of salicin was rapidly metabolised, reaching a peak plasma level of salicylate in just under 2 h. 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 longer 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. 37 (For a more detailed discussion see Chapter 2.)

Clinical trials

A combination of feverfew (600 mg/day) and willow bark (600 mg/day) reduced the frequency and duration of migraine headaches in a prospective, open label clinical trial. 39 For more details see the feverfew monograph.

The following clinical trials were conducted using a potent extract of WBSE. In most cases *S. daphnoides* and *S. purpurea* were prescribed, although other species of willow can probably be used, provided the full spectrum of phytochemicals is present and sufficient salicin content is provided.

A Cochrane Collaboration systematic review examining herbal medicine for low back pain concluded that willow bark seemed to reduce pain more than placebo, but the quality of clinical trial reporting was poor and additional trials against standard treatments are needed. 40, 41 A systematic review of the efficacy of willow bark for musculoskeletal pain found that there was moderate evidence to support willow bark in low back pain and that further trials were required in arthritis. 42 Only minor adverse events were noted for willow bark in the review.

Trials included in these reviews are summarised below.

A small, randomised, double blind, pilot study involving 21 patients indicated a clinically relevant analgesic effect from 2160 mg/day of WBSE, 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 with placebo (40% versus 18%, respectively). 43 The WOMAC (Western Ontario and McMaster Universities) Osteoarthritis Index is a test questionnaire that 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 willow bark for osteoarthritis of the knee and/or hip joint. 21 After a washout period of 4 days, patients received 1360 mg/day of WBSE 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 score. This was

reduced by 14% from baseline values after 2 weeks' treatment with willow bark, compared with an increase of 2% in the placebo group ($p<0.05$). Adverse effects were reported less frequently in the willow bark group than from those taking placebo. Patient diary VAS (visual analogue scales) for pain and physical function confirmed the positive result for willow bark extract and the final overall assessments (by patients and investigators) demonstrated the superiority of willow bark extract over placebo. The analgesic effect of willow bark was mild, estimated to be 40% lower than standard NSAID (non-steroidal anti-inflammatory drug) treatment over the same time period (based on the documented WOMAC pain score reduction after diclofenac treatment at 150 mg/day). However, the analgesic effect of WBSE could increase with longer treatment times (see below).

A randomised, double blind, three-group trial compared oral treatment with one of two doses of WBSE or placebo (lactose) over 4 weeks. 44 A total of 191 patients with acute exacerbation of 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 required tramadol during each week of the study than those taking WBSE ($p<0.001$). A dose-dependent analgesic effect was therefore observed for the WBSE, even though patients in the high-dose group had more severe and prolonged pain at baseline. Furthermore, a statistically significant response in the high-dose group was evident after only 1 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 that was attributed to willow bark extract.

A postmarketing surveillance study confirmed the efficacy of WBSE (containing 240 mg/day of salicin for 4 weeks) in the treatment of low back pain. Forty per cent of patients were pain-free at the end of the treatment period irrespective of whether or not they received additional conventional treatments. 45 Another open, randomised, postmarketing study compared WBSE with rofecoxib (a selective COX-2 inhibitor) in patients with acute exacerbations of low back pain. 46 After 4 weeks'

treatment there was no difference between the two products in terms of pain, the need for additional analgesics and side effects. Each group consisted of 114 patients who received either 1600 mg/day of WBSE containing 240 mg of salicin or 12.5 mg/day of rofecoxib.

In a randomised, double blind, parallel group trial, the therapeutic efficacy and tolerance of WBSE was compared against diclofenac sodium (a conventional NSAID) in patients with knee or hip arthritis. 47 From the 79 patients enrolled, 59 completed the study. The patients were randomly allocated to one of three groups, receiving either 150 mg/day of diclofenac sodium or willow bark extract in two different doses (corresponding to 90 or 180 mg/day salicin, respectively). No additional analgesic NSAID medication was allowed during the study period, lasting over 3 weeks. Outcome measures used were evaluation of pain intensity by a VAS, evaluation of functional capacity and pain intensity during different activities, impairment of daily activity, estimation of whether pain was localised or diffuse, amount of oedema and the intensity and duration of stiffness of the observed joint. Results indicated a good tolerance for the willow bark extract and statistically supported its therapeutically relevant analgesic activity. In terms of pain intensity, an effect comparable to diclofenac sodium was demonstrated. Specific results for the trial included the following:

• Pain intensity (VAS) was reduced by 48% for the NSAID and by 39.5% and 31.3% for the two willow bark groups, respectively

• Functional capacity was significantly ($p<0.05$) improved in all groups (after NSAID treatment 100% of patients were grouped in the lowest ratings of 1 or 2 compared with 90% for the higher dose of willow bark)

• The percentage of symptom-free patients (with various daily activities) increased by similar amounts for all groups.

Not all clinical trials on WBSE have been positive. A 2004 publication contained data for two small randomised, placebo-controlled, double blind trials in patients with osteoarthritis and rheumatoid arthritis, respectively. 48 The osteoarthritis study suggested that the willow bark extract showed no relevant efficacy above placebo. Similarly, the small rheumatoid arthritis trial did not demonstrate a significant therapeutic effect above placebo.

Two large-scale observational studies supporting the safety and efficacy of WBSE in the management of osteoarthritis and chronic low back pain in a clinical setting were presented at conferences. The first study, presented at a Berlin conference in early 2004, involved 922 physicians and 4731 patients in Germany. 49 Over 6 to 8 weeks,

patients with arthritis or back pain took various doses of WBSE (an average of around three tablets/day) and rated their pain intensity from 1 to 10 (with 10 representing pain of the highest intensity). Most of the patients had previously been taking antirheumatic drugs, but had typically discontinued these because of either a lack of efficacy or side effects. During the observation period, only 15.5% needed supplementary antirheumatic drugs in addition to the willow bark. Average pain intensity reduced from 6.4 to 3.7 points in the first 4 weeks of treatment and fell further to 2.7 after 8 weeks, with 97% of patients reporting a reduction in pain and 18% reporting no pain at all. Side effects were judged as minor and occurred in only 1.3% of patients. These were mainly abdominal pain or an allergic skin rash.
The second study was undertaken in Switzerland and involved 204 physicians and 807 patients. 50 Most patients suffered osteoarthritis (44%) or chronic back pain (36%); in 69% of patients the problem had existed for more than 6 months. In 55% of patients the willow bark was prescribed on its own, whereas in 39% it was combined with the conventional medications that the patients were already taking. The average daily dosage of WBSE was 3.4 tablets at the beginning of the study and 2.8 at the end. Throughout the 6 to 8 week observation period, mean pain intensity decreased from 6.4 points to 3.3 and at the final visit 15% of patients were pain free. A substantial reduction of physical impairment was also observed. Suspected adverse reactions occurred in 4.5% of patients and none of them were rated as serious. More than two-thirds of patients rated the tolerability of the willow bark extract as better than conventional antirheumatic drugs. The WBSE used in these two observational studies was standardised to contain 60 mg of salicin per tablet.
Professor Reinhard Saller, a rheumatologist based in Zurich, was interviewed concerning these two studies and his clinical perspective on willow bark extract. 51 He highlighted the high tolerability demonstrated for WBSE in the trials and emphasised that the studies provided useful information concerning its effective dose in a clinical setting. When questioned on the relative value of willow bark extract versus NSAIDs, he suggested that the herbal product had a large advantage because its complex of active principles had an overall modulating effect. The mixture of actives neither provoked a complete blockage nor a maximal stimulation of biochemical phenomena. This resulted in a broader spectrum of action and a greater tolerability than NSAIDs, which he then advised the patients to use on a limited ‘as required’ basis once

they had started willow bark. Given the current disillusionment with COX-2 inhibitors, Professor Saller stressed the advantages of using willow bark extract, which had complex and multiple activities. 52

Toxicology and other safety data

Toxicology

In acute toxicity studies, the LD50 of a liquid willow bark ethanolic extract was 28 mL/kg in mice. 53 No toxic effects were observed in rats orally administered a combination of willow bark and Primula extracts for 13 weeks. 54

Contraindications

Willow bark is contraindicated in those with known allergy, in sensitivity or hypersensitivity to salicylates, and in glucose-6-phosphate dehydrogenase (G6PD) deficient patients (in this condition salicylic acid causes haemolytic anaemia).

Special warnings and precautions

Use with caution in lactating women and in patients combining willow bark with anticoagulants or synthetic salicylates. Willow bark cannot be substituted for aspirin for the prevention of stroke or myocardial infarction. Clinicians should be aware of the unlikely possibility of Reye's syndrome. (Refer to Safety in children section below.)
Because of the tannin content of this herb, use cautiously in highly inflamed or ulcerated conditions of the gastrointestinal tract. In principle, the use of tannins is inappropriate in extreme constipation, iron deficiency anaemia and malnutrition.
The following conditions should be approached with caution when using herbal analgesics: concurrent prescription of powerful analgesics; pain in children; neurological disease; depression and psychosis; history of allergic or anaphylactic reactions.

Interactions

Willow bark may mildly add to the effects of antiplatelet drugs and may interact with anticoagulants, including warfarin. The clinical study previously noted observed very mild, but significant, antiplatelet activity in patients after the consumption of willow bark extract (standardised to 240 mg/day of salicin) for 4 weeks. 20

Use in pregnancy and lactation

Category B1 – no documented increase in frequency of malformation or other harmful effects on the fetus from limited use in women. No evidence of increased fetal damage in limited animal studies.
A combination of willow bark and Primula root extracts did not exert teratogenic effects in rabbits and no negative effects were observed on reproductive function in female rats. 54 Salicylates can cross the placenta and acetylsalicylic acid (aspirin) has been shown to be teratogenic in animals, although there is no conclusive evidence that aspirin causes malformations in humans. 55 Moreover, the salicylates in willow bark do not have the same pharmacology as aspirin.
Willow bark is not advisable during lactation because salicylates are excreted in the breast milk 55 and hypersensitivity reactions might occur.

Effects on ability to drive and use machines

No adverse effects expected.

Side effects

A 2002 review of clinical trials found that 3.8% to 35.8% of 420 patients treated with willow bark extracts (containing 120 mg/day or 240 mg/day of salicin) reported mild adverse events compared to 2.8% to 35.2% of patients who received placebo. 52 In an earlier review, mild adverse events were reported in 3.7% of 733 patients and volunteers treated with three different preparations containing willow bark. 56 The adverse events reported included stomach ache, nausea, headache, dizziness, tiredness, sweating, skin rash and allergic reactions. 52, 56

High doses of tannins lead to excessive astringency on mucous membranes, which has an irritating effect. Gastrointestinal side effects due to willow bark have been attributed to the high tannin content, rather than the salicylate glycosides. 57 Oral administration of salicin (1.4 g/kg) to rats did not cause gastric injury. 58

Acute salicylate poisoning is not expected from the use of willow bark, as the salicylate dose administered in the form of salicylate glycosides is relatively low. Hypersensitivity reactions, which include symptoms such as rhinitis, urticaria, bronchoconstriction, asthma and collapse, can occur from a few milligrams of aspirin and therefore are possible from the administration of willow bark, but the danger is not classed as high. 57 One case of anaphylaxis attributed to a dietary supplement containing willow bark and other ingredients has been reported 59 and another case was noted for WBSE in a clinical trial (see above). 43

A patient with G6PD deficiency presented with acute massive intravascular haemolysis. The patient had been taking a diuretic medication and a herbal combination that contained *Salix caprea*. As salicin is metabolised to salicylic acid, and salicylic acid is a known inducer of haemolysis in G6PD-deficient patients, it was speculated that the herbal preparation might be responsible for the reaction. However, the herbal preparation was not analysed for its salicin content. 60

Overdosage

No incidents have been found in the published literature for willow bark. Overdose resulting from acute ingestion of aspirin (6.5 to 9.8 g) usually produces a serum salicylate level of 300 mg/L or greater. 61 More than 50 g/day of pure salicin would need to be ingested in order to achieve this blood level of salicylate. 21

Safety in children

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 salicylate derivatives, have been implicated. 62 However, it is unknown if the salicylates in willow bark are capable of causing this reaction and no cases have been documented.

Regulatory status in selected countries

Willow bark does not have GRAS status in the USA. However, it is freely available as a ‘dietary supplement’ in the USA under DSHEA legislation (Dietary Supplement Health and Education Act of 1994).
In the UK willow bark is included on the General Sale List and in Germany is covered by a positive Commission E monograph. Willow bark is official in the *European Pharmacopoeia* (2011) and is the topic of an ESCOP monograph.
In Australia willow bark is not included in Part 4 of Schedule 4 of the Therapeutic Goods Regulations and is freely available for sale.

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Witchhazel

(*Hamamelis virginiana* L.)

Synonyms

Hamamelis (Engl), Hamamelidis folium, Hamamelidis cortex (Lat), virginische Zaubernub, Hamamelis, Hexenhasel (Ger), noisietier de la sorcière, hamamélis (Fr), amamelide (Ital), troldnød (Dan).

What is it?

Witchhazel is an American shrub that was used by the Native Americans as a poultice for the treatment of painful swellings and tumours. Pond’s Extract of Witchhazel was once a very popular general household remedy for burns, scalds, insect bites and inflammatory conditions of the skin. The name Hamamelis was adopted from a Greek word to indicate its resemblance to an apple tree. The parts normally used therapeutically are the leaves and bark, which have similar properties. The distilled twig of witchhazel (hamamelis water) is still a popular topical remedy.

Effects

Improves vascular tone; astringent and anti-inflammatory to mucosa; protects against oxidative stress and ultraviolet radiation when used topically; haemostyptic.

Traditional view