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Review

Medicinal plants: *Salix alba* L.

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Abstract

The article presents data on biologically active substances contained in *Salix alba* L. and belonging to various groups of phenolic compounds. From ancient times to the present day, different organs of this willow have been in use for medicinal purposes. The author provides a detailed account of diverse historic and contemporary usages of *S. alba* in medicine. A review of data on modern medications based on raw white willow material includes a brief discussion of possible adverse side effects and contraindications.

Keywords: chemical composition, *Salix alba*, use in medicine

Introduction

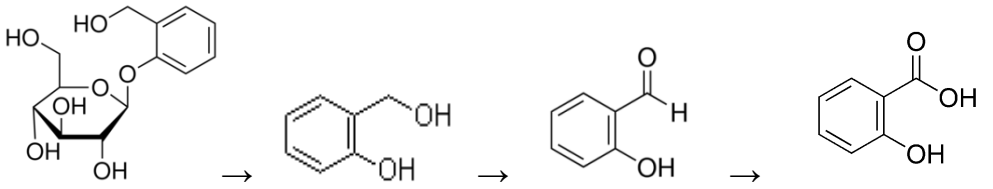
The genus *Salix* L. is of great importance for various spheres of human activity: willows are used to strengthen the shores of water bodies and to fix sand; their shoots are food for many animals; their flowers are important early sources of nectar for honeybees; the bark of many species has tanning properties; wicker furniture is made from willow twigs; a number of species and forms are used as ornamental plants; the use of bark and other organs of willows is of great importance for medicine.

Salix alba L. is one of the most widely known and widespread species of the genus *Salix*. It is rich in a variety of biologically active substances (primarily phenolic compounds) and, since ancient times, has been used for medicinal purposes. This review summarizes what is known about the chemical composition of white willow and the medical usage of its organs and compounds, including medications developed from raw materials in different parts of the world.

Biologically active substances obtained from *Salix alba*

Study of the chemical nature of the active substances of willow began in the 19th century. Salicin, a glucoside of salicyl alcohol, was first isolated in crystalline form from the

bark of white willow in 1828 by the French pharmacist Henri Leroux and Italian chemist Raffaele Piria. Upon enzymatic hydrolysis by salicyl-alcohol β-D-glucosyltransferase, salicin forms salicyl alcohol which is converted into salicylaldehyde and further oxidized to salicylic acid (Fig. 1).



salicin salicyl alcohol salicylaldehyde salicylic acid

Figure 1. Formation of salicylic acid from salicin

Apart from salicin, willow bark contains the glycoside salikortin, which is also a derivative of salicyl alcohol capable of conversion to salicylic acid (Fig. 2).

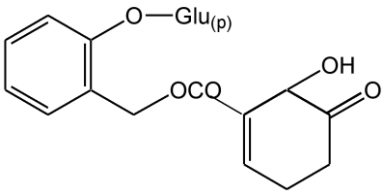


Figure 2. Glycoside salikortin

At present, due to the rapid development of synthetic chemistry, willow bark has lost its original value as a source of salicylic acid, because the method of its extraction from the bark of willow is a long and economically disadvantageous process. Besides, the content of salicin and its derivatives in the bark of white willow is low (Meier *et al*., 1992). However, drugs based on white willow bark and leaves are still in use in many countries, which reflects the presence of a wide range of biologically active substances in the raw materials of this species.

A detailed summary of data on the chemical composition of various organs of white willow is contained in a multi-volume reference book *Rastitelnyve resursy Rossii* [Plant Resources of Russia] (2009). In addition to salicin and salikortin, the following other phenolic alcohols and their glycosides are found in this plant: grandidentatin, triandrin and fragilin in the cortex; salidroside, vimalin and tremuloidin in the leaves (Thieme, 1965; Dytkowska, 1967; Binns *et al*., 1968; Binns and Blunden, 1969; Szabo and Botz, 1999).

Other phenolic compounds identified in the leaves of white willow are: phenol carboxylic acids – chlorogenic, isochlorogenic, gentisic and ferulic (Bate-Smith, 1962; Jaggi and Haslam, 1969; Karl *et al*., 1976); coumarins – esculetin and esculin (Karl, Muller, Pedersen, 1976); flavonoids – quercetin, isoquercetin, rutin, isorhamnetin 3-O-glucoside, isorhamnetin, luteolin 7-glucoside, luteolin, apigenin and its 7-O-(4-O-n-coumaroyl) glucoside, diosmetin, nartsissin, albosid, amentoflavone and cupressus flavone. The following flavonoids are also present in pollen: astragalin, quercimeritrin, quercetin 3,7-di-O-glucoside (Thieme, 1969; Kartusch, 1975; Karl *et al*., 1976; Gorobets *et al*., 1982; Khan and Ansari, 1985; Kuzmichova and Shaluta, 1992).

Eriodictyol, 5,7-dihydroxychromen-4-one and naringenin are found in the extract of white willow bark (Dua *et al*., 2005). Catechins, proanthocyanidins and anthocyanins are present in the bark and leaves. Catechins are represented by (–)-epicatechin, (+)-catechin and gallocatechin (Jaggi and Haslam, 1969; Karl *et al*., 1976; Ohara *et al*., 2003; Esatbeyoglu *et al*., 2010); proanthocyanidins by procyanidins B1, B2, B3, B4 (Karl *et al*., 1976; Ohara *et al*., 2003; Poblocka-Olech and Krauze-Baranowska, 2008); anthocyanins (only in bark) by purpurinidin, cyanidin 3-glucoside and delphinidin 3-glucoside (Bridle *et al*., 1970).

Nitrogen compounds, such as 5-hydroxypipecolic acid, are found in the leaves (Binns *et al*., 1968), and the higher fatty acids, linoleic and linolenic acid are present in the cortex (Tanase and Mocanu, 1969).

Species of willow contain from 2 to 8% of tannins in their leaves and bark, although there are none in willow wood. Rather than in medicine, tannins from willows are mostly used in the tanning industry for the production of heavy leather suitable for premium-quality soles.

The use of white willow in medicine

Of all white willow products, the bark (*Cortex Salicis*) is most often used medicinally. It is harvested from three- to six-year-old branches in the spring, when the sap is flowing, or in early autumn (*Plants for a Future*, 2020). The collected bark is air-dried in the shade with good ventilation, although it is possible to use driers at temperatures not exceeding 50°C. The bark is considered dry if it does not bend but rather breaks with a crack when flexed.

The outer surface of the bark is smooth and gray, gray-green or brown in color. The inner side must be clean, free of wood residues, and pale straw, light pink or light brown in color. It has no odor but tastes bitter and astringent. The raw materials must be stored in linen, paper bags or bales in well-ventilated premises (Zuzuk *et al*., 2005).

In Ancient Greece, willow bark was used as a medicine during the time of Dioscorides; its analgesic, anti-inflammatory and antipyretic properties were known to Hippocrates, Galen and Pliny the Elder. This medicinal raw material was also used in ancient Egypt and Assyria (Norn *et al*., 2009).

Willow was widely used in Arabic medicine. For example, Avicenna recommended to apply the juice of fresh willow bark for resorption of edema or the treatment of jaundice, and a decoction of its bark and fruits for hemoptysis and malignant tumors of the skin. Arabian physicians also considered willow as a good cosmetic remedy for the treatment of dandruff and premature hair loss.

Willow has been widely used in medieval European medicine for centuries. Information about the medicinal properties of willow is included in the well-known *Salerno Health Code* written in the 16th century by philosopher and physician Arnold of Villanova. Medieval European herbalists and medical guidelines recommended tincture of willow bark for colds and fever and powdered bark for the treatment of wounds and abscesses In her book *Physica*, the German abbess and healer Hildegard of Bingen (1098–1179) described the willow as one of the best plants for healing wounds and treatment of rheumatism.

Medieval Italian physician and botanist Pietro Andrea Mattioli (1500–1577) wrote that a decoction of the leaves and bark of the willow is the perfect remedy for rheumatism and gout. His contemporary, the physician and naturalist Adam Lonicer (1527–1587) recommended mixing the powder obtained by grinding the dried bark of willow trees with vinegar and applying to wounds for quick healing (Zuzuk *et al*., 2005). In 1763, Edward Stone reported on the successful treatment of malaria using a willow bark extract (Pasero and Marson, 2010).

In 1876, the antirheumatic effect of salicin was described by T.J. MacLagan, and S. Stricker and L. Riess separately described a similar effect of salicylic acid (Norn *et al*., 2009). Since then, the sodium salt of salicylic acid was included in the pharmacopoeia of a number of countries as an antirheumatic agent. In 1899, a group working at Bayer Company, including Felix Hoffmann, Heinrich Dreser and Arthur Eichengrün, synthesized one of today's most popular drugs, acetylsalicylic acid (Pasero and Marson, 2010). This compound is now popularly known by the commercial name aspirin.

Modern pharmacological studies have confirmed that aqueous and aqueous-alcoholic extracts, tinctures and individual compounds (apigenin, quercetin, salicylic acid) obtained from the bark of white willow have a pronounced anti-inflammatory and analgesic activity (Todorov *et al*., 1959; Gagnier *et al*., 2006; Yakovlev, 2006; Farinacci *et al*., 2008; Drummond *et al*., 2013).

White willow bark reduces pain more slowly than aspirin, but its action is markedly longer. *S. alba,* in combination with *Tanacetum parthenium* Sch. Bip., was shown to be very effective in the treatment of migraine, reducing the frequency, duration and intensity of the painful attacks (Shrivastava *et al*., 2006). The analgesic action of willow bark associated with the presence of salicin is probably due to inhibition of the function of the optic thalamus, which is connected with the transmission of pain sensations. This effect is weak and does not influence the normal activity of the cerebral cortex (Zuzuk *et al*., 2005).

Due to their pronounced anti-inflammatory action, medications based on white willow bark are used in the treatment of diseases of the joints, such as lumbago, sciatica and neuralgia. In Bulgaria, willow bark, as a 20% decoction, is used for the treatment of infectious arthritis and rheumatism, decreasing pain and the swelling of joints, reducing body temperature, and improving appetite and well-being (Minaeva, 1991).

The German *Commission E Monographs*, which are therapeutic guides to herbal medicine, approve *Salix* / Willow for diseases accompanied by fever, rheumatic ailments and/or headaches (*Plants for a Future*, 2020).

The willow medication's effectiveness against gout must be attributed to the enhanced excretion of uric acid, which occurs under the influence of salicylic acid glycosides isolated from willow bark. According to Zuzuk and colleagues, homeopathic remedies for the treatment of arthritis, rheumatism and gout use fresh white willow bark harvested in the morning from three-year-old shoots (Zuzuk *et al*., 2005).

In the form of oral rinses, a decoction of willow bark is recommended for the treatment of inflammation of the mucous membranes of the mouth and upper respiratory tract (Minaeva, 1991).

The pronounced antipyretic effect of extracts and tinctures made from willow bark is associated with an increased rate of heat loss due to the influence of salicin on thermoregulatory centers. Under the influence of salicin, subcutaneous vessels also expand and sweating is increased although, in this case, salicin has a less pronounced effect than salicylic acid (Zuzuk *et al*., 2005).

Not only natural but also synthetic salicylic acid and its derivatives, such as acetylsalicylic acid, salicylamide, methyl salicylate, sodium salicylate, phenyl salicylate, choline salicylate and others are used as anti-inflammatory, antipyretic and analgesic agents.

Relatively recently, Lawrence L. Crawen established anti-aggregative properties of acetylsalicylic acid, which allowed its usage for the treatment and prevention of thrombosis and many cardiovascular diseases. At present combined preparations are being developed

based on salicylic acid and other substances with anti-inflammatory and analgesic effect, which makes it possible to reduce the side effects of salicylates.

The efficiency of willow bark extract has been attributed to the content of salicin and its derivatives. However, based on clinical experience and the data of experimental pharmacological studies, the total amount of salicin present cannot satisfactorily explain the clinical efficacy of willow bark. Experiments *in vivo* and *in vitro* indicate a significant contribution of the fractions of flavonoids and polyphenols. It remains to be seen whether a single compound or combinations are responsible for the observed effects (Nahrstedt *et al*., 2007).

The immunomodulatory properties of aqueous and aqueous-alcoholic extracts of white willow bark may be attributed to the presence of flavonoids and polyphenolic compounds (Farinacci *et al*., 2008). It has been established that white willow produces an antimicrobial effect on a wide range of pathogenic microorganisms.

Willow bark also has astringent, diuretic, antipyretic, hypnotic, sedative and tonic effects. It has been used internally in the treatment of dyspepsia connected with debility of the digestive organs, and its tonic and astringent properties render it useful in convalescence from acute diseases, such as chronic dysentery and diarrhea (*Plants for a Future*, 2020). In the medicine of northwestern India, willow bark is used as an anthelmintic and tonic remedy (Tariq and Tantry, 2012), for the treatment of psoriasis (Kumar and Bhagat 2012), and for teeth cleaning (Kumar *et al*., 2009).

In Russian folk medicine, willow bark is used as a decoction for the treatment of diseases of the spleen, such as jaundice and others. For the treatment of painful varicose veins in the legs, a warm bath (to the knee) with a decoction of willow and oak bark (Minaeva, 1991) may be used. For dandruff, itchiness of the scalp and hair loss, it is recommended to wash the head with a decoction of willow bark and burdock roots (Minaeva, 1991).

The leaves and inflorescences of willow are used in the preparation of medicines to a lesser extent than the bark, but they also possess significant therapeutic properties: leaves can be used as an antipyretic, male inflorescences for the treatment of tachycardia, and leaves and inflorescences for the treatment of neuroses (Budantsev and Lesiovskaya, 2001). Willow flowers are used in Indian ethnomedicine (Mahajan *et al*., 2012).

An infusion of the leaves has a calming effect and is helpful in the treatment of insomnia. When added to bath water, the infusion is of real benefit in relieving widespread rheumatism. The leaves can be harvested throughout the growing season and are used fresh or dried (*Plants for a Future*, 2020).

It has been shown that the pollen of white willow can reduce the damage to chromosomes caused by some anti-cancer drugs (Mytomicin C, Bleomycin and Vincristine), which enables its use as a chemoprotective/chemopreventive medication (Pinto *et al*., 2010).

Medicinal products using white willow as raw material

Medications sold in Europe and the United States include both white willow bark and the bark mixture of *S. alba, S. purpurea* L. and *S.× fragilis* L. The following herbal remedies are available on the market: dried willow bark (in capsules and powder), tinctures, extracts, various teas, and more.

Uroflux, an instant tea for prostate, bladder and kidney complaints (*Nattermann*, Germany), contained, in addition to white willow bark, birch leaves, bearberry leaves, horsetail, goldenrod, rudbeckia roots, licorice roots, restharrow roots and cereal rhizomes but seems to be no longer in use.

The phytopreparation, Linkus ORVI (*Herbion*, Pakistan) is widely used for colds and has an expectorant, anti-inflammatory, mucolytic and antipyretic effect. White willow bark is the main component of this cough syrup although it also includes the leaves of *Justicia vasculosa* (Nees) T.Anderson (= *Adhatoda vasculosa* (Nees) Nees), *Viola odorata* L. leaves and flowers, licorice roots, Chinese tea leaves, *Foeniculum vulgare* L. fruits, *Eucalyptus globulus* Labill. leaves and *Valeriana officinalis* L. rhizomes with roots.

The bark of *Salix alba* is contained in a number of dietary supplements used for the prevention and auxiliary treatment of respiratory diseases.

In the USA, white willow bark is produced as capsules (White Willow Bark, *Sunrider Manufacturing*) and tablets (*GNC* White Willow).

In Russia, employees of *Parapharm* (Moscow) and of the Institute of Physiology, Siberian Branch of the Russian Academy of Medical Sciences (Novosibirsk) developed the dietary supplement, Gerbasprin, for the treatment of patients with inflammatory disease of the respiratory system (Besirishvili and Savitskaya, 2003). It is based on standardized total extracts derived from white willow bark, *Andrographis paniculata* (Burm. f.) Nees, *Rhodiola rosea* L. rhizomes and roots and rose hips. The inclusion of Gerbasprin in complex treatments results in better platelet aggregation. Gerbasprin combines well with anti-inflammatory synthetic drugs, enhancing their effects.

B.M. Zuzuk *et al*. (2005) list the following dietary supplements containing white willow bark.

Alleviate (*Neways*, USA). A solution containing extracts of white willow bark, arnica, ginseng, cayenne pepper, peppermint oil and others. Applications in the treatment of overworked muscles, sprains, dislocations and other injuries, myositis, arthritis of different genesis, neuralgia, neuritis and pain in muscles, joints and spine.

Reumavit (*Bional*, Netherlands). Capsules containing extracts of white willow bark, *Harpagophytum procumbens* (Burch.) DC. ex Meisn., European ash (*Fraxinus excelsior* L.), bittersweet nightshade (*Solanum dulcamara* L.), D-glucosamine, rutin and taurine. They are used for the treatment and prophylaxis of inflammatory diseases of the muscles and joints, including rheumatism and arthritis.

Insti (*Herbalage*, Pakistan). Granules containing white willow bark, *Justicia vasculosa* grass, *Viola odorata* grass, licorice roots and *Valeriana officinalis* rhizomes with roots, used for coughs of different etiology, colds, flu, fever, stuffiness in nose, headache and physical pain.

Pharma med® for the genitourinary system (*Pharma med Inc*., Canada). Capsules containing an extract of European cranberry *Vaccinium oxycoccus* L. (= *Oxycoccus palustris* Pers.), white willow bark, raspberry (*Rubus idaeus* L.) leaves, *Echinacea purpurea* (L.) Moench roots, vitamin C and citric acid. Used as an auxiliary therapy in the treatment of inflammatory diseases of the genitourinary system, for strengthening the immune system, maintenance of normal kidney function and reduction and removal of edema.

Pharma med®, personal monthly system (*Pharma med Inc.*, Canada). Capsules containing the root extract of kawakawa (*Piper methysticum* G.Forst.), extract of primrose (*Primula officinalis* (L.) Hill), white willow bark, ginger (*Zingiber officinale* Roscoe) roots, bearberry leaves, raspberry leaves and others.

Side effects and contraindications

Galenical preparations based on willow bark are practically non-toxic. Nevertheless, stomach upset, nausea, vomiting and gastric bleeding are potential side effects of compounds containing salicylates. An overdose of willow bark can cause nausea, vomiting, inflammation of the stomach and kidneys, skin rash, ringing in the ears, dizziness and a decrease in heart rate.

Medications based on willow are contraindicated for patients sensitive to salicylates, patients with asthma, diabetes, hemophilia, stomach ulcer, diseases of the stomach and duodenum which are accompanied by an increase in acidity of gastric juice, pregnant women and nursing mothers.

Because of the danger of Raye's syndrome, a rare but serious disease associated with the use of aspirin in children, willow bark is contraindicated in children and adolescents under 16.

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