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Activities of *Salix purpurea* (Purple Willow Bark) A Review

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ABSTRACT

Salix purpurea L. (Purple willow bark) is a willow species native to much of Europe, western Asia and North Africa. Purple willow bark contains a particularly valuable raw material aspirin and other salicylic glycosides with analgesic, anti-inflammatory and antioxidant effects. In this present review, an attempt has been made to give an overview of distribution, cultivation, chemical constituents, pharmacological activities, Pharmacodynamic interactions and Pharmacokinetic data of the plant Salix purpurea.

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INTRODUCTION

Salix purpurea L. is a willow species native to much of Europe, western Asia and North Africa. It is a deciduous shrub growing 1-3 m tall, with purple-brown to yellow-brown shoots, turning pale grey on old stems. The leaves are 2–8 cm (rarely to 12 cm) long and 0.3–1 cm (rarely 2 cm) wide; they are dark green above, glaucous green below, and unusually for a willow, are often arranged in opposite pairs rather than alternate. The flowers are small catkins 1.5-4.5 cm long, produced in early spring; they are often purple or red in colour. It is in flower from March to April, and the seeds ripen in May. The species is dioecious (individual flowers are either male or female, but only one sex is to be found on any one plant so both male and female plants must be grown if seed is required) and is pollinated by Bees. The plant is not self-fertile. It is noted for attracting wildlife. [1]

Purple willow bark contains a particularly valuable raw material aspirin and other salicylic glycosides. The bark of *Salix purpurea* (Salicaceae) is traditionally used as an analgesic, antipyretic and anti-inflammatory crude drug material. Commercial preparations prepared from water or ethanol/water extracts of salicis cortex are used for against rheumatic diseases, fever and headache.[2]

It was recently shown that the salicylic alcohol derivatives alone cannot be responsible for the overall efficacy of the crude drug[3] because proanthocyanidins show anti-inflammatory activity *in vivo* and *in vitro*,[4] this group of compounds was investigated in a commercial extract from the bark of *S. purpurea* L., one of the sources of Salicis cortex of the European Pharmacopoeia (2005), prepared by 70% ethanol.[5] Recent research clearly revealed that not only salicylic alcohol derivatives but also the polyphenols significantly contribute to the pharmacological and clinical effects. Standardized extracts rich in polyphenols indicate significant clinical effects[6]and extracts as well as fractions containing polyphenols also showed inhibitory activity *in vitro* on several molecular targets like transcription factors, pro-inflammatory cytokines,[7]and cyclooxygenase and radicle production. Consequently, the overall effect of willow bark extracts can be most likely explained by a multi-component/multi-target principle.[8]

Description of plant

Salix purpurea L. is a medium to tall introduced shrub growing 10 to 20 feet high, with smooth, slender, tough, resilient branches, purplish at first but later changing to grey or olive-

grey. The leaves arise in pairs but not quite oppositely, are smooth tongue shaped, finely-toothed near the tip only, 2 to 4 inches long, bluish-green above and pale below. The catkins are small, arise in almost opposite pairs, and mature in spring before the leaves come out. Male and female flowers are borne on separate plants. Purple osier willow is a solitary shrub, sending up many branches from the base. Growth is rapid, reaching from 2 to 8 feet in two years; often to full height of 15-20 feet in five years. On nutrient-rich sites, it can grow to 25 feet.

Classification

Kingdom:	Plantae
Order:	Malpighiales
Family:	Salicaceae
Genus:	*Salix*
Species:	*S. purpurea*

Cultivation details

Succeeds in most soils, including wet, ill-drained or intermittently flooded soils, but prefers a damp, heavy soil in a sunny position. Plants prefer alkaline or neutral soil, rarely doing well in acid conditions. Said to prefer sandy soil, plants are tolerant of dryish soils. Plants are tolerant of saltwater. A very ornamental plant, it is cultivated for its branches which are used in basket making, there are some named varieties. Plants are coppiced annually for this purpose. A very important food plant for the caterpillars of many butterfly species and a good bee plant, providing an early source of nectar and pollen. Plants in this genus are notably susceptible to honey fungus. Plants should be put into their permanent positions as soon as possible. The species is dioecious, so both male and female plants must be grown if seed is required and is pollinated by Bees. The plant is not self-fertile.

Propagation

Seed - must be surface sown as soon as it is ripe in late spring. It has a very short viability, perhaps as little as a few days. Cuttings of mature wood of the current year's growth, November to February in a sheltered outdoor bed or planted straight into their permanent

position and given a good weed-suppressing mulch. Plant into their permanent positions in the autumn. Cuttings of half-ripe wood, June to August in a frame.

Medicinal use

The bark is anodyne, anti-inflammatory, antiperiodic, antiseptic, astringent, diaphoretic, diuretic, febrifuge, hypnotic, sedative and tonic. It is a very rich source of salicin, which is used in making aspirin. The bark of this species is used interchangeably with *S. alba*. It is taken internally in the treatment of rheumatism, arthritis, gout, inflammatory stages of auto-immune diseases, diarrhoea, dysentery, feverish illnesses, neuralgia and headache. The bark is removed during the summer and dried for later use. The leaves are used internally in the treatment of minor feverish illnesses and colic, cancerous sores and chronic dysentery. The leaves can be harvested throughout the growing season and are used fresh or dried. The twigs are used in the treatment of cancer, dysentery and ulcers. The bark of the stem and roots is anodyne and styptic. It is used in the treatment of rheumatism. The German Commission E Monographs, a therapeutic guide to herbal medicine, approve Salix / Willow for diseases accompanied by fever, rheumatic ailments and headaches.

Other uses

The stems are very tough and flexible and are used in basket making. The plant is usually coppiced annually when grown for basket making, though it is possible to coppice it every two years if thick poles are required as uprights. The bark is much disliked by rabbits, so a closely woven fence of this plant can be used as a protective barrier. Plants can be grown as a hedge, the var. 'Gracilis' is suitable for a small hedge on damp sites. It can be kept dense by annual clipping. The plant has an extensive root system and is used in soil reclamation and stabilization projects along estuaries.

Chemical constituents

The bark of *Salix purpurea* L. contains 4-8% of total salicin (after hydrolysis). Phenol glucosides include salicortin (up to 9%), tremulacin (rarely more than 1%) and salireposide (0.1%-1.2%) with small amounts of syringing and purpurein (up to 0.4%). Other constituents include the yellow chalcone isosalipurperoside (0.15-2.2%), the flavanones eriodictyol-7-glucoside (0.18%-0.4%) and (+) and (-)-naringenin-5-glucoside (0.4-1.5% each),

approximately 0.5% of (+)-catechin and 5% of polyphenols. Young twigs (bark and wood) contain the same constituents in lower concentrations than bark alone.[9]

Pharmacological activities

Anti-inflammatory activity

Although a number of steroidal or non-steroidal antiinflammatory drugs have been developed, researchers are changing their focus to natural products to develop new anti-inflammatory agents due to the side-effects of chemical drugs. As a result, the search for other alternatives seems necessary and beneficial. Many cells and mediators are involved in proceeding inflammation. For example, macrophages are representative inflammatory cells involved in acute or chronic inflammatory responses by over-production of pro-inflammatory cytokines [for example, tumor necrosis factor (TNF)-a, interleukin (IL)-1b and granulocyte/macrophage colony stimulating factor (GMCSF)] and inflammatory mediators.[10,11]

A pharmacological *in vivo* and *in vitro* study on an aqueous extract of the bark of *Salix purpurea* (23-26% total salicin) pointed to contributions of the fraction of polyphenols and flavonoids to the overall effect of willow bark on the inhibition of enzymes of arachidonic acid (AA) metabolism (COX-1, COX-2, HLE isolated enzymes, 5-LOX), inhibition of gene expression of mediators of inflammation, anti-oxidative effects whereas the contribution of salicin derivatives was found to be minor (note that no metabolic activation of the salicins took place). Dose-dependent effects of the extract (50-150 mg/kg) were found in the carrageenan-induced rat paw oedema test and the Randall-Sellitto-test (anti-nociceptive effect), comparable to 150 mg/kg ASA. The results and the mg-mg comparison with regard to salicylic derivatives again suggest that other fractions than salicins distinctly contribute to the effects of the extract.[8]

An aqueous extract of the bark of *Salix purpurea* (DER 16-23:1) at a concentration 50 µg/ml decreased ICAM-1 (Intercellular Adhesion Molecule 1) expression to 40% in human vascular epithelial cells, as compared to control cells, without any sign of toxicity. Flavonoid and chalcone glycosides were not active up to 50 µM, whereas catechol and eriodictyol at the same concentration showed significant reduction of ICAM-1 expression to 50% of controls. Other isolated flavanone glycan like taxifolin, dihydrokaempferol and naringenin showed only weak or moderate inhibitory activity. Eriodictyol was a minor compound in the extract

whereas the catechol content in the extract reached 2.3% determined by HPLC. One of the isolated cyclohexane-1,2-diol glucosides 6'-O-4-hydroxybenzoyl-grandidentin, is a new natural compound. From these *in vitro* data it can be concluded that not only flavonoids and salicin derivatives, but also catechol can probably contribute to the anti-inflammatory activity of willow bark extracts.[12]

An aqueous extract of the bark of *Salix purpurea* 33:1 studied in two inflammation models in rats, the 6 day air pouch model and adjuvant-induced arthritis. The extract was at least as active as acetylsalicylic acid (ASA) on a mg/kg basis in reducing inflammatory exudates and in inhibiting leukocytic infiltration as well as in preventing the rise in cytokines, was more effective than ASA in suppressing leukotrienes, but equally effective in suppressing Prostaglandins. Again, other constituents than salicin are thought to contribute to the overall activity as the extract contains considerably lower amounts of salicylates.[13]

Antipyretic and analgesic activity

Salicin, the major phenolic glycoside present in the bioactive extracts in Salix species is considered to be the pharmacologically active principle due to its structure similarity to aspirin.[14] Salicin administered orally to rats at 5 mmol/kg bwt significantly reduced yeast-induced fever, producing a normal temperature, and completely prevented fever when administered simultaneously with yeast. However, salicin at this dose level did not affect the renal body temperature of afebrile rats. On the other hand, both sodium salicylate and saligenin at 5 mmol/kg lowered body temperature significantly in afebrile rats. Other ingredients of the extract may contribute to the overall analgesic effects. These constituents may include naringenin, catechins and eriodictyol, that inhibit lipoxygenase, hyaluronidase and scavenge free radicals.[15]

Antioxidant activity

An antioxidant is defined as any substance that when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate.[16,17] Antioxidants are of interest to biologists and clinicians because they help to protect the human body against damages induced by reactive free radicals generated in atherosclerosis, ischemic heart disease, cancer, Alzheimer's disease, Parkinson's disease and even in aging process. There are many evidences that natural products and their derivatives

have efficient anti-oxidative characteristics, consequently linked to anti-cancer, hypolipidemic, anti-aging and anti-inflammatory activities.[18,19]

The molecular mechanism of radical scavenging activity of *S. purpurea* could be attributed to the presence of polyphenolic compounds. Oxidation of low density lipoprotein (LDL) by copper ions is strongly inhibited by aqueous extract of the bark of *Salix purpurea* bark in a concentration range between 4 and 7 µg/ml. 10 to 50 µM salicylic acid (SA) stimulate LDL-oxidation whereas higher concentrations (10 to 500 µM) show no effect. Copper chelation seemed to be only partially involved in inhibition of copper-dependent oxidations and only at a certain concentration of extract.[20]

Osteoarthritis and Rheumatoid Arthritis

Müller *et al*. 2010. 350 patients suffering from low back pain and pain due to osteoarthritis were observed during 6 months. They were using a water extract of Salix (DER 16-23:1) (daily dose and compliance not mentioned). The progression of their pain intensity was evaluated using a 100-point visual analogue scale (VAS). Mean improvement for the Salix extract alone was 23.5 on the VAS. Patients combining Salix and NSAIDs reported a mean improvement of 18.8 whereas combination of Salix, NSAIDs and opioids resulted in an improvement of 21.2 (no standard deviation given). The authors conclude that the Salix extract reduces back pain and pain due to osteoarthritis both as monotherapy and in combination with other medicines.[9]

Müller-Fassbender *et al*. 2007 reported about an observational study of 333 patients with osteoarthritis, rheumatoid arthritis or low back pain. The patients were treated with a water extract of Salix (DER 1623:1) during a mean period of 3.3 (+ 0.9) weeks, 85% of the patients receiving a daily dose of 480 mg. Satisfaction rate (good/very good) was reached in 80% of the patients. According to the physicians, the results were comparable to NSAIDs and paracetamol. More than 90% of the patients reported a good to very good tolerability.

Stange *et al.* (2014) followed 436 patients with musculoskeletal pain of different ethology during 24 weeks. The patients were taking a water extract of Salix (16-21:1). The mean visual analogue score (VAS 100) dropped from 58.4 + 22.6 to 31.8 + 22.5 ($P<0.05$ Wilcoxon). NSAIDs were used by 28.9% of the patients (mostly ibuprofen). Adverse effects were reported more often after 3 weeks (4.8%) than after 24 weeks (0.3%).[21]

Pharmacodynamic interactions

Ulrich-Merzenich *et al.* (2013) consider the pharmacodynamic interaction between salicylates and polyphenols as an example of pharmacodynamic anti-inflammatory synergy, resulting in lower active concentrations of salicylates. This synergy may be beneficial in avoiding undesirable effects.

Durak and Gawlik-Dziki (2014) published the results of synergy investigations between coffee and Salix components. They showed that both coffee and purple willow bark are sources of multidirectional antioxidant compounds. Synergism was observed for ability of inhibition of lipid peroxidation and reducing power, whereas in the determination of the ABTS (2,2'-azino-bis (3-ethylbenzothiazoline-6sulphonic acid)) radical scavenging activity the compounds acted antagonistically. Additionally, phytochemicals from willow possess a hydrophilic character and thermostability. According to the authors this may justify their use as an ingredient in coffee beverages.[21]

There seems to be no linear relationship between the number of constituents of willow bark extracts and the number of different targets hit in a biological system on the gene expression level. Interaction studies prove that the number of genetic targets in a biological system does not necessarily increase with the complexity of the treatment. A possible synergism between willow and coffee components. Synergism was observed for ability of inhibition of lipid peroxidation and reducing power.

Pharmacokinetic data

In a 24 hours pharmacokinetic study in 10 healthy volunteers (Schmid *et al.* 2001a), intake of standardized willow bark extract (1360 mg, equivalent to 240 mg salicin, dose divided into 2 tablets at T0h and another 2 tablets at T3h), resulted in salicylic acid as the major metabolite of salicin detected in the serum (86% of total salicylates), besides salicyluric acid (10%) and gentisic acid (4%). Peak levels were reached within 2 hours after oral administration. Peak serum levels of salicylic acid were on average 1.2 mg/L and the AUC was equivalent to that expected form intake of 87 mg acetylsalicylic acid. Considerably higher peak levels of salicylic acid are observed after analgesic doses of acetylsalicylic acid.[22]

Renal elimination occurred predominantly in the form of salicyluric acid (71% of total salicylates), followed by salicylic acid (15%) and gentisic acid (14%). No saligenin or salicin

could be detected in serum or urine. After 24 hours, on average 15.8% of the orally ingested dose of salicin was detected in the urine as salicylates. Since approximately 5% of the salicylates had not yet been excreted by the kidneys after 24 hours, it could be estimated that at least 16.6% of the ingested salicin had been absorbed and metabolized to salicylates.

Based on the *in vivo* findings in rats, it was repeatedly suggested that in humans salicin is also hydrolysed by the flora of the lower intestine prior to absorption of the aglycone (salicyl alcohol). This is contradicted by the studies of Schmid *et al*. (2001), Steinegger *et al.* (1972, 4 g pure salicin)[23]and Pentz *et al.* (1989)[24] combination product of caffeine and willow bark) that found salicylic acid in the serum as early as 1 hour after ingestion, and peak levels recorded after 1-3 hours. This suggests that absorption takes place in the upper intestine, and possibly in the stomach. After oral administration, salicin is obviously hydrolysed before or during absorption. The resulting salicyl alcohol is oxidized to salicylic acid, which is the first detectable metabolite in the serum. After parenteral or rectal administration in humans, salicin is excreted unchanged in the urine.[22]

Contra-indications, Warnings

Precautions associated with salicylate therapy are also applicable to *Salix purpurea*. Therefore individuals with known hypersensitivity to aspirin, asthma, active peptic ulceration, diabetes, gout, haemophilia, hypoprothrombinaemia, kidney or liver disease should be aware of the possible risks associated with the ingestion of willow.[25]

Drug interactions

Drug interactions listed for salicylates are also applicable to *Salix purpurea* and include oral anticoagulants, methotrexate, metoclopramide, phenytoin, probenecid, spironolactone and valproate. Concurrent administration of willow with other salicylate-containing products, such as aspirin, should be avoided. Irritant effects of salicylates on the gastrointestinal tract may be enhanced by alcohol, and barbiturates and oral sedatives have been documented to enhance salicylate toxicity as well as masking the symptoms of overdosage.[26]

CONCLUSION

Extensive literature survey discloses that *Salix purpurea* has a long history of traditional use for a wide range of diseases. These studies on *Salix purpurea* include indicate multiple

actions of the herbal preparation, resulting either synergististic activities of several compounds or individual activities of several compounds. *Salix purpurea* possess several pharmacological properties and contains a huge number of phytochemical compound in it. Thus, this compound could be used in the pharmaceutical industries to produce more drug for the treatment of several diseases. The present review confirms the pharmacological actions and medicinal value of *Salix purpurea*. Future work need to be carried out to identify the efficiency of the different parts of the plant *Salix purpurea*.

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