Salicis cortex
Willow Bark

2017

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Monographs
The Scientific Foundation for Herbal Medicinal Products

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Important Note: Medical knowledge is ever-changing. As new research and clinical experience broaden our knowledge, changes in treatment may be required. In their efforts to provide information on the efficacy and safety of herbal drugs and herbal preparations, presented as a substantial overview together with summaries of relevant data, the authors of the material herein have consulted comprehensive sources believed to be reliable. However, in view of the possibility of human error by the authors or publisher of the work herein, or changes in medical knowledge, neither the authors nor the publisher, nor any other party involved in the preparation of this work, warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for results obtained by the use of such information. Readers are advised to check the product information included in the package of each medicinal preparation they intend to use, to be certain that the information contained in this publication is accurate and that changes have not been made in the recommended dose or in the contraindications for administration.
**FOREWORD**

It is a great pleasure for me to introduce the online era of ESCOP Monographs. Interest in herbal medicinal products continues to stimulate research on herbal substances and the body of knowledge in this field is steadily growing. ESCOP takes account of this by preparing new monographs and - as the only organisation in the field at the moment - particularly through regular revision of our published monographs. In order to provide readers and authorities with balanced compilations of scientific data as rapidly as possible, ESCOP Monographs will be published online from now on. This contemporary way of publishing adds further momentum to ESCOP’s endeavours in the harmonization of European standards for herbal medicinal products.

The Board of ESCOP wishes to express its sincere gratitude to the members of the Scientific Committee, external experts and supervising editors, and to Peter Bradley, the final editor of every monograph published up to March 2011. All have voluntarily contributed their time and scientific expertise to ensure the high standard of the monographs.

Tankred Wegener  
Chair of the Board of ESCOP

**PREFACE**

Over the 15 years since ESCOP published its first monographs, initially as loose-leaf documents then as two hardback books, ESCOP Monographs have achieved a reputation for well-researched, comprehensive yet concise summaries of available scientific data pertaining to the efficacy and safety of herbal medicinal products. The Second Edition, published in 2003 with a Supplement in 2009, covered a total of 107 herbal substances.

The monograph texts are prepared in the demanding format of the Summary of Product Characteristics (SPC), a standard document required in every application to market a medicinal product for human use within the European Union and ultimately providing information for prescribers and users of individual products.

As a change in style, literature references are now denoted by the name of the first author and year of publication instead of reference numbers; consequently, citations at the end of a monograph are now in alphabetical order. This is intended to give the reader a little more information and perspective when reading the text.

Detailed work in studying the pertinent scientific literature and compiling draft monographs relies to a large extent on the knowledge, skills and dedication of individual project leaders within ESCOP Scientific Committee, as well as invited experts. After discussion and provisional acceptance by the Committee, draft monographs are appraised by an eminent Board of Supervising Editors and all comments are taken into account before final editing and approval. In this way a wide degree of consensus is achieved, but it is a time-consuming process.

To accelerate the publication of new and revised monographs ESCOP has therefore decided to publish them as an online series only, commencing in 2011. We trust that rapid online access will prove helpful and convenient to all users of ESCOP Monographs.

As always, ESCOP is indebted to the many contributors involved in the preparation of monographs, as well as to those who provide administrative assistance and hospitality to keep the enterprise running smoothly; our grateful thanks to them all.
NOTES FOR THE READER

From 2011 new and revised ESCOP Monographs are published as an online series only. Earlier monographs are available in two books, ESCOP Monographs Second Edition (2003) and the Second Edition Supplement 2009, but are not available online for copyright reasons.

After purchase of a single monograph, the specific items to be downloaded are:

   Front cover
   Title page
   Verso
   Foreword and Preface
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   The monograph text
   Back cover

Information on the member organizations and people involved in ESCOP’s activities can be found on the website (www.escop.com):

   Members of ESCOP
   Board of Supervising Editors
   ESCOP Scientific Committee
   Board of Directors of ESCOP
ABBREVIATIONS used in ESCOP monographs

AA arachidonic acid
ABTS 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid)
ACE angiotensin converting enzyme
ADP adenosine diphosphate
ALAT or ALT alanine aminotransferase (= SGPT or GPT)
ALP alkaline phosphatase
anti-IgE anti-immunoglobulin E
ASA acetylsalicylic acid
ASAT or AST aspartate aminotransferase (= SGOT or GOT)
ATP adenosine triphosphate
AUC area under the concentration-time curve
BMI body mass index
BPH benign prostatic hyperplasia
b.w. body weight
cAMP cyclic adenosine monophosphate
CI confidence interval
CCl4 carbon tetrachloride
Cmax maximum concentration of a substance in serum
CNS central nervous system
CoA coenzyme A
COX cyclooxygenase
CSF colony stimulating factor
CVI chronic venous insufficiency
CYP cytochrome P450
d day
DER drug-to-extract ratio
DHT dihydrotestosterone
DMSO dimethyl sulfoxide
DNA deoxyribonucleic acid
DPPH diphenylpicrylhydrazyl
DSM Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association)
ECG electrocardiogram
ED50 effective dose in 50% of cases
EDTA ethylenediamine tetraacetate
EEG electroencephalogram
EMA European Medicines Agency
ENT ear, nose and throat
ER oestrogen receptor
ERE oestrogen-responsive element
FSH follicle-stimulating hormone
GABA gamma-aminobutyric acid
Gal galactose
GFR glomerular filtration rate
GGTP gamma-glutamyl transpeptidase
GOT glutamate oxalacetate transaminase (= SGOT)
GPT glutamate pyruvate transaminase (= SGPT)
GSH glutathione (reduced)
GSSG glutathione (oxidised)
HAMA Hamilton Anxiety Scale
12-HETE 12-hydroxy-5,8,10,14-eicosatetraenoic acid
HDL high density lipoprotein
HIV human immunodeficiency virus
HMPC Committee on Herbal Medicinal Products (of the EMA)
HPLC high-performance liquid chromatography
5-HT 5-hydroxytryptamine (= serotonin)
IC50 concentration leading to 50% inhibition
ICD-10 International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICH The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSD International Classification of Sleep Disorders
IFN interferon
IL interleukin
i.m. intramuscular
iNOS inducible nitric oxide synthase
INR  International Normalized Ratio, a measure of blood coagulation (clotting) tendency
i.p.  intraperitoneal
IPSS  International Prostate Symptom Score
i.v.  intravenous
kD  kiloDalton
KM Index  Kuppermann Menopausal Index
kPa  kiloPascal
LC-MS  liquid chromatography-mass spectrometry
LD_{50}  the dose lethal to 50% of animals tested
LDH  lactate dehydrogenase
LDL  low density lipoprotein
LH  luteinizing hormone
5-LOX  5-lipoxygenase
LPS  lipopolysaccharide
LTB_{4}  leukotriene B_{4}
M  molar (concentration)
MAO  monoamine oxidase
MBC  minimum bactericidal concentration
MDA  malondialdehyde
MFC  minimum fungicidal concentration
MIC  minimum inhibitory concentration
Mr  molecular
MRS  Menopause Rating Scale
MRSA  methicillin-resistant *Staphylococcus aureus*
MTD  maximum tolerated dose
MTT  3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW  molecular weight
NBT  nitro blue tetrazolium
NF-κB  necrosis factor kappa-B
NO  nitric oxide
NOS  nitric oxide synthase
n.s.  not significant
NSAID  non-steroidal anti-inflammatory drug
ovx  ovariectomy or ovariectomized
ORAC  oxygen radical absorbance capacity
PA  pyrrolizidine alkaloid
PAF  platelet activating factor
PCR  polymerase chain reaction
PEG  polyethylene glycol
PGE  prostaglandin E
Pgp  P-glycoprotein
PHA  phythaemagglutinin
p.o.  per os
POMS  profile of mood states
PVPP  polyvinylpolypyrrolidone
RANKL  receptor activator of nuclear factor kappa-B ligand
RNA  ribonucleic acid
RT-PCR  reverse transcription polymerase chain reaction
s.c.  subcutaneous
SCI  spinal cord injury
SERM  selective oestrogen receptor modulator
SGOT or GOT  serum glutamate oxalacetate transaminase (= ASAT or AST)
SGPT or GPT  serum glutamate pyruvate transaminase (= ALAT or ALT)
SHBG  sex hormone binding globulin
SOD  superoxide dismutase
SSRI  selective serotonin reuptake inhibitor
STAI  state-trait anxiety inventory
t_{1/2}  elimination half-life
TBARS  thiobarbituric acid reactive substances
TGF-β  transforming growth factor-beta
TNF  tumour necrosis factor
TPA  12-O-tetradecanoylphorbol-13-acetate
URT  upper respiratory tract
URTI  upper respiratory tract infection
UTI  urinary tract infection
VAS  visual analogue scale
VLDL  very low density lipoprotein
SALICIS CORTEX
Willow Bark

DEFINITION
Willow bark consists of the whole or fragmented dried bark of young branches or whole dried pieces of current year twigs of various species of the genus Salix including S. purpurea L., S. daphnoides Vill. and S. fragilis L. The drug contains not less than 1.5 per cent of total salicylic derivatives, expressed as salicin (C13H18O7; Mr 286.3) and calculated with reference to the dried drug.

The material complies with the monograph of the European Pharmacopoeia [Willow Bark].

CONSTituENTS
The characteristic constituents are derivatives of salicin, mainly salicortin, 2'-O-acetylsalicortin and/or tremulacin [Meier 2014]. Young twigs (bark plus wood) contain the same constituents in lower concentrations, when compared to the bark alone. Further constituents, like polyphenols, flavanones, and chalcone glycosides, including procyanidins are now also considered to be characteristic of willow bark, as they have been shown to attribute to its beneficial effects [Fiebich 2014; Narstedt 2007; Freischmidt 2015].

The bark of Salix purpurea L. may contain 6-8.5%, and the bark of S. fragilis 4-10%, of total salicin (determined after hydrolysis) [Meier 1985a]. Phenol glucosides present include salicortin (up to 10%), tremulacin (rarely more than 1%) and saligenin-p-glucoside (0.1-1.2%), with small amounts of syringin and purpurein (up to 0.4%) [Egloff 1991 to 1991; Meier 1985b]. Other constituents include the yellow chalcone isosalipurposide (0.15-2.2%), the flavanones eriodictyol-7-glucoside (0.18-4.4%), and (+)- and (-)-naringenin-5-glucoside (up to 1.5% each) [Meier 1985b/1988; Freischmidt 2015], approximately 0.5% of (+)-catechin and other polyphenols [Shao 1991], as well as flavan-3-ols and dimeric and trimeric procyanidins [Jürgenliemk 2007; Kaufeld 2014]. The bark of S. alba L. contains over 4% of total salicin [Meier 1985a]. Phenol glucosides present include salicortin (3-11%), tremulacin (up to 1.5%) and salicin (up to 1%), and a small amount of syringin (up to 0.2%) also occurs [Egloff 1982; Julkunen 1989; Shao 1991; Meier 1985b]. Other constituents include the yellow chalcone isosalipurposide (0.2-1.5%), the flavonones (+)- and (-)-naringenin-5-glucoside (0.3-1.5% each) and naringenin-7-glucoside (0.3-1.5%) [Meier 1987/1985b], approximately 0.5% of (+)-catechin and other polyphenols [Shao 1991]. The bark of Salix daphnoides Villars contains over 4% of total salicin [Meier 1985a]. Phenol glucosides present include salicortin (3-11%), tremulacin (up to 1.5%) and salicin (up to 1%) and saligenin-p-glucoside (up to 0.2%) also occurs [Egloff 1982; Julkunen 1989; Shao 1991; Meier 1985b]. Other constituents include the yellow chalcone isosalipurposide (0.2-1.5%), the flavanones (+)- and (-)-naringenin-5-glucoside (0.3-1.5% each) and naringenin-7-glucoside (0.3-1.5%) [Meier 1987/1985b], approximately 0.5% of (+)-catechin and other polyphenols [Shao 1991]. The bark of Salix daphnoides Villars contains over 4% of total salicin [Meier 1985a]. Phenol glucosides present include salicortin (3-11%), tremulacin (up to 1.5%) and salicin (up to 1%) and saligenin-p-glucoside (up to 0.2%) also occurs [Egloff 1982; Julkunen 1989; Shao 1991; Meier 1985b]. Other constituents include the yellow chalcone isosalipurposide (0.2-1.5%), the flavanones (+)- and (-)-naringenin-5-glucoside (0.3-1.5% each) and naringenin-7-glucoside (0.3-1.5%) [Meier 1987/1985b], approximately 0.5% of (+)-catechin and other polyphenols [Shao 1991]. The bark of S. purpurea x daphnoides contains over 4% of total salicin [Meier 1985a]. Phenol glucosides present include salicortin (3-11%), tremulacin (up to 1.5%) and salicin (up to 1%) and saligenin-p-glucoside (up to 0.2%) also occurs [Egloff 1982; Julkunen 1989; Shao 1991; Meier 1985b]. Other constituents include the yellow chalcone isosalipurposide (0.2-1.5%), the flavanones (+)- and (-)-naringenin-5-glucoside (0.3-1.5% each) and naringenin-7-glucoside (0.3-1.5%) [Meier 1987/1985b], approximately 0.5% of (+)-catechin and other polyphenols [Shao 1991].

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CLINICAL PARTICULARS

Therapeutic indications

For the relief of fever associated with common cold and headache [Mayer 1949; Bradley 1992; Wagner 1995; Meier 1998; Kaul 1999; Blumenthal 2000; März 2002; Wichtl 2009; Schilcher 2010]. Efficacy in these indications is plausible on the basis of human experience and long-standing use.
Dosage and method of administration

**Dosage**

- **Adults**: oral use for low back pain and mild rheumatic conditions.
  - Daily dose of a hydroalcoholic or aqueous extract, equivalent to 120-360 mg of total salicin [Schmos, 2000a; 2001a; Christakis, 2000b; 2005b; Lardos, 2004; Beer, 2008; Wichtl, 2009].

- **Adults**: oral use for fever, common cold and headache:
  - Dried bark: 2-3 g (3-4 times daily);
  - Liquid extract: 1-3 ml (3-4 times daily).

- **Identities**:
  - Dose: same as for adults.
  - Children: generally not recommended for children and adolescents under 18 years of age. For ages 12 to 17 years the product should not be used without medical advice.

**Method of administration**

For oral administration:

**Duration of use**

No restriction. No severe adverse events were reported in investigations of long term treatment with willow bark extracts, including clinical studies with a duration of use of 6-24 weeks involving a total of 1,371 patients, and a 6 month observational study including 436 patients [Uehleke, 2013; Vlachojannis, 2014].

**Contra-indications**

A history of aspirin allergy. In cases of sensitivity to salicylates, the use of willow bark preparations should be avoided [Cullotta, 2003; Wiegmann, 2005; Vasquez, 2006].

**Special warning, and special precautions for use**

The treatment of children with willow bark extracts is not recommended, because of the structural similarity of salicylic derivatives in willow bark to acetylsalicylic acid. The use of synthetic acetylsalicylic acid or aspirin in children is still associated with a history of aspirin allergy. In cases of sensitivity to salicylates, the use of willow bark preparations should be avoided [Cullotta, 2003; Wiegmann, 2005; Vasquez, 2006].

**Interaction with other medicinal products and other forms of interaction**

Following a daily dose of willow bark extract, corresponding to 240 mg salicin, patients' platelet aggregation was minimally inhibited, whereas compared with inhibition by a cardioprotective dose of 100 mg acetylsalicylic acid. Therefore it is possible that willow bark may modify the effects of oral anticoagulants [Jants, 2001].

**Pregnancy and lactation**

No data available. In accordance with general medical practice, the product should not be used during pregnancy and lactation without medical advice.

**Effects on ability to drive and use machines**

None known.

**Undesirable effects**

Adverse reactions were attributed to willow bark in 4 patients, including skin rash, swollen eyes and pruritus [Christakis, 2000a, 2001b].

**Overdose**

No case of overdose reported.

**In vivo experiments**

- **Anti-inflammatory effects and mechanism of action**: The hen's egg chorioallantoic membrane test system [Luepke, 1985; Luepke, 1986] has been used to study the anti-inflammatory effect of the willow bark constituents salicin and tremulacin. One of their anti-inflammatory effects is delayed in comparison with saligenin (salicylic alcohol), sodium salicylate and acetyl salicylic acid, indicating that the active principles may be metabolites of salicin and tremulacin [Reger, 1972].

- **Anti-inflammatory effects and mechanism of action**: An extract inhibited LPS-induced COX-2-mediated PGE2 release and weakly inhibited TNF-α, IL1β and IL6 release from human monocytes, but had no direct effect on COX-1 or COX-2. The controls, salicin and acetylsalicylic acid, had no effect on any of the parameters [Fieth, 2004].

- **Anti-inflammatory effects and mechanism of action**: An extract inhibited LPS-activated monocyte mRNA expression of COX-2 and transcription factor NF-κappaB [Bonatto, 2010].

- **Anti-inflammatory effects and mechanism of action**: Catechol, a bioactive degradation product of salicortin, reduced TNF-α, IL-6, IL-1β and IL-8 mRNA expression in human endothelial cells [Kaufeld, 2012].

- **Anti-inflammatory effects and mechanism of action**: A purified 2,3-trans procyanidin fraction from willow bark demonstrated redox-sensitive endothelium-dependent relaxation in porcine coronary arteries [Kaufeld, 2014].

- **Anti-inflammatory effects and mechanism of action**: As flavanone and chalcone glycosides, including procyanidins, in willow bark extracts are considered to contribute to the efficacy of willow bark, as has been demonstrated in various experiments [Reichbach, 2004; Nair, 2007; Vlachojannis, 2009; Frei, 2010; Kaufeld, 2014], a quantitative determination method using hydrolysis of the aglycones, naringenin, eriodictyol and chalconaringenin has been developed for use in willow bark preparations [Frei, 2010].

- **Anti-angiogenic effects and cytotoxic activity**: An endothelial cell (ECV304) treated with saligenin (2-5µg/ml) for 24 hours, migratory properties were reduced, tubular formation was inhibited and the mRNA expression of vascular endothelial growth factor (VEGF) was decreased. Angiogenesis was suppressed by blocking the reactive oxygen species production and extracellular signal-regulated kinase (ERK) activation. Indications that salicin significantly inhibits angiogenic activity in endothelial cells [Kong, 2012].

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leucocyte migration (by 13%, p < 0.01) in rats, and on serotonin-induced ear oedema (by 43%, p < 0.001) and acetic-acid induced writhing (p < 0.01 to p < 0.001) in mice. Inhibition of leukotriene B, biosynthesis in pleural leucocytes (obtained ex vivo from rats 24 hours after intra-pleural injection of carrageenan) also supported the activity of taremicarin a human inflammatory animal model [Cheng 1994].

In the rat air pouch model, a willow bark extract showed a significant increase of reduced glutathione (GSH) levels, in vitro and in vivo. It also raised superoxide dismutase activity; the extract was more potent than acetylsalicylic acid or rofecoxib [Khayyal 2005].

The contribution of polyphenols and flavonoids to the mechanism of action and overall effect of aqueous extracts of S. piperata, and S. daphnoides has been shown. However, in vivo and in vitro studies suggest that the clinical efficacy of willow bark cannot be entirely explained by the total salicin fraction alone [Nachtstedt 2007].

Antipyrtyic effect

Salicin administered orally to rats at 5 mmol/kg b.w. significantly reduced yeast-induced fever, producing a normal body temperature, and completely prevented fever when administered simultaneously with yeast. However, salicin at this dose level did not affect the rectal 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 [Kao et al. 2002].

A tumour activity, inhibition of tumour angio genesis and apoptosis

In a mouse model, salicin at 10 mg/kg/d i.p. significantly inhibited tumour growth. Angiogenesis during tumour growth was reduced by the salicin treatment, as measured by two markers, the level of haemoglobin and the expression of CD31 on endothelial cells. This indicates that salicin might inhibit tumour progression by reducing angiogenesis within the tumour [Kong 2014].

Pharmacological studies in humans

Platelet aggregation

In a randomized, placebo-controlled, double-blind study, patients with acute exacerbations of chronic low back pain were treated with either oral willow bark extract corresponding to 240 mg of salicin (n = 19) or placebo (n = 16) daily for 28 days; a third group of patients suffering from chronic ischaemic heart disease (n = 16) received 100 mg of acetylsalicylic acid daily during the study period. Arachidonic acid-induced platelet aggregation, measured in blood samples drawn from the patients 24 hours after each treatment, was minimally inhibited by the inhibitory effect of salicin at this dose level. The mean percentages of inhibition by acetylsalicylic acid. The mean percentages of maximal arachidonic acid-induced platelet aggregation were 61% 78% and 95% in the willow bark extract, placebo and acetylsalicylic acid groups respectively [Krivo et al. 2001].

Clinical Studies

Controlled studies

In a randomized, double-blind, placebo-controlled parallel study, patients with degenerative rheumatic conditions (51 patients) were treated daily for 14 days with either a standardized extract of willow bark (n = 11, 240 mg salicin/d) or placebo (n = 10). Pain intensity was decreased in 8/10 patients in the willow bark group and in 5/10 patients in the placebo group. No severe adverse reactions were reported in any of 11 patients receiving willow bark; 1 patient dropped out due to stomach ache, which appeared to be unrelated to taking the preparation. A similar number of slight adverse events (headache, stomach ache, head ache) were reported in both groups [Schallner 1997].

An standardized willow bark extract in coated tablets was evaluated in patients with osteoarthritis in a randomized, double-blind, placebo-controlled study at an oral dosage corresponding to 240 mg of salicin (n = 39) or placebo (n = 39) daily for 2 weeks following a washout phase with placebo for 4–6 days. Efficacy was assessed by means of the WOMAC Osteoarthritis Index. The WOMAC pain score in the willow bark group decreased significantly (-14%, p = 0.049 compared to that of the placebo group (+2%). The final overall assessment showed significant superiority of the willow bark extract over placebo (patients’ assessment, p = 0.007; patients’ assessment, p = 0.0002) and demonstrated a moderate analgesic efficacy in osteoarthritis [Schmid 2000 / 2001a].

In a randomized, double-blind, placebo-controlled, three-arm study with an exacerbation of chronic low back pain were assigned to one of three treatment groups: a standardized willow bark extract in coated tablets corresponding to either 200 mg (n = 28), 400 mg (n = 28), or placebo (n = 28), daily for 4 weeks. Efficacy was assessed using the Arhus Low Back Pain Index, and the opioid analgesic tramadol was the rescue medication. From intention-to-treat analysis, the number of pain-free patients without rescue medication (responders) in the last week of the study was significantly higher (p < 0.001) in the verum groups and also of a dose-dependent effect: 27 out of 70 (39%) in the 200 mg group and 20 out of 70 (29%) in the 400 mg group and compared to 4 out of 70 (6%) in the placebo group. Significantly more patients in the placebo group required tramadol (p < 0.01) during each week of the study. Willow bark extract thus appears to be a useful and safe treatment for low back pain [Chrubasik et al. 2000a].

Two randomized, placebo-controlled clinical trials, one on hip or knee osteoarthritis and the other in active rheumatoid arthritis, were conducted for 4 weeks, comparing a standardized willow bark extract (240 mg salicin) with placebo, and in one of these trials also with diclofenac. Neither study found significant efficacy for willow bark extract when compared with placebo. However, as was expected, the difference between placebo and diclofenac was highly significant (p<0.0002) [Biegert 2004].

In a randomized, double-blind, parallel group trial, the efficacy and tolerability of 2 doses of willow bark extract (90 or 180 mg salicin/d) were compared to diclofenac sodium (75 mg/d) for 6 weeks in patients with knee or hip osteoarthritis. Neither NSAIDs were allowed. Analgesic activity and pain intensity of both groups treated with the extract were statistically comparable to that of the diclofenac sodium group. Tolerance of the extract was considered as good [Lardos et al. 2004].

Open studies

An elderly, open, uncontrolled clinical study to various acute and chronic rheumatic conditions and respiratory tract infections (n = unknown), reported anti-rheumatic, anti-inflammatory and anti-pyretic activity in 70% of the treated cases [Javer 1999].

In an open, randomized, controlled, post-marketing study, patients with acute exacerbations of low back pain were assigned to treatment with a willow bark extract corresponding to 240 mg of salicin (n = 114) or the synthetic anti-rheumatic rofecoxib, a selective COX-2 inhibitor (12.5 mg, n = 112) daily for 4 weeks. No patients were free to use additional conventional treatments if necessary. About 20 patients were pain-free (visual analogue
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<td>Schaffner 1997</td>
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<td>Pilot study</td>
<td>R / D-B / P-C</td>
<td>n = 11:10</td>
<td>Painful arthritis (degenerative disease)</td>
<td>Extract (240 mg salicin/d)</td>
<td>2 weeks</td>
<td>*n.s. Better pain reduction for the extract</td>
<td>ADE: 30:30</td>
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<td>Schmid 2000/2001a</td>
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<td>Osteoarthritis</td>
<td>Extract (240 mg salicin/d)</td>
<td>2 weeks</td>
<td>*** Sign. decrease of WOMAC-score (p&lt;0.047)</td>
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<td>Chrubasik 2000a</td>
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<td>R / D-B / P-C</td>
<td>n = 78:70:70</td>
<td>Exacerbation of chronic lower back pain</td>
<td>Extract (120 mg salicin/d), Extract (240 mg salicin/d) Placebo</td>
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<td>Rescue medication, tramadol, allowed for all groups.</td>
<td>*** Sign. Number of responders to the extract requiring no rescue medication was significantly higher than with placebo (p&lt;0.001). Sign. more use of tramadol in the placebo-group (p&lt;0.001).</td>
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<td>Biegert 2004 (first trial)</td>
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<td>R / D-B / P-C / P-R-C</td>
<td>n = 43:43:41</td>
<td>Cox- or gonarthrosis (hip or knee)</td>
<td>Extract (240 mg salicin/d), Diclofenac (100 mg/d) Placebo</td>
<td>6 weeks</td>
<td>*n.s. decrease of WOMAC score for extract vs. placebo. Significant for diclofenac vs. placebo (p=0.0002).</td>
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<tr>
<td>Biegert 2004 (second trial)</td>
<td></td>
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<td>Pilot study</td>
<td>R / D-B / P-C</td>
<td>n = 13:13:13</td>
<td>Active rheumatoid arthritis</td>
<td>Extract (240 mg salicin/d) Placebo</td>
<td>6 weeks</td>
<td>*n.s. decrease of VAS-Pain score for extract (15%) vs. placebo (4%).</td>
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<tr>
<td>Lardos 2004</td>
<td></td>
<td></td>
<td>R / D-B / P-C, 3-arm</td>
<td>n = 17:22:21</td>
<td>Cox- or gonarthrosis (hip or knee)</td>
<td>Extract (90 mg salicin/d), Extract (180 mg salicin/d) Diclofenac (150 mg/d)</td>
<td>3 weeks</td>
<td>*** Sign. Extract pain score statistically comparable to diclofenac. Extract well tolerated</td>
<td></td>
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<tr>
<td>Open studies</td>
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<tr>
<td>Mayer 1949</td>
<td></td>
<td></td>
<td>open study, uncontrolled</td>
<td></td>
<td></td>
<td>Among others, acute-chronic rheumatic conditions</td>
<td>3-6 g/d powdered drug</td>
<td></td>
<td>70% of these conditions showed a tendency to lower disease activity.</td>
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<tr>
<td>Chrubasik 2001a</td>
<td></td>
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<td>open, P-R-C, post-marketing + rescue therapy</td>
<td>n = 114:114</td>
<td>Acute exacerbations of low back pain</td>
<td>Extract (240 mg salicin/d), Rofecoxib 2.4 mg</td>
<td></td>
<td>*** Sign. Comparable number of pain-free patients in both groups. ADEs comparable</td>
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<tr>
<td>Chrubasik 2001b</td>
<td></td>
<td></td>
<td>open, non-randomized, 3-arm/ P-R-C, Post-marketing surveillance</td>
<td>n = 15:112:224</td>
<td>Acute exacerbations of low back pain</td>
<td>Extract (120 mg salicin/d), Extract (240 mg salicin/d), Conventional therapy</td>
<td>4 weeks</td>
<td>* Relatively lower pain relief with willow bark extract at 240 mg/d, compared to 120 mg/d.</td>
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<tr>
<td>Peer 2008</td>
<td></td>
<td></td>
<td>open, P-R-C, prospective cohort study</td>
<td>n = 88:40</td>
<td>Degenerative cox- or gonarthrosis (mild to fairly severe cases)</td>
<td>Extract (120-240 mg salicin/d) Standard therapy (= pos. ref.)</td>
<td>6 weeks</td>
<td>Extract has comparable efficacy to positive ref., at 6 weeks. Tolerability better for extract.</td>
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</table>

**Clinical study design:** R = randomized, D = double-blind, B = placebo-blind, P = physician-blinded, C = control, R-C = randomized control, P-R-C = physician-randomized control, P-C = physician-controlled, B-P-C = pharmacist blind, B-P-R-C = pharmacist-blinded, R-B-P-C = pharmacist-blinded, B-R-P-C = pharmacist randomized. **No. patients:** n = verum: placebo: positive control. **Diagnosis:** Painful arthritis (degenerative disease). **Verum medication:** Extract (240 mg salicin/d). **Placebo and/or Reference therapy:** Placebo and/or Conventional therapy. **Duration of treatment:** Duration of treatment. **Outcome:** Outcome of the study. **Safety:** Safety of the study.
Hydrolysis of salicortin
[Steinegger 1972; Fötsch 1989a]. Salicin was stable under acidic conditions (0.5% hydrochloric acid), even after incubation with human saliva at pH 7.2 for 1-4 hours (1 to 4 equiv. to 60 mg salicin); co-medication was possible 6-8 weeks. * n.s. Moderate reduction of pain: 3-4 tabs better than 1-2 tabs. The extract was well tolerated. More ADEs in co-medication-treated patients. ** p<0.01; *** p<0.001. N = 176 AEs were regarded as unrelated to the extract.

**Pharmacology is in vitro**

Hydrolysis of salicin
Salicin was stable under acidic conditions (0.5% hydrochloric acid, with or without pepsin) and reduced no saligenin (salicylic acid), even after incubations with human saliva at pH 7.2 [Steinegger 1972; Fötsch 1989a].

Hydrolysis of salicortin
Salicortin was exchanged after 1 hour of incubation in artificial gastric juice (pH 1.0). After 6 hours of incubation with artificial intestinal juice pH 7.4 to 7.6 at 37°C salicortin was degraded to salicin at t0.5 = 4.02 hours [Meier 1987; Meier 1990].

Enzymatic hydrolysis and esterification
Both β-glucosidase extracted from almonds (EC 3.2.1.21) and β-glucosidase derived from guinea pig liver converted salicin and salicortin to saligenin [Julkunen 1992; Gopalakrishnan 1992]. However, salicylate derivatives acetylated on the sugar moiety (2'-O-acetylsalicortin and 2'-O-acetylsalicylic acid) and tremulacin were not degraded by β-glucosidase. Non-specific esterases (EC 3.1.1.1) from rabbit and porcine liver transformed salicortin to salicin (98.1%), acetylsalicylic acid to acetylsalicin (73.5%) and tremulacin to tremulacin (67.9%) [Julkunen 1992]. Acetyl- and formyl-proteases degraded salicortin to salicin and tremulacin to tremuloidin [Wutzke 1991].

Erythrocyte membrane permeability and protein binding
Transport of salicin and saligenin into erythrocytes was rapid for salicin (1 minute to saturation) and delayed for salicin (4 hours to saturation). The process was reversible, release being rapid for salicin and slower for saligenin. Saligenin and salicin behaved like human serum albumin but salicin has a significantly higher affinity [Matsumoto 1993].

Metabolic transformation by homogenized kidney, liver and lung
Salicin was transformed into salicylic acid by homogenized liver, kidney and lung. Gentisic acid was qualitatively detectable in homogenized liver after incubation with salicin. Gentisic acid was significantly higher than in the positive reference; salicortin to saligenin [Fötsch 1989a].

Intestinal metabolism
Salicin and saligenin were hydrolysed by intestinal bacteria to its main aldehyde saligenin [Fötsch 1989a]. Salicortin was partially metabolized to saligenin and salicylic acid after incubation with homogenized kidney from rats [Adamcik-Janic 1961].

Transport through intestinal wall
Transport of salicin and saligenin through the isolated intestinal wall was confirmed using the closed off posterior section of the male rat intestine. When salicin and saligenin were injected into the closed intestine, both passed the ileum wall unchanged. Salicin appeared to permeate the intestinal wall faster than saligenin [Fötsch 1989a].

**Pharmacokinetic properties**

**Pharmacokinetics in vitro**

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<thead>
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<th>Study</th>
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* ADE = Adverse drug event; sign. = significant; pos. ref. = positive reference drug.

**R** = randomized; **D-B** = double-blind; **P-C** = placebo-controlled; **P-R-C** = positive-reference-controlled; **C** = controlled.

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Pharmacokinetics in animals

Serum concentration-time curve and metabolism in rats

After oral administration of salicin to male Wistar rats at 1 mg/kg (0.266 mg/kg) the urinary metabolites were: unchanged salicin (ca. 25% of the dose), salsolinol (ca. 0.1%), salicylic acid (ca. 30%), conjugated salicylic acid (ca. 5%) and gentisic acid (ca. 2%). After oral administration of a total of 2.5 g of salicin in successive daily doses of 1 mmol/kg, only unchanged salicin was identified in the faeces [Fötsch 1989a].

The concentration of the metabolite salicylic acid was determined in the serum of rats after oral administration of salicin, 300 mg/kg or sodium salicylate (29 mg/kg). With salicin, it was detected after the first 2 hours, but then it appeared in the serum, gradually increased and peaked at 5 hours with a Cmax = 8.44 µg/ml. After administration of sodium salicylate, salicylic acid appeared rapidly and reached a maximum concentration at 1.5 hours with a Cmax = 104.2 µg/ml. Elimination was slower after administration of sodium salicylate than after salicin. The relative bioavailability of salicylic acid from salicin was only 3.25% of that from sodium salicylate [Fötsch 1990].

Plasma levels of salicin, saligenin and salicylic acid were measured and compared to sodium salicylate after oral administration of each compound to rats at 1, 2.5 and 5 mmol/kg. Salicin appeared to be a prodrug which was gradually transported to the lower part of the intestine, hydrolysed to saligenin by intestinal bacteria, and converted to salicylic acid by absorption. Salicin absorption is slow compared to that of saligenin or salicylic acid [Aabo 2002].

In rats, administered 100 mg/kg of oral salicin, catechol and salicylic acid were detected in serum, after serum processing with metabolizing enzymes. The predominant metabolite was catechol sulfate. Unconjugated catechol could not be detected [Knuth 2013].

Metabolism of radioactively labelled salicin in mice

14C-labelled salicin (8.9 mg/mouse) was rapidly and completely metabolized after oral administration to mice. Free salicylic acid was detected in the blood, elimination was mainly by the renal route. Salicin (4 mg/mouse) and renelsalin (11 mg/mouse) were partially metabolised. The metabolite gentisic acid was transiently detected in the small intestine [Wurtele 1991].

Pharmacokinetics in humans

Absorption, distribution, metabolism and elimination

Salicin (4 g, corresponding to 1230 mg of saligenin) and a separate experiment, 2.4 g of sodium salicylate were taken as single medication by volunteers in a study and compare the kinetics. The maximum plasma concentration of free salicylate was reached about 4 hours after administration of salicin with a Cmax = 100 µg/ml. In comparison, sodium salicylate yielded Cmax = 29.5 µg/ml, also after about 4 hours. Metabolites equivalent to more than 25% of the administered salicin were recovered in 24-hour urine: salicylic acid (51%), salicyl glucuronide (14%), salicylic acid (12%), gentisic acid (5%) and saligenin (4%), together with a small amount of unchanged salicin [Steinegger 1972]. The urinary metabolic spectrum of oral acetylsalicylic acid in man [Dünnendahl 1982] was very similar to that of salicin taken orally [Meier 1990]. The metabolism of acetylsalicylic acid is transiently detected in the small intestine [Wurtele 1991].

Absorption and metabolism of willow bark extract

Twelve male volunteers took 3 tablets containing willow bark extract (standardized to provide a total dose of 55 mg salicin) and cola nut extract. The plasma Cmax of salicylic acid was 130 ng/ml, reached 3 hours after administration, and the plasma half-life was calculated as 2.5 hours. An exceptional increase in the plasma level of salicylic acid observed in one volunteer 4-6 hours after administration was ascribed to the effects of eating lunch during this period. Administration of a second dose of 3 tablets four hours after the first dose produced a Cmax of 37 ng/ml at 1 hour after the second dose. This level was increased further by a third dose of 3 tablets eight hours after the first dose [Penz 1989].

A standardized willow bark extract preparation corresponding to 240 mg of salicin was administered to 10 healthy volunteers in two equal doses at 0 and 4 hours. Urine and serum collected over a 24-hour period showed that salicylic acid was the major metabolite in serum (86% of total salicylates). Peak levels of salicylic acid were reached after 2 hours (1.2 mg/l) and then again under the curve (AUC). Equivalent to that expected from an intake of 87 mg of acetylsalicylic acid. From this study it was concluded that willow bark extract leads to much lower serum salicylate levels than observed after anesthetic doses of synthetic salicylates. The formation of salicylic acid alone does not therefore explain the analgesic or anti-rheumatic effects of willow bark [Penz and Kuehnel 2001].

Quantities of gentisic, salicylic and salicylic acids found in human plasma from persons not taking aspirin drugs, were assumed to be derived from vegetable food containing salicylic and derived compounds, such as can be found in cucumbers, melons, cherries and berries [Knuth 2013].

Erectile safety data

Acute toxicity

A hydroethanolic (30%) willow bark extract, administered to mice, yielded an LD50 of 28 ml/kg. With a dry extract of willow bark the LD50 could not be reached [Leslie 1978; März 2002].

Repeated dose, chronic and reproductive toxicity

A hydroethanolic (30%) extract of willow bark (53% of a combination product, including primula root extract, and a plasmolyse of Candida utilis) was administered by gavage to 50 rats for 13 weeks, at a dose of 25 mg/kg. No adverse events were reported during this period and there was no negative effect on reproduction in female rats. Teratogenic effects were not observed in rabbits during this period [Leslie 1979; März 2002].

Mutagenicity and carcinogenicity

No data available.

Induction of gastric lesions

Oral administration of salicin did not induce gastric lesions in rats even at a dose of 5 mmol/kg. However, saligenin and sodium salicylate did induce severe gastric lesions in a dose-dependent manner in the range of 1-5 mmol/kg [Akao 2002].

Prediction of adverse events

Using an in vivo screening tool in rats (gene expression profiling) to predict possible adverse events due to herbal medicines products containing salicinates and the antidepressant imipramine, it was found that imipramine crossed the threshold level for adverse events several times, whereas the willow
Clinical safety data

In studies involving 6993 patients and healthy volunteers treated with various preparations containing willow bark extract or willow bark, mild adverse events were reported [Mayer 1999; Zerwes 1999; Schäffner 1997; Krivov 2001; Schmid 2000; 2001a; Chuubasik 2000a; 2001a; 2001b; Blumenthal 2004; Lardos 2004; Werner 2004; Beer 2008; Saller 2008; Knuth 2013; Uehleke 2013].

No significant adverse reactions were reported in 9 out of 11 patients treated daily for 14 days with a standardized extract of willow bark (240 mg salicin/d). One patient dropped out due to a stomach ache, which appeared to be unrelated to taking the preparation [Schäffner 1997].

In a 2-week randomized study involving osteoarthritis patients, the number of patients experiencing adverse events was the same in the placebo group (16 out of 39) as in those treated with willow bark extract corresponding to 240 mg of salicin per day (16 out of 39). However, more adverse events were reported in the placebo group (28) than in the verum group (17), the most frequent being salicylic skin reactions and gastrointestinal upsets. The most important adverse event in the verum group was a skin rash starting on day 10, however the patient did have a medical history of frequent allergic reactions [Schmid 2000; 2001a].

In a 2-week randomized, three-arm study in patients with low back pain (n = 240), an allergic reaction (skin rash, swollen eyes, urticaria) reported by 1 patient receiving low-dose willow bark extract (equivalent to 2 × 20 mg of salicin/d) was attributable to the extract, dizziness reported by 12 patients taking the extract and the higher dose (2 × 120 mg of salicin/d) was attributed to tramadol rescue medication. In the placebo group, 3 patients reported dizziness and other symptoms attributed to tramadol, and reported mild gastrointestinal ailments [Chrubasik 2000].

In 27 patients treated with willow bark extract (corresponding to 120 or 240 mg of salicin only), occasional mild adverse events occurred as well as 3 cases of allergy which could be attributed to the willow bark [Chrubasik 2001b].

During a 2-day treatment of 12 male volunteers with 12 tablets, containing a combination of willow bark extract (166.6 mg, standardized to 11% total salicin) and a dry extract of cola nut (38 mg, standardized to 25% caffeine), no adverse events were reported [Pentz 1989].

In a 4-month double-blind placebo-controlled study involving 85 patients with chronic arthritic pain, treated daily with 2 tablets of a combination product containing 200 mg of powdered willow bark and five other herbs, 3 adverse events were reported, that could not be directly related to willow bark: one dyspeptic symptom one of headache and one of breathlessness (Mi 1996).

An extensive review of willow bark studies supported the hypothesis that the extract is less prone to cause adverse reactions in the stomach than are known to be caused by acetylsalicylic acid. This appears to be because willow bark does not inhibit cyclo-oxygenase in the stomach wall, since its active metabolite is generated in the intestines and not after stepwise degradation as intact glucosides; the development of stomach lesions is therefore unlikely [Kauf 1999; März 2002]. Another review of the safety of willow bark extract treatments concluded that the incidence of adverse effects is low [Chrubasik 2009].

Peak levels of salicylic acid in the serum of 10 healthy volunteers who received a willow bark extract corresponding to 240 mg of salicin per day were approximately 1.4 mg/L. In contrast, peak levels of 35-50 mg/L have been reported after the intake of 120 mg of acetylsalicylic acid. Therefore, the observed adverse effect of willow bark may not be attributed to salicyclic acid alone. It can be postulated that other constituents (e.g. polyphenols, tannins, flavonoids, salicin, saligenins and others) may contribute to the overall effects of willow bark [Schmid 2000; 2001; Narstedt 2007]; and it may consequently be considered to have a broader mechanism of action and to be safer, than aspirin [Chrubasik 2000a; Ako 2002; Fabic 2005; Clausen 2005; Narstedt 2006; Vlachojannis 2011].

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http://dx.doi.org/10.1002/ptr.981


Willow bark - Salicis cortex. European Pharmacopoeia, Council of Europe.

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<td>Couch Grass Rhizome</td>
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The second edition of ESCOP Monographs, published as a hardback book in 2003 with a Supplement in 2009, has been widely acclaimed for its authoritative information on the therapeutic uses of herbal medicines. Monographs covering a total of 107 herbal substances include extensive summaries of pharmacological, clinical and toxicological data, and copious references to scientific literature form an important part of each text.

Although publication in the form of books was convenient in the past, ESCOP recognizes that online publication now offers a number of advantages, not least in facilitating rapid publication of individual monographs as soon as all stages of preparation have been completed. Commencing from 2011, therefore, new and revised monographs will be published online only.

The European legislative framework for herbal medicines has advanced considerably over the past decade. Directive 2004/24/EC introduced a simplified registration procedure for traditional herbal medicinal products in EU member states and imposed a 2011 deadline for the registration of certain products on the market. The Committee on Herbal Medicinal Products (HMPC), established in 2004 as part of the European Medicines Agency, has made substantial progress in the preparation of Community Herbal Monographs and associated documentation to provide a more harmonized approach to the scientific assessment of herbal medicinal products throughout the European Community.

Whether the evaluation of a herbal medicine is based on evidence of clinical efficacy (well-established use) or on experience and historical use of that product (traditional use) those involved at all levels of the regulatory process need access to detailed, reliable and structured summaries of the available efficacy and safety data. ESCOP monographs meet that requirement and offer an invaluable source of scientific information on herbal medicines to regulators, manufacturers, academics, researchers, health professionals and numerous others.