Cortex Rhamni Purshianae

Definition

Cortex Rhamni Purshianae consists of the dried bark of *Rhamnus purshiana* D.C. (Rhamnaceae) (*1–5*). Cascara (*2*) and Cascara Sagrada (*5*) are also official names of the drug.

Synonyms

Frangula purshiana (D.C.) A. Gray ex J.C. Cooper (*3*, *5*), *Rhamnus purshianus* D.C. (*4*). Although the species name in the British, French, German and European pharmacopoeias is given as *purshianus*, the correct species name is *purshiana* according to the *International code of botanical nomenclature* (Tokyo code) (*4*; J. Morley, personal communication, 1998).

Selected vernacular names

Amerikanischen Faulbaum, bear wood, bitter bark, cascara bark, cascararinde, chittem bark, cortex cascara sagradae, écorce de cascara, purshiana bark, quishron moquaddas, Rhamnus, sacred bark (*1*, *6–8*).

Geographical distribution

Indigenous to south-western Canada and the Pacific north-west of the United States of America (*8–10*).

Description

A tree, 4–10 m high, with reddish-brown bark and hairy twigs. Leaves petiolate, elliptical, acuminate, serrulate, or sometimes entire, with 10–15 pairs of veins, dull green upper surface and pubescent underside. Inflorescence an axillary umbellate cyme of small greenish flowers. Fruit a turbinate, purplish-black drupe, about 8 mm long, composed of 3 indehiscent cocci (*8*).

Plant material of interest: dried bark

The fresh bark contains free anthrones and must be dried for at least 1 year or artificially aged by heat or aeration before therapeutic use (*1*, *5*, *8*).

General appearance

Occurs in quills, slightly channelled or nearly flat pieces; usually 1–5 mm thick, usually varying greatly in length (up to 20 cm) and width (up to 2 cm). Outer surface brown, purplish-brown or brownish-red, usually more or less completely covered by a whitish coat of lichens, epiphytic moss and foliaceous liverwort; shows occasional lenticels that are orientated transversally. Inner surface light yellow to reddish-brown or almost black, with fine longitudinal striations; turns red when treated with dilute alkali (Bornträger's test). Fracture short and granular in outer part and somewhat fibrous in the inner part (*1*, *3*, *5*).

Organoleptic properties

Odour: faint, but characteristic; taste: bitter, nauseous and persistent (*1*, *11*).

Microscopic characteristics

Cork frequently bearing dense masses of lichen tissues, and formed of 10 or more rows of small, flattened, thin-walled cells with yellowish-brown contents. Cortex narrow, yellowish-grey, consisting of a few layers of collenchyma and several layers of parenchyma, containing starch granules and scattered cluster crystals of calcium oxalate; showing numerous scattered, bright, ovoid groups of sclereids, usually encircled by cells containing prismatic crystals of calcium oxalate. Phloem brownish-yellow, traversed by numerous wavy medullary rays (1–5 cells wide and 15–25 cells deep); consists of alternating bands of lignified fibres, surrounded by crystal sheath containing prismatic crystals of calcium oxalate, and of soft sieve tissue and parenchyma with brown walls; contains scattered cluster crystals of calcium oxalate and starch grains; each fibre 8–15 µm in diameter. Groups of sclereids also found in outer part of phloem; sclereids possess thick, stratified, pitted walls. Parenchyma may contain yellow substance which turns crimson with dilute alkali (Bornträger's test) (*1*, *5*).

Powdered plant material

Yellowish-brown to dusky yellowish-orange. Bundles of partly lignified phloem fibres accompanied by crystal sheaths containing prismatic crystals of calcium oxalate; groups of sclereids accompanied by crystal sheaths; cluster crystals of calcium oxalate, 5–20 µm, occasionally up to 45 µm, in diameter; some parenchymatous cells contain yellow substance which turns crimson when treated with dilute alkali (Bornträger's test); cork cells and frequently epiphytes—latter may be liverworts (entire or in fragments, having a lamina one cell thick without a midrib and composed of isodiametric cells) or mosses (having a lamina 1 cell thick composed of elongated cells and possessing a midrib several cells thick); starch grains spheroid, up to 8 µm in diameter (*1*, *3*, *5*).

General identity tests

Macroscopic, microscopic and microchemical (Bornträger's test) examinations (*1*, *3*, *5*) and thin-layer chromatography for characteristic hydroxyanthracene glycosides (*3*, *12*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign matter

Not more than 1% (*3*).

Total ash

Not more than 7% (*1*, *3*).

Water-soluble extractive

Not less than 23% (*1*).

Loss on drying

Not more than 10% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, acid-insoluble ash, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

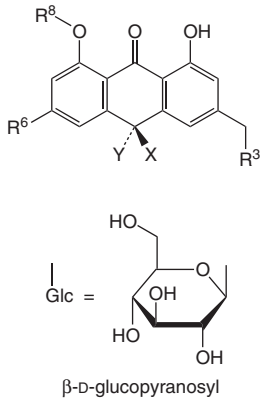
Chemical assays

Contains not less than 8.0% hydroxyanthracene glycosides of which not less than 60% consists of cascarosides, both calculated as cascaroside A. Quantitative analysis is performed by spectrophotometry at 515 nm (*3*, *5*). A high-performance liquid chromatography method for the quantitative analysis of cascarosides has been reported (*16*).

Major chemical constituents

The active constituents are hydroxyanthracene glycosides (6–9%). Of these, 70–90% are C-10 glycosides, with the 8-*O*-glycosides, aloins A and B, and 11-desoxyaloins A and B (chrysaloins A and B) accounting for 10–30%. The diastereoisomeric pairs, cascarosides A and B and cascarosides C and D and cascarosides E and F constitute 60–70% of the total *O*-glycosides. Other major hydroxyanthracene glycosides (10–20%) include the hydroxyanthraquinones, chrysophanol-8-*O*-glucoside and aloe-emodin-8-*O*-glucoside (*7*, *17–19*).

In the fresh bark, anthraquinones are present in the reduced form, and are converted by oxidation from their corresponding parent anthraquinone glycosides during drying and storage (*10*). The structures of the major anthracene glycosides are presented below.



	X	Y	R^3	R^6	R^8
aloin A	Glc	H	OH	H	H
aloin B	H	Glc	OH	H	H
cascaroside A	Glc	H	OH	H	Glc
cascaroside B	H	Glc	OH	H	Glc
cascaroside C	Glc	H	H	H	Glc
cascaroside D	H	Glc	H	H	Glc
cascaroside E	Glc	H	H	OH	Glc
cascaroside F	H	Glc	H	OH	Glc
chrysaloin A	Glc	H	H	H	H
chrysaloin B	H	Glc	H	H	H

Medicinal uses

Uses supported by clinical data

Short-term treatment of occasional constipation (*8*, *17*, *20*, *21*).

Uses described in pharmacopoeias and in traditional systems of medicine

As a cathartic (*1*).

Uses described in folk medicine, not supported by experimental or clinical data

Internally for treatment of diabetes and externally for skin irritations (*6*).

Pharmacology

Experimental pharmacology

Laxative effects

The laxative effects of Cortex Rhamni Purshianae are due primarily to the anthraquinone glycosides and cascarosides A–D (*7*, *22*). After oral administration of Cortex Rhamni Purshianae, the hydroxyanthracene glycosides are not absorbed in the upper intestine, but are hydrolysed in the colon by intestinal bacteria to form the pharmacologically active metabolites. These metabolites are partially absorbed in the colon and act as a stimulant and irritant to the gastrointestinal tract, as does senna (*21*, *23–25*). The mechanism of action, similar to that of senna, is twofold. Firstly, there is stimulation of colonic motility, resulting in increased propulsion and accelerated transit of faeces through the colon (which reduces fluid absorption from the faecal mass). Secondly, there is an increase in paracellular permeability across the colonic mucosa, probably due to inhibition of sodium/potassium-transporting adenosine triphosphatase or inhibition of chloride channels (*23*, *26*). The increased permeability results in increased water content in the colon (*21*, *26*).

The laxative effect of Cortex Rhamni Purshianae is not generally observed until 6–8 hours after oral administration. Hydroxyanthracene glycosides are excreted predominantly in the faeces but are also excreted to some extent in urine, producing an orange colour; anthrones and anthranols will also pass into breast milk (*23*).

Toxicity and overdose

As with other anthraquinone laxatives, the major symptoms of overdose are intestinal pain and severe diarrhoea with consequent loss of fluid and electrolytes (*27*). Treatment of overdoses should be supportive with generous amounts of fluid. Electrolyte levels should be monitored, particularly those of potassium. This is especially important in children and the elderly (*27*).

Clinical pharmacology

None.

Contraindications

Cortex Rhamni Purshianae should not be administered to patients with intestinal obstruction and stenosis, atony, inflammatory diseases of the colon (such as ulcerative colitis, irritable bowel syndrome, Crohn disease), appendicitis,

severe dehydration with water and electrolyte depletion, or chronic constipation (*20*, *24*, *27*). As with other stimulant laxatives, Cortex Rhamni Purshianae is contraindicated in patients with cramps, colic, haemorrhoids, nephritis or any symptoms of undiagnosed abdominal disorders such as pain, nausea or vomiting (*27*). Owing to the pronounced action on the large intestine and insufficient toxicological investigations, Cortex Rhamni Purshianae and other anthranoid laxatives should not be administered to pregnant women (*28*, *29*). As anthranoid metabolites may appear in breast milk, Cortex Rhamni Purshianae should not be used during lactation, since there are insufficient data to assess potential pharmacological effects in the breastfed infant (*29*). Use of Cortex Rhamni Purshianae in children under 10 years is contraindicated (*20*).

Warnings

Products containing Cortex Rhamni Purshianae should only be used if no effect can be obtained through a change of diet or by the use of bulk-forming laxatives. Patients should also be warned that certain constituents of the bark are excreted by the kidney and may colour the urine orange, which is harmless. Cortex Rhamni Purshianae and other stimulant laxatives should not be used in patients with abdominal pain, nausea or vomiting. The use of stimulant laxatives for longer than 2 weeks requires medical supervision. Rectal bleeding or failure to have a bowel movement after taking a laxative may indicate a serious condition. Chronic use may result in aggravation of constipation with laxative dependence, a need for increased dosages and disturbances of water and electrolyte balance (e.g. hypokalaemia). Chronic use may also lead to colonic dysfunction (atonicity) and melanotic pigmentation of the colonic mucosa (pseudomelanosis coli), which is harmless. Laxative abuse resulting in diarrhoea and consequent fluid and electrolyte losses (mainly of potassium) may cause albuminuria, haematuria, and cardiac and neuromuscular dysfunction. Neuromuscular dysfunction may arise particularly in the case of concomitant use of cardiotonic glycosides (e.g. digoxin, digitalis or strophanthin), diuretics, corticosteroids or liquorice root (*27*).

Precautions

General

Cortex Rhamni Purshianae and other laxatives containing anthraquinone glycosides should not be used continuously for longer than 1–2 weeks, because of the risk of electrolyte imbalance (*27*).

Drug interactions

Increased intestinal transit time may result in reduced absorption of orally administered drugs (*30*). Electrolyte imbalances, such as hypokalaemia, may potentiate the effects of cardiotonic glycosides (e.g. digoxin, digitalis or

strophanthin). Hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs (e.g. quinidine) that change sinus rhythm by affecting potassium channels. Hypokalaemia caused by drugs such as thiazide diuretics, adrenocorticosteroids or liquorice root may be enhanced, and electrolyte imbalance may be aggravated (*21*).

Drug and laboratory test interactions

Anthranoid metabolites may not be detectable in faeces or urine by standard methods. Thus faecal excretion measurements may not be reliable (*30*). Urinary excretion of certain anthranoid metabolites may cause discoloration of the urine which is not clinically relevant, but may cause false-positives in urinary urobilinogen tests and in estrogen measurements using the Kober procedure (*31*).

Carcinogenesis, mutagenesis, impairment of fertility

Although chronic use of anthranoid-containing laxatives has been hypothesized to play a role in colorectal cancer, no causal relationship has been demonstrated (*32–35*).

No specific data on carcinogenicity or mutagenicity are available for Cortex Rhamni Purshianae or the cascarosides. Data for aloin derived from aloe indicate no genotoxic risk. Emodin derived from aloe showed both positive and negative results in vitro, but was negative in vivo. Emodin was mutagenic in the *Salmonella*/microsome assay, but gave inconsistent results in gene mutation assays (V 79). It showed positive results in the test for unscheduled DNA synthesis with primary rat hepatocytes, but negative results in the sister chromatid exchange assay (*20*).

Pregnancy: teratogenic effects

See Contraindications. Administration of aloin A to rats at doses up to 200 mg/kg body weight had no embryotoxic, teratogenic or fetotoxic effects (*36*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Adverse reactions

Single doses of Cortex Rhamni Purshianae may result in cramp-like discomfort of the gastrointestinal tract, which may require a reduction of dosage (*21*).

Overdose can lead to colicky abdominal spasms and pain, as well as the formation of thin, watery stools.

Long-term laxative abuse may lead to electrolyte imbalance (hypokalaemia and hypocalcaemia), metabolic acidosis, malabsorption of nutrients, weight loss, albuminuria and haematuria (*37*, *38*). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant laxatives are repeatedly used. Secondary aldosteronism may occur after prolonged use due to renal tubular damage. Steatorrhoea and protein-losing gastroenteropathy with hypoalbuminaemia have also been reported after long-term laxative abuse (*39*). Pseudomelanosis coli has been observed in individuals taking anthraquinone laxatives for extended time periods (*27*, *38*). The pigmentation is harmless and usually reversible within 4–12 months after the drug is discontinued (*38*). Conflicting data exist on other toxic effects after long-term use such as intestinal-neuronal damage (*38*, *40*). In incontinent patients using anthranoid laxatives, prolonged exposure of the skin to faeces may cause skin damage (*41*).

Use of the fresh bark of *Rhamnus purshiana* may cause severe vomiting, with possible abdominal spasms (*23*). One case of occupational asthma and rhinitis has been reported (*42*).

Dosage forms

Finely cut crude drug, powder, dried extracts, extract (*5*), fluidextract (*5*), other liquid and solid preparations (*5*, *7*). Store in a tightly sealed, light-resistant container (*1*, *3*).

Posology

The correct dosage for the treatment of occasional constipation is the smallest dosage necessary to maintain a soft stool. Daily dosage: 0.3–1.0 g crude drug in a single dose (*20*); all preparations standardized to contain 20–30 mg of hydroxyanthracene derivatives calculated as cascaroside A; taken at bedtime, or in two divided doses, one in the morning and one at bedtime (*20*, *21*).

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