Cortex Granati

Definition

Cortex Granati consists of the dried root or trunk bark of *Punica granatum* L. (Lythraceae) (*1–3*).

Synonyms

Punica nana L. (Punicaceae) (*4*).

Note: According to current botanical authorities, *Punica granatum* belongs to the Lythraceae family (*5*).

Selected vernacular names

Anar, anara, anar-ke-per, Carthaginian apple, dadam, dadima-phalam, dalima, dalimb, dalimbay, dalimbuhannu, dalimo, darakte-naiar, darimba, darinko bokra, daru, delima, delum, delun, dhalima, dila dae lok, dlima, ende limau, gangsalan, glima glineu mekah, granada, granade, granado, Granatbaum, granatum, grenadier, grenadillo, gul armini, gulnar, jaman, jeliman, kupchaphala, lelo kase, madalai, madalam, madalangkai, matalam, mathalanarkom, melograno, mkoma manga, nar, pomegranate, posnar, qsur roman, qsur rommam, quishr-al-romman, quishr-romman, ranato, romã, roman, romeira, rommam, roman amruj, romanzeira, roumammam-goulnar, ruman, rumau, sekiryuu-karpi, seog-ryu, seokryupi, shajratur-rummam, sham-al-rumman, shih liu pi, shiliupi, shukadana, talima, thab thim, thap thim, zakuro-juhi (*1*, *3*, *4*, *6–12*).

Geographical distribution

Native to the Middle East (eastern Mediterranean to northern India), and now widely cultivated in warm regions throughout the world (*6*, *8*, *9*).

Description

A deciduous shrub or small tree, erect, up to 7 m high, much branched from the base; branches slender; branchlets often ending in spines, the young ones quadrangular or almost tetrapterous. Leaves: simple, oppo-

site, verticillate, oblong-lanceolate, glabrous, 1–9 cm long and 0.5–2.5 cm wide; apex acute, obtuse or emarginate; base cuneate. Flowers: 1–5 at the highest leaf axil of branchlets, 1 terminal, sessile or subsessile. Calyx: 2–3 cm long, red or pale yellow; lobes erectopatent to recurved; petals round or obtuse, red or white. Fruit, a berry, globose, 5–13 cm in diameter, with a leathery rib enclosing numerous seeds, variously coloured, yellowish-green, white, reddish brown or rarely blackish-purple. Seeds: numerous, red, pink or yellowish white (*6*, *7*, *9*).

Plant material of interest: root and stem bark

General appearance

Stem bark: curved pieces or quills; up to 15 cm long, 0.5–3.0 mm thick: outer surface, yellowish to blackish-brown, with occasional greyish patches of lichens, longitudinally wrinkled and marked; small, broadly elliptical lenticels; inner surface, light yellow to light brown, finely striated; fracture, very short and granular.

Root bark: flat, irregular, curved, or recurved small pieces; outer surface, brownish yellow, rough, with darker patches and conchoidal depressions due to exfoliation of the outer portion, but no lenticels; inner surface, yellow, smooth, with irregular darker brown patches. Other characteristics similar to those of stem bark (*1–3*).

Organoleptic properties

Odour: slight; taste: astringent and slightly bitter (*1*, *2*).

Microscopic characteristics

Cork, formed of several alternating layers of suberized thin-walled cells and of lignified cells with greatly thickened inner tangential walls. Cortex, consisting of parenchyma containing small starch granules; crystals of calcium oxalate from scattered prisms to rosette clusters; and large sc1ereids, which are isolated, rarely in small groups, with very thick and strongly stratified walls, up to 400 µm long and 200 µm broad. Phloem shows numerous cells containing cluster crystals of calcium oxalate in more or less tangential rows, and parenchyma cells with numerous small starch granules or amorphous tannin masses. Medullary rays, 1–2 cell rows with occasional cells containing numerous small prisms (*1–3*).

Powdered plant material

Yellowish brown to dark brown, characterized by fragments of parenchyma containing numerous starch granules and crystals of calcium oxalate; sclereids with very thick and pitted walls; fragments of cork with

prominent, thickened and lignified walls; numerous calcium oxalate crystals, prisms, 6–10 µm long and rosette cluster crystals up to 15 µm in diameter; starch granules, abundant, simple, 2–10 µm in diameter, or rarely compound; occasional long wood fibres, 15–20 µm in diameter, associated with pitted vessels; bast fibres absent (*1*, *3*).

General identity tests

Macroscopic and microscopic examinations, microchemical tests (*1–3*, *13*) and thin-layer chromatography (*3*, *13*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*14*).

Foreign organic matter

Not more than 2% (*1*, *2*).

Total ash

Not more than 15% (*2*).

Acid-insoluble ash

To be established in accordance with national requirements.

Water-soluble extractive

To be established in accordance with national requirements.

Alcohol-soluble extractive

To be established in accordance with national requirements.

Loss on drying

To be established in accordance with national requirements.

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European Pharmacopoeia* (*15*) and the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*14*).

Radioactive residues

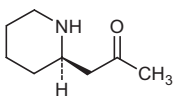
Where applicable, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*14*).

Chemical assays

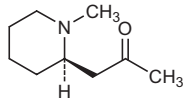
Contains not less than 0.4% of total alkaloids.

Major chemical constituents

The major biologically active constituents are alkaloids and tannins. Isopelletierine, methylpelletierine, methylisopelletierine, pseudopelletierine, norpseudopelletierine and related alkaloids totalling 0.5–0.9%. The tannins present at up to 22% in the bark include punicalin, its 2-*O*-galloyl derivative and punicalagin (*12*, *17*, *18*). The structures of pelletierine, *N*-methylisopelletierine, pseudopelletierine, and the tannins punicalin and punicalagin are presented below.

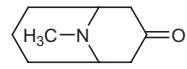


Pelletierine



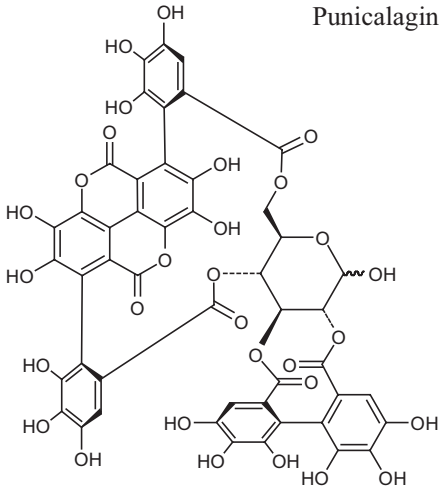
and enantiomer

N-Methylisopelletierine

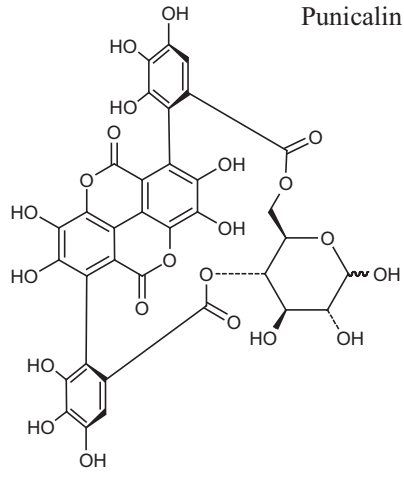


Pseudopelletierine

Punicalagin



Punicalin



Medicinal uses

Uses supported by clinical data

No information was found.

Uses described in pharmacopoeias and well established documents

Used orally for the treatment of diarrhoea and intestinal parasites (*7*, *19*).

Uses described in traditional medicine

Used orally to treat dyspepsia, sore throat, menorrhagia, leukorrhoea and ulcers (*12*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

An aqueous and a 95% ethanol extract of the bark had weak activity in vitro against *Bacillus cereus*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* at a concentration of 25.0 mg/well (*20*). A decoction of the crude drug inhibited the growth of *Trichophyton tonsurans, T. rubrum*, *T. simii*, *Trichosporon beigelii*, *Microsporum fulvum, M. gypseum* and *Candida albicans* when added to the nutrient medium at a concentration of 5% (*21*).

Anthelminthic and molluscicidal activities

Pelletierine, an alkaloid constituent of the bark, was active against tapeworms (*Taenia solium*), but was not active against other intestinal parasites (*4*). At a concentration of 1:10 000, pelletierine hydrochloride kills tapeworms within 5–10 minutes (*22*). This alkaloid acts by causing the tapeworm to relax its grip on the intestinal walls and thereby making it possible to be expelled by cathartics. The molluscicidal activity of the crude drug against the snail *Lymnaea acuminata* was found to be both time- and dose-dependent. An ethanol extract of the bark was effective in killing the test animals, with a 24 h median lethal concentration of 22.42 mg/l (*23*). The extract was not toxic to the fish, *Colisa fasciatus*, which shares the same habitat with the snail (*23*).

Antiuraemic activity

Administration of a decoction of the bark in the drinking-water, at a dose of approximately 150.0 mg/kg body weight (bw), prevented casein/adenine-induced kidney failure in rats (*24*).

Pharmacokinetics

The metabolism of punicalagin, a water-soluble ellagitannin isolated from the crude drug, was assessed in rats (*25*). The animals were treated with repeated oral administration of a 6% punicalagin-containing diet for 37 days. Punicalagin and related metabolites were identified by high performance liquid chromatography–diode array detector–mass spectrome-

try–mass spectrometry (HPLC-DAD-MS-MS) in plasma, liver and kidneys. Five punicalagin-related metabolites were detected in liver and kidney, that is, two ellagic acid derivatives, gallagic acid, 3,8-dihydroxy-6H-dibenzo[b,d]pyran-6-one glucuronide, and 3,8,10-trihydroxy-6H-dibenzo[b,d]pyran-6-one (*25*).

Toxicology

In animal experiments, intragastric administration of very large doses (not stated) of the alkaloids isolated from the bark caused respiratory arrest and death (*26*). Punicalagin has been reported to be toxic to cattle and rats (*25*). The chronic toxicity of punicalagin was assessed in rats. Treatment consisted of repeated oral administration of a 6% punicalagin-containing diet for 37 days. Feedstuff intake, food utility index and growth rate were lower in treated rats during the first 15 days, but no significant adverse effects were observed. No significant differences were found in treated rats in any blood parameter analysed (including the antioxidant enzymes glutathione peroxidase and superoxide dismutase) with the exception of urea and triglycerides, which remained low throughout the experiment (*25*).

Clinical pharmacology

Toxicology

Ingestion by humans of more than 80.0 g of drug may cause severe vomiting with blood, dizziness, fever, tremor and collapse. After 10 hours to 3 days temporary blindness may occur, which usually resolves after several weeks. Ingestion of pelletierine may cause visual disturbances with mydriasis (dilated pupils), dizziness and headache, as well as long-lasting anaesthesia or somnolence. Further symptoms of overdose include colic, cold sweat, dizziness, headache, muscle cramps, weakness or paralysis of the lower extremities, nausea, cardiac and respiratory collapse (*27*).

Adverse reactions

Common adverse events observed in humans include dizziness, visual disturbances, weakness, calf spasms and tremors. Large overdoses (> 80.0 g) of the crude drug may lead to dizziness, mydriasis, severe headache, vertigo, vomiting, lethargy, collapse and possible death due to the alkaloid content (*26*).

Contraindications

Hypersensitivity or allergy to the bark.

Warnings

For diarrhoea lasting for longer than 3 days, contact a health care provider. For diarrhoea associated with fever, nausea and vomiting, or bloody stools, contact a health care provider. Do not exceed recommended dosage.

Precautions

General

No information was found.

Drug interactions

No information was found.

Drug and laboratory test interactions

No information was found.

Carcinogenesis, mutagenesis, impairment of fertility

The genotoxic effects of the crude drug were examined in established human cell lines, Raji and P3HR-1. Cells were treated with a decoction of the bark at various concentrations for 24 and 48 hours in vitro. Cell growth and viability were dose-dependently reduced. No apparent chromosomal aberrations were induced by the treatment. Administration of a bark extract induced apoptotic DNA fragmentation (*28*).

Pregnancy: teratogenic effects

No information was found.

Pregnancy: non-teratogenic effects

Due to the lack of safety data, the use of Cortex Granati during pregnancy is not recommended.

Nursing mothers

Due to the lack of safety data, the use of Cortex Granati during breastfeeding is not recommended.

Paediatric use

Due to the lack of safety data, the use of Cortex Granati in children under the age of 12 years is not recommended.

Other precautions

No information was found.

Dosage forms

Crude drug, extracts and tablets. Store in a cool dry place (*19*).

Posology

Oral daily dose: 3–9 g for decoction (*19*).
Daily dose: 20 g root bark fluidextract (1:1) in 59% ethanol for the treatment of *Taenia* infestation (*27*).

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