Boldo

Species (Family)

Peumus boldus Molina (Monimiaceae)

Synonym(s)

Boldus, *Boldus boldus* (Mol.) Lyons

Part(s) Used

Leaf

Pharmacopoeial and Other Monographs

BHP 1996[G9]
BP 2001[G15]
Complete German Commission E[G3]
ESCOP 1996[G52]
Martindale 32nd edition[G43]
PDR for Herbal Medicines 2nd edition[G36]
Ph Eur 2002[G28]
WHO volume 1 1999[G63]

Legal Category (Licensed Products)

GSL[G37]

Constituents[G2,G22,G41,G52,G58,G62,G64]

Alkaloids Isoquinoline-type. 0.25–0.7%. Pharmacopoeial standard not less than 0.1% alkaloid calculated as boldine.[G15,G28] Boldine 0.06% (major, disputed), isoboldine, 6a,7-dehydroboldine, isocorydine, isocorydine-*N*-oxide, norisocorydine, laurolitsine, laurotetanine, *N*-methyllaurotetanine, reticuline (aporphines); (−)-pronuciferine (proaporphine) and sinoacutine (morphinandienone).[1–4]

Flavonoids Flavonols (e.g. isorhamnetin) and their glycosides.[5,6]

Volatile oils 2.5%. Some 38 components have been identified, including *p*-cymene 28.6%, ascaridole 16.1%, 1,8-cineole 16.0%, linalool 9.1%, terpinen-4-o1 2.6%, α-terpineol 0.9%, fenchone 0.8% and terpinolene 0.4%.

Other constituents Coumarin 0.5%, resin and tannin.

Food Use

Boldo is listed by the Council of Europe as a natural source of food flavouring (category N3). This category indicates that boldo can be added to foodstuffs in the traditionally accepted manner, although insufficient information is available for an adequate assessment of potential toxicity.[G16] In the USA, boldo is approved for food use in alcoholic beverages only.[G64]

Herbal Use[G2,G4,G32,G43,G52]

Boldo is stated to possess cholagogue, liver stimulant, sedative, diuretic, mild urinary demulcent, and antiseptic properties. It has been used for mild digestive disturbances, constipation, gallstones, pain in the liver or gall bladder, cystitis, rheumatism, and specifically for cholelithiasis with pain.[G2,G7,G64] The German Commission E approved use for treatment of dyspepsia and mild spastic gastrointestinal complaints.[G3]

Dosage

Dried leaf 60–200 mg or by infusion three times daily;[G7] 2–5 g as a tea.[G52]

Liquid extract 0.1–0.3 mL (1:1 in 45% alcohol) three times daily.[G7]

Tincture 0.5–2.0 mL (1:10 in 60% alcohol) three times daily.[G7]

Pharmacological Actions

In vitro and animal studies

Boldo has exhibited choleretic (highest activity in rats), diuretic, stomachic and cholagogic properties.[G41,G52] The choleretic activity may be due to synergy between flavonoids and alkaloids.[G52] Experiments in rats have failed to demonstrate choleretic activity after oral administration of 400 or 800 mg/kg aqueous ethanolic extract, intraduodenal administration of 200 mg or 800 mg/kg, and intravenous administration of 32.5–130 mg/kg of a dry ethanolic extract.[7]

An aqueous ethanolic extract (equivalent to 0.5–1.0 mg/mL dried ethanolic extract) and also boldine (33 µg/mL) gave significant hepatoprotection against *t*-butyl hydroperoxide-induced hepatotoxicity in rat hepatocytes *in vitro*.[7] Boldine at a concentration of 0.015 mol/L inhibited microsomal lipid peroxidation in a rat liver preparation by 50%.[8] A dried aqueous ethanolic extract (0.06–0.115%) of boldine at a dose of 500 mg/kg gave 70% protection against carbon tetrachloride-induced hepatotoxicity in mice, and boldine alone (10 mg/kg) gave 49% protection.[7] An aqueous ethanolic extract of boldo at doses of 50 and 100 mg/kg administered intraperitoneally showed anti-inflammatory activity in the rat paw carrageenan-induced oedema test, whereas boldine alone appeared to be inactive.[7]

Boldine showed concentration-dependent relaxant activity on isolated rat ileum (EC_{50} 1.7×10^{-4} mol/L), and acted as a competitive antagonist of acetylcholine and as a non-competitive antagonist of barium.[9] Boldine at low micromolar concentrations prevented oxidation in rat brain homogenate and lipid peroxidation of red cell plasma membranes, led to inactivation of lysozymes, indicating high reactivity of free radicals.[10]

Boldo essential oil contains terpinen-4-ol, the irritant and diuretic principle in juniper oil.

Clinical studies

Boldo, in combination with cascara, rhubarb and gentian, has been reported to exhibit a beneficial effect on a variety of symptoms such as loss of appetite, digestion difficulties, constipation, flatulence and itching.[11,12] Rhubarb and gentian were found to be more effective with respect to appetite-loss related symptoms, and boldo and cascara more effective in constipation-related symptoms.

Two preparations containing extracts of boldo and cascara have been documented to increase biliary flow without altering the lithogenic index or bile composition.[13] Boldine may provide relief to patients with gallstones for whom surgery is not an option or drugs have not been effective.[G56] The choloretic action of boldine releases bile and its diuretic action increases fluid secretion, possibly cleansing sediment or bacteria from the biliary tract.[G56] Treatment of 12 human volunteers with boldo dry extract resulted in prolongation of intestinal transit time.[G4]

Ascaridole, a component of the volatile oil, previously found a clinical use as an anthelmintic agent.[14] However, this use has declined with the development of synthetic compounds with lower toxicity and a wider range of activity.

Side-effects, Toxicity

Boldo volatile oil is stated to be one of the most toxic oils.[G58] Application of the undiluted oil to the hairless backs of mice has an irritant effect.[15] The oil contains irritant terpenes, including terpinen-4-ol, the irritant principle in juniper oil.

An acute oral LD_{50} value for boldo oil has been given as 0.13 g/kg body weight in rats, with doses of 0.07 g/kg causing convulsions.[15] The acute dermal LD_{50} in rabbits has been reported as 0.625–1.25 g/kg.[15] No acute toxicity was observed in rats given oral doses of 3 g/kg of dry aqueous ethanolic extract.[G52] In mice, an aqueous ethanolic extract (1 : 1) had an LD_{50} of 6 g/kg (intraperitoneal administration).[G52] The LD_{50} values of total alkaloids and of boldine in mice were 420 and 250 mg/kg (intraperitoneal administration), respectively.[G52] Total alkaloids (intraperitoneal administration) given to dogs produced vomiting, diarrhoea and epileptic symptoms with a recovery after 50 minutes.[G52]

Boldine was not genotoxic as indicated by the SOS chromotest with *Escherichia coli*, or in the Ames test, and did not induce mutations in *Saccharomyces cerevisiae*.[16] Boldine did not induce an increase in the frequency of chromosome aberrations in human lymphocytes *in vitro*, or in mouse bone marrow cells *in vivo*. There were no signs of genotoxicity in mouse bone marrow, as assessed by the micro nucleus test.[16]

Contra-indications, Warnings

Excessive doses of boldo may cause renal irritation, because of the volatile oil, and should be avoided by individuals with an existing kidney disorder. Boldo is contraindicated in individuals with obstruction of bile duct or severe liver disease. For gallstone patients, it should only be used after consultation with a physician.[G3] Ascaridole is toxic and use of the oil is not recommended.[G58]

Pregnancy and lactation The safety of boldo taken during pregnancy has not been established. In view of the potential irritant nature of the volatile oil, the use of boldo during pregnancy should be avoided.

Pharmaceutical Comment

The chemistry of boldo is well documented, and some pharmacological data are available. Clinical studies have described choleretic activity, although further well-designed studies are required to establish this. The reputed diuretic and mild urinary antiseptic properties of boldo are probably attributable to the irritant volatile oil. In view of the toxicity data and

the irritant nature of the volatile oil, excessive use of boldo should be avoided. Boldo is not recommended for long-term use.[G56]

References

See also General References G2, G3, G9, G10, G15, G16, G22, G28, G31, G36, G37, G41, G43, G52, G54, G56, G57, G58, G62 and G64.

1 Urzúa A, Acuña P. Alkaloids from the bark of *Peumus boldus*. *Fitoterapia* 1983; 4: 175–177.

2 Urzúa A, Torres R. 6a,7-Dehydroboldine from the bark of *Peumus boldus*. *J Nat Prod* 1984; 47: 525–526.

3 Hughes DW *et al.* Alkaloids of *Peumus boldus*. Isolation of laurotetatine and laurolitsine. *J Pharm Sci* 1968; 57: 1619–1620.

4 Hughes DW *et al.* Alkaloids of *Peumus boldus*. Isolation of (+)-reticuline and isoboldine. *J Pharm Sci* 1968; 57: 1023–1025.

5 Bombardelli E *et al.* A new flavonol glycoside from *Peumus boldus*. *Fitoterapia* 1976; 46: 3–5.

6 Krug H, Borkowski B. Neue Flavonol-Glykoside aus den Blättern von Peumus boldus Molina. *Pharmazie* 1965; 20: 692–698.

7 Lanhers MC *et al.* Hepatoprotective and anti-inflammatory effects of a traditional medicinal plant of Chile, *Pneumus boldo*. *Planta Med* 1991; 57:110–115

8 Cederbaum AI *et al.* Inhibition of rat liver microsomal lipid peroxidation by boldine. *Biochem Pharmacol* 1992; 44: 1765–1772.

9 Speisky H *et al.* Activity of boldine on rat ileum. *Planta Med* 1991; 57: 519–522.

10 Speisky H *et al.* Antioxidant properties of the alkaloid boldine in systems undergoing lipid peroxidation and enzyme inactivation. *Biochem Pharmacol* 1991; 41: 1575–1581.

11 Borgia M *et al.* Pharmacological activity of a herbs extract: A controlled clinical study. *Curr Ther Res* 1981; 29: 525–536.

12 Borgia M *et al.* Studio policentrico doppio-cieco doppio-controllato sull'attività terapeutica di una nota associazione di erbe medicamentose. *Clin Ter* 1985; 114: 401–409.

13 Salati R *et al.* Valutazione delle proprietà coleretiche di due preparati contenenti estratti di boldo e cascara. *Minerva Dietol Gastroenterol* 1984; 30: 269–272.

14 Wagner H, Wolff P, eds. *New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity*. Berlin: Springer-Verlag, 1977.

15 Boldo leaf oil. *Food Chem Toxicol* 1982; 20(Suppl.B): 643.

16 Moreno PRH *et al.* Genotoxicity of the boldine aporphine alkaloid in prokaryotic and eukaryotic organisms. *Mutat Res* 1991; 260: 145–152.