Overdose
No case of overdose reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

In vitro experiments

Anti-inflammatory effects
A purified flavonoid extract obtained from blackcurrant leaf inhibited the biosynthesis and release of prostaglandins (IC_{30}: 1.03 mg/ml flavonoids) in isolated perfused rabbit heart. The flavonoid extract was 2.2 and 3.6 times more effective than isoquercitroside and rutin respectively [Pham Huu Chanh 1986].

Di- and trimeric prodelphinidins isolated from blackcurrant leaf were investigated for their effects on the metabolism of human chondrocytes and potential inhibition of COX-1 and COX-2. At the end of a 12-day incubation with 10 µg/ml of prodelphinidin, proteoglycans and type II collagen production were significantly increased in human chondrocytes ($p<0.025$ and $p<0.01$). Under the same conditions, inhibition of PGE_2 synthesis was observed in the presence of di- and trimeric prodelphinidins at a dose of 10 µg/ml ($p<0.025$ and $p<0.01$ respectively). An *in vitro* test on purified COX-1 and COX-2 showed a preferential inhibition of COX-2 (53.2±4.0%) compared to COX-1 (8.1±13.9%) at a concentration of 10^{-5} M dimeric procyanidin. However, no effect was observed on COX activity in the whole blood assay [Garbacki 2002].

In human endothelial LT2 cells, pre-treated for 24 h with a proanthocyanidin-enriched fraction from blackcurrant leaf (mixture of catechin, gallocatechin, di- and trimeric prodelphinidins) [Tits 1992 a] and activated with TNF-α, the cell adhesion immunoglobulin was dose dependently and significantly (10, 30 and 60 µg/ml) inhibited ($p<0.05$ or $p<0.01$). The same fraction did not significantly modify expression of IL-8 and vascular endothelial growth factor 165 (mediators involved in inflammatory processes associated with angiogenesis) [Garbacki 2005].

Antioxidant effects
Antioxidant properties of methanolic crude extracts from fresh blackcurrant leaf (2.4 g in 50 ml) of three different varieties were demonstrated by measuring the inhibition of lipid oxidation induced in rat liver microsomes by ferrous sulfate-ADP-ascorbic acid (IC_{50}: 6.44-7.29µl of methanolic extract per ml) or by *t*-butyl hydroperoxide (IC_{50}: 8.63-9.31 µl of methanolic extract per ml) [Costantino 1993].

A dry extract containing 11.9% flavonol glycosides (not further defined) suppressed the oxidation of erythrocyte membrane lipids induced by UV-C (IC_{50}: 22.8-24.2 µg/ml) and 2,2'-azobis (2-amidinopropane) dihydrochloride (IC_{50}: 7.15-7.25 µg/ml). The control substance, Trolox, showed IC_{50} values of 13.3-15.9 µg/ml and 3.6-4.2 µg/ml respectively [Bonarska-Kujawa 2014].

In vivo experiments

Anti-inflammatory effects
A 14%-ethanolic extract from blackcurrant leaf (60 g per litre), administered orally at 1 and 10 ml/kg b.w., produced dose-dependent anti-inflammatory effects corresponding respectively to 30% and 54% reductions in carrageenan-induced rat paw oedema compared to controls. Comparable activities were observed with reference substances: indometacin produced 63% reduction at 2.5 mg/kg and 66% at 5 mg/kg; niflumic acid produced 19% reduction at 25 mg/kg and 70% at 50 mg/kg. A 21-day oral treatment with the extract reduced oedema compared to control animals by 30% at 0.33 ml/kg, 42.5% at 1 ml/kg and 46% at 10 ml/kg, the last being statistically identical with the activities of indometacin at 1.66 mg/kg (49% reduction) and niflumic acid at 12.5 mg/kg (53% reduction). A 21-day oral treatment with a lyophilizate of the 14%-ethanolic extract (1 g of lyophilizate equivalent to 30 ml of extract or 1.8 g of leaf) gave an ED_{50} of 0.67 g/kg for the lyophilizate compared to 0.43 mg/kg for indometacin. The efficacy of the blackcurrant leaf extract was apparent in both the proliferative and exudative phases of inflammation [Declume 1989].

A lyophilizate prepared after maceration of blackcurrant leaf (100 g/litre) in 15% ethanol for 10 days at 20°C and administered intraperitoneally to rats exhibited potent anti-inflammatory activity in comparison with controls [Mongold 1993]. In the carrageenan-induced rat paw oedema test at 50 and 100 mg/kg b.w., the lyophilizate produced dose-dependent inhibition of inflammation ($p<0.01$), its effect at 100 mg/kg (70% inhibition) being similar to that of indometacin at 5 mg/kg (77% inhibition). In the cotton pellet-induced granuloma test, the lyophilizate at 150 mg/kg reduced inflammation by 18.6%, comparable to the 24% reduction with indometacin at 3 mg/kg. In the Freund adjuvant-induced arthritis test, the lyophilizate produced a dose-dependent reduction in inflammation of 18.7% at 150 mg/kg and 34.6% at 300 mg/kg, the latter being statistically identical to the 37.7% reduction obtained with indometacin at 3 mg/kg [Mongold 1993].

Prodelphinidins isolated from blackcurrant leaf, administered intraperitoneally, had a dose-dependent anti-inflammatory effect in the carrageenan-induced rat paw oedema model: 18%, 40% and 55% reductions in inflammation with 5, 10 and 40 mg/kg respectively. In a similar experiment, a crude aqueous extract from blackcurrant leaf produced 57% inhibition at 60 mg/kg, comparable to 44% with indometacin at 4 mg/kg and 47% with aspirin at 200 mg/kg [Tits 1992b].

Treatment of rats with a proanthocyanidin-enriched fraction from blackcurrant leaf [Tits 1992 a] (10, 30, 60 and 100 mg/kg, i.p.) significantly ($p<0.05$) reduced paw oedema induced by carrageenan in a dose and time-dependent (from 0 to 4 h) manner and also dose-dependently significantly inhibited ($p<0.05$) carrageenan-induced pleurisy in rats. The same fraction at 30 mg/kg also significantly lowered ($p<0.05$) TNF-α, IL-1β and nitrite/nitrate levels in pleural exudate [Garbacki 2004].

In rats treated with the same fraction (10, 30 and 60 mg/kg, i.p.) before intrapleural injection of carrageenan, exudate volume was significantly reduced ($p<0.05$ or $p<0.01$) in a dose-dependent manner (31, 37 and 55% respectively) 4 hours after injection. Infiltration of polymorphonuclear leucocytes was also significantly inhibited ($p<0.01$) in a dose-dependent manner (64, 73 and 75% respectively) [Garbacki 2005].

Analgesic effects
A lyophilizate prepared after maceration of blackcurrant leaf (100 g/litre) in 15% ethanol for 10 days exhibited potent analgesic activity, which may be of peripheral origin, in the acetic acid-induced writhing test after single dose i.p. administration to mice. The lyophilizate had an ED_{50} of 61.5 mg/kg and a therapeutic index (LD_{50}/ED_{50}) of 17.7. Paracetamol (acetaminophen) administered to the control group gave a higher ED_{50} of 132 mg/kg and a lower therapeutic index of 3.8 [Mongold 1993].

Diuretic activity
A fluid extract (1:1) of blackcurrant leaf showed a salidiuretic action (diuretic quotient 1.56) in rats when administered orally at a dose equivalent to 1500 mg dried leaf/kg; this was similar

to the effect of furosemide at 50 mg/kg (diuretic quotient 1.52) [Rácz-Kotilla 1977].

The potassium-sodium ratios in blackcurrant leaf and blackcurrant leaf decoction were found to be 128:1 and 242:1 respectively, which may contribute to a diuretic effect [Szentmihályi 1998].

Antihypertensive effects
A fluid extract (1:1) of blackcurrant leaf had an antihypertensive effect on cats, with an antihypertensive quotient of 1.82 at an oral dose equivalent to 400 mg dried leaf/kg, the effect lasting for 15-20 minutes; tolazoline had comparable antihypertensive quotients, 1.69 at 0.75 mg/kg and 2.12 at 1.0 mg/kg, but the effect lasted for only 5 minutes [Rácz-Kotilla 1977].

An infusion of blackcurrant leaf (20 g/litre), administered intravenously to normotensive rats at a dose equivalent to 360 mg dried leaf/kg b.w., produced a rapid fall of 45% in arterial blood pressure and the decrease was still 30% after 30 minutes [Lasserre 1983].

Pharmacokinetic properties
No data available.

Preclinical safety data
A lyophilized 14%-ethanolic extract (1 g of lyophilizate equivalent to 1.8 g of blackcurrant leaf), administered orally to rats at 2 g/kg/day for 21 days or 1.34 g/kg/day for 28 days, revealed no signs of toxicity and no gastric ulceration was observed [Declume 1989].

Rats treated orally for 28 days with a lyophilizate prepared after maceration of blackcurrant leaf (100 g/litre) in 15% ethanol for 10 days had no gastric ulceration. Compared to control animals no changes were apparent in food and fluid consumption or b.w., nor in results from blood analysis and histopathological evaluation of 14 different organs. In an acute toxicity study of the same lyophilizate in mice, the i.p. LD_{50} was 1.09 g/kg; oral doses up to 3 g/kg showed no overt toxicity [Mongold 1993].

The i.p. LD_0 and LD_{50} values of a blackcurrant leaf fluid extract (1:1) in mice were 22 and 49 g/kg respectively [Rácz-Kotilla 1977].

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E/S/C/O/P
MONOGRAPHS

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