

REVIEW ARTICLE

A Systematic Review on the *Rosa canina* Effect and Efficacy Profiles

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Rose hip, rose hip and seed and rose hip seed, all were negatively monographed by the German Commission E due to insufficient evidence of effects and effectiveness. Therefore a comprehensive review of the literature was conducted to summarize the pharmacological and clinical effects of *Rosa canina* L. to reevaluate its usefulness in traditional medicine.

For various preparations of rose hip and rose hip and seed, antioxidative and antiinflammatory effects have been demonstrated. Lipophilic constituents are involved in those mechanisms of action. The proprietary rose hip and seed powder Litozin[®] has been employed successfully in a number of exploratory studies in patients suffering from osteoarthritis, rheumatoid arthritis and low back pain. However, the sizes of the clinical effects for the different indications need to be determined to assure clinical significance.

There is also a rationale behind the use of Litozin[®] as part of a hypocaloric diet based on the rose hip probiotic, stool regulating and smooth muscle-relaxing actions, as well as the rose hip seed lipid-lowering, antiobese and antiulcerogenic effects. Further research is needed to clarify the importance of the reported promising experimental effects in clinical use and to characterize the optimum rose hip seed oil preparation for topical use in the treatment of skin diseases. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: *Rosa canina*; rose hip; rose hip seed; pharmacological effects; clinical efficacy.

INTRODUCTION

The rose hip (or rose haw) is the pseudofruit of the rose plant. Rose hips of some species, especially *Rosa canina* (dog rose), are known as valuable sources of vitamin C. In 1990, the German Commission E published three monographs on the traditional use of various species of the genus *Rosa* L.: rose hip (*Rosae pseudofructus*, the ripe, fresh or dried seed receptacle, freed from seed and attached trichomes), rose hip and seed (*Rosae pseudofructus cum fructibus*, the ripe, fresh or dried pseudofruits including the seed) and rose hip seed (*Rosae fructus*, the ripe, dried seed) (Blumenthal, 1998). The weight of a rose hip and seed ranges from 1.25 to 3.25 g of which 71% constitutes the pericarp and approximately 29% the seed. A highly significant positive correlation was found between the fruit weight and the percentage of fruit flesh, but a moderate negative correlation between fruit weight and percentage dry matter (Uggla *et al.*, 2003).

In traditional medicine, 2–5 g of the plant material is used to prepare an aqueous extract, e.g. for a cup of tea, taken 3 to 4 cups per day. An infusion of rose hip and seed contained less vitamin C than a decoction over 10 min (Winckelmann, 1938; Peplau, 1941). The vitamin C content decreased considerably within 24 h

(Bogdan and Veturia, 1994). However, in a maceration the vitamin C content increased within 48 h (Peplau, 1941). Tea from the dried fruit contained more vitamin C than tea from half-dried (still moist) (Bogdan and Veturia, 1994) or frozen (Yavru and Kadioglu, 1997) fruit. Spiro and Chen (1993) measured the vitamin C concentration in aqueous infusions of rose hip sieved into narrow size ranges of 600–710 g, 850–1000 g and 1180–1400 g. To prevent aerial oxidation, the experiments were carried out under anaerobic conditions. The rate of vitamin C extraction decreased with increasing particle size but it showed little variation with temperatures from 70 to 90 °C or with the pH of the extracting medium. Optimum temperature and infusion periods to achieve the maximum content of vitamin C in the tea from dried or divided frozen fruit were found to be 60 °C and 360 min (dried fruit) and 60 °C and 270 min, respectively (Yavru and Kadioglu, 1997).

Dried rose hips contained more folate per 100 g than fresh rose hip. However, in commercial products, e.g. soups, only minor amounts of folate and vitamin C were found, probably because the duration of the preparation and high temperatures might have destroyed both active constituents (Stralsjö *et al.*, 2003). Three different brands of tea bag containing dried rose hip were mixed and pulverized and 0.5 g was taken to determine minerals and trace elements. Fourteen minerals were identified in the powder Ca 18 mg/kg, Mg 1909 mg/kg, Fe 267 mg/kg, Al 157 mg/kg, Mn 244 mg/kg, Zn 22 mg/kg, Cu 5 mg/kg, Sr 59 mg/kg, Ba 47 mg/kg, Ni 2.9 mg/kg, Cr 0.9 mg/kg, Co 0.4 mg/kg,

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Pb 0.3 mg/kg and Cd 0.1 mg/kg and were detected in tea (prepared from 0.5 g rose hip in 25 mL water for 30 min at 95 °C) in percentages of 6%, 72%, 14%, 4%, 20%, 28%, 60%, 25%, 52%, 25%, 66%, 27% and not detectable, respectively (Basgel and Erdemoglu, 2006). Chen and Spiro (1993) determined the concentrations of nine inorganic and organic cations and anions by ion chromatography in a German rose hip tea. The major cation present was potassium (1.16%) followed by calcium (0.6%), sulphate (0.21%), sodium (0.18%) and magnesium (0.15%). Minute amounts of chloride, phosphate and organic acids were found in equilibrium infusions at 80 °C.

Since the evidence for some of the health claims attributed to the rose hip parts was not sufficiently documented and for others not documented at all (Table 1), therapeutic indication was not recommended by the Commission E for any of the plant parts or preparations thereof. The aim of this systematic review was to update the knowledge on the effects and efficacy of *Rosa canina* L.

METHODS

Computerized literature searches were carried out (OVID(MEDLINE), PUBMED and COCHRANE COLLABORATION LIBRARY back to 1985) to identify studies with *Rosa canina* ('or' rose hip). Hand searches were performed by searching the authors' own files and the bibliographies of all located papers. No restrictions regarding the language of publication were imposed. Authors CC and SC extracted the data independently and discussed the findings and any disagreements.

Pharmacological properties from *in vitro*, *in vivo* and human pharmacological studies

Various preparations and isolated constituents from rose hip, rose hip and seed and rose hip seed have been studied in a variety of *in vitro* and *in vivo* tests.

Antioxidative activity. An extract was prepared by adding 50 mL of methanol/HCl 2% (95:5 v/v) to 20 g of rose hip and seed, homogenized and centrifuged. The extract contained 6 mg/mL of polyphenols expressed as gallic acid equivalents (pH differential method) and was assayed within 1 h of preparation. Superoxide radical scavenging activity expressed as % inhibition of nitroblue tetrazolium was 86% and the lipid peroxidation IC₅₀ 3.8 µg/mL (Costatino *et al.*, 1994). Likewise, extract prepared with 70% aqueous acetone from 500 mg ground lyophilized rose hip and seed (the supernatants were dried and the solid residue dissolved in methanol) containing 13 mg of gallic acid equivalents inhibited the oxidation of methyl linoleate *in vitro* (Kähkönen *et al.*, 1999).

Gao and coworkers (2000) investigated a crude extract prepared with 50% ethanol from powdered rose hip sine fructibus and its phenolic, ascorbinic and lipophilic fractions. For these, undiluted crude extract was extracted twice with CHCl₃, dried and dissolved in ethanol 95% (lipophilic fraction containing about 0.06 mg β-carotene

equivalents/g dried powder). The aqueous phase was used as the ascorbic fraction (ascorbate content about 15 mg/g dried powder) and after incubation with ascorbate oxidase as the ascorbate-free extract (phenolic fraction, containing about 60 mg/g gallic acid equivalents dried powder). A battery of tests was employed: the ferric-reducing antioxidant power assay, the Trolox-equivalent cation radical scavenging assay, the 2,2'-azobis(2,4-dimethylvaleronitrile)- and the 2,2'-azobis(2-amidino-propane)hydrochloride-induced lipid peroxidation and the ascorbate-ferric ion-induced lipid peroxidation assays. High antioxidative activities were seen in all assays. The phenolic fraction made a major contribution to the antioxidative activity. However, the lipophilic component was the most effective when the results were compared based on the relation between total antioxidant capacity and the content of antioxidants. Ascorbate acted as an antioxidant in all assays except the ascorbate-ferric ion-induced lipid peroxidation (Gao *et al.*, 2000). Likewise, Daels-Rakotoarison and co-workers (2002) prepared a rose hip extract deprived of vitamin C. Crushed rose hip was macerated in acetone/water (60/40, v/v), the filtrate concentrated, the remaining phase washed with dichloromethane then with ethyl acetate and concentrated under low pressure and excess chloroform leading to a precipitate which was dried and used for the experiments. This extract contained mainly phenolics (proanthocyanidins 132 mg%, flavonoids 15 mg%, no vitamin C) and inhibited oxygen radicals in both cell-free and cellular systems. The IC₅₀ values were 5.7 mg/L, 1.3 mg/L and 2.3 mg/L in scavenging superoxide anions, hydrogen peroxide and hypochlorous acid, respectively. For cellular experiments, the IC₅₀ values were quite similar (Daels-Rakotoarison *et al.*, 2002). In an earlier study from Russia, an anthocyanin derivative, pelargonidin-3,5-diglucoside prepared from *Rosa canina*, had a pronounced radioprotective effect in the absence of toxic effects (increased mouse survival) (Akhmadieva *et al.*, 1993).

The ischemia/reperfusion injury in the mouse colon is another established model to study the antioxidative effect of agents. The rose hip powder containing 863 mg% vitamin C and 82% carbohydrates, had a significantly additive effect on the *Lactobacillus plantarum* DSM 9843-inhibitory effect on caecal malondialdehyde (MDA) as an index of lipid peroxidation. A positive correlation between MDA and Enterobacteriaceae count was found. The authors concluded that rose hip and *L. plantarum* should be used as a pre-treatment to tissue injuries, e.g. colon surgery, organ transplantation and vascular surgery (Hakansson *et al.*, 2006).

Antiinflammatory activity. The chemoluminescence assay is another measure of oxygen radical generation by activated polymorphonuclear neutrophils (PMN). Rose hip and seed aqueous extract at concentrations of 500 µg/mL and higher inhibited chemoluminescence of PMN activated by opsonized zymosan and also chemotaxis of the human cells. Sole aqueous rose hip seed extract was significantly less active, whereas an aqueous extract from the seed receptacle freed from seed was more active than extract from rose hip and seed up to a dose of 1000 µg/mL (Kharazmi and Winther, 1999). A galactolipid was identified as the co-active ingredient for the inhibitory effect on chemotaxis in PMN (Larsen *et al.*, 2003).

Table 1. Constituents in the rose hip components and traditional use (modified after Anonymous, 1998; Blumenthal, 1998; Hyattum, 2002; Böhm *et al.*, 2003; Salminen *et al.*, 2005; Koponen *et al.*, 2007; Nowak 2005; 2006a, b; Özcan, 2002)

	Rosae pseudofructus	Rosae fructus	Rosae pseudofructus
Constituents	up to 1.8% of total ascorbic acid; 3% malic and citronic acid; up to 11% pectin acid; up to 8.3% (pro)anthocyanins including lycopene up to 35 mg/100 g; flavonoids (isoquercetin, kempferol, rutin, quercetin, hyperoside, tiliroside); up to 15% total sugar; up to 3% fatty oil (55% linoleic acid, 20% linolenic acid, 0.08% carotenoids); elagitannins, ellagic acid, galactolipid, vitispiran	up to 10% fatty oil with unsaturated fatty acids and polyunsaturated fatty acids (2.5% palmitic, 2% stearic, 52% linoleic, 17% linolenic, 2% arachidonic acid; traces of essential oil; tannins, mucilage; up to 12% proteins, up to 1.5% phospholipids; minerals; galactolipid, conjugated phenolic acids	up to 2.4% of total ascorbic acid (10–20% dehydroascorbic acid); 3% malic and citronic acid; up to 8.3% (pro)anthocyanins; up to 11% pectin; flavonoids; in the fruit flesh up to 0.02% carotenoids (β - and γ -carotene, xanthophyll, lutein); phenolic acids
Traditional Use	prevention and treatment of common colds; influenza-like infections; infectious diseases; for vitamin C deficiencies; fever; general exhaustion; gastric spasms; prevention of gastritis and gastric ulcers; diarrhea; as a laxative; for gallstones and gallbladder discomforts; urinary tract diseases and discomforts; as a diuretic; for gout, arthritis, sciatica, diabetes, inadequate peripheral circulation, as an astringent, for lung ailments, as an eye rinse	for diseases and ailments of the kidneys and lower urinary tract; as a diuretic; for arthritis, rheumatism, gout, sciatica; for Colds; as a laxative; for fever; for vitamin C deficiency and for 'blood purification'	prevention and treatment of common colds; chills influenza-like infections; infectious diseases; for vitamin C deficiencies; gastric juice deficiencies; bowel disorders; to aid digestion; for gallstones and biliary complaints and colics; complaints and disorders of the urinary tract; edema, as a diuretic; for arthritis and rheumatoid disorders; as an eyewash, for worm diseases

An aqueous extract prepared from rose hip seed did not inhibit the prostaglandin biosynthesis and platelet activating factor-induced exocytosis of elastase (Tunon *et al.*, 1995). However, a recent short communication reported that if rose hip and seed were extracted with organic solvents (e.g. methanol, dichloromethane and hexane) both COX-1 (sheep seminal vesicles) and COX-2 (human recombinant) were inhibited *in vitro*. However, the aqueous extract was also ineffective in these tests. The methanol extract was the most potent with IC₅₀ values of 12 μ g/mL and 19 μ g/mL for COX-1 and COX-2, respectively (Jäger *et al.*, 2007). Lipophilic extracts of rose hip *sine fructibus* had lower IC₅₀ values in the COX-1 and COX-2 *in vitro* assay than lipophilic extracts from rose hip and seed and even inhibited LOX (Wenzig *et al.*, 2007; Wenzig, personal communication 2007).

In *Rosa canina* root, constituents with inhibitory effects on inflammatory mediators of cartilage destruction, such as Il-1R, Il-1 and TNF-R were found (Yesilada *et al.*, 1997). It remains to be established if such ingredients are also contained in rose hip or rose hip seed.

Two types of rose hip and seed extracts (solvents water and ethanol 80%) were screened in mice for antiinflammatory and antinociceptive activity. The mice were treated once (for acute administration) or for 7 days (for subacute administration) by gastric gavage with 3496 mg/kg of the aqueous extract or 2628 mg/kg of the ethanol extract (which corresponds to a human dose of 10 g per day). The ethanol extract showed a greater inhibitory effect compared with the aqueous extract on carrageenan-induced and PFE₁-induced hind paw edema, on acetic acid-induced increase in capillary permeability and on p-benzoquinone-induced writhing. The activity of the extracts was not increased significantly by subacute administration. Fractions of the ethanol extract prepared with hexane, trichloromethane, ethyl acetate, butanol and the remaining water fraction were then tested. The ethyl acetate and *n*-butanol fractions displayed anti-inflammatory and antinociceptive activities at a dose of 919 mg/kg without inducing acute toxicity (Deliorman Orhan *et al.*, 2007), indicating that the antiinflammatory principle is probably lipophilic.

PMN chemotaxis before and after consuming 45 g of rose hip and seed powder over 28 days inhibited chemotaxis of isolated polymorphonuclear neutrophils *ex vivo/in vitro* (Kharazmi and Winther, 1999). In a cross-over human pharmacological study, in which the volunteers first received 45 g rose hip and seed powder over 28 days and thereafter 10 g powder per day, it was shown that the antiinflammatory effect in terms of *ex vivo/in vitro* chemotaxis of PMN was dose-dependent (Winther *et al.*, 1999). Moreover, C-reactive protein (a marker of inflammation) as well as creatinine values decreased significantly. After stopping the intake of the powder, these values increased to the pre-values again (Kharazmi and Winther, 1999; Winther *et al.*, 1999).

Effects on body fat, plasma and biliary lipids. An 80% acetone extract from rose hip and seed (50 mg/kg) or seed (12.5 and 25 mg/kg) were found to show substantial inhibitory effect on the gain of body weight and/or weight of visceral fat (total weight of epididymal, mesenteric and paranephric fats) without affecting food intake in mice for 2 weeks after administration of the extracts and with no obvious toxic effect (Ninomiya *et al.*, 2007). Extracts from the rose hip (pericarp or

shell) 100 and 200 mg/kg/day did not show such an effect. In addition, plasma triglyceride and free fatty acid levels were significantly reduced on day 14 following the rose hip and seed or the rose hip seed lipophilic extract. As main constituent, *trans*-tiliroside was identified, that inhibited dose-dependently body weight gain and visceral fat weight in a dose of 0.1–10 mg/kg/day. Structurally similar constituents such as kaempferol 3-O- β -D-glucopyranoside, kaempferol and *p*-coumarin acid at a dose of 10 mg/kg/day had no significant antiobese effects. A single dose of *trans*-tiliroside at a dose of 10 mg/kg increased the expression of peroxisome proliferator-activated receptor-mRNA levels in liver tissue after 24 h. The authors suggested that lipid metabolism was promoted by the oral administration of *trans*-tiliroside (Ninomiya *et al.*, 2007).

Plasma lipids of male golden Syrian hamsters fed diets supplemented with 15% (w/w) rose hip seed (species not stated), sunflower, olive and coconut oils were assessed for 4 weeks. Whereas the oils with a low polyunsaturated index of 1.3 (olive oil) and 0.03 (coconut oil) increased all blood lipids, total cholesterol, HDL cholesterol and triglycerides were not affected by the oils with a high polyunsaturated index of 17.6 (rose hip oil) and 9.2 (sunflower oil). The authors suggested that the content of *n*-6 linoleic acid might be responsible for this (Gonzales *et al.*, 1997). In an earlier study (Gonzalez *et al.*, 1989), the group fed rats with a diet with 20% corn or rose hip oil or without any oil (control) over 35 days. Bile flow was similar in the groups, but cholesterol concentrations and biliary cholesterol output were higher in the rats receiving rose hip oil, as was the cholesterol/phospholipid ratio as an indicator for promoting the development of gallbladder stones. Rat plasma cholesterol and triglyceride concentrations were significantly lower after the rose hip oil diet than in the control animals. This was attributed to lower concentrations of VLDL and HDL cholesterol, resulting in a higher LDL/HDL cholesterol ratio compared with the control.

Hepatocyte membrane fluidity expressed by the anisotropy of fluorescence polarization of 1,6-diphenyl-1,3,5-hexatriene was decreased by the rose hip seed and corn oils. The authors suggested that based on the increased cholesterol/phospholipid ratio the hepatocyte cholesterol synthesis might be stimulated by the oils. In this study an oil of the *Rosa moschata* species has been used, but it seems likely that the results are similar for *Rosa canina* seed oil since the linoleic/linolenic fatty acid ratios of both oils are similar (Gonzalez *et al.*, 1989; Özcan, 2002). Likewise, in rats fed *ad libitum* diets containing 5% or 15% rose hip (probably seed) oil for 15 or 60 days, the plasma concentrations of cholesterol and triglycerides were not affected, although the plasma cholesterol tended to be lower in rats fed with the 15% oil (Lutz *et al.*, 1993). During the first 15 days of the 5% and 15% rose hip oil diet, higher concentrations of cholesterol were measured in the bile, whereas the biliary concentration of phospholipids and bile acids decreased. An elevated cholesterol/phospholipid ratio is generally considered as lithogenic, thus the lithogenic index was higher in the rats fed with 15% oil (Lutz *et al.*, 1993).

Antiulcerogenic and probiotic effects. An aqueous extract prepared from 10 g rose hip seed with a yield of

21% in a dose of 2 g/kg prevented gastrointestinal lesions caused by 96% ethanol if administered 15 min prior to the ethanol administration. The ulcer index, defined as the sum of lesions in mm, was zero (Gürbüz *et al.*, 2003). Likewise, no ulcers were seen in experiments in mice investigating the analgesic and antiinflammatory effect of aqueous and ethanol rose hip seed extracts and fractions obtained with lipophilic solvents (Deliorman Orhan *et al.*, 2007).

In a human pharmacological investigation, 22 healthy volunteers received a proprietary rose hip drink over 3 weeks and another 26 volunteers, a rose hip drink containing oats fermented with *Lactobacillus plantarum* 9843. In both groups, the numbers of faecal bifidobacteria and lactobacilli were significantly increased. No changes were seen in the numbers of anaerobes, Gram-negative anaerobes or total aerobes during administration. During the period of intake, the volunteers receiving the fermented drink experienced a significant increase in stool volume and a significant decrease in flatulence and slightly softer stools, whereas the stool volume was slightly decreased during the intake of proprietary rose hip drink (Johansson *et al.*, 1998). Unfortunately, it was not stated whether rose hip or rose hip and seed was used nor the dose administered daily.

Effect on blood glucose. Male hamsters were fed with diets containing 15% rose hip, olive or coconut oil for 4 weeks. Thereafter, the intestines were removed. The concentrations of glucose in the serosal solution was quantified in pieces of everted intestine at 20, 40 and 60 min. The mucosal solution contained 0.6% glucose. A lower concentration of glucose was observed in the group with the olive oil diet although this was only statistically significant when compared with the rose hip and coconut oil diet groups (Gonzales Barra *et al.*, 1995).

The effects of aqueous and ethanol extracts on blood glucose were investigated in rabbits. For the aqueous extract, 50 g of dried rose hip and seed were macerated with 500 mL water, boiled for 30 min and the filtrate evaporated to dryness; the yield was 23% of the starting material and dissolved in 15 mL water or 35 mL of 70% glucose. For the ethanol extract, 70 g of dried rose hip and seed was extracted with 96% ethanol; the yield was 17% of the starting material and dissolved in 10 mL water. The rabbits were divided into seven groups of five animals each. After collecting a fasting blood sample, group 1 (control) was given orally 1 mL/kg saline, groups 2 and 3 aqueous rose hip and seed extract (2 g/kg and 4 g/kg of original dry starting material), groups 4 and 5 ethanol rose hip and seed extract (200 mg/kg and 400 mg/kg), group 6 (glucose control) 70% glucose 1 g/kg and group 7 aqueous extract 2 g/kg suspended in glucose solution. None of the extracts had a blood glucose lowering effect (Can *et al.*, 1992). However, for the constituent *trans*-tiliroside a blood glucose lowering effect after glucose loading (1 g/kg i.p.) was demonstrated in doses up to 10 mg/kg/day (Ninomiya *et al.*, 2007).

Effects on urine excretion and composition. Twenty rats were given 5 mL of water or tea prepared from 5 g or 10 g powdered rose hip and seed per 100 mL, respectively. Urinary excretion was determined after 45 and

60 min and after 4 h. A 40% reduced excretion of urine volume was observed with the rose hip and seed 10% infusion after 45 min. The author suggested that the initially reduced diuresis might have been caused by the pectin-containing mucilage of the rose hip and seed preparation (Jaretzki, 1941). An infusion of rose hip seed had only a minor diuretic effect in a self-experiment and in healthy volunteers. Excretion of urea, sodium and calcium were not affected (Peplau, 1941). In rats, an oral infusion of rose hip seed 2% had no effect on urea and chloride excretion, nor on uric acid, sodium and calcium excretion, whereas the chloride and uric acid excretion was increased by 11% following administration of the 5% infusion of rose hip and seed (Jaretzki, 1941). Likewise, Grases and coworkers (1992) did not observe any diuretic effect during 12 days and no effect on creatinine, phosphate and oxalate concentrations and excretion when water was replaced by a rose hip seed infusion 5 g/L (prepared with boiling water and filtered) in rats receiving a balanced diet. However, calciuria decreased and citraturia increased, indicating a possible beneficial effect of rose hip seed tea in calcium oxalate urolithiasis. While magnesium chloride decreases urine pH, such an acidifying effect was not observed during concomitant administration of the rose hip seed infusion (Grases *et al.*, 1992).

Effects on muscle tone and nerve conduction. In 1941, Peplau did a battery of experiments with an ethanol fluid and aqueous rose hip and rose hip and seed extracts prepared according to DAB 6. On isolated frog hearts, the aqueous and ethanol rose hip preparation decreased ventricular contractions in a dose equivalent to 10–50 mg crude dried drug. Decoctions (20 min) and ethanol extracts of rose hip seed equivalent to 10–20 mg increased dose-dependently the cardiac muscle tone.

In decapitated frogs in which the aorta was connected to a saline reservoir and the abdominal vein to a device that counted the number of drops of the perfusate, aortal injection of 2–6 mL of ethanol or aqueous extracts of rose hip decreased the drop number from 16–18 to 10–11, indicating a vasoconstrictive effect. When using 0.5 mL of a 10% rose hip seed aqueous extract the number of drops only tended to decrease (Peplau, 1941). In isolated rat and mouse smooth muscle preparations from the uterus the muscle tone decreased following the rose hip seed administration. There was no difference attributable to species (each $n = 8$). A decrease in the mean muscle tone of the uterus was observed after 0.5–1.5 mL ethanol fluid extract, and paralysis of the uterus following 2.5–7 mL. Isolated smooth muscle preparations from the small intestine and the colon of both species were more sensitive to rose hip preparations. For the small intestine and the colon, the doses for relaxation and paralysis were 0.1–0.2 mL and 0.2–0.5 mL, respectively.

In contrast, 4 mL and 10 mL of a 10% decoction of rose hip seed increased uteri muscle tone dose-dependently. Whereas the contractility was doubled, the number of contractions per minute decreased. Similar results were achieved for the isolated small intestine and the colon muscle preparations. Neither rose hip nor rose hip and seed extracts had any impact on nerve conduction in an isolated nerve–muscle preparation (details not stated; Peplau, 1941).

Antimutagenic and anticancerogenic effects. Rose hip (unclear if *cum* or *sine fructibus*) boiled at 100 °C and then stewed for 10 min was investigated in mutagenicity and antimutagenicity tests (Ames test). Raw, boiled juice, boiled leaves and dried seeds of rose hip were not found to be mutagenic in *Salmonella typhimurium* TA 100. Raw rose hip decreased the sodium azide mutagenicity by 44% which was in the range of raw nettle herb. Unfortunately, this experiment did not test whether there was a difference between rose hip and rose hip seed (Karakaya and Kavas, 1999).

Dried rose hip seed (100 g) was extracted with petroleum ether, with ethanol 95% and water, with yields of 0.3%, 5.9% and 10%, respectively. Whereas the aqueous rose hip seed extract showed only a poor cytotoxic effect on Yoshida ascites sarcoma cells ($LD_{50} > 10$ mg/mL), the ethanol and petroleum ether extracts demonstrated a significant cytotoxic effect with LD_{50} values of 3.9 and 1.2 mg/mL, respectively, indicating a possible anticancerogenic effect (Trovato *et al.*, 1996).

Antimicrobial effects. Methanol, dichloromethane and *n*-hexane rose hip seed extracts were assessed for their antibacterial activity against 11 pathogenic Gram-positive and Gram-negative bacterial species. Only the methanol extract demonstrated a weak antibacterial effect and only against *E. coli* 8110 (Kumarasamy *et al.*, 2002).

Dried rose petals were homogenized in 70% acetone and filtered. The acetone extract was then concentrated and extracted with diethylether, butanol and ethyl acetate, successively. The ethyl acetate extract had the highest minimal inhibitory concentration (MIC) of β -lactams against methicillin-resistant *Staphylococcus aureus* and also reduced the MICs of benzylpenicillin and ampicillin. Two polyphenols were isolated: tellimagrandin I was more effective than rugosin B and had a synergistic effect to oxacillin in reducing the MIC in methicillin-resistant *Staphylococcus aureus*. The MICs of oxacillin were reduced from 128–512 μ g/mL to 1–2 μ g/mL, restoring the effectiveness of β -lactams against methicillin-resistant *Staphylococcus aureus*. Tellimagrandin I also significantly reduced the MIC of tetracycline in some strains of methicillin-sensitive *Staphylococcus aureus* (Shiota *et al.*, 2000).

The group also showed that inactivation of penicillin binding proteins is involved in this mechanism of action as well as a partial inhibition of β -lactamase. Since the chelating agents and radical scavengers tested did not affect the MICs of oxacillin in the bacteria, the authors concluded that the activity of constituents is not exerted via an antioxidative effect (Shiota *et al.*, 2004).

The petroleum ether, ethanol and aqueous extracts investigated in the study on the cytotoxic effects of rose hip seed (Trovato *et al.*, 1996) were also tested for their antimycotic activity on strains of *Candida albicans*. The ethanol rose hip seed extract had a modest but significant antimycotic effect (Trovato *et al.*, 2000).

OTHER EFFECTS

Peplau (1941) also did some toxicological experiments with the aqueous and ethanol extracts described above. Frogs receiving 0.5–1.5 mL of a 9-month-old batch (vitamin C content 60 mg%) into the dorsal lymph

sac did not show any abnormal signs, nor to a freshly prepared extract. A decoction equivalent to 0.25–0.75 g crude rose hip or 0.5–1.5 mL of a decoction of rose hip seed were also well tolerated, as were subcutaneous administration of rose hip aqueous and ethanol extracts in rodents. However, a concentrated ethanol rose hip extract resulted in death of all mice and rats, although rats were slightly more sensitive, being centrally depressed for hours before they died. For the rose hip ethanol fluid extract, a minimum lethal dose could not be determined in frogs. In mice the dose was 0.9–1.1 mL and in rats 0.7–0.9 mL. For rose hip seed a minimum lethal dose could not be determined in any of the species.

On isolated frog hearts, aqueous and ethanol rose hip preparations caused diastolic cardiac arrest in doses equivalent to 16–21 mg. After washing out the rose hip solutions, a 30% increased contractility was observed associated with positive inotropic and negative chronotropic effects. The cardiac arrest was reversible in all cases by washing the isolated heart with isotonic saline, even after a duration of 4–5 min.

Decoctions (20 min) and ethanol extracts of rose hip seed caused diastolic cardiac arrest at a dose of 47 mg (decoction) and 39 mg (ethanol extract). Cardiac arrest was also reversible, even after several minutes of cardiac arrest.

None of the rose hip and rose hip seed preparations caused hemolysis on isolated human erythrocytes in dilutions of 1:1 000 000 to 1:10.

In a human pharmacological study, healthy smokers received randomly and double-blind either a rose hip drink with 11.2 g rose hip powder per day ($n = 18$) or a test product with roughly the same amount of rose hip containing in addition *Lactobacillus plantarum* 299v 5×10^7 colony-forming units ($n = 18$). Compared with the test product, the proprietary rose hip drink was not effective in decreasing systolic blood pressure, plasma leptin, fibrinogen, F2-isoprostanes and interleukin-6.

Whereas *ex vivo/in vitro* the generation of oxygen species in resting and phorbol myristate acetate-activated monocytes was not affected, the adhesion to native and stimulated human umbilical vein endothelial cells was significantly decreased. The authors concluded that the proprietary rose hip drink – in contrast to that with *Lactobacillus plantarum* – had no impact on cardiovascular risk factors in smokers (Naruszewicz *et al.*, 2002).

CLINICAL STUDIES

Six clinical studies were identified. Four of them were carried out with a rose hip and seed powder from the subspecies *lito*. The quality of all studies is summarized in Table 2a and b using different classifications (Chrubasik *et al.*, 2003; 2004; Gagnier *et al.*, 2004). A systematic review (Chrubasik *et al.*, 2006) that had identified four studies investigating Litozin^R in patients suffering from osteoarthritic complaints (Warholm *et al.*, 2003; Rein *et al.*, 2004a; Rein *et al.*, 2004b; Winther *et al.*, 2005) discovered that 2 of them were subgroup analyses (Rein *et al.*, 2004a; Winther *et al.*, 2005). Whereas a later systematic review (Rosnagel *et al.*, 2007b) on the effectiveness of *Rosa canina* in osteoarthritis also included the two studies by Warholm and co-workers (2003) and Rein and co-workers (2004), a recent systematic review did not identify the subgroups and presented a meta-analysis with all four studies, favouring the effectiveness of Litozin^R (Christensen *et al.*, 2007). Recently presented exploratory studies were carried out in patients suffering from inflammatory rheumatic complaints (Rosnagel *et al.*, 2007a) and chronic low back pain (Chrubasik *et al.*, in press).

Although evidence of the effectiveness is only moderate for osteoarthritis (two exploratory clinical studies of good quality, Chrubasik *et al.*, 2006) and

Table 2a. A eligibility criteria specified, B randomization appropriate, C treatment allocation concealed, E similarity at baseline, F outcome measures and control interventions explicitly described, G co-interventions comparable, H outcome measures relevant, I adverse events and J drop-outs fully described, K sample size based on a priori power calculation, L intention-to-treat analysis, N point estimates and measures of variability presented for the primary outcome measure, O appropriate timing giving a Total Score (TS) of 13

	<i>Phytomedicine</i> 2004; 11: 383–391	<i>Curr Ther</i> <i>Res Clin Exp</i> 2003; 64: 21–31	<i>Ann Rheum Dis</i> 2007; 66(Suppl 2): 603	<i>Ann Rheum Dis</i> 2007; 66(Suppl 2): 625	<i>Am J Gastroenterol</i> 2000; 95: 1231–1238
	$n = 112$	$n = 100$	$n = 89$	$n = 152$	$n = 60$
	5 g/day vs placebo cross-over over 3 months	5 g/day vs placebo Parallel over 4 months	5 g/day vs placebo Parallel over 6 months	5 g or 10 g/day Open over 12 months	?? g/day Open over 4 weeks
A	OA multiple sites	hip, knee	rheumatoid arthritis	chronic low back pain	Irritable bowel syndrome
B	yes	yes	yes	no	yes
C	yes	yes	yes	no	yes
E	yes	don't know	don't know	not applicable	don't know
F	yes	yes	yes	yes	yes
G	yes	yes	yes	not applicable	yes
H	yes	yes	yes	yes	yes
I	yes	yes	yes	yes	no
J	yes	yes	yes	yes	yes
K	no	no	don't know	no	no
L	yes	yes	yes	yes	no
N	no	no	not stated	yes	no
O	yes	yes	yes	yes	no
% of TS	85%	80%	69%	62%	54%

Table 2b. Internal and external validity items in chronologically listed studies investigating the proprietary rose hip and seed powder Litozin[®] (methods in Chrubasik *et al.*, 2003); 1 Warholm *et al.*, 2003, 2 Rein *et al.*, 2004b; 3 Rossmagel *et al.*, 2007b; 4 Chrubasik *et al.*, in press; 5 Nobaek *et al.*, 2000; * baseline evaluation too short

Study Number from Table 1	Internal			Validity			External			Validit		
	Randomization and/or allowance for confounding	Blinding and masking of outcome assessment	Attrition-number of Dropouts and intention-to-treat and/or sensitivity analyses	Appropriate tests of null and alternative hypotheses in pre-specified POM and/or MV testing null alt	Inclusion and exclusion criteria and/or baseline description of patients and their complaints	Treatment type and availability of additional treatments	Setting (number of centres)	Validated outcome measures included	Duration of Study (m months) (w weeks)	Number of patients with adverse events		
1	Y	Y	2V, 2P 13V, 14P	N	Y	Y	1	Y	4m 3mV, 3mP	2V, 2P 10V, 10P		
2	Y	Y	Y	N	Y	Y	1	Y	6m	14V, 26P 27V with n = 33 not stated		
3	Y	Y	11V, 4P 75V	N	Y	Y	2	Y	12m	not stated		
4	not stated	N	Y	N	Y	Y	1	Y	4w			
5	Y	Y	5V, 3P	N	Y	Y*	1	Y				

poor for rheumatoid arthritis and chronic low back pain (one exploratory study only for each indication) there is no doubt of the overall anti-inflammatory and analgesic potential of Litozin[®]. Studies that objectify the effect sizes are urgently needed to assure clinical significance before the rose hip and seed powder may be considered in treatment guidelines. As a specific adverse event in rare cases, allergy may occur. Allergy with generalized exanthema and gastrointestinal complaints may even occur after drinking rose hip tea (Leonart *et al.*, 2007). Otherwise, only minor gastrointestinal adverse events have been observed, mainly due to inappropriate concomitant liquid consumption: in the case of irritable bowel syndrome with constipation, 300–500 mL is required, since the plant fibres absorb the liquid, increase the stool volume and act as a laxative, in the case of irritable bowel syndrome with diarrhea, the powder should be taken with only small amounts of liquid. As generally suggested for plant intake, a gap of 2 h should be considered between the intake of powder and the intake of other medications so as not to risk any interaction in absorption.

A rose hip preparation (not clear whether it was rose hip or rose hip and seed) was investigated in a randomized double-blind study including 60 patients suffering from irritable bowel syndrome. They started to register their intestinal complaints 2 weeks before the administration of the products by means of a questionnaire. Patients receiving the proprietary rose hip drink as placebo profited less than those receiving additional *Lactobacillus plantarum* 9843, but abdominal pain was reduced in both groups (Nobaek *et al.*, 2000). A 2 week baseline recording is a very short time to describe irritable bowel syndrome complaints and likewise, the treatment period of 4 weeks was not long enough to objectify the effects. Since rose hip may exert some effects on the gastrointestinal tract it has not been well chosen as a placebo.

Recently, the powder Litozin[®] has been used as part of a hypocaloric diet in a dosage of 2 × 5 g per day (Vlachojannis *et al.*, 2007). Future research in this field is needed in the light of the rose hip probiotic, stool regulating and muscle-relaxant and the rose hip seed lipid-lowering, antiobesity and antiulcerogenic effects.

The topical use of rose hip seed oil in eczema, trophic ulcers of the skin, neurodermitis, cheilitis etc may also be promising, as observed in an exploratory study including 75 patients testing topical rose hip seed oil together with an oral polyvitamin preparation of fat-soluble vitamins (Shabykin and Godorazhi, 1967). Because the oil and the vitamins may have had a synergistic effect, this study is not listed in Table 2. A new extraction procedure may provide solvent-free oils by supercritical fluid extraction or carbon dioxide extraction while in the case of other extractions evaporation of the solvent is needed (Szentmihalyi *et al.*, 2002). Since the content of bioactive constituents in the oils prepared with ultrasound, microwave, sub- and supercritical fluid extraction was different, clinical studies are necessary to determine which oil is the best for topical use. Contact allergy to rose oil of other species, e.g. the flower petals of *Rosa damascena*, has been observed (Cockayne and Gawkrödger, 1997) and might therefore also be possible with topical use of *Rosa canina* oil. A rose hip keratitis was observed in a patient following rubbing his eyes after he ate a rose hip fruit (species not stated; Venkatsh *et al.*, 2005).

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