Folium Cynarae

Definition

Folium Cynarae consists of the dried basal leaves of *Cynara cardunculus* L. (Asteraceae) (*1–4*).

Note: The fresh lower part of the flower head is official in the *African pharmacopoeia* (*5*).

Synonyms

Cynara scolymus L. was the name of the plant cited in the above-mentioned pharmacopoeias and monographs. However, the correct name of the plant is *Cynara cardunculus* L. (Asteraceae) according to the currently accepted nomenclature (*6*).

Selected vernacular names

Alcachofa, alcachofra, alcaucil, alcaucoe, artichaut, artichaut commun, artichiocco, artichoke, artichoke thistle, Artischocke, artiskok, carcioffa, carciofo, carciuffolo, cardo alcachofero, cardo de comer, cardo senzaspine, cardoon, dofital 'roza, edible thistle, enginar, garden artichoke, Gemüseartischocke, globe artichoke, hathi choka, hatichuk, kangar, kangar I dahri, kharshoul, kharsuf, kunjor, Scotch thistle, som-eonggeongqui (*2*, 3, *5*, *7–13*).

Geographical distribution

Native to the Mediterranean, northern Africa and southern Europe, and the Canary Islands; cultivated in subtropical regions (*8*, *14*, *15*).

Description

A large herbaceous perennial, thorny plant, approximately 1.5 m in height. The leaves are large, alternate, deeply dentate. The tall purple flowers are grouped in large capitulums, 10–15 cm in diameter borne by hardy ramified grooved stems, with sessile and almost entire leaves (*5*, *14*, *16*).

Plant material of interest: dried leaves

General appearance

Leaves are very large, up to approximately 50 cm long by 25 cm wide with a long petiole approximately 1 cm thick; lamina deeply pinnatifid, forming flat, lanceolate segments with coarsely-toothed margins; upper surface brownish-green, lower surface greyish-white and densely covered with trichomes; segments with pinnate venation, the side veins terminating in a short point on each marginal tooth; midrib and petiole deeply grooved on the upper surface, the lower surface prominently raised, with several longitudinal ridges and covered with long, whitish trichomes (*1*, *2*, *17*).

Organoleptic properties

Odour: faint, slightly sour; taste: salty at first, then bitter (*1*, *2*, *17*).

Microscopic characteristics

Lamina: The dorsiventral view reveals a fairly large and loosely packed palisade layer of cells. Cells of the upper epidermis have straight to slightly sinuous anticlinal walls, whereas the cells of the lower epidermis are more wavy-walled. Anomocytic stomata on both surfaces, more numerous on the lower surface, with covering trichomes scattered on the upper epidermis, especially over the veins, very abundant on the lower epidermis; individual trichomes mostly of the whiplash type with several small cells forming the uniseriate bases and very long, narrow and sinuous terminal cells intertwining to form a felted mass covering the surface; other less numerous, uniseriate covering trichomes composed of 4–6 cells, tapering to a blunt apex with the cells sometimes more or less globular to ovoid; fairly large glandular trichomes also abundant on both surfaces, with short, 1- or 2-celled stalk and a spherical head filled with a brownish secretion.

Midrib and petiole: Epidermal cells rectangular and longitudinally elongated, with scattered glandular and covering trichomes similar to those in the lamina. Transverse section shows bands of collenchyma below both the upper and lower epidermises; a large vascular bundle in each ridge on the lower surface, and a number of smaller bundles arranged in an arc surrounding the groove on the upper surface; vascular bundles composed of a dense group of pericyclic fibres with thick, lignified walls, a wide area of thin-walled sieve tissue and a lignified xylem containing small vessels, tracheids and xylem parenchyma; below each xylem group a mass of lignified fibres, which, in the larger bundles, extends as a narrow layer on either side of the vascular tissue to join with the fibres of the pericycle; ground tissue composed of large-celled, rounded parenchyma, some with lignified walls (*1*, *2*).

Powdered plant material

Greyish-green to brown powder with faint odour; fragments of the lamina with more or less sinuous walls and anomocytic stomata; covering trichomes, scattered or in felted masses and large, glandular trichomes with brown contents; groups of lignified fibres and vessels from the midrib and petiole, the larger vessels with reticulate thickening (*1*, *2*).

General identity tests

Macroscopic and microscopic examinations (*1*, *2*, *17*), and thin-layer chromatography (*1*, *2*).

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 (*18*).

Foreign organic matter

Not more than 2.0% (*1*, *2*).

Total ash

Not more than 15.0% (*1*, *2*).

Acid-insoluble ash

Not more than 4% (*2*).

Water-soluble extractive

Not less than 25.0% (*2*).

Loss on drying

Not more than 8% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*19*). For other pesticides, see the *European pharmacopoeia* (*19*) and the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*18*) and pesticide residues (*20*).

Heavy metals

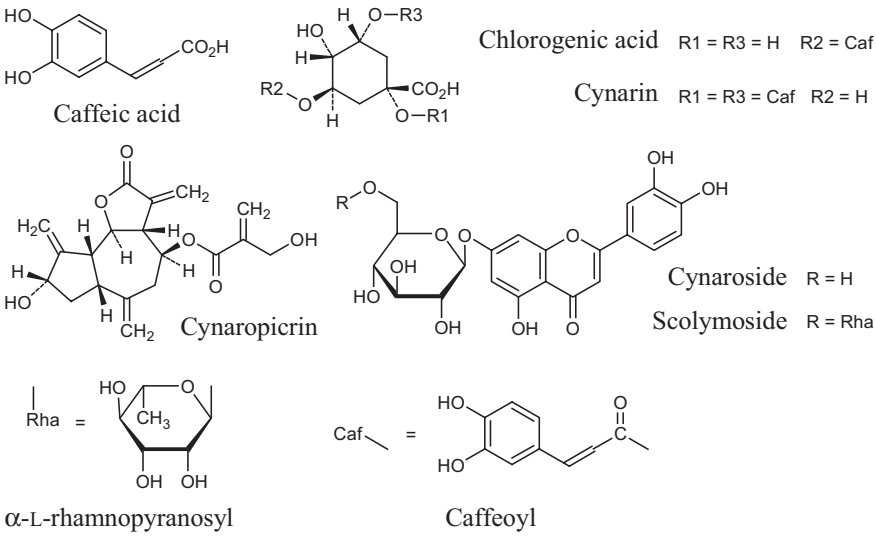
For maximum limits and analysis of heavy metals, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*18*).

Radioactive residues
Where applicable, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*18*).

Other purity tests
Chemical tests to be established in accordance with national requirements.

Chemical assays
To be established in accordance with national requirements.

Major chemical constituents
Contains up to 6% phenolic acids, including 1-*O*-caffeoylquinic acid, 3-*O*-caffeoylquinic acid (chlorogenic acid), caffeic acid, 4-*O*-caffeoylquinic acid, 5-*O*-caffeoylquinic acid, 1,5-di-*O*-caffeoylquinic acid (cynarin); up to 5% sesquiterpene lactones, with cynaropicrin being the primary component, followed by dehydrocynaropicrin, grosheimin and their derivatives; and flavonoids (0.35–0.75%) including scolymoside, cynaroside and cynarotrioside (*7*, *16*, *17*, *21*). The structures of chlorogenic acid, caffeic acid, cynarin, cynaropicrin, scolymoside, cynaroside α-L-rhamnopyranosyl and caffeoyl are presented below.



Medicinal uses
Uses supported by clinical data
Treatment of digestive complaints (e.g. dyspepsia, feeling of fullness, flatulence, nausea, stomach ache and vomiting) (*15*, *22*, *23*). Adjunct treatment of mild to moderate hypercholesterolaemia (*22*, *24–27*).

Uses described in pharmacopoeias and well established documents

Orally for the treatment of atherosclerosis and kidney dysfunctions (diuretic) (*5*).

One study has indicated that the crude drug may be of benefit for the treatment of irritable bowel syndrome (*28*), but further randomized controlled clinical trials are needed before any therapeutic recommendations can be made.

Uses described in traditional medicine

Oral treatment of anaemia, diabetes, fever, gout, rheumatism and urinary stones (*7*, *9*, *29*).

Pharmacology

Experimental pharmacology

Antiatherosclerotic and antihypercholesterolaemic activities

A dried aqueous extract of the leaves (4.5:1) inhibited cholesterol biosynthesis from ^{14}C-acetate in primary cultured rat hepatocytes in a concentration-dependent biphasic manner with moderate inhibition (approximately 20%) being noted between 0.007 and 0.1 mg/ml and stronger inhibition at 1 mg/ml (80%). Replacement of ^{14}C-acetate by ^{14}C-mevalonate largely prevented the inhibitory effects of the extracts, indicating inhibition of the activity of hydroxyl-methyl-glutaryl-CoA-reductase. Stimulation of hydroxyl-methyl-glutaryl-CoA-reductase activity by insulin was efficiently blocked by the extract. Cynaroside and its aglycone luteolin, constituents of the extract, were mainly responsible for enzyme inhibition (*30*). The effect of an extract of the leaves in vivo was investigated in four groups of 10 rats each fed an atherosclerogenic diet. Group one was administered 110 mg/kg body weight (bw) powdered leaves; group two, 80.0 mg/kg bw powdered *Cynara cardunculus*; group three, 10.0 mg/kg bw heparaxal; and group four served as the control. Examination of tissue after 120 days showed that the leaf extract prevented formation of atherosclerotic changes, prevented serum cholesterol increase, caused a decrease in lipid phosphate, slightly increased the level of glycoproteins in the blood, prevented an increase in serum γ-globulin, decreased albumin, glycoproteins and liver cholesterol, and increased γ-globulin and γ-globulin fractions. *Cynara cardunculus* showed a similar but weaker activity (*31*). A methanol extract of the leaves was shown to reduce serum triglyceride levels in olive oil-loaded mice. Oral administration of the extract, at doses between 125 and 500.0 mg/kg bw, significantly suppressed serum triglyceride elevation 2 h after administration of olive oil. In contrast, 6 h after administration of olive oil, increases in triglyceride level were observed in the groups that

received the extract at doses of 125.0 and 250.0 mg/kg bw. Orlistat, a lipase inhibitor, completely suppressed the serum triglyceride elevation at 250.0 mg/kg bw. Clofibrate, a hypolipidaemic medicine, also suppressed the triglyceride level at doses of 250.0 and 500.0 mg/kg bw. Three sesquiterpenes (cynaropicrin, aguerin B and grosheimin) from the extract were isolated as the active components (*32*).

Antihepatotoxic activity

The effects of an aqueous extract of the leaves on taurolithocholate-induced cholestatic bile canalicular membrane distortions were studied in primary cultured rat hepatocytes using electron microscopy. Artichoke extracts at concentrations between 0.08 and 0.5 mg/ml were able to prevent the formation of canalicular membrane transformations in a dose-dependent manner when added simultaneously with the bile acid. However, prevention also occurred when the hepatocytes were preincubated with the extracts, indicating that absorption of the bile acid to components of the extracts was not involved (*33*).

The hepatoprotective activity of cynarin against carbon tetrachloride (CCl_4)-induced toxicity in isolated rat hepatocytes was compared with other phenolic compounds. Only cynarin and, to a lesser extent, caffeic acid showed a cytoprotective effect (*34*). Treatment of rats with three consecutive doses of 500.0 mg/kg bw of an extract of the crude drug, administered by gavage 48, 24 and 1 h before CCl_4 intoxication, produced a significant decrease in glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase (also known as alanine aminotransferase or ALT), direct bilirubin and glutathione levels, thus indicating a reduction in the potential for hepatotoxicity (*35*).

Primary cultures of rat hepatocytes exposed to *tert*-butyl hydroperoxide were used for characterizing the antioxidative and hepatoprotective potential of an aqueous extract of the crude drug and some selected constituents. Addition of *tert*-butyl hydroperoxide to the culture media resulted in enhanced lipid peroxidation as measured by the production of malondialdehyde and enhanced cytotoxicity detected by leakage of lactate dehydrogenase. The extract added prior to or simultaneously with *tert*-butyl hydroperoxide reduced both phenomena with a median effective concentration (EC_{50}) of 95.0 and 12.0 µg leaf powder/ml, respectively. Furthermore, the aqueous extract prevented the loss of intracellular glutathione caused by *tert*-butyl hydroperoxide. Several polyphenolic and flavonoid constituents of the extract were found to reduce malondialdehyde production. The median effective concentration values were 8.1, 12.5, 15.2 and 28 µg/ml for caffeic acid, chlorogenic acid, cynarin and cynaroside, respectively (*36*).

Primary rat hepatocyte cultures exposed to *tert*-butyl hydroperoxide or cumene hydroperoxide were used to assess the antioxidative and protective potential of aqueous extracts of the leaves. Both hydroperoxides stimulated the production of malondialdehyde, particularly when the cells were pretreated with diethylmaleate in order to diminish the level of cellular glutathione. Addition of the extract did not affect basal malondialdehyde production, but prevented the hydroperoxide-induced increase of malondialdehyde formation in a concentration-dependent manner when presented simultaneously with or prior to the peroxides. The effective concentrations were as low as 0.001 mg/ml (*37*).

Antioxidant activity

A study measured the effects of aqueous and ethanol extracts of the leaves on intracellular oxidative stress stimulated by inflammatory mediators, tumour necrosis factor alpha and oxidized low-density lipoprotein (ox-LDL) in endothelial cells and monocytes. Both extracts inhibited basal and stimulated reactive oxygen species production in endothelial cells and monocytes, in a dose-dependent manner. In endothelial cells, the ethanol extract (50.0 µg/ml) significantly reduced ox-LDL-induced intracellular reactive oxygen species production by 60% ($p < 0.001$) and the aqueous extract (50 µg/ml) reduced ox-LDL-induced intracellular reactive oxygen species production by 43% ($p < 0.01$). The ethanol extract (50 µg/ml) reduced ox-LDL-induced intracellular reactive oxygen species production in monocytes by 76% ($p < 0.01$). Effective concentrations of 25–100 µg/ml were well below the cytotoxic levels of the extracts which started at 1.0 mg/ml as assessed by lactate dehydrogenase leakage and trypan blue exclusion (*38*).

An aqueous dried extract (9:2) of the leaves was studied in human leukocytes to assess activity against oxidative stress. The extract (median effective concentration 0.23 µg/ml) produced a concentration-dependent inhibition of oxidative stress when cells were stimulated with agents that generate reactive oxygen species: hydrogen peroxide, phorbol-12-myristate-13-acetate and *N*-formyl-methionyl-leucyl-phenylalanine. Cynarin, caffeic acid, chlorogenic acid and luteolin, constituents of artichoke leaf extracts, also showed a concentration-dependent inhibitory activity in the above models, contributing to the antioxidant activity of the extract in human neutrophils (*39*).

Choleretic effects

Two aqueous alcoholic extracts of the fresh leaves (total extract containing 19% caffeoylquinic acids, at a dose of 200.0 mg/kg bw and a semi-purified extract containing 46% caffeoylquinic acids, at a dose of 25.0 mg/kg bw) were assessed in rats. Intraperitoneal administration stimulated

choleresis, and significantly increased bile dry residue and total cholate secretion ($p < 0.05$). Intragastric administration of the same extracts (400.0 mg/kg bw, total extract and 200.0 mg/kg bw of the semipurified extract) also increased gastrointestinal motility by 11% and 14%, respectively ($p < 0.05$) (*40*).

The effects of an extract of the crude drug on bile flow and the formation of bile compounds in anaesthetized rats after acute administration and repeated oral administration (twice a day for 7 consecutive days) were studied. A significant increase in bile flow was observed after acute treatment with the extract as well as after repeated administration. The choleretic effects of the extract were similar to those of the reference compound dehydrocholic acid. Total bile acids, cholesterol and phospholipid were determined by enzymatic assays. At the highest dose (400.0 mg/kg bw), a significant increase was observed after single and repeated administration ($p < 0.01$) (*41*).

The choleretic effects of four extracts of the leaves (not described) were assessed in vivo in a study in rats. Extracts 1, 2 and 4 did not show significant choleretic activity at a dose of 1.0 and 2.0 g/kg bw. Extract 3, however, was found to induce an increase of bile flow, which was gradual and sustained. Cynarin and chlorogenic acid, administered as pure compounds, did not show choleretic activity at any of the doses tested and neither of them decreased the malondialdehyde content in liver (*42*).

Toxicology

The oral and intraperitoneal median lethal doses of a hydroalcoholic extract of the leaves in rats were 2.0 g/kg and 1.0 g/kg bw, respectively (*40*). The oral median lethal dose of cynarin in mice was 1.9 g/kg bw. Intraperitoneal administration of cynarin to rats for 15 days, at doses between 50.0 and 400.0 mg/kg bw per day produced no macroscopic, haematological or histological abnormalities. Intraperitoneal administration of cynarin to rats for 40 days at a dose between 100.0 and 400.0 mg/kg bw per day increased body and kidney weight, as well as producing some degenerative changes in the liver (*43*). External application of a leaf extract to the skin of white rats, at doses of 1.0–3.0 g/kg bw for 21 days, did not produce any toxic effects or have any cumulative effects on haematological parameters or the biochemistry of rats. No skin-irritating or eye-irritating effects were observed in guinea-pigs (*44*).

Clinical pharmacology

Antidyspeptic effects

A multicentre open study assessed the effects of a dried aqueous leaf extract (3.8–5.5:1, 320 mg per capsule) in 553 patients with dyspeptic com-

plaints. The daily dose was 4–6 capsules (containing 320.0 mg of extract per capsule) per day, for an average of 43.5 days. Digestive complaints declined significantly, by 71%, over the treatment period ($p < 0.001$). Compared with the baseline data on subjective symptoms, a reduction in abdominal pain (76%), emesis (88%), meteorism (66%) and nausea (82%) was observed. In a subgroup of 302 patients, total cholesterol decreased by 11.5% and triglycerides by 12.5% (*25*). In a similar study, the same extract was assessed in a 6-month open trial involving 203 patients with dyspepsia. The daily dose administered was 3–6 capsules (each capsule containing 320.0 mg of the extract). After 21 weeks of treatment, symptoms such as vomiting, abdominal pain, nausea and flatulence decreased by 84%, 78%, 77% and 70%, respectively. Total blood cholesterol and triglycerides were reduced by 10.9% and 11%, respectively. Data from 159 patients indicated that low-density lipoprotein-cholesterol decreased by 15.8% and high-density lipoprotein-cholesterol increased by 6.3%. Global efficacy as assessed by physicians was good to excellent in 85.7% of patients. No adverse reactions were reported (*26*).

In a double-blind, randomized controlled trial, 247 patients with functional dyspepsia were treated with either a commercial extract of the crude drug (2 × 320.0 mg of plant extract three times daily) or a placebo. The primary outcome measured was the sum score of the patient's weekly rating of the overall change in dyspeptic symptoms (four-point scale). Secondary variables were the scores for each dyspeptic symptom and the quality of life as assessed by the Nepean Dyspepsia Index. Of the 247 patients enrolled, data from 244 patients (129 given active treatment, 115 given placebo) were suitable for inclusion in the statistical analysis (intention-to-treat). The overall improvement in symptoms over the 6 weeks of treatment was significantly greater in patients treated with the commercial extract than in those treated with the placebo (8.3 ± 4.6 versus 6.7 ± 4.8, $p < 0.01$). Similarly, patients treated with the commercial extract showed significantly greater improvement in the global quality of life scores (Nepean Dyspepsia Index) than the placebo-treated patients (-41.1 ± 47.6 versus -24.8 ± 35.6, $p < 0.01$). The preparation tested was significantly better than the placebo at alleviating symptoms and improving the disease-specific quality of life in patients with functional dyspepsia (*45*).

Antihypercholesterolaemic and lipid-lowering effects

Two randomized controlled clinical trials assessed the effects of a dried aqueous extract of the leaves on cholesterol levels in 187 patients (*24, 27*). The first, a randomized, double-blind, placebo-controlled pilot study involving 44 healthy volunteers, assessed the effect of an extract of the crude drug on cholesterol levels. Patients were randomly assigned to receive

either 640.0 mg of the extract or a placebo three times daily for 12 weeks. No significant effects on serum cholesterol were found. However in subgroup analysis, significant cholesterol-lowering effects were observed in subjects with a total cholesterol level of > 210 mg/dl ($p < 0.022$) (*27*).

The second placebo-controlled study assessed the safety and efficacy of a dried aqueous extract of fresh artichoke (25–35:1). Patients received either 1800 mg of artichoke extract as coated tablets, each containing 450.0 mg extract, or a placebo. Patients ($n = 143$) with hyperlipoproteinaemia – initial total cholesterol of > 7.3 mmol/l (> 280 mg/dl) received 1.8 g of a dried leaf extract per day or the placebo for 6 weeks. Changes in total cholesterol and low-density lipoprotein-cholesterol from baseline to the end of treatment showed a statistically significant superiority of the dry artichoke extract over the placebo ($p = 0.0001$). Observed reductions in total cholesterol levels were 18.5% in those who received the extract and 8.6% in those who received the placebo after 6 weeks of treatment (*24*). The decrease in low-density lipoprotein-cholesterol in the group treated with the extract was 22.9% and was 63% in those treated with the placebo. The ratio of low-density lipoprotein to high-density lipoprotein showed a decrease of 20.2% in the group that received the extract and 7.2% in the group that received the placebo. No drug-related adverse events were reported (*24*).

In a randomized, placebo-controlled clinical trial, two groups of 30 patients presenting various dislipidaemic profiles were treated for 50 days with either cynarin, 2 × 250 mg tablets per day, or a placebo. Cynarin was able to induce a significant reduction of hypercholesterolaemia ($p < 0.001$), the level of pre-β-lipoproteins ($p < 0.01$), the β/α-lipoprotein ratio ($p < 0.01$) and patient's body weight (*46*).

Several uncontrolled studies have found that cynarin reduced total serum cholesterol in patients after treatment with oral doses of 750–1500 mg per day. Oral administration of cynarin to 17 patients, at a dose of 1000 mg/day, for 4 weeks resulted in a significant decrease in total cholesterol (15%, $p < 0.005$) (*9*).

Choleretic effect

A randomized, double-blind, placebo-controlled trial assessed the choleretic effects of a dry aqueous extract of the leaves (4.5–5:1) in 20 male volunteers with acute or chronic metabolic disorders. The treatment group ($n = 10$) received a single intraduodenal dose of the extract at a dose of 1.92 g/day in 50 ml of water on an empty stomach, while the control group received a placebo of similar appearance. Crossover to the alternative treatment followed an 8-day washout period. The outcomes included intraduodenal bile secretion measured using multi-channel probes. Com-

pared with baseline values, 60 minutes after administration there was a significant increase in bile secretion in the treatment group (151%) as compared with the placebo group ($p < 0.01$) (*23*).

Irritable bowel syndrome

Irritable bowel syndrome, characterized by abdominal pain and altered bowel habit, has symptoms that overlap with those of dyspepsia. Since the crude drug is used for the treatment of dyspepsia, a postmarketing surveillance study was performed to assess its effects on irritable bowel syndrome. A subgroup of patients ($n = 279$) with symptoms of irritable bowel syndrome was identified from a sample of individuals ($n = 553$) with dyspeptic syndrome who were being monitored in a postmarketing surveillance study of the extract for 6 weeks. Analysis of the data from the subgroup with irritable bowel syndrome revealed significant reductions in the severity of symptoms including abdominal pain, bloating, flatulence and constipation, and favourable evaluations of overall effectiveness by both physicians and patients (*28*).

Pharmacokinetics

A study to investigate the absorption, metabolism and disposition of artichoke leaf extract was performed using two different extracts (*47*). The extracts were administered to 14 healthy volunteers in a crossover study. Each subject received doses of both extracts. The administered dose of extract A contained caffeoylquinic acids equivalent to 107.0 mg caffeic acid and luteolin glycosides equivalent to 14.4 mg luteolin. The administered dose of extract B contained caffeoylquinic acids equivalent to 153.8 mg caffeic acid and luteolin glycosides equivalent to 35.2 mg luteolin. Urine and plasma analysis were performed by a validated high-performance liquid chromatography method using 12-channel coulometric array detection. None of the genuine target extract constituents could be detected in the plasma or urine of the subjects. However, caffeic acid, its methylated derivates ferulic acid and isoferulic acid and the hydrogenation products dihydrocaffeic acid and dihydroferulic acid were identified as metabolites derived from caffeoylquinic acids. Except for dihydroferulic acid, all of these compounds were present as sulfates or glucuronides. Peak plasma concentrations of total caffeic acid, ferulic acid and isoferulic acid were reached within 1 h and declined over 24 h showing almost biphasic profiles. By contrast, maximum concentrations for total dihydrocaffeic acid and dihydroferulic acid were observed only after 6–7 h, indicating two different metabolic pathways for caffeoylquinic acids. Luteolin administered as glucoside was recovered from plasma and urine only as sulfate or glucuronide, but neither in the form of genuine glucosides nor

as free luteolin. Peak plasma concentrations were reached rapidly within 0.5 h. The elimination showed a biphasic profile (*47*).

Adverse reactions

Gastrointestinal complaints included mild diarrhoea, accompanied by abdominal cramps, upper abdominal pain, nausea and heartburn. Allergic reactions may occur in sensitized patients (*22, 25*).

No significant adverse events other than gastrointestinal discomfort have been reported from open or controlled clinical trials (*24–27*, *48*).

Contraindications

Hypersensitivity or allergies to artichokes and other plants from the Compositae/Asteraceae, and obstruction of the bile ducts (*15*).

Warnings

Possible interaction with coumarin-type anticoagulants.

Precautions

General

Patients with gallstones should seek the advice of a health care provider prior to use.

Carcinogenesis, mutagenesis, impairment of fertility

The genotoxic effects of flavonoid constituents present in the crude drug (quercetin and luteolin) were assessed in two short-term bacterial assays (*49*). In *Salmonella typhimurium* (strains TA1538 uvrB- and TA1978 uvrB+) the flavonoids did not induce damage in the DNA as recognized by UvrABC nuclease. Results of the SOS-chromotest in *Escherichia coli* K-12 strains PQ37 and PQ243 indicated that the flavonoids only weakly induced the SOS system (*49*).

Drug interactions

No information was found.[1]

Pregnancy: teratogenic effects

Due to the lack of safety and efficacy studies, the use of the crude drug during pregnancy is not recommended.

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[1] A report of a potential drug interaction with Folium Cynarae or its preparations and with coumarin-type anticoagulants such as phenprocoumone and warfarin has been recorded by a national regulatory authority.

Pregnancy: non-teratogenic effects
Due to the lack of safety data, the use of the crude drug during pregnancy is not recommended.

Nursing mothers
Due to the lack of safety data, the use of the crude drug during breastfeeding is not recommended.

Paediatric use
Due to the lack of safety data, the use of the crude drug for the treatment of children under the age of 12 years is not recommended.

Other precautions
No information was found.

Dosage forms
Crude drug, extracts and other Galenical preparations for internal use.

Posology
(Unless otherwise indicated)
Average oral daily dose: for hypercholesterolaemia and dyspepsia, 1–2 g of a dried aqueous extract (*24*, *27*, *45*). Adult daily dose: 5–10 g of crude drug; or equivalent preparations (*15*, *17*).

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