

Artichoke

Species (Family)

Cynara scolymus L. (Asteraceae/Compositae)

Synonym(s)

Globe Artichoke.

Globe artichoke should not be confused with Jerusalem artichoke, which is the tuber of *Helianthus tuberosa* L.

Part(s) Used

Leaf

Pharmacopoeial and Other Monographs

BHP 1996^(G9)

Complete German Commission E^(G3)

Martindale 32nd edition^(G43)

Mills and Bone^(G50)

PDR for Herbal Medicines 2nd edition^(G36)

Legal Category (Licensed Products)

GSL^(G37)

Constituents^(1,2,G41)

Acids Phenolic, up to 2%. Caffeic acid, mono- and dicaffeoylquinic acid derivatives, e.g. cynarin (1,5-di-O-caffeoylquinic acids) and chlorogenic acid (mono derivative).

Flavonoids 0.1–1%. Flavone glycosides e.g. luteolin-7 β -rutinoside (scolymoside), luteolin-7 β -D-glucoside and luteolin-4 β -D-glucoside.

Volatile oils Sesquiterpenes β -selinene and caryophyllene (major); also eugenol, phenylacetaldehyde, decanal, oct-1-en-3-one, hex-1-en-3-one, and non-*trans*-2-enal.

Other constituents Phytosterols (taraxasterol and β -taraxasterol), tannins, glycolic and glyceric acids, sugars, inulin, enzymes including peroxidases,⁽³⁾ cynaropicrin and other sesquiterpene lactones, e.g. grosheimin, cynarotriol.^(4,5) The root and fully devel-

oped fruits and flowers are devoid of cynaropicrin; highest content reported in young leaves.⁽⁶⁾

Food Use

Artichoke is listed by the Council of Europe as a natural source of food flavouring (category N2). This category indicates that artichoke can be added to foodstuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product.^(G16) In the USA, artichoke leaves are approved for use in alcoholic beverages only, with an average maximum concentration of 0.0016% (16 ppm).^(G41)

Herbal Use

Artichoke is stated to possess diuretic, choleric, hypocholesterolaemic, hypolipidaemic, and hepatostimulating properties.⁽⁷⁻⁹⁾ Modern use of artichoke is focused on its use in the treatment of hyperlipidaemia, hyperlipoproteinaemia, non-ulcer dyspepsia and conditions requiring an increase in choleresis. There is also interest in the potential hepatoprotective properties of globe artichoke, although this has not yet been tested in controlled clinical trials.^(10,11)

Dosage

The German Commission E recommends an average daily dose of 6 g drug, or an equivalent dose of extract (based on the herb-to-extract ratio) or other preparations, for dyspeptic problems.^(G3,G56) A recommended dosage regimen for liquid extract (1:2) is 3–8 mL daily.^(G50)

Dosages used in clinical trials of globe artichoke leaf extract have assessed the effects of dosages of up to 1.92 g daily in divided doses for up to six months.⁽¹²⁾

Pharmacological Actions

Several pharmacological properties have been documented for artichoke leaf, including inhibition of cholesterol biosynthesis, hypolipidaemic, anti-oxidant and hepatoprotective activity. It remains unclear which of the constituents of artichoke are responsible for its pharmacological activities. The

dicafeoylquinic acids, which include cynarin, are likely to be an important group of constituents in this respect.^(11,G50) The sesquiterpene lactones, such as cynaropicrin, and flavonoids, such as luteolin glycoside, may also exert biological effects.⁽¹¹⁾

***In vitro* and animal studies**

Hypolipidaemic, hypocholesterolaemic and choleric activity Hypolipidaemic, hypocholesterolaemic and choleric activities are well documented for globe artichoke leaf extract and particularly for the constituent cynarin; this literature has been reviewed.^(10,11)

Globe artichoke leaf extract not only increases cholesterolemia and, therefore, cholesterol elimination, but also has been shown to inhibit cholesterol biosynthesis.⁽¹⁰⁾ Preparations of globe artichoke leaf extract inhibit cholesterol biosynthesis in a concentration-dependent manner in studies in cultured rat hepatocytes.^(13,14) Low concentrations (<0.1 mg/mL) of globe artichoke extract achieved around 20% inhibition, whereas 65% inhibition was noted with concentrations of 1 mg/mL. Luteolin was considered to be one of the most important constituents for this effect, and it was suggested that a possible mechanism of action might be indirect inhibition of hydroxymethylglutaryl-CoA reductase (HMG-CoA).⁽¹⁴⁾ Other *in vitro* studies have documented a concentration-dependent inhibition of *de novo* cholesterol biosynthesis in cultured rat and human hepatocytes for globe artichoke leaf extract 0.03–0.1 mg/mL.⁽¹⁵⁾

Several other experimental studies have documented lipid-lowering effects for globe artichoke leaf extract and cynarin *in vivo*.^(10,11) A study in rats explored the hypocholesterolaemic, hypolipidaemic and choleric effects of purified (containing 46% caffeoylquinic acids, calculated as chlorogenic acid) and total extracts of globe artichoke leaf (containing 19% caffeoylquinic acids, calculated as chlorogenic acid).⁽⁷⁾ The purified extract was found to be more potent than the total artichoke extract: purified extract 25 mg/kg intraperitoneally reduced plasma triglyceride and cholesterol concentrations by 33% and 45%, respectively, whereas reductions of only 18% and 14%, respectively, were observed with the total extract (100 mg/kg intraperitoneally).⁽⁷⁾ Both purified (25 mg/kg intraperitoneally) and total extract (200 mg/kg intraperitoneally) significantly enhanced bile secretion following treatment, compared with baseline values; the increase in bile secretion seen with the purified extract was still statistically significant 3 hours after treatment. The more potent pharmacological activities observed with the purified extract were attributed to the higher concentration of monocateoylquinic acids

(e.g. chlorogenic, neochlorogenic) compared with dicafeoylquinic acids (e.g. cynarin) present.

Another study investigated the effects of cynarin on total cholesterol concentrations in serum and liver of rats given ethanol (6 g/kg/day by gavage over three days).⁽¹⁶⁾ In rats given ethanol alone, serum cholesterol concentrations rose significantly by 44%, compared with controls ($p < 0.01$). Rats given ethanol plus cynarin (30 mg/kg intraperitoneally 30 minutes before gavage) showed a significant reduction in serum cholesterol concentrations, compared with controls ($p < 0.05$).

Antioxidant and hepatoprotective activity *In vitro*, a luteolin-rich globe artichoke leaf aqueous extract (flavonoid content around 0.4% w/w) retarded low-density lipoprotein (LDL) oxidation in a concentration-dependent manner (determined by a prolongation of the lag phase to conjugated diene formation).⁽¹⁷⁾ The same tests carried out with the pure aglycone luteolin at concentrations of 0.1–1 $\mu\text{mol/L}$ showed that this constituent had a similar concentration-dependent effect on LDL oxidation in this model. Luteolin-7-O-glucoside also demonstrated a concentration-dependent reduction in LDL oxidation, but was less potent than luteolin.

Several *in vitro* and *in vivo* studies have investigated the antioxidative and hepatoprotective properties of globe artichoke leaf extracts, and their constituents, against liver cell damage induced by different hepatotoxins.

The hepatoprotective effect of polyphenolic compounds isolated from artichoke has been investigated *in vitro* using rat hepatocytes.⁽⁸⁾ Cynarin was the only compound reported to exhibit significant cytoprotective activity, with a lesser action demonstrated by caffeic acid. A standardised extract of globe artichoke (Hepar-SL forte) significantly inhibited the formation of malondialdehyde induced by *tert*-butylhydroperoxide (*t*-BHP) in a concentration-dependent manner within 40 minutes of incubation, compared with control.⁽¹⁸⁾ The protective antioxidant effect of globe artichoke was reported to be significant, compared with control, even at a concentration of 1 $\mu\text{g/mL}$. A reduction in *t*-BHP-induced cell death with globe artichoke extract was also observed. Further studies assessed the antioxidative and protective potential of the same extract (Hepar-SL forte) in cultures of primary rat hepatocytes exposed to *t*-BHP.⁽¹⁹⁾ Incubation of cultured hepatocytes with globe artichoke extract and *t*-BHP inhibited *t*-BHP-induced malondialdehyde formation in a concentration-dependent manner. Globe artichoke extract was significantly effective, compared with control, at concentrations down to 0.001 mg/mL. Furthermore,

concentrations of globe artichoke extract down to 0.005 mg/mL significantly enhanced hepatocyte survival. The antioxidative effect of the extract was not affected by various pretreatments (including tryptic digestion, boiling and acidification), although it was sensitive to alkalisation. Incubation with the globe artichoke constituents chlorogenic acid and cynarin resulted in significant inhibition, and incubation with both compounds was reported to have a synergistic effect, although an additive effect may be a more accurate description of the findings. Chlorogenic acid and cynarin were not solely responsible for the antioxidative effect, as reduction of malondialdehyde formation by the extract was at least twofold that seen with the chlorogenic acid and cynarin.⁽¹⁹⁾ The antioxidative and hepatoprotective potential of globe artichoke extract was confirmed in other studies which also indicated that several constituents of the extract may contribute to the effects.⁽²⁰⁾

The effects of globe artichoke leaf extract and its constituents have also been investigated for activity against oxidative stress in studies using human leukocytes.⁽²¹⁾ Globe artichoke leaf extract demonstrated a concentration-dependent inhibition of oxidative stress induced by several agents, such as hydrogen peroxide and phorbol-12-myristate-13-acetate, that generate reactive oxygen species. The constituents cynarin, caffeic acid, chlorogenic acid and luteolin also showed concentration-dependent inhibitory activity in these models.

In vivo hepatoprotectivity against tetrachloromethane-induced hepatitis has been documented for globe artichoke leaf extract (500 mg/kg) administered orally to rats 48 hours, 24 hours and 1 hour before intoxication.⁽⁹⁾ Concentrations of liver transaminases were significantly lower in rats given globe artichoke leaf extract, compared with those in controls. A hepatoregenerating effect has also been described for an aqueous extract of globe artichoke leaf administered orally to rats for three weeks following partial hepatectomy.⁽²²⁾ Regeneration was determined by stimulation of mitosis and increased weight in the residual liver when animals were sacrificed in globe artichoke-treated rats, compared with controls. In a similar study, aqueous extract of globe artichoke leaf (0.5 mL daily for five days preceding hepatectomy) was found to be more potent than a root extract.⁽²³⁾

Clinical studies

Several clinical trials have explored the choleric and hypolipidaemic properties of globe artichoke leaf extract, and its effects in patients with symptoms of dyspepsia.

A randomised, double-blind, placebo-controlled, crossover trial involving 20 male volunteers assessed the choleric effects of a single intraduodenal dose (1.92 g in 300 mL water) of the globe artichoke leaf extract Hepar-SL forte.⁽²⁴⁾ Intraduodenal bile secretion, the primary outcome variable, was measured using multichannel probes starting 30 minutes after drug administration and continuing for up to 4 hours afterwards. An increase in bile secretion was observed in both groups; maximal increases for globe artichoke leaf extract and placebo were 152% at 60 minutes after drug administration, and 40% at 30 minutes, respectively. Differences between globe artichoke leaf extract and placebo were statistically significant at 30, 60 and 90 minutes after drug administration ($p < 0.01$) and at 120 and 150 minutes after drug administration ($p < 0.05$). In another randomised controlled trial, 60 patients with dyspepsia received a combination preparation containing extracts of globe artichoke 50 mg, boldo (*Peumus boldus*) 30 mg and chelidonium (*Chelidonium majus*) 20 mg per tablet, or placebo, three times daily for 14 days.⁽²⁵⁾ The volume of bile secreted, measured using a duodenal probe, increased significantly in the treatment group, compared with the placebo group ($p < 0.01$). Also, an improvement in symptoms was reported for 50% of the treatment group, compared with 38% of the placebo group. There are also clinical studies in the older literature (some of which were placebo-controlled trials, whereas others were open, uncontrolled studies) which report choleric effects with globe artichoke leaf extract. These trials have been summarised in several reviews.^(10,24,G50)

The effects of globe artichoke leaf extract have also been monitored in several postmarketing surveillance (phase IV) studies in patients with non-specific gastrointestinal complaints, including dyspepsia,⁽¹²⁾ functional biliary tract complaints, constipation and gastric irritation.⁽¹¹⁾ The studies monitored the effects of globe artichoke leaf extract (Hepar-SL forte; one capsule contains 320 mg standardised aqueous extract; drug-extract ratio: 3.5 to 5.5 : 1) up to six capsules daily for six weeks⁽¹¹⁾ or six months.⁽¹²⁾ Both studies reported improvements in clinical symptoms and reductions in serum total cholesterol and triglyceride concentrations, compared with baseline values. A subgroup analysis of 279 patients with at least three of five symptoms of irritable bowel syndrome reported significant reductions in the severity of symptoms and favourable evaluations of overall effectiveness by both physicians and participants.⁽²⁶⁾ The findings from postmarketing surveillance studies provide supporting data for the effects of globe artichoke leaf extract,

but these are open studies and do not include a control group and, therefore, are not designed to assess efficacy.

The efficacy of globe artichoke leaf extract in patients with hyperlipoproteinaemia has been assessed in a randomised, double-blind, placebo-controlled, multicentre trial involving 143 patients with initial total cholesterol concentrations of >7.3 mmol/L (>280 mg/dL).⁽²⁷⁾ Participants received globe artichoke leaf extract (CY450; drug-extract ratio: 25 to 35:1) 1800 mg daily in two divided doses, or placebo, for six weeks. At the end of the study, mean total cholesterol concentrations had decreased by 18.5% to 6.31 mmol/L and by 8.6% to 7.03 mmol/L in the CY450 and placebo groups, respectively ($p < 0.0001$). CY450 treatment also led to a significant reduction in LDL cholesterol, compared with placebo ($p = 0.0001$). There was no difference between CY450 recipients and placebo recipients in blood concentrations of the liver enzyme gamma-glutamyltransferase (GGT).

A published abstract reports the findings of a previous randomised, double-blind, placebo-controlled trial of a globe artichoke leaf extract (Hepar-SL forte; 640 mg three times daily for 12 weeks) involving 44 healthy volunteers.⁽¹⁵⁾ Mean baseline total cholesterol concentrations for participants in this study were low (placebo group: 203.0 mg/dL; globe artichoke extract group: 204.2 mg/dL). Subgroup analysis suggested lipid-lowering effects with globe artichoke extract for participants with baseline total cholesterol concentrations of >200 mg/dL. However, numbers of participants included in this analysis were small. The study indicates only that trials in patients with hyperlipoproteinaemia are required.

A series of three open, uncontrolled studies involved the administration of pressed globe artichoke juice (obtained from fresh leaves and flower buds) 10 mL three times daily for up to 12 weeks to a total of 84 patients with secondary hyperlipidaemia (total cholesterol ≥ 260 mg/dL).⁽²⁸⁾ After six weeks' treatment, total cholesterol, LDL cholesterol and triglyceride concentrations decreased, whereas high-density lipoprotein cholesterol tended to increase. Another uncontrolled study involved the administration of cynarin to 17 patients with familial type IIa or type IIb hyperlipoproteinaemia for whom blood lipid concentrations were maintained with dietary treatment alone.⁽²⁹⁾ Cynarin was taken 15 minutes before meals at either 250 mg or 750 mg daily dose. Over a period of three months, cynarin was reported to have no effect on mean serum cholesterol and triglyceride concentrations.⁽²⁹⁾ The results were in agreement with the findings of some previous workers, but

also in contrast to other studies that have reported cynarin to be effective in lowering serum concentrations of cholesterol and triglycerides when taken in daily doses ranging from 60 mg to 1500 mg.⁽²⁹⁾

Side-effects, Toxicity

A randomised, double-blind, placebo-controlled trial involving 143 patients with hyperlipoproteinaemia reported a similar frequency of adverse events for globe artichoke leaf extract (CY450) and placebo groups.⁽²⁷⁾ A total of 28 adverse events were reported during the study, 26 of which related to mild changes in laboratory values. The relationship to the globe artichoke was considered to be 'unlikely' in all cases.

Postmarketing surveillance (phase IV) studies have monitored patients with non-specific gastrointestinal complaints receiving treatment with globe artichoke leaf extract (Hepar-SL forte; up to 1.92 g daily for six weeks⁽¹¹⁾ or six months⁽¹²⁾). In one study involving 533 patients with non-specific gastrointestinal complaints, including dyspepsia, functional biliary tract complaints, constipation and gastric irritation, seven adverse events (weakness, hunger, flatulence) were reported (1.3% of participants).⁽¹¹⁾ No serious adverse events were reported. A second postmarketing surveillance study involved 203 patients with symptoms of dyspepsia who received globe artichoke leaf extract up to 1.92 g daily for up to six months.⁽¹²⁾ It was reported that no adverse events were recorded during the study, and that the physician's overall judgement of tolerability was given as 'good' or 'excellent' in 98.5% of cases.

Allergic contact dermatitis, with cross-sensitivity to other Compositae plants, has been documented for globe artichoke.^(30,G51) A case of occupational contact urticaria syndrome in a 20-year-old woman has been reported in association with globe artichoke. The woman developed acute generalised urticaria, angioedema of the hands, forearms and face, and respiratory symptoms after handling globe artichokes. The clinical history and results of skin-prick tests indicated that the woman had developed type I allergy to globe artichoke antigen(s).⁽³¹⁾ An isolated case of allergy to ingested globe artichoke has also been described.⁽³²⁾

Cynaropicrin and other sesquiterpene lactones with allergenic potential have been isolated from globe artichoke.^(30,G53) Purified globe artichoke extract is more toxic than a total extract. LD₅₀ values (rat, by intraperitoneal injection) have been documented as greater than 1000 mg/kg (total extract) and 265 mg/kg (purified extract).⁽⁷⁾

Contra-indications, Warnings

Globe artichoke yields cynaropicrin, a potentially allergenic sesquiterpene lactone.^(G51) Individuals with an existing hypersensitivity to any member of the Compositae family may develop an allergic reaction to globe artichoke.

Pregnancy and lactation In view of the lack of toxicity data, excessive use of globe artichoke should be avoided during pregnancy and lactation.

Pharmaceutical Comment

Globe artichoke is characterised by the phenolic acid constituents, in particular cynarin. Experimental studies (*in vitro* and *in vivo*) support some of the reputed uses of artichoke. Traditionally, the choleric and cholesterol-lowering activities of globe artichoke have been attributed to cynarin.⁽⁷⁾ However, studies in animals and humans have suggested that these effects may in fact be due to the monocaffeoylquinic acids present in globe artichoke (e.g. chlorogenic and neochlorogenic acids). Clinical trials investigating the use of globe artichoke and cynarin in the treatment of hyperlipidaemia generally report positive results. However, further rigorous clinical trials are required to establish the benefit of globe artichoke leaf extract as a lipid- and cholesterol-lowering agent. Hepatoprotective and hepatoregenerating activities have been documented for cynarin *in vitro* and in animals (rats). However, these effects have not yet been documented in clinical studies.

References

See also General References G3, G9, G16, G19, G36, G41, G43, G49, G50 and G51.

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