

Clinical uses of artichoke leaf extract

Artichoke, or *Cynara scolymus*, is a native plant to southern Europe, northern Africa, and the Canary Islands.¹⁻⁴ Artichoke is a member of the Asteraceae, or daisy, family and is thought to be one of the oldest used medicinal plants. It has been pictured in ancient Egyptian drawings and was used by the ancient Greeks and Romans to aid in digestion.³ The portion of the artichoke plant used as a medicinal remedy is the leaf extract.¹⁻⁴ Artichoke leaf extract has been used for a variety of purposes, including alcohol-induced hangovers, chronic albuminuria, hyperlipidemia, irritable bowel syndrome (IBS), jaundice, liver dysfunction, and snake bites.^{1,2,4,5} It has also been used as a diuretic and to manage postoperative anemia.^{1,5}

Mechanism of action. Artichoke leaf extract consists of up to 2% phenolic acids (chlorogenic acid, cynarin, and caffeic acid), up to 4% sesquiterpene lactones, and 1% flavonoids (scolymoside, cynaroside, and luteolin).² Artichoke also contains phytosterols, tannins, sugars, starch, and inulin.⁴

Artichoke leaf extract is thought to act as a choleric, stimulating bile flow from the liver to the gallbladder. This action is attributed to chlorogenic

acid, cynarin, and scolymoside and may contribute to the extract's potential to alleviate alcohol-induced hangovers and dyspepsia.² Cynaroside and luteolin may play a role in reducing cholesterol by indirectly inhibiting hydroxymethylglutaryl-coenzyme A reductase.⁴ Phytosterols may inhibit exogenous cholesterol absorption and therefore may reduce cholesterol levels.^{4,6}



Clinical studies. Hyperlipidemia. The effect of artichoke leaf extract (Cynarin, Pharma-Schwarz GmbH, Farmitalia, Milan, Italy) on the lipid levels of patients with familial type IIa ($n = 15$) or type IIb ($n = 2$) hyperlipidemia was studied.⁷ Over the three-month study period, nine patients received 250 mg of artichoke leaf extract once daily, and eight patients received 750 mg given as 250 mg three times daily. Each dose was given 15 minutes before a meal. All patients were assessed for secondary hyperlipidemia, and none were attributed to a secondary cause. Six months before study initiation, patients started a standardized, basic fat-modified diet. In the 250-mg treatment group, the mean total cholesterol concentration decreased from 381 to 375 mg/dL and the mean triglyceride concentration slightly increased from 154 to 156 mg/dL. In the 750-mg treatment group, the mean total cholesterol concentration increased from 372 to 382 mg/dL and the mean triglyceride concentration increased from 167 to 232 mg/dL. None of the results were statistically significant. In four patients, the artichoke leaf extract dosage was increased to 1.5 g daily for three to six months, yielding no further changes in cholesterol levels. No adverse effects were reported. The authors concluded that artichoke leaf extract has no lipid-lowering effect in familial type II hyperlipidemia.

Too few patients were enrolled in this study to draw strong conclusions, and the daily dose of artichoke leaf extract

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was low compared with the recommendations of a reputable reference.⁸ However, the basic fat-modified diet was a positive intervention for these patients. Though not statistically significant, total cholesterol levels increased in the 750-mg treatment group.

In another study of patients with hyperlipidemia, a series of three related prospective randomized trials were conducted.⁹ Patients included in trial 1 ($n = 60$) had to have the following lipid values: total cholesterol, ≥ 260 mg/dL; low-density-lipoprotein (LDL) cholesterol, ≥ 200 mg/dL; triglycerides, ≥ 220 mg/dL; and high-density-lipoprotein (HDL) cholesterol, ≤ 40 mg/dL. Other inclusion criteria included a diagnosis of secondary hyperlipidemia or primary hyperlipidemia of Fredrickson type IIa, IIb, or IV. Trial 1 was six weeks in duration and designed to determine if lipid values were affected by artichoke leaf extract administered three times daily (given as 10 mL of pressed artichoke juice for each dose), which components of the lipid panel were affected, and to what extent those components were affected. The artichoke leaf extract was described as being prepared from artichoke fresh leaves and flower buds; therefore, the extract was not a commercially available preparation. The mean total cholesterol decreased from 269 to 265 mg/dL, mean LDL cholesterol decreased from 208 to 204 mg/dL, and mean triglycerides decreased from 349 to 332 mg/dL. The mean HDL cholesterol increased from 65 to 67 mg/dL. The results were not statistically significant. Trial 2 included 30 patients from trial 1 to determine if there was a further reduction in lipid levels with an additional 6 weeks (for a total of 12 weeks) of treatment with artichoke leaf extract. Mean total cholesterol decreased from 284 to 263 mg/dL, mean LDL cholesterol decreased from 244 to 206 mg/dL, and mean triglycerides decreased from 326 to 284 mg/dL. Mean HDL cholesterol increased from 59 to 66 mg/dL. Again, the results were not statistically significant. In trial 3, patients

who did not participate in trials 1 and 2 who had (1) secondary hyperlipidemia or Fredrickson type IIb or IV primary hyperlipidemia and (2) a total cholesterol concentration ≥ 300 mg/dL or triglyceride levels of ≥ 450 mg/dL were studied ($n = 24$). Trial 3 was 12 weeks in duration and designed to determine if extreme hyperlipidemia would respond to treatment with artichoke leaf extract. The mean total cholesterol decreased from 290 to 282 mg/dL, the mean LDL cholesterol decreased from 188 to 186 mg/dL, and the mean triglyceride level decreased from 481 to 460 mg/dL. The mean HDL concentration remained unchanged at 38 mg/dL. The author concluded that there may be value in using artichoke leaf extract for hyperlipidemia treatment for a longer duration. Although the results of this study were not statistically significant, patients' cholesterol levels were reduced with artichoke leaf extract treatment. One limitation of this study is that a commercially available preparation was not used, so it would be difficult to reproduce the study's results. Also, a 10-mL dose was given, and it is difficult to extrapolate a milligram-equivalent dosage for reproducibility.

Petrowicz et al.¹⁰ conducted a study of artichoke leaf extract using healthy volunteers without hyperlipidemia. In a randomized, placebo-controlled, double-blind, pilot study, 44 volunteers were given either artichoke leaf extract as 640-mg capsules (Hepar-SL forte) three times daily or placebo for 12 weeks to determine the effect of artichoke leaf extract treatment on lipoprotein metabolism. The mean total cholesterol levels in both groups were initially normal (205 mg/dL in the placebo group and 204.2 mg/dL in the treatment group). Subgroup data analysis showed that patients with a baseline total cholesterol concentration of >200 mg/dL had significantly greater reductions in total cholesterol than patients with lower baseline levels. Mean HDL cholesterol levels increased with treatment, though not significantly. No major adverse effects were observed or reported.

Englisch et al.¹¹ enrolled 143 patients with hyperlipidemia into a random-

ized, placebo-controlled, double-blind, multicenter, Phase III clinical trial conducted over six weeks to evaluate the cholesterol-reducing properties and clinical efficacy of artichoke leaf extract. The primary outcome measures were the change in total cholesterol and γ -glutamyltranspeptidase (GGT) values. Secondary outcome measures were changes in LDL cholesterol, HDL cholesterol, aspartate transaminase (AST), and alanine transaminase (ALT) levels. Patients had an initial total cholesterol of >280 mg/dL and were enrolled in the study if they had not taken any lipid-lowering drugs within the two weeks before enrollment. Patients were randomized to receive either 1800 mg of artichoke leaf extract daily, given as two 450-mg coated tablets (900 mg) in the morning and in the evening before meals, or placebo tablets. Artichoke leaf extract was given as a standardized, commercially available preparation (Valverde Artischocke bei Verdauungsbeschwerden, Novartis Consumer Health, Munich, Germany). At six weeks, the mean total cholesterol concentration decreased from 299 to 244 mg/dL in the treatment group and decreased from 297 to 271 mg/dL in the placebo group ($p = 0.0001$). Mean LDL cholesterol decreased from 212 to 164 mg/dL in the treatment group and from 201 to 188 mg/dL in the placebo group ($p = 0.0001$). The mean triglyceride concentration decreased in the treatment group from 202 to 190 mg/dL and in the placebo group from 201 to 181 mg/dL. Mean HDL cholesterol slightly decreased in the treatment group, from 45 to 44 mg/dL, and slightly increased from 46 to 47 mg/dL in the placebo group. Changes in triglycerides, HDL cholesterol, GGT, AST, and ALT were not statistically significant. A total of 28 adverse effects were reported and occurred with similar frequency in both groups. Of the 28 adverse effects, 26 were mild changes in laboratory test values, while the other 2 were coronary bypass surgery and pacemaker implantation—both thought to be unrelated to artichoke leaf extract therapy. Decreased appetite was reported by 14 patients. No dietary interventions

were conducted in conjunction with artichoke leaf extract therapy. A commercially available preparation of artichoke leaf extract was used in this study; therefore, its results may be reproducible in other patients.

Patients with moderate hyperlipidemia were included in a matched control study by Lupattelli et al.¹² Moderate hyperlipidemia was defined as an LDL cholesterol concentration exceeding 130 but less than 200 mg/dL or triglyceride levels over 150 but less than 250 mg/dL. The primary purpose of this study was to investigate the effects of artichoke leaf extract treatment on brachial flow-mediated vasodilation (FMV) and lipid levels in patients with hyperlipidemia. Endothelial dysfunction can represent the first stage of atherogenesis and is evaluated by brachial FMV, which can be reduced in the presence of lipid disorders. Eighteen moderately hyperlipidemic patients were included in the study, as well as 10 hyperlipidemic patients matched for age, sex, and lipid values. Patients were excluded if they had an increased cardiovascular risk, diabetes mellitus, hypertension, a family history of early cardiovascular disease, a history of ischemic heart disease, peripheral arterial disease, or cerebrovascular disease. Patients were given 20 mL/day of frozen artichoke juice dissolved in water that contained a few drops of lemon juice. Patients also began an isocaloric hypolipidic diet. During the study, daily physical activity was assessed and did not change from baseline. Brachial FMV increased in the treatment group from 3.3% to 4.5% ($p < 0.001$) and remained unchanged in the control group (3.1%). The mean total cholesterol concentration decreased in the treatment group (from 261 to 244 mg/dL [$p < 0.05$]) and in the control group (from 267 to 249 mg/dL [$p < 0.001$]). The mean LDL cholesterol concentration also decreased in both groups (from 174 to 160 mg/dL in the treatment group [$p < 0.05$] and from 180 to 164 mg/dL in the control group [$p < 0.001$]). The mean triglyceride value increased from 156 to 165 mg/dL in the treatment group ($p < 0.05$) but decreased from 136 to 126 mg/dL in the control

group. The mean HDL cholesterol concentration slightly decreased in the treatment group (from 56 to 52 mg/dL) and remained unchanged in the control group (60 mg/dL). The changes in total cholesterol, LDL cholesterol, HDL cholesterol, and brachial FMV were not statistically significant between groups. No adverse effects were reported during the study. The main limitation of this study is that a commercially available preparation of artichoke leaf extract was not used, making reproducibility difficult.

Dyspepsia. The efficacy of artichoke leaf extract was evaluated in a randomized, open-label, dose-ranging study of healthy patients with self-reported dyspepsia.¹³ A total of 516 participants were randomized to receive either 320 or 640 mg of artichoke leaf extract daily (Cynara, LichtwerPharma, Bournemouth, United Kingdom) for two months. Efficacy was assessed in the 454 participants who completed the study using a questionnaire that included the Nepean Dyspepsia Index (NDI), which measures symptoms and quality of life, and the Spielberger State-Trait Anxiety Inventory. Adverse effects were not assessed. In both groups, a significant reduction in all dyspeptic symptoms occurred ($p < 0.01$). The mean global dyspepsia score was reduced by about 40% in both groups. A significant increase in quality-of-life scores occurred in both groups ($p < 0.001$). Quality-of-life scores were higher in the 640-mg treatment group than in those receiving 320 mg; however, the difference was not statistically significant. A statistically significant reduction in state and trait anxiety scores occurred in both groups. In state (but not trait) anxiety scores, there was a statistically significant difference between the dosage groups, with patients receiving 640 mg having a greater reduction in anxiety than those receiving 320 mg ($p = 0.03$).

Holtmann et al.¹⁴ conducted a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of artichoke leaf extract in treating functional dyspepsia. A total of 247 patients with functional dyspepsia were randomized to receive two 320-mg artichoke

leaf extract capsules (Hepar-SL forte, Lichtwer Pharma AG, Berlin, Germany) or two placebo capsules three times daily for six weeks. The primary endpoint was the sum score of the patient's weekly rating of the overall change in dyspeptic symptoms using a 4-point scale (range of sum scores was 0 to 18, with higher numbers indicating more improvement). Secondary endpoints were the scores of each dyspeptic symptom and quality of life (assessed by the NDI). Adverse effects were also assessed. Patients receiving artichoke leaf extract had greater improvement in sum scores of dyspeptic symptoms than did patients receiving placebo (8.3 versus 6.7, respectively) ($p < 0.01$). Patients receiving artichoke leaf extract had statistically significant decreases in the intensity of fullness ($p = 0.005$), flatulence ($p = 0.0112$), and early satiety ($p = 0.0032$), but did not have significant decreases in the intensity of nausea, vomiting, or epigastric pain compared with patients receiving placebo. Patients receiving artichoke leaf extract had greater improvement in quality-of-life scores than did those receiving placebo (−41.1 versus −24.8, respectively) ($p < 0.01$). In the treatment group, 45 adverse effects were reported by 29 patients; in the placebo group, 25 adverse effects were reported by 18 patients (25.7% of all adverse effects were classified as gastrointestinal, and 18.6% were classified as "body as a whole").

IBS. Data from a postmarketing surveillance study of patients with dyspeptic syndrome who were treated with two 320-mg capsules of artichoke leaf extract (Hepar-SL) three times daily for six weeks were used to evaluate a subset of patients with IBS ($n = 279$).¹⁵ Individual symptoms, overall effectiveness, and adverse effects were assessed. Significant decreases in the severity of all symptoms (abdominal pain, abdominal cramps, bloating, flatulence, and constipation) were achieved. Approximately 84% of physicians and patients rated the overall effectiveness of artichoke leaf extract as good or excellent. Seven adverse effects were reported, three of which were attributed to artichoke leaf extract (one

report of hunger and two reports of increased flatulence).

Data from the randomized, open-label, dose-ranging study of healthy patients with self-reported dyspepsia¹³ were used to evaluate a subset of patients with IBS.¹⁶ A total of 208 participants from that study were identified as having IBS. The frequency of IBS, bowel patterns, and NDI score were assessed before and two months after treatment with 320 or 640 mg of artichoke leaf extract (Cynara). After treatment, the rate of IBS decreased by 26.4% ($p < 0.001$). At baseline, 18% of patients reported "normal" bowel patterns; after treatment, 39% reported normal bowel patterns. The NDI total symptom score decreased by 41% ($p < 0.001$) and the total quality-of-life score increased by 20% ($p < 0.001$) after treatment. No significant differences were detected between the two dosage groups.

Alcohol-induced hangovers. Pittler et al.¹⁷ conducted a randomized, double-blind, placebo-controlled trial to evaluate the effectiveness of artichoke leaf extract in preventing alcohol-induced hangovers. Fifteen healthy adult volunteers (10 women and 5 men) were randomized to receive three 320-mg artichoke leaf extract capsules for a total dose of 960 mg (Cynara) or three placebo capsules immediately before and after one drinking episode (the type and amount of alcohol required to induce a hangover were predefined by each patient). After a one-week washout period, the participants received the opposite treatment for a second drinking episode. Participants consumed the same food before each drinking episode. The primary endpoint was the difference in hangover severity scores between the treatments. Secondary endpoints were differences in scores on a mood profile questionnaire and cognitive performance test. Adverse effects were also assessed. Measurements were taken 1 hour before and 10 hours after the drinking episodes. The average number of alcohol units consumed, amount of nonalcoholic drinks, and duration of sleep were similar between the treatment groups. No significant

differences were detected between the treatments for any of the endpoints. One participant developed facial flushing during treatment with artichoke leaf extract; no adverse effects were reported during treatment with placebo. Too few patients were included in this study to draw strong conclusions.

Dosage. The dosages of artichoke leaf extract used in the clinical trials varied. In the hyperlipidemia trials, dosages used were 250 mg three times daily, 640 mg three times daily, and 900 mg two times daily.^{7,9-12} For dyspepsia, 320 mg once daily, 640 mg once daily, and 640 mg three times daily were used.¹³ For IBS, 640 mg of artichoke leaf extract three times daily was used.¹⁶ For relief of alcohol-induced hangovers, 960 mg immediately before and after one drinking episode was used.¹⁷ The dosage recommended by one source is 6 g daily in divided doses, which is significantly higher than the doses used in the aforementioned studies.⁸

Adverse effects. Artichoke leaf extract may increase flatulence, and there have been reports of weakness and hunger.^{1,2} Several patients in one study reported decrease in appetite.¹¹ Artichoke leaf extract may cause an allergic reaction in patients, especially those sensitive to plants from the Asteraceae family (chrysanthemums, daisies, echinacea, marigold, and ragweed). Allergic contact dermatitis can occur after handling the artichoke plant.² Acute macroglossia (edema of the tongue), allergic rhinitis, asthma attacks, and urticaria have been associated with artichoke ingestion.^{18,19}

Precautions and contraindications. Patients with bile-duct obstruction or gallstones should not take artichoke leaf extract, as it may worsen either of these conditions due to the potential for bile-flow stimulation.^{1,2,5,8} Also, patients with known allergic reactions to any of the plants in the Asteraceae family should not ingest artichoke leaf extract.^{2,4}

Interactions. There are no known or reported drug or supplement interactions with artichoke leaf extract.

Discussion. While the efficacy of artichoke leaf extract in hyperlipidemia is unclear, efficacy in reducing the symp-

toms of dyspepsia and IBS (e.g., bloating, flatulence) has been demonstrated. Artichoke leaf extract has not been shown to be effective in the treatment of alcohol-induced hangovers.

Artichoke leaf extract therapy has several limitations. The doses used in the summarized studies may not have been adequate enough to result in clinically significant outcomes, as one source recommends the use of 6 g of artichoke leaf extract daily.⁸ Also, some studies used commercially available preparations of artichoke leaf extract (Cynara, Hepar-SL forte) while other investigators manufactured their own formulation of artichoke leaf extract. Another limitation is the difference in the dosage regimens used in the studies (once, twice, or thrice daily). In addition, dietary modifications were made for patients in some but not all of the studies.

Conclusion. Artichoke leaf extract supplementation may alleviate some symptoms associated with dyspepsia or IBS. The role of artichoke leaf extract in hyperlipidemia treatment is less clear. No evidence supports the use of artichoke leaf extract for treating alcohol-induced hangovers.

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