Artichoke leaf extract – Recent findings reflecting effects on lipid metabolism, liver and gastrointestinal tracts.

K. KRAFT

Summary

In various molecular, cellular and *in vivo* test systems, artichoke (*Cynara scolymus* L.) leaf extracts show antioxidative, hepatoprotective, choleretic and anti-cholestatic effects as well as inhibiting actions on cholesterol biosynthesis and LDL oxidation. Recently, active ingredients responsible for the main effects have been identified. Thus, luteolin seems to be of crucial importance for the inhibition of hepatocellular *de novo* cholesterol biosynthesis. The anti-dyspeptic actions ware mainly based on increased choleresis. Regarding clinical data, lipid-lowering, antiemetic, spasmolytic, choleretic and carminative effects have been described, along with good tolerance and a low incidence of side effects. Due to its specific mechanisms of action, the future use of artichoke leaf extract for the prevention of arteriosclerosis can be expected.

Key words: Artichoke leaf extract, luteolin, lipids, antioxidant, dyspepsia, atherosclerosis, nausea.

Introduction

Both, traditional and more recent literature make reference to the fact that artichoke leaf extracts alleviate abdominal pain and have choleretic, lipid-lowering and hepatoprotective effects. However, it has only been possible in the last few years to evaluate the underlying mechanisms of action. Experimental and clinical results for artichoke leaf extract complement each other, a rare phenomenon in phytotherapy. Artichoke leaf extract is suitable for treating chronic gastrointestinal, metabolic, and cardiovascular diseases. Additionally, carminative, spasmolytic and antiemetic effects, have been verified through recent investigations, confirming that the dyspeptic syndrome is a traditional indication for artichoke leaf extract. (Monography: Cynarae folium 1988 [corr. 1990])

Plant, drug and ingredients

The artichoke (*Cynara scolymus* L.) belongs to the Asteraceae. It has been used medically since the 4th century B. C. Theophrast (371 B. V., Lesos), a pupil of Aristotle, was one of the first to describe the plant in depth. The modern artichoke is a derivative of the wild artichoke, *Cynanara cardunculus*, a prolific composite. Linné also counted *Carduus marianus* (milk thistle, today: *Silybum marianum*) as being part of this genus (Mayr and Fröhlich, 1965). The history of the artichoke as a medicinal plant has been dealt with in reviews by Mayr and Fröhlich (1965) and by Ernst (1995).

The extract is manufactured from the leaves (Cynarae folium). The 10th edition of the French Pharmacopoeia includes a monograph of the drug. The essential ingredients of artichoke extract are caffeic acid, chlorogenic acid, cynarin (1,5-di-caffeoylquinic acid), luteolin and the glycosides scolymoside and cynaroside. Modern extracts are manufactured using highly standardized procedures (Wagenbreth *et al.*, 1996).

Mechanisms of action

Fig. 1 summarizes the mechanisms of action of artichoke leaf extract. The graph also includes relevant experimental findings, although in a very brief form.

Choleresis and dyspepsia

Recent liver cell culture experiments demonstrated a clear increase of the secretion of biliary substances, and an elevated number and size of the secreting bile ducts within



Fig. 1. Action mechanisms of artichoke leaf extract.

the liver cells after administration of 0.1 mg/ml artichoke leaf special extract. Artichoke leaf extract caused accumulation of pericanalicular vesicles which were visualized by electron microscopy (Gebhardt, 1996 d). Clear dose dependency of the choleretic effect was depicted in the isolated perfused rat liver (Matuschowski *et al.*, 1996). These findings conclusively support the results of experimental and clinical studies, which have demonstrated stimulation of choleresis.

In double-blind clinical studies, high-dose extracts of artichoke leaves caused a considerable increase in choleresis (Kirchhoff *et al.*, 1993 and 1994) (Fig. 1), most likely due to increased production of bile acids (Kirchhoff *et al.*, 1993). A double-blind, randomized, placebo-controlled clinical study showed that artichoke leaf extract significantly (p < 0.01) increased the amount of bile secretion into the duodenum of healthy volunteers as compared with placebo recipients (Kirchhoff *et al.*, 1994) (Fig. 2).

This effect is obviously responsible for the successful treatment of the so-called dyspeptic syndrome (irritable stomach, nervous gastropathy, meteorism and flatulence, irritable colon, functional biliary tract disease).

In a further randomized, placebo-controlled clinical study, 60 patients with idiopathic dyspepsia (non-ulcer dyspepsia, irritable stomach) were investigated (Kupke *et al.*, 1991). Symptoms, such as upper abdominal pain, heartburn, bloating, constipation, diarrhea, nausea and vomiting were recorded. The volume of bile secretion, measured with a duodenal probe, increased significantly (p < 0.01) in

the active constituent group as compared with the placebo group. An improvement in symptoms was seen in 50% of patients after 14 days of treatment with artichoke leaf extract. This confirmed the findings of earlier clinical investigations of similar design (Hammerl and Pichler, 1957; Struppler and Rössler, 1957).

In a post marketing surveillance study, 417 patients with hepatic and biliary tract disease were treated for four weeks with artichoke leaf extract (Held, 1991).

They suffered from upper abdominal pain, bloating, meteorism, constipation, lack of appetite and nausea. Prior to the study, the average duration of the symptoms was four months. The patients were examined prior to the therapy as well as after the first and fourth week of treatment. Improvement of symptoms occurred after one week in 65 to 77% of patients. After four weeks, this proportion increased to 80 to 92%. Depending on the symptom, complaints disappeared in 52 to 82% of cases (Table 1).

 Table 1. Change in dyspeptic symptoms after 4 weeks treatment

 with artichoke leaf extract (Held, 1991).

Variable	No symptoms (%)	Improved (%) (cumulative)
Upper abdominal pain	59,2	85,5
Bloating	55,1	91,1
Meteorism	52,1	87,2
Constipation	56,2	78,4
Nausea	82,2	90,3



Fig. 2. Increase in biliary secretion after artichoke leaf extract (Kirchhoff et al., 1994).

A recently completed post marketing surveillance study (Fintelmann and Menßen, 1996; Fintelmann, 1996 a) was conducted under the conditions of routine treatment in patients with dyspeptic syndrome (n = 553). In this observation, subjective complaints declined in a clinically impressive and statistically significant manner within 6 weeks of

treatment (Fig. 3). The therapeutic efficiency of artichoke leaf special extract was assessed by physicians as excellent or good in *ca.* 87% of patients, as minimal in 8 patients, and as insufficient in 6 patients. Thus, the proportion of patients with below-average effects was *ca.* 3%.

98% of patients believed that the effect of the artichoke



Fig. 3. Regression of selected symptoms (mean extent of residual symptoms in % in relation to the baseline value on admission to the study [= 100%]) after approx. 6 weeks of treatment with artichoke leaf extract in patients with dyspeptic complaints (p < 0.001 for initial/post comparison of the presented variables) (Fintelmann, 1996 a; Fintelmann und Menßen, 1996).



Fig. 4. Inhibition of cholesterol biosynthesis by artichoke leaf extract: concentration-dependent incorporation of [¹⁴C]-labelled acetate in the fraction of non-saponifiable lipids on cultivated liver cells (*, p < 0.01; ... control) (Gebhardt, 1995 a, 1995 c).

leaf extract was considerably better, somewhat better or equal to that achieved during previous treatment with other drugs. Thus, artichoke leaf extract appears to be a good therapeutic option in dyspeptic syndrome.

Lipid lowering and anti-atherosclerotic effects

There are numerous clinical hints of lipid lowering effects by artichoke leaf extract preparations. They work by affecting hepatic cholesterol synthesis. The incorporation of $[^{14}C]$ -labelled acetate into the fraction of non-saponifiable



Fig. 5 a. Structure of cynaroside (luteolin-7-O-glucoside), prodrug of luteolin. Computer calculated 3-dimensional structure (Software "Lipop"; University of Straßburg).

lipids was investigated in primary cultures of rat hepatocytes. This procedure gives reliable, comparative data on the relative synthesis rate of cholesterol and sterol precursors under the effect of test substances. In 1995, a significant (p < 0.01) concentration-dependent reduction in hepatic *de novo* cholesterol synthesis was demonstrated after 2 hours incubation with artichoke leaf extract (0.01–1 mg/ml) (Fröhlich and Zigler, 1973; Gebhardt *et al.*, 1996) (Fig. 4). Cytotoxic effects were not observed within this concentration range.

The inhibiting effect was confirmed in numerous studies on isolated human hepatocytes (Gebhardt, 1996 e). Therefore, artichoke leaf extract not only increases choleresis and thereby cholesterol elimination (Kirchhoff *et al.*, 1993 and 1994; Kupke *et al.*, 1991; Hammerl and Pichler, 1957, 1959; Struppler and Rössler, 1957; Adam and Kluthe, 1979; Beggi and Dettori, 1931; Cima and Bonora, 1959; Panizzi and Scarpati, 1954; Preziosi *et al.*, 1959; Preziosi, 1962; Schreiber *et al.*, 1970), it also reduces *de novo* cholesterol biosynthesis. Inhibiting effects which could lead to a pattern shift of the sterol precursors of cholesterol were not observed (Gebhardt, 1995 c).

In animal experiments, lipid-lowering effects of the extract and its ingredients have been demonstrated (Fröhlich and Zigler, 1973; Samochowiec *et al.*, 1971; Wojcicki, 1976; Wojcicki, 1978; Samochowiec, 1959 and 1962; Lietti, 1977).

According to the most recent findings, the constituent luteolin plays a crucial role in the inhibiting effect of artichoke leaf extract on cholesterol synthesis (Gebhardt, 1996c). Luteolin is released from its glucoside (which has a weaker effect) by β -glucosidase in the digestive tract as well as in liver cells and other cells. Luteolin causes inhibition of cholesterol biosynthesis up to 60% at EC₅₀ values of 30 μ M. In HepG2-cells, an 80% maximum effect is reached with slightly higher EC₅₀ values (Gebhardt, 1996c).

Luteolin obviously acts below the level of HMG-CoA reductase, the key enzyme of cholesterol biosynthesis. In addition, the total extract shows effects on HMG-CoA reductase, which probably occur via other interactions, indirect-



Fig. 5 b. Chemical structure of luteolin.



Fig. 6. Inhibition of cholesterol synthesis by artichoke leaf extract.

ly via activation of inhibitory mechanisms or inhibition of activating mechanisms (Fig. 6). Thus artichoke leaf extract appears to inhibit lipid synthesis at several levels. Accumulation of undesired sterol compounds described for some synthetic lipid-lowering agents is thus not to be expected with artichoke leaf extract (Gebhardt, 1995 c).

In addition to findings from animal experiments (Fröhlich and Zigler, 1973; Samochowiec *et al.*, 1971; Wojcicki, 1976 and 1978; Samochowiec, 1959 and 1962; Lietti, 1977), there are many clinical data in the literature proving the lipid-lowering effects of artichoke leaf extracts. Fig. 7 gives a summary in a very simplified and shortened version. Differences between the investigational conditions of the various studies were not considered.

Recently, in a double-blind, monocentre, randomized, placebo-controlled comparative group study, the lipid-lowering potential of artichoke leaf extract was investigated in clinically healthy volunteers (n = 44). Volunteers with total cholesterol baseline values above 220 mg/dl experienced a significant decrease as compared with placebo recipients; the higher the baseline value, the larger the reduction in lipids. In contrast, protective HDL cholesterol had a tendency to increase (Petrowicz *et al.*, 1996).

In 1995, Fintelmann published the results of a post-marketing surveillance study (Fintelmann and Menßen, 1996; Fintelmann, 1996 a,b), which was conducted as a structured, multicenter investigation of 557 patients who were treated with a special extract from artichoke leaf. The average daily dose in the random sample was *ca.* 1.5 g extract and the average duration of treatment was 43.5 days. In patients whose cholesterol values were routinely determined (n = 302), serum cholesterol and serum triglyceride concentrations dropped significantly (p < 0.001) (cf. Fig. 8).

As early as the 1930s, favorable effects of artichoke leaf extract on cholesterol-containing deposits in arteries, ocular fundus, and skin were known (Tixier, 1939). In rats, artichoke leaf extracts inhibited the increase in serum lipids and the manifestation of atherosclerotic plaques induced by an atherogenic diet (Samochowiec, 1959 and 1962).

The recent demonstration of a concentration-dependent inhibition of LDL oxidation by artichoke extract *in vitro* (Gebhardt, 1996 e) confirm these earlier findings. As oxidized LDL cholesterol plays an important role in the pathogenesis of arteriosclerosis due to its cytotoxicity and atherogenicity, artichoke leaf extracts might be suitable as a prophylactic measure (Esterbauer *et al.*, 1990 and 1991; Steinberg *et al.*, 1989; Witztum and Steinberg, 1991; Bobyrev *et al.*, 1989; Gebhardt, 1995 d).

Hepatocellular protection due to antioxidative effects

Previous animal experiments encompassing various liver damage models (chlorinated hydrocarbons, ethanol) (Adzet et al., 1987; Samochowiec et al., 1971; Wojcicki, 1978) es-



Lipid lowering effects [%] induced by artichoke leaf extracts [various published data]

Fig. 7. Review of clinical data on lipid decrease caused by artichoke leaf extract. The bars show the mean values of the percentage drop listed. The data relate to cholesterol or triglycerides. Separate recording was carried out when measuring both parameters (references: 1 = Wojcicki et al. 1982; 2 = Picart 1936; 3 = Roffo 1943; 4 = Wojcicki and Winter 1975; 5 = Wojcicki et al. 1981; 6 = Herrmann 1947; 7 = Siedeck et al. 1963; 8 = Hammerl and Pichler 1959; 9 = Vorberg 1980; 10 = Dorn 1994; 11 = Palacz et al. 1981).

tablished the following after prior treatment with artichoke leaf extract: an increase in tissue regeneration, an intrahepatic increase in perfusion, an increase in the number of binucleate hepatocytes and RNA content, and stimulation of cell division (Adzet et al., 1987; Maros et al., 1966, 1968). These observations suggest hepatoprotective systems showed strong antioxidative effects for artichoke leaf extract (Gebhardt 1995 b,d and 1996 a,b,d,f; Gebhardt et al., 1996). In liver cell cultures, malondialdehyde production, which was induced by coumen hydroperoxide (Gebhardt, 1996 a,b) or t-butylhydroperoxide (t-BHP) (Gebhardt, 1995 d, 1996 b) (Fig. 9), was inhibited by artichoke leaf extract in a concentration-dependent manner. Significant effects could be demonstrated even with 1 mg extract/ml incubation fluid. At the same time, the death of hepatocytes triggered by t-BHP were reduced (Gebhardt, 1995 d). As already mentioned, the antioxidatant effect is not limited to the liver.

A cytotoxic effect of 1 mg artichoke leaf extract was ruled out using cultivated liver cells (Gebhardt, 1995 a,d).

The hepatotoxic effect of carbon tetrachloride is mainly caused by the cytochrome P_{450} dependent production of a CCl₃ radical (Recknagel and Glende, 1973; Wolf *et al.*, 1980). The mitochondrial reduction of a tretrazolium salt into a dyed formazan (MTT test) is used as demonstration of cellular damage (cytolysis). if the cells are damaged, the formazan formation is reduced. After adding an artichoke leaf extract (10 mg/ml) to a medium containing CCl₄, the death of isolated liver cells could be prevented. Inhibition was demonstrated within 3 hours and even more so after 24 hours (p < 0.001). The reduction in formazan formation due to CCl₄ was inhibited by 75% (Gebhardt, 1995 b) (Fig. 10). In this respect, a certain analogy may be seen to a hepatoprotective effect of extracts from the milk thistle (*Silybum marianum*) or its extract containing a mixture of flavonoids (silymarin) (Fintelmann and Albert, 1980; Ferenci *et al.*, 1989; Salmi and Sarna, 1982). Silymarin also possesses an antioxidative effect (Bindoli *et al.*, 1977; Muriell and Mourelle, 1990; Letteron *et al.*, 1990). However, silymarin does not have any inhibiting effects on cholesterol synthesis or choleretic effects.

Recently the active substances responsible for the antioxidative effect of the extract have been identified. They represent a mixture of polyphenols and flavonoids, i. e. caffeic acid, chlorogenic acid, cynarin, luteolin-7-O-glucoside (cynaroside) and luteolin (Gebhardt, 1996 a). Up to now, the hepatoprotective effect of artichoke leaf extract has not been proven in controlled clinical trials.

Further effects

Incubation with artichoke leaf extract prevented cholestasis, which was triggered by lithocholic acid in liver cell cultures, and which could be seen under the electron microscope as characteristic changes in canalicular membranes (Gebhardt, 1996 d). Clinical investigations covering the importance of this effect of artichoke leaf extract are not yet available.

Clinical observation of outpatients with dyspeptic syndrome showed that artichoke leaf extract had a strong anti-



lipid concentration [mg/dl] ±S.E.M.

Fig. 8. Decrease in total cholesterol and serum triglyceride concentrations (mg/dl) during six weeks observation (arithmetic mean \pm SEM) (Fintelmann, 1996a).

MDA-Production (pmol/mg protein)



Artichoke leaf extract [µg/ml] (+ t-BHP)

emetic effect (cf. Fig. 11) (Held, 1991, 1992; Fintelmann, 1996a). Score reduction, measured in relation to the initial value was *ca*. 82% for nausea, 88% for emesis, *ca*. 66% for meteorism and *ca*. 76% for nausea and 88% for emesis, *ca*. 66% for meteorism, *ca*. 76% for abdominal pain (Fintelmann and Menßen, 1996). These findings show that this well tolerated phytopharmaceutical drug might also be applied in nausea of other genesis, i. e. as adjuvant medication in oncology.

Tolerability and contraindications

The tolerability of artichoke leaf extract ranges from good to very good in the literature. A post marketing surveillance study of 417 patients showed a very good to good tolerance in 95% of cases (global assessment by the physician) (Held, 1991 and 1992). In a similar investigation on 553 patients, 1.3% of patients experienced mild adverse drug reactions such as flatulence, feeling of weakness and hunger (Fintelmann and Menßen, 1996; Fintelmann, 1996 a,b). In a placebo-controlled double-blind study there were also no significant differences between the artichoke leaf extract and placebo with respect to side effects (Petrowicz et al., 1996). Interactions with other drugs are unknown (Saller et al., 1995). As is the case for other composite flowers, local atopic reactions (type IV) have been reported after skin contact with the fresh plant (so-called artichoke harvesters disease, Meding, 1983; Gougerot, 1936; Sidi and Dobkevitch, 1950; Santori, 1932). Although so far there have been reported allergic

Fig. 9. Inhibiting effect of artichoke leaf extract on production of malondialdehyde stimulated by the oxidant t-butylhydroperoxide (t-BHP). Concentration-dependent hepatoprotective effect of various concentrations of artichoke leaf extract (* = significantly different to cultures incubated with t-BHP, p < 0.01; ** = significantly different to the control, p < 0.01) (Gebhardt, 1995a).

reactions following oral intake of artichoke leaf extract (Fintelmann and Menßen, 1996; Fintelmann, 1996 a,b), caution should be exercised when encountering known allergies to other composites.

The following contraindications may be deduced from the action profile: cholelithiasis, bile duct occlusion and allergy to composites.

The good tolerability and the very low rate of side effects confirm that drug safety is high in the case of artichoke leaf extract.

Conclusions

• Artichoke leaf extract is one of the few phytopharmaceutical drugs whose clinical effects have been confirmed to a great extent by basic biomedical research. In particular, antioxidative, choleretic, anti-cholestatic and hepatoprotective effects as well as inhibition of cholesterol synthesis have been demonstrated.

• The major components responsible for essential effects of the extract have been identified.

• Clinical investigations show that artichoke leaf extract has carminative, spasmolytic and choleretic properties.

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Absorption (A550 nm -A690 nm)



Fig. 10. Inhibition of CCl_4 induced damage of hepatocytes by artichoke leaf extract. Photometric determination of mitochondrial formazan formation as a gauge of cell damage after incubation with CCl_4 with and without extract after 3 hours (light bars) and after 24 hours (dark bars) (* p < 0.01; ** p < 0.001) (Gebhardt, 1995b).

Thus, this phytopharmaceutical drug is very suitable for treating the dyspeptic syndrome.

• The extract has an antiemetic and lipid-lowering effect in clinical practice. According to current findings, it affects the pathomechanisms of atherosclerosis by inhibiting hepatocellular cholesterol synthesis at different levels, by increased elimination of cholesterol due to choleresis, and by inhibition of LDL oxidation. Accumulation of undesired sterol compounds, as in the case of direct HMG-CoA reductase inhibitors, is not to be expected.

• Artichoke leaf extract is well tolerated and has few side effects.

• Since artichoke leaf extract is a phytopharmaceutical drug and thus has the basic advantage of a lower starting threshold for medical intervention than synthetic preparations as well as fewer risks at lower therapeutic costs, it might possibly be used for primary prevention of secondary diseases of atherosclerosis.

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Fig. 11. Antiemetic effect of artichoke leaf extract in patients with dyspeptic syndrome. Course of symptom scores for nausea (n = 292) and vomiting (n = 94) during treatment with artichoke leaf extract (p < 0.01 for initial/post comparison of the variables between initial and conclusion) (Fintelmann und Menßen, 1996).

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Address

K. Kraft, Rheinische Friedrich-Wilhelms-Universität, Medizinische Poliklinik, Wilhelmstr. 35–37, D-53111 Bonn, Germany

Tel.: 0228-287-2373; Fax: 0228-287-2266