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Health-promoting properties of artichoke in preventing cardiovascular disease by its lipidic and glycemic-reducing action

Proprietà di promozione sulla salute del carciofo mediante prevenzione delle malattie cardiovascolari grazie alla sua azione ipolipodemizzante ed ipoglicemizzante

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ABSTRACT: ***Health-promoting properties of artichoke in preventing cardiovascular disease by its lipidic and glycemic-reducing action. M. Rondanelli, F. Monteferrario, S. Perna, M.A Faliva, A. Opizzi.***

The artichoke, *Cynara scolymus*, is one of the most ancient plants grown in the world, and its extracts, obtained from different parts of the plant (leaves, fruits and roots), have been used as medicaments from time immemorial. The pharmacological and therapeutic effects of the artichoke on the liver had already been well known in the 17th century. Modern studies started in the last century confirmed the stimulating properties of artichoke extracts on the liver and gallbladder. The ensuing wave of research was initially focused on the patent liver-stimulating, diuretic and choleretic effects exerted by artichoke preparations on both animals and man, then discovering such other therapeutic properties as the hypolipemizing activity, antioxidant activity and hypoglycemizing activity. This review enumerates the most significant studies that have highlighted these therapeutic properties. Complementary medicine information needs to be incorporated into clinical practice and patient and professional education, in addition to adequate education about proper nutrition. Awareness of the widespread use of complementary and alternative medicine by people with metabolic disorders is crucial for healthcare professionals in order to prevent cardiovascular disease.

Keywords: artichoke, caffeic acid derivatives,* Cynara scolimus*, cholesterol, flavonoids, glycemia.

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Introduction

Cynara scolymus extracts obtained from different parts of the plant (leaves, fruits and roots) have been used as medicaments since ancient times [1-3]. Traditional medicine made use of the artichoke a choleretic, diuretic, laxative, appetite-stimulant, anti-gout medication and depurative [4]. The interest in the artichoke as a medicament was lost around the mid-19th century, however, and was then revived again in the first half of the 20th century, when French scientists had described artichokes as potential drugs against liver disorders. In the 1960s, one of the active ingredients found in the artichoke – called cynarin – was identified and successfully marketed as a liver-protecting agent. In a short time, this active ingredient was isolated, and some Italian researchers identified its chemical structure, thus enabling its synthesis. Some cynarin-based synthetic preparations were used to treat liver and gallbladder disorders, as well as to reduce lipid and cholesterol values, even if, over the years, they were then replaced by drugs that were more specific for these diseases. In the last ten years, however, the aqueous extract from artichoke leaves has regained an acknowledged medical value in Germany: it has been officially certified as safe and effective if it is obtained through a process complying with the relevant international pharmaceutical regulations. The extract has been used as a dietary supplement indicated for treatment of hyperlipidemia [5, 6]. In addition, Pharmacopoeias have approved its use as a hepatic stimulant and appetite stimulant, particularly in children [7-10]. Artichoke leaves, whether fresh or dry, are presently included in the official European monographs on herbal products, and the plant is mentioned in the most important collections of medicinal herbs and phytotherapy and general pharmacognosy books [11-15], which approve use of artichoke as a choleretic, diuretic, hepatoprotective and liver-stimulating substance. As far as Italy is concerned, the artichoke is mentioned in the Italian

Pharmacopoeia X Edition [9] as a dry nebulization extract titrated with caffeoylquinic acids calculated as chlorogenic acid min. 13% and max. 18%.

Complementary medicine information needs to be incorporated into clinical practice and patient and professional education, in addition to adequate education about proper nutrition [16]. Awareness of the widespread use of complementary and alternative medicine by people with metabolic disorders is crucial for healthcare professionals in order to prevent cardiovascular disease [17].

Chemistry of the biologically active molecules found in the artichoke

From a chemical point of view, artichoke leaves contain different molecules with important pharmacological activities: caffeic acid derivatives, flavonoids, sesquiterpenic lactones, anthocyans, in particular cyanidin and tannins, volatile oils, including terpenoids, carotenoids, saturated, unsaturated and polyunsaturated fatty acids, including linoleic, palmitic, oleic and stearic acids, other unsaturated compounds, like hydroxymethyl acrylic acid and polyacetylene, citric, malic, lactic, succinic and glycemic acids, monosaccharides, oligosaccharides and polysaccharides of different kinds, such as, for example, various sugars, mucilages, pectins, inulin, amino acids and proteins, like L-asparagine, and a large number of enzymes, including oxidase, peroxidase, cynarase, ascorbinase, protease, ashes, potassium, magnesium, calcium and traces of other metals.

Caffeic acid derivatives

Many of the pharmacological activities of artichoke leaf extracts were attributed – at least initially – to the presence of caffeoylquinic acids (CQS). [18-20]. In literature, these compounds are also called, more generically, "caffeic acid derivatives" or "ortodihydrophenols"; they are synthetically obtained from the condensation of a quinic acid molecule with one or two caffeic acid molecules.

Historically, chemical investigations on these component began in 1840, when a certain Mr. Gritteau isolated a substance that is known today as cynarin. The true nature of this substance was discovered by Chabrol [21] and his collaborators in 1931. Studies on the chemical nature of cynarin developed over the years, and in 1965 some Authors [22] demonstrated that this substance actually corresponded to 1,5- dicaffeoylquinic acid. Today cynarin can also be obtained through an easy and cheap semi-synthesis method that does not require use of any chromatographic step [23]. This procedure is based on the separation of the fraction rich in 1,5-dicaffeoylquinic acid, the isomerization of the compound and, owing to its higher polarity, on the simple isolation of cynarin from the reaction mix. In addition to cynarin, other monocaffeoylquinic acids have also been isolated from artichoke leaves: chlorogenic acid (or 5-O-caffeoylquinic acid) and crypto-chlorogenic acid (or 4-O- caffeoylquinic acid) [24, 25].

The highest content in caffeoylquinic acids can be found in the leaf at the end of the first vegetation year [26]. But these acids can also be found in small quantities in all the other parts of the plant. Pharmacologically, these compounds have exhibited choleretic effects (that is, they stimulate the biliary flow) and, in part, a cholesterol-reducing action.

Flavonoids

The chief flavonoids identified in leaves (0.1 to 1%) are luteolin [27-30] and three luteolin glycosides: cynaroside (luteolin-7-O-glucopiranoside), scolymoside (luteolin-7-O-rutinoside), and cynarotrioside (luteolin-7-O-rutinosil-4-O-glucopiranoside). In addition, recent analyses also highlighted the presence of rutin, apigenin, quercetin and other flavonoids together with luteolin and its glycosides [31, 32]. It now seems to have been ascertained that these compounds – in particular luteolin – seem to exert a pharmacological effect on cholesterolemia through at least two different mechanisms: on the one hand they modulate cholesterol absorption and, on the other, they slow down endogenous cholesterol synthesis by inhibiting HMG-CoA-reductase synthesis. In addition, these substances can also enhance the production of biliary acids and exhibit a marked antioxidant activity in the liver and serum.

Sesquiterpenic lactones

In addition to flavonoids and caffeoylquinic acid derivatives, artichoke leaves also contain a number of sesquiterpenic lactones (cynarotriol, cynaropicrin), which are responsible for the typical bitter taste of the artichoke [27, 33]. The highest contents in these substances were measured in young leaves immediately after flowering; on the contrary, they are absent in roots, ripe fruits and flowers. These components are endowed with hypocholesterolemizing antiinflammatory activity.

Other components

Other components found in the artichoke include: anthocians, and in particular cyanidin and tannins [34]; more than 30 volatile oils, including terpenoids [35], carotenoids [36]; saturated, unsaturated and polyunsaturated fatty acids, including linoleic, palmitic, oleic and stearic acids [37]; other unsaturated compounds, such as hydroxymethyl acrylic acid and polyacetylene [38]; citric, malic, lactic, succinic and glycemic acids [39]; monosaccharides, oligosaccharides and polysaccharides of different kinds, such as, for example, various sugars, mucilages, pectins, inulin [40, 41]; amino acids and proteins, like L-asparagine, and a large number of enzymes [42], including oxidase, peroxidase, cynarase, ascorbinase, protease [43]; ashes, potassium, magnesium, calcium and traces of other metals.

Pharmacology of the artichoke

The pharmacological and therapeutic characteristics of cynarin and the other active ingredients found in the artichoke leaves are described below and schematically listed as follows: 1. Hypolipemic and cholesterol biosynthesis-inhibiting properties. 2. Antioxidant properties. 3. Hypoglycaemic properties. 4. Liver-protecting properties. 5. Choleretic properties.

1. Action on lipid metabolism

A large number of studies demonstrated that Artichoke extracts act on lipid metabolism by decreasing production of cholesterol and endogenous triglycerides and supporting their excretion or the natural re-distribution through the organism. They also strengthen bile production by increasing the quantity of biliary acids and cholesterol discharged with bile. Since bile is the chief route to eliminate cholesterol, the stimulation of biliary secretion by artichoke extracts results in causing the physiological reduction of cholesterol in the liver and serum. In literature, there are also a number of studies highlighting a direct action of artichoke extracts on the endogenous synthesis of cholesterol. A number of reserchers investigated these activities closely through both experimental and clinical settings. Del Vecchio [44] had highlighted, *in vitro*, that the artichoke extract aided cholesterol esterification in serum, while, together with this effect, Obrecht also observed an action on atherosclerotic plaques. Preziosi and colleagues [45] tested the effects of an intravenous administration of cynarin and caffeic acid on serum cholesterol of the rabbit. In these animals, significant results were obtained following administration of doses of over 100 mg/kg, and the reduction in cholesterol levels lasted for more than 72 hours, with the maximum reduction occurring between the fourth and sixth hours from administration [45, 46]. The action was more effective on esterified cholesterol rather than on free cholesterol; the activity of caffeic acid was found to be equivalent to that of cynarin, even if its duration was shorter. The action of these two compounds seems to be ascribable to inhibition of liver cholesterol biosynthesis, rather than to the increase in serum cholesterol solubilization or esterification power [47]. Gebhardt investigated the possible mechanisms of action of the different components of the artichoke cholesterol synthesis inhibition [48]. An aqueous extract from artichoke leaves was used in high doses to inhibit cholesterol biosynthesis, in a dose-dependent manner, starting from 14C-acetate in a culture of rat hepatocytes. The failure in cholesterol synthesis seems to be linked to some inhibition of HMG-CoA reductase by the artichoke extracts. This hypothesis was then compared with the results obtained with mevastatin - an HMG-CoA inhibitor. The comparison yielded similar results, although the action of artichoke extracts lies in the modulation of the activity of HMG-CoA reductase, rather than in a true inhibition. The effects seem to be induced chiefly by flavonoids, such as luteolin and cynaroside, and, to a lesser extent, by cynarin and caffeic acid. These early studies were then followed by a considerable number of investigations using both artichoke extracts and cynarin alone, which demonstrated to possess good therapeutic efficacy in patients with normal or high cholesterol and triglyceride levels in serum; these results were then reviewed by Schilcher and Heil in 1992, by Wegener [49] and Schmidt in 1995, by Kraft [50] in 1997 and by Wegener and Fintelmann in 1999 [51]. The Table 1 and 2 provide an overview of

Table 1. - Results of studies on the effects of cynarin and artichoke extracts on cholesterol serum from 1959 to 1994 (meta-analysis by Wegener and Schmidt).

Authors and publication year	Number of patients	Treatment length in weeks	Daily dose (mg)	Total Cholesterol (mg/dl)		
				From	to	Reduction %
Mancini *et al*. (1961)	23	8	1500	256 ± 40	192 ± 20	25
Caruzzo *et al*. (1969)	1	4	1000	n.a.	Reduction	Not available
Cairella and Volpari (1971)	24	4	1000	283 ± 7	247 ± 5	13
Hammerl *et al*. (1973)	132	52-80	60	310	214	31
Eberhardt (1973)	12/10	5	1500	234 ± 38	199 ± 54	15
Montini *et al*. (1975)	30/30	7	500	ca. 300	ca. 240	20
Pristautz (1975)	60	8.5	60	298 ± 6	266 ± 9	11
Heckers *et al*. (1977)	9	12	250	381 ± 31	375 ± 38	2
Adam and Kluthe (1979)	7	11	1000	275 ± 85	213 ± 53	23
Vorberg (1980)	50	4	1200	306 ± 50	260 ± 61	15
Wegener (1994)	170	6	1920	267	228	14.5
Wójcicki and Kadikow (1974)	20	3	500 (wk 1) 450 (wk 2/3)	1085 ± 516	819 ± 179	25
Wójcicki and Winter (1975)	10	4	900	203 ± 11	153 ± 11	25
Wójcicki *et al*. (1979)	43	4	750	293 ± 15	260 ± 12	11
Palacz *et al*. (1981)	43	52	900	–	Slight reduction	–
Wójcicki *et al*. (1981)	30	6	900	203 ± 6	179 ± 15	12

Table 2. - Results of studies on the effects of cynarin and artichoke extracts on triglycerides serum from 1959 to 1994 (meta-analysis by Wegener and Schmidt).

Authors and publication year	Numebr of patients	Treatment length in weeks	Daily dose (mg)	Triglycerides (mg/dl)		
				from	to	Reduction %
Hammerl *et al*. 1973)	132	52-80	60	228	174	24
Mars and Brambilla 1974)	15/15	8.5	1000	237 ± 64	155 ± 47	35
Montini *et al*. 1975)	30/30	7	500	ca. 230	ca. 200	13
Pristautz 1975)	60	8.5	60	369 ± 11	303 ± 25	18
Vorberg 1980)	50	4	1200	196 ± 55	174 ± 80	11
Wójcicki and Kadikow 1974)	20	2	450 (wk 1) 500 (wk 2)	704 ± 231	513 ± 177	27
Wójcicki and Winter 1975)	10	4	900	143 ± 75	117 ± 43	18
Wójcicki *et al*. 1979)	43	4	750	547 ± 97	363 ± 43	33
Wójcicki *et al*. 1981)	30	6	900	135 ± 17	71 ± 8	47
Palacz *et al*. 1981)	43	52	900	–	–	27.9

the results of the studies conducted to assess the effect of the administration of the artichoke extract on lipid metabolism in man.

It is impossible to draw any correlations among the different results because of the lack of standardisation of the methods and substances used in the studies. Nonetheless, all the studies, except one, demonstrated statistically significant improvements in cholesterol and triglycerides levels. As a matter of fact, Heckers [52] administrated daily doses of 250 and 750 mg synthesis cynarin preparations for three months in 17 outpatients affected by familial type IIa or IIb hypercholesterolemia without observing any significant improvements in cholesterol and triglycerides levels, and came to the conclusion that cynarin was relatively ineffective as a therapeutic regimen in hyperlipemia. After the Polish investigator Wojcicki and collaborators had conducted studies with cynarin in the rat, they studied the influence of this compound, and then of artichoke extracts, in men of different ages affected by primitive or secondary hypercholesterolemia. First, they assessed the influence of cynarin on serum lipid levels of 20 diabetic patients, of 20 to 77 years of age, with clofibrate-resistant hypercholesterolemia [53]. Cynarin was administered for 21 days: through i.m. injections (0.5 g/die) for the first ten days and then through three tablets a day (each containing 0.15 g cynarin) for the remaining days. Both cholesterol and triglycerides decreased considerably. Cynarin was then administered in patients affected by hypercholesterolemia alone. In this case, the agent was administered through the intravenous route at a daily dose of 1 g for 21 days, and then orally at a daily dose of 0.75 g for another 21 days. This study suggests that the hypocholesterolemizing action of cynarin could be enhanced by treatment with higher doses and/or for longer periods of time. Other investigations with cynarin [54] or artichoke extracts confirmed their beneficial effects in patients affect by hyperlipemia. For example, the decrease in cholesterol, triglycerides (to –62% of the baseline value), free fatty acids, phospholipids and lipoproteins was observed in 30 healthy elderly individuals (aged 75 years on the average) following daily administration of 0.45 or 0,9 g extract, containing 0.09% polyphenols, for six weeks. The administration of different doses of two different artichoke preparations for 27 or 45 weeks was compared in individuals with primary hypertriglyceridemia unaffected by treatment with clofibrate; this study resulted in the improvement of serum triglycerides levels in 39 out of 73 patients (58.5 %; mean value of the overall results), with the normalization of 12 cases (16.8%). The fraction of phospholipids and free fatty acids in blood was then assessed in 38 patients affected by hypertriglyceridemia and treated with two different doses of 0.25 g (no = 22) and 0.5 g (no = 16) artichoke extract three times a day for 27 or 45 weeks. Statistically significant improvements of cholesterol in serum were observed after 45 weeks in the patients treated with the higher dose ($p < 0.02$). As far as phospholipids were concerned, changes were observed only in lecithin levels ($p < 0.02$) in both treatment groups; on the contrary, lysolecithin, sphyngomielin, phosphatidylcholine, phosphatidylethanolamine, lysophosphatidylethanolamine and cardiolipin levels remained statistically unchanged. High LDL levels, together with high cholesterol and triglycerides levels, are a risk factor for various degenerative vascular diseases, and in particular for arteriosclerosis. A multicentre, double-blind, randomised, placebo-controlled clinical trial was published by Englisch and collaborators in 2000 [55]. This trial analysed the efficacy and tolerability of an aqueous artichoke extract with respect to hypercholesterolemia. The preparation was formulated in coated tablets containing 450 mg artichoke extract. The trial enrolled 143 adult patients (aged between 35 and 69 years) with total baseline cholesterol levels higher than 280 mg/dl; they received 1,800 mg artichoke extract or placebo a day

for more than 6 weeks and were forbidden to consume such other medications as antibiotics or statins during the experiment. Primary endpoints were cholesterol and triglycerides levels in serum, and secondary endpoints were the values of liver enzymes. The reductions in total cholesterol levels were initially comparable between the two groups, but after the seconds week, the cholesterol level began to increase in the group treated with placebo, while it decreased in the treated group. At the end of treatment, the reduction in total cholesterol levels (-18.5% in comparison with –8.6% in the placebo group) and LDL cholesterol levels (-22.9% in comparison with –6.3% in the placebo group) in the treated group was statistically significant ($p = 0.0011$ and $p = 0.0001$, respectively) in comparison with placebo. In the authors' opinion, these results are almost comparable to those obtained with statins. The LDL/HDL ratio decreased by 20.2% in the treated group and by 7.2% in the placebo group, although the HDL cholesterol levels remained unchanged. Contrary to the results obtained in other studies, triglycerides levels were not affected by the administration of artichoke. Finally, no statistically significant difference in liver enzymes was observed between the two groups. Only two cases of poor tolerability were reported in the 12 individuals who did not complete the trial. A recent trial conducted by Bundy and Walzer [56] in 2008 examined 131 healthy adult individuals affected by slight to moderate hypercholesterolemia., with total cholesterol levels in plasma amounting to 6.0-8.0 mmol/l. The trial was aimed at assessing the effects of artichoke leaf extracts on lipid plasma levels and the general wellbeing of the individuals. The volunteers were randomised into two groups: one received 1,280 mg artichoke extract every day for 12 weeks, and the other a placebo. In the treated group, total cholesterol levels in plasma decreased on the average by 4.2%, while they increased in the control group (by 1.9% on the average); this means that the difference between the groups is statistically significant ($p = 0.025$). On the other hand, there was no significant difference in LDL cholesterol, HDL cholesterol and triglycerides between the groups. Following either treatment, the enrolled individuals reported an improvement of their subjective sensation of wellbeing, without any significant difference between the groups. In conclusion, consumption of the artichoke leaf extract resulted in a modest but favourable, statistically significant, difference in total cholesterol after 12 weeks. Our present knowledge has now ascertained that, in spite of the presence of high quantities of lipids in the blood, the first step towards the development of an atheromatous plaque must take place in the vascular endothelium owing to tissue lesions or oxidative processes. Most of the recent *in-vitro* experiments have highlighted that the artichoke and its active ingredients not only induce the reduction of circulating cholesterol levels, but may also exert a positive effect on the vascular endothelium performance, thus succeeding in preventing atherosclerosis. Lupattelli and collaborators [57] examined 18 moderately hypocholesterolemic individuals (LDL cholesterol ranging between 130 and 200 mg/dl, triglycerides between 150 and 250 mg/dl) and 10 individuals affected by high hypercholesterolemia (LDL cholesterol >200 mg/dl, triglycerides >250 mg/dl), aged between 36 and 60 years. The patients were not treated with a hypocholesterolemizing therapy during the study period and received 20 ml/die artichoke juice dissolved in water for 6 weeks. In addition to the usual lipid parameters in the blood, the levels of various soluble adhesion molecules, such as VCAM-1, ICAM-1 and E-selectin, were also measured; these molecules are hyper-expressed in dyslipidemic individuals. Finally, the brachial arteria diameter and flow-mediated vasodilatation (FMV) of the brachial arteria – two measures of the arterial dilatation capacity – were verified. At the end of treatment, an increase in triglycerides levels and a decrease in total and LDL cholesterol ($p < 0.05$ for all of them) were recorded in the treated patients; even if the controls showed a significant decrease in the latter parameters ($p < 0,01$ for both). There was also a reduction in VCAM-1 and ICAM-1 ($p < 0,05$ for both), but not in E-selectin. Brachial FMV increased significantly ($p < 0,01$), and a subsequent analysis demonstrated that the changes in adhesion molecule levels and brachial FMV were well correlated ($p < 0,05$); on the contrary, no correlation was observed between LDL cholesterol and brachial FMV. In a subsequent discussion on these results, the Authors pointed out that the potential beneficial effect of the artichoke on the vasodilatation capability, as observed in their study, seemed to be mediated by its antioxidant property, rather than by the hypocholesterolemizing effect. The latest meta-analysis on the hypocholesterolemizing action secondary to the administration of artichoke extract was conducted by Pittler and collaborators [58]. In this meta-analysis the authors reviewed 2 clinical trials conducted with correct methods and involving 167 patients affected by moderate hypercholesterolemia. The dry artichoke extract, titrated with caffeoylquinic acid 15%, reduced total cholesterol from 7.74 mmol/l. to 6.31 mmol/l after 42 treatment days ($p<0.01$), while the placebo reduced it from 7.69 mmol/l to 7.03 mmol/l. The adverse effects recorded in either trial were almost negligible.

Finally, an interesting recent research randomized, double-blind, placebo-controlled clinical trial was performed on 92 overweight subjects with primary mild hypercholesterolaemia for 8 weeks [59]. Verum supplementation with 2-daily oral assumptions (before lunch and dinner) of film-coated tablets of 250 mg of standardized artichoke leaf extract (>20% caffeoylquinic acids, >5% flavonoids and >5% cynaropicrin) was associated with a significant increase in mean high-density lipoprotein (HDL)-cholesterol ($p<0.001$) and in mean change in HDL-cholesterol (HDL-C) ($p=0.004$). A significantly decreased difference was also found for the mean change in total cholesterol ($p=0.033$), low-density lipoprotein (LDL)-cholesterol ($p<0.001$), total cholesterol/HDL ratio ($p<0.001$) and LDL/HDL ratio ($p<0.001$), when verum and placebo treatment were compared.

These data indicates that dry artichoke extracts can be useful to lower cholesterol levels, but other adequately rigorous clinical trials still have to be published to confirm these results. In short, the action of the artichoke extract on cholesterolemia is especially linked to the increase in choleresis and,

therefore, to the excretion of biliary salts and acids rich in cholesterol, but also to a direct action on the liver, which it is known to play a major role in lipid.

The Artichoke seems to be able to stimulate the following mechanisms of cholesterol metabolism by the liver: 1) more effective uptake and subsequent intra-hepatocyte metabolism of chylomicron remnants; 2) stimulation of apolipoprotein synthesis by the liver, with the consequent improvement of lipid metabolism; 3) increased uptake of LDLs and HDLs by the liver with the improvement of their intra-hepatocyte metabolism; 4) hepatic HDL synthesis stimulation induced by increased formation of apolipoproteins A1 and A2 by the liver. It is well known that these apolipoproteins, also produced by the intestine, are essential for the formation of circulating HDLs; 5) increase in HTGL and LCAT synthesis by the liver.

2. Antioxidant action

The artichoke leaf extract induces the concentration-dependent inhibition of induced oxidative stress in human neutrophils. Cynarin, caffeic acid, chlorogenic acid and luteolin have been found to be the active ingredients that play the major role in the antioxidant protective activity. The antiradical properties of aqueous and alcoholic artichoke extracts, as well as their capability of inhibiting lipid peroxidation, were recently confirmed. As demonstrated by several studies conducted by Samochowiec [60], artichoke extracts possess efficacious properties against the oxidative stress induced by inflammatory process mediators and LDL oxidation. The radical-scavenger properties of the extract, documented by *in-vitro* copper-induced oxidative prevention of LDLs, are due to the presence of flavonoids and, in particular, luteolin. Flavonoids act as hydrogen donors (reducing action) and as chelating substances capable of binding to catalyzing metals. In practice, they act as antioxidants because they seize reactive oxygen species (ROS) and transform them into less aggressive radicals, thus sacrificing themselves and, at the same time, saving physiological antioxidants (carotenoids, glutathione, vit. C and vit. E). The major role played by antioxidants in the reduction of oxidative and degenerative damage to cells and, consequently, to the tissue is by now widely known. A recent Italian study conducted in 2008 [61] was aimed at demonstrating the liver-protecting properties of polyphenolic artichoke extracts (AE) on rat hepatocytes and human hepatoma cells. The hepatocytes were exposed to H2O2 generated *in situ* by glucose-oxdase and then treated with AE, or pure chlorogenic acid (Cha) or a well-known antioxidant, N, N'-difenyl-p-phenylenediamine (DPPD). The addition of glucose-oxidase to the cell culture induced deplezione intracellular gluthatione depletion (GSH), malon dialdehyde accumulation (MDA) in the cultures – an indicator of lipid peroxidation – and cell death. These results demonstrated that cells treated with AE were protected against the oxidative stress caused by glucose-oxidase to a similar extent to that of DPPD. In addition, AE, wa well as Cha, prevented total loss of GSH and MDA accumulation. On the contrary, hepatoma cell treatment with AE for 24 hours determined reduced cell viability in a dose-dependent manner; however, Cha did not exert any noteworthy effect on the cell death rate. The results of this study indicate that AE has a potential market as an antioxidant that protects hepatocytes from oxidative stress. In addition, AE reduces viability of human liver cancer cells by supporting their apoptosis.

3. Hypoglycemizing action

A few compounds found in the artichoke exhibited a significant hypoglycemizing activity *in vitro*.

Chlorogenic acid was identified by Arion and collaborators as a powerful and specific glucose-6-phosphate-translocase inhibitor [62]. This enzyme is essential for the formation of endogenous glucose during the gluconeogenesis process, as well as for the glycolytic process. Chlorogenic acid also seems to be able to reduce the absorption of the carrier-favourite intestinal glucose.

All this may contribute to a slight reduction of glycemia values, which is particularly significant in non-insulin-dependent diabetic individuals. Matsui and collaborators [63] isolated some caffeoylquinic acid derivatives involved in the inhibitory activity of α-glucosidase and demonstrated that caffeoylquinic acids exerted a moderate hypoglycemizing effect. Another compound that is found in artichoke leaves in considerable quantities and affects glucide metabolism is inulin [64]; this compound belongs to the family of fruit-oligosaccharides (FOS) and exerts important effects on the intestinal transit, in which it modulates cholesterol and triglycerides concentrations in the blood and improves intestinal bacterial flora composition. Various authors have described the hypoglycemizing activity of the artichoke consumed as food. Vinik [65] in 2002 and, more recently, Nazni [66] in 2006 confirmed that the edible parts of the plant have good hypoglycemizing properties, especially due to the presence of high quantities of alimentary fibre.

Moreover, recently a randomized, double-blind, placebo-controlled clinical trial was performed in 39 overweight subjects for 2 months. The net change of the glycaemia was reduced significantly only in the intervention group; intervention consisted in 3-daily oral assumptions (before breakfast, lunch and dinner) of film-coated tablets of 200 mg of standardized *Cynara scolymus* flowering buds extract. Finally, in the supplemented group, the homeostasis model assessment (HOMA) decreased significantly after intervention; these parameters did not change in the controls [67].

4. Liver-protecting action

Among the many therapeutic properties that have been traditionally ascribed to the artichoke, the liver-protecting action is not certainly the least important, to the extent that its use was recommended to patients affected by hepatitis, jaundice, cirrhosis and liver steatosis. Cynarin and caffeoylquinic acids are thought to be the substances that are chiefly responsible for the protective action against such hepatotoxic agents as carbon tetrachloride. The liver-protecting action manifests itself in the reduction of liver malondialdehyde and blood enzymes AST (Aspartate aminotransferase) and ALT (Alanine

aminotransferase), whose increase in serum indicates altered liver performance due to hepatotoxic damage. The extracts with a higher content in phenol derivatives exert a greater effect on the bile flow and a better liver-protecting action. Nevertheless, single administrations of chlorogenic acid in equivalent quantities to those found in the extract do not produce any choleretic or protective effects. At least two of the earliest studies on the artichoke had tried to demonstrate its usefulness in arsenic-poisoned individuals [68]. Artichoke leaf extracts were tested *in vivo* by Maros [69] to verify their regeneration effects on liver cells. In one experiment, an aqueous artichoke leaf extract, administered orally in partially hepatectomized rats in 0.5 ml/day doses for 21 days, significantly increased liver tissue regeneration as measured from the residual liver weight, mitotic index and liver cell rate. In other experiments using the same methods the artichoke extract accelerated liver weight increase, induced marked hyperaemia and increased both binucleated hepatocyte rate and the liver cell content in ribonucleic acid. According to the majority of the recent research, luteolin and other polyphenols [48] seem to affect hepatocyte proliferation induced by different growth factors, including insulin. The action against exogenous toxic agents was also the subject of various investigations. Adzet and collaborators [70] reported that an aqueous artichoke extract (containing 2.2% caffeoylquinic acids and 0.9% luteolin), administered orally in the rat in doses of 500 mg/kg body weight 48 hours, 24 hours and 1 hour before inducing acute liver intoxication with carbon tetrachloride, significantly improved the liver performance; this was evidenced by the decrease in GSH (glutathione) liver content and total bilirubin, direct bilirubin, GOT and GPT levels in the plasma. Only cynarin, of the three caffeoylquinic acids, exhibited notable liver-protecting properties against release of both GOT and GPT. Various polyphenol components [48] of the artichoke leaf have been analysed and seem to contribute to the liver-protecting and antioxidant actions; this disagrees with the results obtained by Adzet [70], who had ascertained that only cynarin and, to a lesser extent, caffeic acid were active. These results are of great clinical interest, because this strong protective action is not probably limited to hepatocytes alone. For example, as already mentioned, these substances also inhibit LDL cholesterol oxidation and, consequently, may prevent atherosclerosis. In 2003 Speroni and collaborators [71] tested four different marketed artichoke leaf extracts, containing different quantities of active ingredients, in an animal model. The study results demonstrated that the extract with the highest content in phenols exerted the best results in terms of biliary excretion and liver-protecting activities. The histological examination of liver samples of mice poisoned with CCl4 highlighted steatosis, necrosis, small fibrosis areas and leukocyte migration; the hepatocytes showed dilatation of the endoplasmic reticulum with polyribosome detachment and disaggregation, as well as cell swelling with clarity of mitochondrial vacuoles. Similar aspects also remain unchanged in samples taken from rats treated with chlorogenic acid and cynarin. On the contrary, the liver parenchyma of rats treated with the extract having the highest content in phenols exhibited an almost normal anatomy, without any major damage to the endoplasmic reticulum or cell mitochondria.

5. Choleretic action

The artichoke performs a "amphocholeretic" role, regulating the biliary flow by either decreasing an exceedingly high biliary secretion or increasing it whenever it is reduced by toxic factors. The whole phytocomplex enhances choleresis through the simultaneous stimulation of the enzymatic, functional and antitoxic activities of the liver, liver regeneration and blood flow increase. In fact, it joins the biliary activity to the liver activity, thus justifying its indication against dyspepsia accompanied by a sensation of a full stomach, abdominal pain, meteorism, nausea and vomiting.

Experiments conducted *in vitro* demonstrated that the dry aqueous extract from artichoke leaves in primary hepatocyte cultures can induce bile secretion from biliary canaliculi, and that pure or more or less diluted juices squeezed from fresh leaves exert a dose-dependent choleretic effect on the isolated, perfused rat liver; in an experiment conducted by Matuschowski [72] in 1996, the bile flow increased by 112 to 150%, with a peak after 20 minutes from administration. The hepatobiliary and hepatoprotective effects of artichoke leaf preparations were demonstrated not only by *in-vitro* experiments, but also by a number *in-vivo* studies. Doses amounting to 200 mg/kg of an hydro-alcoholic extract from fresh artichoke leaves (19% of caffeoylquinic acids) and to 25 mg/kg of an hydro-alcoholic extract from fresh artichoke leaves – with the latter extract being purified and enriched in phenolic compounds (46% of caffeoylquinic acids) – were administered in the rat by the parenteral route. Both extracts stimulated choleresis by increasing the content in dry bile residue and total cholate excretion (flow collection through incannulation of the bile duct). These same extracts, administered orally in doses of 400 mg/kg for the total extract and 200 mg/kg for the enriched extract, increased intestinal propulsion by 11% and 14% respectively, as was highlighted in the studies conducted by Saenz Rodriguez and collaborators in 2002 [73] and in those conducted by Speroni in 2003 [71]. Much more recently, in 1993, the choleretic action of the standardized extract was investigated by Kirchhoff [74] in a cross-over, double-blind, randomised, placebo-controlled pilot study. A single 1.92 g dose was administered in 20 male patients (mean age 26 years), divided into two groups: the first group (A) received the active treatment and then placebo after an 8-day washout period; the second group (B) received placebo in the first stage and the active treatment in the second. The mean increase in secreted bile volume was considerably higher in treated individuals (I-A and II-B) than in the placebo groups (I-B and II-A); in particular, the greatest effect was reached after 1 hour, but the effects were still evident after 3 hours (always $p < 0,01$ times from the measurements between 30 and 180 minutes in comparison with the baseline values). During the discussion, the authors pointed out that

this data was of an unquestionable clinical importance; in addition, the artichoke extract consumed after a meal may be able to affect enzyme digestion and the intestinal motor function for an actual length of time of about 120-150 minutes. This means that the extract can be recommended for treatment of dyspepsia, especially when the cause can by ascribed to dyskinesia of biliary ducts or fat absorption disorders. Neither side effects nor changes in laboratory parameters were observed during this study. In 1998, Schulz reported the results of a small placebo-controlled clinical trial. The administration of 1,920 mg artichoke extract in 20 volunteers increased bile flow by 127.3% and 151.5% after 30 and 60 minutes respectively. The effects of the artichoke on gastrointestinal disorders associated to poor elimination of biliary acids were investigated in an observation study conducted by Held [75] in 1991, in which 403 patients affected by hepatic insufficiency and disorders in the biliary duct were treated for 4 weeks with standardised artichoke extract containing 375 mg dry extract per tablet. The overall results were considered as "very good" by 37.4% of the patients (34.9% of the physicians) and as "good" by 46.9% of the patients (52.3% of the physicians). Twelve patients (2.9%) dropped out of the study - 4 because of diarrhoea and 2 because of excessive flatulence. The same extract was used in a similar study conducted by Wegener in 1994. The extract was administered at the average dose of 4.75 tablets a day (corresponding to 1,520 mg) in 170 patients affected by different gastrointestinal disorders, including dyspepsia (34%), irritable colon (16%), constipation (22%), functional biliary duct disorders (21%), and others. After 6 weeks' treatment, there was an unexpected marked reduction of vomiting (95%), nausea (85%) and abdominal pain (75.5%). Abdominal pain, inappetence and meteorism also improved. According to the patients, the results were generally considered as excellent (22%) or good (67%). Unwanted side effects (weakness and a sensation of hunger) were observed only in 1.2% of the patients. Another large multicentre phase IV clinical trial, with treatment lasting 43.5 days on the average, was conducted by Fintelmann and Menßen [76] in 1996 in 553 patients (mean age 54.7 years) suffering from dyspepsia. The administration of 3 to 6 tablets of standardised extract containing 375 mg dry extract per tablet resulted in the significant reduction of dyspeptic symptoms within 6 treatment weeks and the improvement of general symptoms in 70% of the cases. In comparison with baseline values, the subjective reduction of symptoms was about 66% for meteorism, 76% for abdominal pain, 82% for nausea and 88% for vomiting. According to the physician's opinion, the general average therapeutic efficacy, on the basis of a classification scale ranging from 1 (excellent) to 5 (poor), amounted to 1.95. The effects were considered as "good" or "excellent" in about 87% of the patients and occurred within 10 days from treatment. Only slight side effects were recorded (weakness and flatulence). Other more recent studies were also conducted to ascertain the capability of the artichoke extract of improving dyspepsia symptoms.

Riassunto

Il carciofo, Cynara scolymus*, è una delle più antiche piante coltivate nel mondo, ed suoi estratti, ottenuti da diverse parti della pianta (foglie, frutti e radici), sono stati utilizzati come medicamenti da tempo immemorabile. Gli effetti farmacologici e terapeutici del carciofo sul fegato erano già noti nel 17 ° secolo. Gli studi moderni, iniziati nel secolo scorso, hanno confermato le proprietà stimolanti degli estratti di carciofo sul fegato e sulla cistifellea. La ricerca in questo campo è stata inizialmente concentrata sugli effetti diuretico e coleretico, esercitati dagli estratti di carciofo sia sugli animali sia nell'uomo. Poi sono state dimostrate altre importanti proprietà terapeutiche, come l'attività ipolipemizzante, l'attività antiossidante e ipoglicemizzante. Questa review enumera gli studi più significativi che hanno evidenziato queste proprietà terapeutiche. Informazioni in merito alla possibilità terapeutiche offerte dalla medicina complementare evidence-based devono essere diffuse e tali possibilità terapeutiche integrate nella pratica clinica, anche per le persone con disturbi metabolici al fine di prevenire le malattie cardiovascolari.*

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