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Review article

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Pharmacological studies on artichoke leaf extract -An edible herb of Mediterranean origin

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Abstract:

Artichoke leaf consists of the fresh or dried leaf of Cynara scolymus Artichoke leaf extract is made from the long, serrated basal leaves of the plant in which is found the highest concentration of biologically active compounds .Artichoke extract is one of the few herbal remedies where the clinical and experimental trials have complemented each other. Both experimental and clinical effects have been verified through extensive biomedical herbal remedy research. Specifically, antioxidant, choleretic, hepatoprotective, bile-enhancing and lipid-lowering effects have been demonstrated, which correspond with its historical use. Ongoing research seems to indicate that artichoke does indeed have medicinal qualities. Most significant appears to be its beneficial effect on the liver. In animal studies, liquid extracts of the roots and leaves of artichoke have demonstrated an ability to protect the liver, and possibly even to help liver cells regenerate. Although research is not yet conclusive, scientists are optimistic that its long-standing use in humans for digestive and bowel problems is indeed justified. It may also play a role in lowering cholesterol and thus help to prevent heart disease. Boiled wild artichoke reduces postprandial glycemic and insulinemic responses in normal subjects but has no effect on metabolic syndrome patients. This article intends to review the wide ranging pharmacological effects of artichoke

Key words *:* Artichoke, Cynara scolymus , antioxidant, choleretic, hepatoprotective, bile-enhancing and lipid-lowering, postprandial glycemic and insulinemic responses, metabolic syndrome, HIVinhibitor.

Introduction:

Cynara scolymnus - the actual artichoke plant - is one of the oldest known cultivated plants in the world with a 2000-year history. It is a tall thistle-like plant of the compositae family and is related to the better known Milk thistle-Silybum marianum. The immature flower of the artichoke plant, the rather strange-looking bud, has been used as a vegetable over the centuries. It has a high bitter index and is enjoyed for its slightly bitter taste.

Figure 1 **: Artichoke :whole plant**

History

Used as a food and a medical remedy as early as the 4th century B.C., the artichoke plant has a long history. At the time, a pupil of Aristotle named Theophrastus was one of the first to describe the plant in detail. Enjoyed as a delicacy, an appetizer and digestive aid by the aristocracy of the Roman Empire, it later seems to have fallen into oblivion until the 16th century, when medicinal use of the artichoke for liver problems and jaundice was recorded. In 1850 a French physician successfully used extract of artichoke leaves in the treatment of a boy who had been sick with jaundice for a month and had made no improvement from the drugs used at that time. This accomplishment inspired researchers to find out more about the effects of this extract, and their research resulted in the knowledge we have today about the constituents of the extract and its mechanisms of action.

The artichoke is one of the oldest cultivated plants.[1] It was first grown in Ethiopia and then made its way to southern Europe via Egypt. Its image is found on ancient Egyptian tablets and sacrificial altars. The ancient Greeks and Romans considered it a valuable digestive aid and reserved what was then a rare plant for consumption in elite circles. In sixteenth-century Europe, the artichoke was also considered a "noble" vegetable meant for consumption by the royal and the rich.

In traditional European medicine, the leaves of the artichoke (not the flower buds, which are the parts commonly cooked and eaten as a vegetable) were used as a diuretic to stimulate the kidneys and as a "choleretic" to stimulate the flow of bile from the liver and gallbladder. (Bile is a yellowish-brown fluid manufactured in the liver and stored in the gall- bladder; it consists of numerous substances, including several that play a significant role in digestion.) In the first half of the twentieth century, French scientists began modern research into these traditional medicinal uses of the artichoke plant.[1] Their

work suggested that the plant does indeed stimulate the kidney and gallbladder. Mid-century, Italian scientists isolated a compound from artichoke leaf called cynarin, which appeared to duplicate many of the effects of whole artichoke. Synthetic cynarin preparations were used as a drug to stimulate the liver and gallbladder and to treat elevated cholesterol from the 1950s to the 1980s; competition from newer pharmaceuticals has since eclipsed the use of cynarin.

Figure 2 **Artichoke :Herbarium**

Tolerability and contraindications**:** [6]

Artichoke leaf extract is well tolerated and has few side effects in recommended dosages. The use of the artichoke plant as food in many countries over hundreds of years supports its safety. More important, however, is that several rigorous studies report the absence of adverse effects when using a standardized extract compared to placebo. In a large safety study, only one out of 100 subjects reported mild side effects such as transient increase in flatulence.

Local eczematous reactions have been reported after occupational exposure and skin contact with the fresh plant or its dried parts. Such an allergy should be considered a contraindication for internal use of the extract, although no reactions to orally ingested extract have been observed so far. Because of its bile stimulating effect, the extract should not be taken by individuals with gallstones or other bile duct occlusion.

Availability: [6]

A new artichoke extract is now available in the United States, giving Americans a chance to discover its merits. While the German artichoke products, cited in most European studies, typically contain 3% caffeoylquinic acids, this new artichoke extract is standardized to contain 15% caffeoylquinic acids, calculated as chlorogenic acid.

Artichoke leaf extract - its effects on gastro intestinal tract: [3, 4, 8]

The importance of effective liver function for overall health in general, and proper gastrointestinal function in particular, is rarely emphasized in health discussions in this country. One reason might be that there is neither laboratory evidence nor specific physical symptoms to reveal an overburdened liver in the beginning stages. The symptoms may be non-specific, such as general malaise, fatigue, headache, epigastric pain, bloating, nausea or constipation. Discomfort following meals and intolerance of fat are also notable indications of disturbances in the biliary system.

It is estimated that at least 50% of patients with dyspeptic complaints have no verifiable disease. Because of the liver's essential role in detoxification, even minor impairment of liver function can have profound effects. It is therefore important to take such chronic complaints seriously. In Germany and France, for example, physicians frequently prescribe herbal liver remedies such as artichoke extract with good results, when presented with these chronic but nonspecific symptoms. We may have something to learn here.

The proven basis for the beneficial effects of artichoke leaf extract on the gastrointestinal system is the promotion of bile flow. Bile is an extremely important substance that is produced by the liver and stored in the gallbladder. It is secreted into the small intestine, where it emulsifies fats and fat-soluble vitamins and improves their absorption. Good bile flow is also essential for detoxification, which is one of the major tasks of the liver. The liver is constantly bombarded with toxic chemicals from the environment: the food we eat, the water we drink and the air we breathe. Bile serves as a carrier for these toxic substances, delivering them into the intestine for further elimination from the body. This is the major route for excretion of cholesterol. Yet another feature of the bile is helpful here: its promotion of intestinal peristalsis, which helps prevent constipation.

When the excretion of bile is inhibited for various reasons (cholestasis), toxins, including cholesterol, stay in the liver longer with damaging effects. One of the causes of inhibited bile flow is obstruction of the bile ducts by the presence of gallstones. Other common reasons for impairment of the bile flow within the liver itself are, for example, alcohol ingestion, viral hepatitis and certain chemicals and drugs. In the initial stages of liver dysfunction, laboratory tests, such as serum bilirubin, alkaline phosphatase, SGOT, LDH and GGTP, often remain normal, and it is not adequate to rely on such tests alone. Symptoms that may indicate reduced liver function are general malaise, fatigue, digestive disturbances and sometimes increasing allergies and chemical sensitivities.

Excessive alcohol consumption is by far the most common cause of impaired liver function in the United States. It stimulates fat infiltration into the liver cells, causing the so-called fatty liver. Some livers are very sensitive to even minute amounts of alcohol; others are more tolerant. Recent research suggests that the fatty liver condition is more serious than previously believed, as it may develop to more advanced liver disease, such as inflammation, fibrosis and cirrhosis.

Because of its long historical use for liver conditions it seemed reasonable to investigate the artichoke plant scientifically, and the first clinical studies were conducted in the 1930s with encouraging results. In the 1990s the interest has been intensified, and several excellent clinical studies have been conducted during the last few years: Realizing the importance of adequate bile flow for health, German researchers set out to confirm the earlier findings of bile promoting effect of the artichoke plant in

a controlled double-blind study on healthy volunteers. (Kirchhoff et al.,1994). The participants were given a one-time dose of artichoke extract or placebo, and their bile secretion was measured with special techniques over the following hours. The bile secretion was found to be significantly higher in the group that received the artichoke extract.

Another clinical study showed an improvement of symptoms in 50% of patients with dyspeptic syndrome after 14 days of treatment with artichoke leaf extract. The study involved 60 patients with non-specific symptoms such as upper abdominal pain, heartburn, bloating, constipation, diarrhea, nausea and vomiting. In the placebo group, as a comparison, improvements of less distinct quality were noticed in 38% of the participants. (Kupke et al., 1991).

Interesting results were also demonstrated in a large open label study of 417 participants with liver or bile duct disease. Most of these patients had had longstanding symptoms, some of them for many years. They suffered from upper abdominal pain, bloating, constipation, lack of appetite and nausea. These patients were treated with artichoke leaf extract for four weeks. After one week around 70% of the patients experienced improvement of their symptoms, and after four weeks the percentage was even higher (approx. 85%). (Held 1991).

Even more remarkable improvement was shown in another recently completed open label study (Fintelmann, 1996), where 553 outpatients with non-specific dyspeptic complaints were treated with a standardized artichoke leaf extract. The subjective complaints declined significantly within 6 weeks of treatment. Improvements were found for vomiting (88%), nausea (83%), abdominal pain (76%), loss of appetite (72%), severe constipation (71%), flatulence (68%) and fat intolerance (59%). Ninety-eight percent of the patients judged the effect of the extract to be considerably better, somewhat better or equal to that achieved during previous treatment with other drugs. The dosage used in this study was 1-2 capsules three times daily of the preparation Hepar SL Forte. One capsule contained 320 mg of dry extract of artichoke leaves, standardized to provide 3% of caffeoylquinic acid.

The study by Fintelmann not only confirmed the efficacy of the artichoke extract for dyspepsia, but also demonstrated a significant effect of the extract on fat (lipid) metabolism. The researchers found a significant decline in both the cholesterol and triglyceride levels in the blood, which confirmed a discovery, made as early as in the 1930s.

Artichoke and its effects on cardiovascular health: [1, 2, 4-8]

Early research on the ability of artichoke leaf extract to promote digestion led to the discovery of its application for cardiovascular health. Researchers noted that artichoke leaf helped reduce cholesterol levels and prevent atherosclerotic deposits. More recent research confirms these findings.

In one 12-week, double-blind study, artichoke leaf extract was found to decrease cholesterol levels significantly in those who had high (more than 220mg/dI) cholesterol levels to begin with. Artichoke leaf extract had a tendency to increase HDL (good) cholesterol levels. The study also found that those subjects with the highest beginning cholesterol levels showed the most significant change.

A six-week study of more than 300 subjects showed an average reduction in serum cholesterol of nearly 12 percent, and a reduction in serum triglycerides of nearly 13 per cent.

The discovery that artichoke leaf extract reduces elevated cholesterol levels opens up exciting perspectives in the prevention and treatment of arteriosclerosis and coronary heart disease.

It was as early as the 1930s that scientists first discovered that artichoke extract had a favorable effect on atherosclerotic plaques in the arteries (Tixier, 1939). Later animal studies, in which rats were fed a high-fat diet, also showed that artichoke extract prevented a rise in serum cholesterol levels and the manifestation of atherosclerotic plaque (Samochowiec, 1959 and 1962).

In addition to findings in animal experiments (Frohlich and Ziegler, 1973; Samochowiec et al., 1971; Wojcicki 1976 and 1978; Samochowiec 1959 and 1962; Lietti 1977), a number of early case reports and uncontrolled studies indicated clinical effectiveness of the artichoke extract on human cholesterol levels (Hammerl and Pichler 1957, Hammerl et al., 1973).

Recent research confirms these earlier findings. The above mentioned study by Fintelmann demonstrated a significant reduction in cholesterol and triglyceride levels in spite of the relatively short duration of the study (6 weeks). On an average there was an 11.5% reduction in serum cholesterol, from 264 mg/dl initially to 234 mg/dl. Serum triglycerides were similarly reduced from 215 mg/dl initially to 188 mg/dl, corresponding to a decrease of 12.5%. Although this was an open study, its reliability is buttressed by the relatively large number of patients (302) and the very high level of statistical significance attained for the main results.

Very interesting results came out of an excellent double blind clinical trial, conducted by Petrowicz in 1996. It studied the cholesterol-lowering effect of artichoke leaf extract on 44 healthy individuals under strictly controlled conditions over a 12-week period. There was a significant decrease of cholesterol levels in the volunteers who had high initial levels (greater than 220 mg/dl). In fact, the higher the initial cholesterol value, the more significant was the reduction in cholesterol levels. It was also observed that the protective HDL cholesterol levels showed a tendency to increase. Although the cholesterol-lowering effect of artichoke extract has been known for a few decades, the mechanism behind it has not been clear. Current research is increasing our understanding in this respect.

Artichoke extract has been found to affect the cholesterol metabolism in two different ways. It not only increases the breakdown of cholesterol to bile salts and enhances their elimination through increased bile production and flow; it also inhibits the internal production of cholesterol in the liver.

The inhibiting effect of artichoke leaf extract on cholesterol synthesis was demonstrated in some very interesting studies by Gebhardt (1995, 1996 and 1997) on rat hepatocytes (liver cells). A highly significant concentration-dependent inhibition of cholesterol synthesis was found. The 1997 study indicates that artichoke leaf extract reduces the formation of cholesterol in a physiologically favorable, long-lasting manner. This reduction of cholesterol synthesis persisted for hours following the period of exposure.

The study further indicates that artichoke extract may work through indirect inhibition of the enzyme HMGCoA-reductase, which might avoid problems known to occur with strong direct inhibitors of HMGCoA-reductase during long-term treatment. The indirect inhibition was supported by the fact that artichoke leaf extract effectively blocked insulin-dependent stimulation of HMGCoA-reductase without affecting insulin in general. HMGCoA-reductase is a key enzyme in cholesterol synthesis, and HMGCoA-reductase inhibitors generally reduce total cholesterol, LDL cholesterol and triglyceride levels.

***Artichoke extract as hepatoprotective*:** [9, 10]

The concept of hepato-protection basically reflects an appreciation of the liver's critical role in many aspects of metabolism and the importance of improving the liver's function by protecting it from damage. Antioxidants are among the many compounds that can offer significant protection of the liver.

Artichoke extract has demonstrated a strong antioxidant potential and hepato-protective effect in recent research on animals. It protects the liver and the animal from the damaging effects of toxins, such as carbon tetrachloride and other environmental chemicals in a manner similar to that of silymarin from the milk thistle. Like milk thistle, artichoke extract stimulates the regeneration of damaged liver tissue. The usefulness of artichoke for preventing or reducing build-up of fat in the liver from chronic alcohol consumption is noteworthy.

The regenerative effect of artichoke leaf extract was studied on rats after removal of part of the liver. (Maros et al., 1966, 1968). Clear signs of regeneration were observed, such as increase in liver tissue and liver cell content of RNA, stimulation of cell division and increase of blood circulation in the liver.

Studies of hepato-protective action have only been done in animals, as the common procedure involves exposure to toxins. The basic research method for this type of investigation is to give the test substance, in this case artichoke leaf extract, to the animal prior to or simultaneously with administration of a toxic substance and observe the results.

Such studies were undertaken by Adzet et al. (1987) using artichoke leaf extract against carbon tetrachloride-induced poisoning in rats and indicated a clear reduction of liver injury. Another investigation by Adzet (1987) on isolated rat liver cells (hepatocytes) exposed to the same chemical tested the activity of the different polyphenolic compounds in artichoke extract. Cynarin, which is a caffeoylquinic acid and a major constituent of the extract, was found to be responsible for the main cell-protective action.

In another study on ethanol treated rats by Samochowiec (1971) a significant reduction (28%) of fatty acid esters was found with cynarin treatment. Cynarin also reduced levels of serum and liver cholesterol in ethanol-intoxicated rats according to a study by Wojiciki (1978).

More recently Gebhardt (1995) demonstrated hepato-protective effects against carbon tetrachloride-induced toxicity on liver cells from rats, and again cynarin was found to be the compound responsible for the cell protective effect. When studying rat liver cells exposed to t-BHP (tertiary butylhydroperoxide), Gebhardt (1997) found that artichoke leaf extract significantly prevented oxidative damage to hepatocyte membranes and that chlorogenic acid and cynarin were the main contributors to this strong antioxidant effect. The findings also suggested that the cell protection should not be limited to the hepatocytes, opening the possibility that inhibition of low-density lipoprotein oxidation and other atherosclerosis-preventing actions may occur.

These studies all demonstrate a pronounced antioxidant potential by artichoke leaf extract. However, more research is needed here to fully understand the hepatoprotective mechanisms and to reveal the scope of the hepatoprotective effects.

Potential health benefits: [10]

The polyphenolic constituents of artichoke extract are by now widely recognized to be powerful antioxidants. One of the caffeoylquinic derivatives in particular, chlorogenic acid, has been repeatedly investigated during the last couple of years, with interesting results pointing to new territories, such as HIV, cancer, glucose metabolism and more.

Chlorogenic acid was tested in a study of chemically induced precursor lesions to colorectal cancer in rats (Morishita et al., 1997). Significant results were achieved both in preventing and reducing these lesions in the group that was treated with chlorogenic acid.

An investigation on HIV replication in tissue cultures demonstrated that caffeoylquinic acids are a potentially important class of HIV inhibitors that can contribute to our understanding of the mechanisms for viral integration into the host cells. These compounds act at a site distinct from that of current HIV therapeutic agents and are promising leads to new anti-HIV therapeutics. An important observation in this study was also that caffeoylquinic acids are effective against the virus at only one hundredth the concentration at which they exhibit toxicity. (Robinson et al., 1996; McDougall et al., 1998).

Another potential field for further exploration is the glucose metabolism in the liver. A study from Germany in 1998 found chlorogenic acid to be an effective inhibitor of the so-called hepatic glucose-6-phosphatase system, which regulates blood glucose levels. Such a Gl-6-P inhibitor may be useful for the reduction of inappropriately high rates of glucose output from the

liver, which is often found in non-insulin-dependent diabetes. (Hemmerle et al., 1997).

Numerous animal studies have indicated that chlorogenic acid is effective in inhibiting carcinogenic reactions, and plays an integral role in modulating the carcinogenic potential of toxic chemicals. (More et al., 1986; Tanaka et al., 1993; Kitts et al., 1994; Kono et al., 1995). These results might suggest possible future application of this natural substance to chemoprevention of cancer.

One particularly interesting feature of chlorogenic acid is its antioxidant effect against a substance called peroxynitrite. It has been shown, for example, that chlorogenic acid prevents oxidative damage to DNA by scavenging peroxynitrite (Grace et al., 1998). Now, why may this be important?.

Peroxynitrite is a cytotoxic agent that forms in the body from the reaction between superoxide and nitric oxide. Through recent research it is established that peroxynitrite is one of the major damaging oxidants produced in humans. Peroxynitrite formation is particularly associated with ischemic injuries, inflammation and neurodegenerative diseases, and damages biologically important molecules through a number of mechanisms.

As our tissues are continually exposed to damaging "reactive oxygen species" or free radicals, it is important to have effective defense mechanisms to protect against or repair the damage caused by these free radicals. Major defense mechanisms include certain enzymes, such as superoxide dismutase, and antioxidants such as vitamin C, vitamin E and glutathione. Oxidative stress occurs when the production of damaging radicals overwhelms the antioxidant defenses. Chlorogenic acid may prove to add substantial force to these defenses. Peroxynitrate as well as chlorogenic acid will most likely remain a focus of research for many years to come. Chlorogenic acid in artichoke leaf has been identified as a potent antioxidant, and researchers are examining its possible application in treating cancer, diabetes and HIV, Chlorogenic acid has also been shown to be an antioxidant against peroxynitrite, one of the most damaging oxidants, and one that is associated with heart disease, neurodegenerative diseases and inflammatory disease.

In one study, chlorogenic acid was shown to both prevent and reduce existing precancerous lesions in the colons of rats. Other studies have suggested that chlorogenic acid helps inhibit carcinogenic reactions and lessens the potential of certain chemicals to be carcinogenic.

A study on the application of artichoke leaf for diabetes found that chlorogenic acid helps regulate glucose metabolism, preventing the risk of high rates of glucose output found in diabetic patients.

A study on HIV replication showed that caffeoylquinic acids have promise as HIV inhibitors, and that they may be effective against the virus at only 1/100th the concentration at which they exhibit toxicity.

Conclusion:

Artichoke leaf extract has proven to be a safe and natural way to maintain and improve general health, because of its many applications to essential physiological functions. As a nutritional supplement and antioxidant it can safely be used as an adjunct to conventional therapies.

Summary:

Artichoke is one of the safest herbal drugs with almost no adverse effects in most of the subjects . It has proven wide ranging therapeutic applications. Its consumption as a regular food stands as an evidence for its safety. Current research activities on artichoke show strong indications of its pharmacological effects as antispasmodic, antimicrobial and antifungal agent. It shows strong hypocholesteremic activity along with improved endothelial function in, thereby assists in prevention of heart related ailments in par with statins. Its hypoglycemic effects on studies conducted are remarkable. The structure of some of the caffeoylquinic acids obtained from phytochemical screening of artichoke show significant receptor level interactions with HIV, on which *in* vivo and *in* vitro trials are in progress.

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