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REPORT

THE ARTICHOKE

More than just a gourmet food

A digestive aid, artichoke is also a promising phytopharmaceutical that aids in the prevention of arteriosclerosis, among other ills.

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The artichoke plant is best known for its "heart," the bottom part of its spiky flower bud that many of us have learned to appreciate as both a delicacy and as a nutritious vegetable. However, other parts of this tall thistle-like plant, which never reach the dinner table, have proven to be even more beneficial for our health. Clinical studies show its large basal leaves to be effective for improving digestion and liver function as well as cholesterol levels.



Since ancient times, humans have looked to nature for help to cure diseases. Up until modern times most remedies were derived from the plant kingdom, and even today a large percentage of our current pharmaceutical drugs are based on plant extracts from various parts of the world. Many old herbal remedies, however, have fallen into oblivion with the development of modern medicine.

Artichoke extract is one of the few phytopharmaceuticals whose experiential and clinical effects have been confirmed to a great extent by bio-medical research. Its major active components have been identified, as have some of its mechanisms of action in the human body. In particular, antioxidant, liver-protective, bile-enhancing and lipid-lowering effects have been demonstrated, which correspond well with the historical use of the plant. More research is needed to determine in detail the mechanisms of action for these effects. However, there appears to be evidence enough to suggest a potential role for artichoke extract in some areas where modern medicine does not have much to offer.

What is artichoke?

Cynara scolymus - 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.

The plant is native to the Mediterranean countries and was originally cultivated from the wild artichoke-*Cynara cardunculus*. It is not to be confused with the Jerusalem artichoke-*Helianthus tuberosus*-a potato-like tuber originally grown by Native American Indians. In the United States, the wild artichoke has been known and used as a delicious food only for a few decades. Today artichoke is grown in southern Europe, north Africa, South America and also to a large extent in California, where four counties devoted to its cultivation claim to be "The Artichoke Center of the World."

Artichoke has a long 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 extract

The artichoke leaf extract is made from the long, deeply serrated basal leaves of the artichoke plant. This part is chosen for medicinal use, because the concentration of the biologically active compounds is higher here than in the rest of the plant. The most active of these compounds have been discovered to be the flavonoids and caffeoylquinic acids. These substances belong to the polyphenol group and include chlorogenic acid, caffeoylquinic acid derivatives (cynarin is one of them), luteolin, scolymoside and cynaroside.

Cynarin was the first constituent of the extract to be isolated in 1934. Interestingly, it is found only in trace amounts in the fresh leaves, but is formed by natural chemical changes that take place during drying and extraction of the plant material. Cynarin was originally believed to be the one active component of the extract. Today the whole complex of compounds is considered important, since it has not yet been completely clarified which component is responsible for each effect. It is claimed that neither cynarin alone nor fresh plant material achieves the potency of the dried total extract. (Kirchhoff et al., 1994).

Chlorogenic acid, another major component of the artichoke leaf extract, has recently become known as a powerful antioxidant with exciting potential in many applications. Laboratory investigations are ongoing all over the world with promising findings for future clinical application in areas such as HIV, cancer and diabetes.

Most of the modern research on artichoke has been done with the German artichoke extract Hepar SL forte, standardized to contain 3% caffeoylquinic acids. A new, even more potent extract, standardized at 15% caffeoylquinic acids-calculated as chlorogenic acid-is now available on the American market.

Biological effects

The original use of artichoke since ancient times has been as an aid for indigestion and insufficient liver function. The mechanism of action, however, has been essentially unknown. Recent findings have provided a new foundation for our understanding and discovered additional benefits of the extract, such as antioxidant and lipid-lowering effects.

Effects on the gastrointestinal system

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.

Cardiovascular protection

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 (Samochowicz, 1959 and 1962).

In addition to findings in animal experiments (Frohlich and Ziegler, 1973; Samochowicz et al., 1971; Wojcicki 1976 and 1978; Samochowicz 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 & 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.

Another important observation in Gebhardt's study was that the extract did not interfere with other stages of the pathway leading to cholesterol synthesis, which is why adverse effects due to accumulation of sterol precursors are not to be expected. The study also revealed that the components of the extract responsible for its cholesterol-inhibiting effect are chlorogenic acid, cynaroside and particularly luteolin. Cynarin, which for a long time was believed to be the active principle in this respect, seems instead to have its main influence on the bile promoting and hepato-protective mechanisms.

The importance of these studies becomes clear when we take a look at the health situation in America today. It is an astounding fact that approximately 50% of American adults (100 million people) have high (>240 mg/dl) or borderline-high (200-239 mg/dl) serum levels of total cholesterol. It is also a disconcerting fact that an estimated two thirds of these people do not receive any form of therapy, according to the National Heart, Lung and Blood Institute. High cholesterol levels are universally accepted as a major risk factor for coronary heart disease (CHD), and there is strong evidence from large clinical trials according to the American Heart Association, that reduction of cholesterol levels benefits patients with CHD.

Coronary heart disease is the single leading cause of death in America today. Statistics estimate 1,100,000 cases of new and recurrent coronary attacks per year in America, and one third will lead to death. High mortality, widespread personal suffering as well as a substantial economical impact on the total cost of our health care systems, demand multiple approaches to this devastating situation.

What is cholesterol?

Cholesterol is a form of fat or lipid. We get it in two ways: externally from the food we eat, and internally from our own normal metabolic processes. Although a high blood level is a risk factor for coronary heart disease, it does not mean that cholesterol is altogether bad. Cholesterol is necessary for the body to function properly. It is, for example, used to build cell membranes and to manufacture sex hormones. There is the so-called "good" cholesterol, known as HDL cholesterol, and the "bad" form known as LDL cholesterol. The terms HDL and LDL refer to the lipoprotein carriers of cholesterol in the blood.

The measurement of total cholesterol in the blood includes low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol. The oxidized LDL form is very damaging to our arteries. HDL cholesterol, on the other hand, is beneficial for us. The American Heart Association currently recommends that LDL cholesterol levels should be under 130 mg/dl, HDL cholesterol should be above 35 mg/dl and total cholesterol should be under 200 mg/dl. The total cholesterol-to-HDL ratio should be no higher than 4, and the LDL-to-HDL ratio should be no higher than 2.5. The risk of heart disease can be reduced by raising HDL cholesterol as well as lowering LDL cholesterol.

How do we raise HDL cholesterol? It has actually been shown that regular exercise is an effective way to raise HDL cholesterol. Exercise is one of the non-drug therapies recommended by the American Heart Association. Physical inactivity is shown to be a clear risk factor for CHD, while regular exercise 3-4 times a week can help control both lipid levels, hypertension and overweight problems.

The lowering of LDL cholesterol, however, has more to do with diet. Consumption of hydrogenated oils, saturated fats, alcohol and high sugar intake interfere with normal cholesterol metabolism and raise the blood levels of LDL cholesterol. The lack of important nutrients found in vegetables and fruits also play a role in this regard. The American Heart Association offers detailed recommendations for a healthy diet in its program for prevention and treatment of coronary heart disease. It does little good, however, to eat a low cholesterol diet if we are overproducing cholesterol internally or not removing it from the blood at the normal

rate. Normal bile production and bile flow are therefore of crucial importance for a balanced cholesterol metabolism.

When a healthy lifestyle is not enough to keep cholesterol levels within an acceptable range, drug therapies are usually offered. A variety of cholesterol-reducing pharmaceutical drugs have been developed, such as fibric acids (Lopid), bile acid sequestrants (Questran), nicotinic acid (Niacin), and HMG-CoA reductase inhibitors (Lipitor, Mevacor, Pravachol, Zocor and others), some of which unfortunately have very serious side effects. More therapeutic options are urgently needed.

There is evidence enough to support artichoke leaf extract as a gentle, non-toxic aid and adjunct to other therapies in the prevention and treatment of high cholesterol levels and coronary heart disease. Further research and well-designed controlled clinical studies are of course needed to clarify in detail the lipid-lowering mechanisms and further evaluate potential efficacy and safety. Its safety profile and demonstrated efficacy suggest that artichoke leaf extract fills an important gap.

Hepato-protection

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 Wojciki (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.

Further effects

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.

Tolerability and contraindications

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

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.

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.

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