ARTICHOKE LEAF EXTRACT FOR TREATING HYPERCHOLESTEROLAEMIA

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A B S T R A C T

Background: Hypercholesterolaemia is directly associated with an increased risk for coronary heart disease and other sequelae of atherosclerosis. Artichoke leaf extract (ALE), which is available as an over-the-counter remedy, has been implicated in lowering cholesterol levels. Whether ALE is truly efficacious for this indication, however, is still a matter of debate.

Objective: To assess the evidence of ALE versus placebo or reference medication for treating hypercholesterolaemia defined as mean total cholesterol levels of at least 5.17 mmol/L (200 mg /dL).

Search strategy: We searched MEDLINE, Embase, Amed, Cinahl, CISCOM and the Cochrane Controlled Trial Register. All databases were searched from their respective inception until June 2001. Reference lists of articles were also searched for relevant material. Manufacturers of preparations containing artichoke extract and experts on the subject were contacted and asked to contribute published and unpublished material.

Selection criteria: Randomized controlled trials of ALE mono-preparations compared with placebo or reference medication for patients with hypercholesterolaemia were included. Trials assessing ALE as one of several active components in a combination preparation or as a part of a combination treatment were excluded.

Data collection and analysis: Data were extracted systematically and methodological quality was evaluated using a standard scoring system. The screening of studies, selection, data extraction and the assessment of methodological quality were performed independently by two reviewers. Disagreements in the evaluation of individual trials were resolved through discussion.

Main results: Two randomised trials including 167 participants met all inclusion criteria. In one trial ALE reduced total cholesterol levels from 7.74 mmol/l to 6.31 mmol/l after 42 ± 3 days of treatment whereas the placebo reduced cholesterol from 7.69 mmol/l to 7.03 mmol/l ($p=0.00001$). Another trial did state that ALE significantly ($p<0.05$) reduced blood cholesterol compared with placebo in a sub-group of patients with baseline total cholesterol levels of more than 230 mg/dl. Trial reports and post-marketing surveillance studies indicate mild, transient and infrequent adverse events.

Reviewers' conclusions: Few data from rigorous clinical trials assessing ALE for treating hypercholesterolaemia exist. Beneficial effects are reported, the evidence however is not compelling. The limited data on safety suggest only mild, transient and infrequent adverse events with the short term use of ALE. More rigorous clinical trials assessing larger patient samples over longer intervention periods are needed to establish whether ALE is an effective and safe treatment option for patients with hypercholesterolaemia.

BACKGROUND

Hypercholesterolaemia is directly associated with an increased risk of coronary heart disease (CHD) and other sequelae of atherosclerosis [Pi-Sunyer 1993, Verschuren 1995, Expert Panel 1988, Muldoon 1990, Holme 1990]. Effective non-pharmacologic treatment consists largely of dietary interventions and increased physical activity and is considered the treatment of choice for primary and secondary prevention of CHD [Tang 1998, Pyörälä K 1994]. Conventional lifestyle management programs, however, are burdened with notoriously poor compliance which often render them impractical. Standard drug therapy includes bile acid sequestrants, nicotinic acid, fibric acids and HMG-CoA reductase inhibitors (statins) [Expert Panel 1993]. None of these pharmacological options is free of adverse events [Expert Panel 1993] and some have been associated with potential carcinogenicity [Newman 1996]. A harmless yet effective treatment option would therefore be of considerable interest.

Artichoke leaf extract (ALE) has been suggested as such an option. Artichoke (Cynara scolymus) is a herbaceous perennial native to southern Europe, northern Africa and the Canary islands. Traditionally, it has been used for jaundice and liver insufficiency. Animal experiments implied a marked reduction of serum cholesterol after induced hypercholesterolaemia [Samochowiec 1962a, Samochowiec 1962b, Samochowiec 1959, Lietti 1977] and several case reports and uncontrolled clinical studies confirmed these findings [Hammerl 1959, Dorn 1995, Siedek 1963, Vorberg 1980, Wojcicki 1975, 1981]. In addition, the suggested mechanism of action of ALE indicates that it may have beneficial effects. In vitro studies on cultured hepatocytes, for instance, suggested that ALE inhibits the incorporation of 14C-labelled acetate into the non-saponifiable lipid fraction and thus reduce cholesterol biosynthesis [Gebhardt 1995, Gebhardt 1996a]. Other studies suggested indirect inhibitory effects exerted at the level of HMGCoA reductase, a key enzyme in cholesterol biosynthesis [Fintelmann 1996a, Gebhardt 1996a, Gebhardt 1997].

Quantitative measurements show that artichoke extract inhibits cholesterol biosynthesis in a concentration dependent manner [Artner-Dworzak 2000, Gebhardt 1996b]. Cynarine (1.5-di-caffeoyl-D-quinic acid) has been suggested as the principal active component of artichoke [Panizzi 1954]. More recent findings, indicate a role for the flavonoid luteolin in the inhibiting effects of on cholesterol synthesis [Gebhardt 1997]. Today, artichoke containing preparations are promoted, particularly in Europe, as aids to reduce cholesterol levels and are freely available, for instance, through the internet. Whether artichoke extract is truly efficacious for this condition is, however, still a matter of debate. This study is an attempt to determine whether ALE is effective for reducing cholesterol levels in patients with hypercholesterolaemia.

OBJECTIVES

To assess the evidence (harms and benefits) of ALE versus placebo or reference medication for treating hypercholesterolaemia.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials (RCTs). Studies with a parallel group design or cross-over studies were included if comparing ALE with placebo or reference medication. No restrictions regarding the language of publication were imposed (Egger 1997).

Types of participants

Studies were included if participants were patients with hypercholesterolaemia defined as a mean total cholesterol level of at least 5.17 mmol/L (200 mg /dL).

Types of intervention

Trials were included if performed using oral preparations containing ALE as the only component (mono-preparation). Trials assessing ALE as one of several active components in a combination preparation or as a part of a combination treatment were excluded. A minimum duration of follow-up was not specified as a criterion.

Types of outcome measures

Total serum cholesterol, cholesterol subfractions and adverse events as reported in the included trials.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Cochrane Heart Group search strategy

All publications describing (or which might describe) RCTs of ALE compared with placebo or reference medications for treating hypercholesterolaemia were sought using the following databases:

- MEDLINE was searched from 1966 to June 2001.
- Embase (1980 to June 2001).
- Amed (1985 to June 2001).
- Cinahl (1982 to June 2001).
- CISCOM (1960 to June 2001).
- and the Cochrane controlled trials register (CCTR) Issue 2, 2001.

In addition, manufacturers of commercial artichoke preparations and experts on the subject were contacted and asked to contribute published and unpublished material. Furthermore, our own files were searched for relevant publications. The bibliographies of the studies thus retrieved were searched for further trials. Primary authors of studies reporting insufficient data for statistical pooling were asked to provide additional information.

The search terms used were artichoke, Cynara scolymus, cynarin, Artischocke (the German common name for Cynara scolymus) and included trade names: Hepar SL, Valverde, Hewechol, Hepagallin, CY450 and Cynatol.

METHODS OF THE REVIEW

Data were extracted systematically according to methods used, outcome measures, patient characteristics, interventions and results. Methodological quality was evaluated according to allocation concealment, blinded assessment of outcomes and loss to follow-up. In addition, the scoring system developed by Jadad (Jadad 1996), which quantifies the likelihood of bias inherent in the trials, based on the description of randomisation, blinding and withdrawals was used. The screening of studies, selection, data extraction and the assessment of methodological quality were performed independently by the two reviewers. Disagreements in the evaluation of individual trials were resolved through discussion. The assessment of publication bias, heterogeneity and sub-group analyses are not possible due to the scarcity of the available data and will be performed in future reviews.

- DATA ANALYSIS
- Continuous variables have been expressed as the mean change from baseline to follow up, and the standard deviation difference from baseline to follow up for each comparison group. A weighted mean difference (WMD) and 95% CI have been calculated for each study. Data from each study were pooled as appropriate using a random effect model.

Should more data become available we plan to assess publication bias using a funnel plot based in the data for the primary outcome measure. If there is asymmetry in the funnel plot this will be discussed as reasons other than publication bias will also need to be considered (Sterne 2001). Because trials found may not have been carried out according to a common protocol there will usually be variations in patient groups, clinical settings, concomitant care etc. Although some difference in treatment effect is to be expected, if it is greater than that we would expect by chance, it is important to then consider if it is appropriate to pool data. Therefore we plan to assess homogeneity of trial data by using the Mantel-Haenszel chi-square test of heterogeneity. Trial data will be considered to be heterogeneous if $p<0.10$. If significant heterogeneity is present, an attempt will be made to explain the differences based on the patient clinical characteristics and interventions of the included studies. In addition, relative risk will be calculated data using the conservative, random effects method. If heterogeneity is removed using this method it will be considered safe to pool the data (Thompson 2001, Deeks 2001).

DESCRIPTION OF STUDIES

We prepared a QUOROM statement to describe the articles found from our searches (Moher 1999). Six potentially relevant studies described as randomised trials were identified (Englisch 2000, Petrowicz 1997, Dorn 1995, Kirchoff 1994, Kupke 1991, Montini 1975). No unpublished studies were found. Four studies were excluded for the following reasons: not testing a mono-preparation (Kupke 1991); not testing whole artichoke leaf extract (Montini 1975); not measuring cholesterol levels (Kirchoff 1994); not controlled although described as randomised (Dorn 1995). Two RCTs assessing oral preparations containing artichoke leaf extract for treating patients with hypercholesterolaemia were included in this review (Englisch 2000, Petrowicz 1997). Both trials were conducted double-blind and placebo-controlled.

METHODOLOGICAL QUALITY

In both trials the assessment of treatment outcomes was performed in a blinded fashion and a relatively low loss to follow up is reported. However in both trials the method of allocation concealment is not clear. Twelve of 143 patients (8.4%) dropped out in one trial (Englisch 2000), while for the study by Petrowicz (Petrowicz 1997) additional data provided by the manufacturer showed none of the 44 participants dropped out. According to the scoring system developed by Jadad and colleagues (Jadad 1996) both trials scored at least 3 of 5 points. One trial (Petrowicz 1997) scored the maximum on this scale based on the data provided by the manufacturer.

RESULTS

Englisch and colleagues (Englisch 2000) conducted a randomised, placebo-controlled, double-blind, multicentre trial. Patients, aged between 18 and 70 years with total cholesterol levels of > 7.3 mmol/l (>280 mg/dl) who had not taken any lipid lowering drugs within two weeks of enrolment were included. Ninety-six women and 47 men were randomised to receive either 1800 mg ALE or placebo daily for 6 weeks. Cholesterol lowering drugs and antibiotic treatment were prohibited during the treatment phase.

Total cholesterol levels for patients on ALE decreased by 18.5% or 1.43 mmol/l (from 7.74 mmol/l at baseline to 6.31 mmol/l after 42 ± 3 days of treatment). Total cholesterol levels for patients taking placebo also decreased by 8.6% or 0.66 mmol/l (from 7.69 mmol/l at baseline to 7.03 mmol/l). The difference between the artichoke and placebo groups was statistically significant ($p<0.00001$, 95% CI = 0.49-1.05). Low density lipoprotein levels were also significantly lower for patients receiving ALE showing a mean decrease 1.26 mmol/l compared with patients taking placebo where the mean decrease was 0.33 mmol/l ($p<0.00001$, 95% CI = 0.57 - 1.29). There were no differences between placebo and ALE group for the blood levels of either high density lipoprotein or triglyceride. Although dietary habits were recorded, the food intake was not strictly controlled in the entire patient sample. In the sample, which included out-patients as well as hospitalised patients the latter, however, received a standardised and constant hospital alimentation.

The assessment of global tolerability indicated good to excellent ratings in 68 of 71 patients in the artichoke group. Twenty eight adverse events of which 26 were mild changes in laboratory parameters are reported. These were judged by the authors as 'unlikely' to be related to the artichoke preparation and were similar in number in both treatment and placebo groups. Data are provided for the liver enzymes gamma-GT, AST, ALT and GLDH. There were no relevant changes in these parameters.

In their article, which is available only as an abstract Petrowicz and colleagues (Petrowicz 1997) report a randomised, placebo-controlled, double-blind pilot study assessing healthy volunteers. Forty-four healthy volunteers aged between 20-49 years, were randomly allocated to receive either 1920 mg artichoke extract daily or indistinguishable placebo for a 12-week treatment period. There were no significant effects on serum cholesterol levels in the total sample. Sub-group analyses were performed in 24 patients with baseline total cholesterol levels of more than 200 mg/dl. The data suggest that patients with an initial total cholesterol level of more than 230 mg/dl experienced a significant reduction in total cholesterol levels compared with patients who received placebo ($p=0.015$). Total cholesterol levels at baseline are reported for the two groups together and therefore it was not possible to assess whether baseline data were comparable for both groups. No major adverse events were reported in either group.

DISCUSSION

The limited evidence, which is available is not sufficient to recommend ALE as a treatment option for hypercholesterolaemia. However, a modest positive effect on total cholesterol levels and low density lipoprotein levels are reported. These result update and extend the findings of a previous systematic review (Pittler 1998). More rigorous randomised controlled trials, assessing larger patient samples over longer treatment periods and including careful study of relevant cardiovascular outcome measures and safety aspects are required (Ernst 2001).

Both reviewed trials were of adequate methodological quality although the study by Petrowicz is reported as an abstract only and assessed a relatively small sample. Treatment outcomes were assessed in a blinded fashion and the loss to follow-up was relatively low. Both trials scored at least 3 of 5 points for methodological quality on the scoring system developed by Jadad (Jadad 1996). None of the trials was, however, flawless. The concealment of treatment allocation, for instance, is unclear in both trials and compliance with the treatment regimen seems not to have been formally assessed. In addition, dietary intake was not rigorously controlled for in the largest trial (Englisch 2000), which would have been important in this sample of predominantly overweight out-patients (mean body mass index: 28.2). Furthermore, one trial (Petrowicz 1997) reports insufficient data for independent replication and further contacts did not produce the relevant data. Methodological weaknesses may detract from the validity of trial results and distort the findings (Moher 1998). The size of the effect reported in the reviewed trials is similar to the relative cholesterol reduction attributable to garlic which ranges between 4% and 6% (Stevinson 2000). The percentage reduction of total cholesterol attributable to dietary advice after at least six months of intervention was 5.3% (Tang 1998). Compared with conventional pharmaceutical options of lowering cholesterol, however, the effect of ALE is unimpressive. For statin drugs, for instance, systematic reviews of randomised clinical trials have reported reductions in total cholesterol from baseline between 17% and 32% compared with 0.6% for placebo (Herbert 1997, Ross 1999).

The traditional use of a plant-based remedy implies relative safety but provides no proof whether such remedies are without adverse events (Ernst 1998). The two reviewed trials indicate the absence of serious adverse events in patients treated with 1.8 to 1.9 g of ALE daily. A post-marketing surveillance study assessed 417 patients and reported good to excellent tolerability of artichoke extract in 95% of patients (Held 1992). 553 outpatients were assessed in a more recent post-marketing surveillance study (Fintelmann 1996b). Mild adverse events were reported by 1.3% of the assessed patients (flatulence n = 5, hunger n = 1, weakness n = 1). Another post-marketing study on 203 patients over a 23-week period corroborates this and reports the absence of adverse events (Fintelmann 1997, Fintelmann 1999). Overall from the evidence of the reviewed trials and post-marketing surveillance studies it seems that ALE is relatively well tolerated. These findings are confirmed by the Commission E monographs of the German Federal Institute for Drugs and Medical Devices and the American Botanical Council (Blumenthal 2000).

REVIEWERS' CONCLUSIONS

Implications for practice

Few data from rigorous clinical trials assessing ALE for treating hypercholesterolaemia exist. Beneficial effects are reported, the evidence however is not compelling. The

limited data on safety suggest mild, transient and infrequent adverse events with the short term use of ALE.

Implications for research

The lipid-lowering effects of artichoke leaf extract are supported by in vitro and animal experiments. More rigorous clinical trials assessing larger patient samples over longer intervention periods are needed to establish whether ALE is an effective and safe treatment option for patients with hypercholesterolaemia.

ACKNOWLEDGEMENTS

POTENTIAL CONFLICT OF INTEREST

None.

TABLES

Characteristics of included studies

Study	Englisch 2000
Methods	randomised, double-blind 2 parallel armsquality (Jadad): 3
Participants	143 caucasian patients aged between 18 and 70 years. Total cholesterol level of greater than 7.3 mmol/l (equivalent to 280 mg/dl). Placebo Armn= 72Mean age 49.7 yearsTreatment armn=71Mean age 54.2 years
Interventions	Treatment Arm: 900 mg artichoke dry extract twice daily. 1800 mg per day.Control Arm: placebo. Duration of treatement: 6 weeks
Outcomes	total cholesterol reductionLOW DENSITY LIPOPROTEIN HIGH DENSITY LIPOPROTEINTRIGLYCERIDEMean reduction of total cholesterol was 18.5% (1.43mmol/l) for the treatment group and 8.6% for the placebo group (0.66 mmol/l). Statistically significant.
Notes	12 drop outsDietary fat intake recorded as HIGH in 11 patients in the Treatment arm compared with 30 in the Placebo arm. Significant percentage reduction in total cholesterol levels compared with placebo
Allocation concealment	B

Study	Petrowicz 1997
Methods	randomised, double-blind 2 parallel armsquality (Jadad): 5 (data provided by manufacturer)
Participants	44 entered / drop outs not reported
Interventions	Treatment Arm: 640 mg artichoke leaf extract three times daily. 1920 mg per day. Control Arm: Placebo.Duration of Treatment 12 Weeks
Outcomes	Total cholesterol reduction
Notes	No effect in total patient population. Sub-group analysis in patients with initial total cholesterol levels of above 210 mg/dl showed that artichoke leaf extract significantly reduced total cholesterol compared with placebo. But this was on few patients therfore data is of limited power, n=7 Control/placebo arm and n=10 in the treatment arm.
Allocation concealment	B

Characteristics of excluded studies

Study	Reason for exclusion
Dorn 1995	Was not a randomised controlled trial although it was described as a randomised controlled trial
Kirchoff 1994	Did not measure blood cholesterol
Kupke 1991	Did not test a mono-preparation
Montini 1975	Did not test whole artichoke leaf extract

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** indicates the major publication for the study*

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GRAPHS

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

01 Artichoke leaf extract vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Total cholesterol reduction (mmol/l)	1	143	Weighted Mean Difference (Random) 95% CI	0.77 [0.49, 1.05]
02 LDL-cholesterol reduction (mmol/l)	1	143	Weighted Mean Difference (Random) 95% CI	0.93 [0.57, 1.29]
03 HDL-cholesterol reduction (mmol / l)	1	143	Weighted Mean Difference (Random) 95% CI	0.05 [-0.19, 0.29]
04 Triglycerides reduction (mmol/l)	1	143	Weighted Mean Difference (Random) 95% CI	-0.10 [-0.46, 0.26]

Artichoke leaf extract for treating hypercholesterolaemia

Reviewer(s)	Pittler MH, Thompson Coon J, Ernst E
Contribution of Reviewer(s)	Conception and design: MH Pittler, E Ernst Literature searches: MH Pittler, J Thompson Coon Analysis and interpretation of the data: MH Pittler, J Thompson Coon, E Ernst Drafting of the article: MH Pittler, E Ernst Critical revision of the article for important intellectual content: MH Pittler, J Thompson Coon, E Ernst Final approval of the article: MH Pittler, J Thompson Coon, E Ernst
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Most recent changes	Information not supplied by reviewer
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	Information not supplied by reviewer
Date reviewers' conclusions section amended	Information not supplied by reviewer
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SOURCES OF SUPPORT

External sources of support

- none UK

Internal sources of support

- Department of Complementary Medicine, University of Exeter UK

SYNOPSIS

Insufficient evidence of artichoke leaf extract for cholesterol reduction in people with high cholesterol

Too much cholesterol in the blood can lead to cholesterol depositing on the walls of the arteries (major blood vessels). This blocks the arteries and can cause heart attacks and strokes. High cholesterol can be lowered by quitting smoking, dietary changes and exercise. Some drugs such as statins are used, but these can have adverse effects. Artichoke (Cynara scolymus) leaf extract (ALE) is a herbal remedy marketed as an aid to lowering cholesterol. The review found that few studies have rigorously researched this topic in people with high cholesterol. ALE might be effective and relatively safe, but further research is needed.

KEYWORDS

Humans; Hypercholesterolemia[*drug therapy]; *Phytotherapy; Plant Extracts[therapeutic use]; Plant Leaves[chemistry]; Randomized Controlled Trials; Vegetables[*chemistry]