June 2003 · Vol. 52, No. 6

ORIGINAL RESEARCH

Herbs for serum cholesterol reduction

A systematic review

Joanna S. Thompson Coon, PhD, BSc (Hons); Edzard Ernst, MD, PhD, FRCP (Edin)
Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, United Kingdom

Practice Recommendations

- There is some evidence from randomized clinical trials that guggul (*Commiphora mukul*), fenugreek (*Trigonella foenum-graecum*), artichoke (*Cynara scolymus*), yarrow (*Achillea wilhelmsii*), holy basil (*Ocimum sanctum*), red yeast (*Monascus purpureus*) rice, eggplant (*Solanum melongena*), and arjun (*Terminalia arjuna*) reduce serum cholesterol.
- The evidence is not conclusive for any of the products, although preliminary clinical trials seem promising; further research is warranted.
- Safety profiles from clinical trials appear encouraging, but the long-term safety has not been established; herb-drug interactions may be possible with milk thistle (*Silybum marianum*), Asian ginseng (Panax ginseng), guggul, and fenugreek.
- It is important for physicians to discuss the use of complementary and alternative therapies with their patients.

- Objectives To systematically review the clinical evidence for herbal medicinal products in the treatment of hypercholesterolemia.
- Study Design A systematic review of randomized clinical trials of herbal medicinal products used to lower serum cholesterol. Systematic literature searches were conducted in 6 electronic data-bases. The reference lists of all papers and our files were searched for more relevant publications. Experts in the field and manufacturers of identified herbal medicinal products were contacted for published and unpublished data. No language restrictions were imposed.
- Outcomes Measured All randomized clinical trials of serum cholesterol reduction, in which mono-preparations of herbal medicinal products were administered as supplements to human subjects, were included.
- Results Twenty-five randomized clinical trials involving 11 herbal medicinal products were identified. Guggul (*Commiphora mukul*), fenugreek (*Trigonella foenum-graecum*), red yeast rice, and artichoke (*Cynara* scolymus) have been most extensively studied and have demonstrated reductions in total serum cholesterol levels of between10% and 33%. The methodological quality as assessed by the Jadad score was less than 3 (maximum, 5) for 13 of the 25 trials.
- Conclusions Many herbal medicinal products have potential hypocholesterolemic activity and encouraging safety profiles. However, only a limited amount of clinical research exists to support their efficacy. Further research is warranted to establish the value of these extracts in the treatment of hypercholesterolemia.

Two recent surveys of patients undergoing cardiac surgery reported that 75% (263 of 376) and 81% (224 of 246) of

patients currently use some form of complementary medicine (including herbs, vitamins, supplements, megavitamins, prayer, relaxation, spiritual healing, massage, imagery, and lifestyle and diet modifications).[1,2]

Many herbal medicinal products are promoted for hypercholesterolemia, including some of the top-selling supplements. It is therefore vital to establish both the efficacy of these herbal supplements in reducing serum cholesterol levels and their relative safety. This review is an attempt to systematically summarize the evidence from randomized clinical trials for the efficacy and safety of lipid-lowering herbal medicinal products.

METHODS

Identification of clinical trials

To identify clinical trials involving herbal medicinal products with hypocholesterolemic properties, we conducted systematic literature searches in the following electronic databases (all from their inception to May 2001): MEDLINE (via PubMed), EMBASE, CINAHL, AMED (Alternative and Allied Medicine Database, British Library Medical Information Centre), the Cochrane Library (Issue 2, 2001), and CISCOM (Research Council for Complementary Medicine, London, UK). The search strategy is summarized in **Appendix A** (available online at **http://www.jfponline.com**).

Further relevant papers were located by hand-searching the reference lists of all papers and departmental files. In addition, experts in the field and manufacturers were contacted to provide published and unpublished material.

Inclusion and exclusion criteria

Only randomized clinical trials investigating serum cholesterol reduction of monopreparations of herbal medicinal products administered as supplements were included. These could be placebo-controlled or equivalent trials. All retrieved data including uncontrolled trials, case reports, and preclinical and observational studies were reviewed for safety data. No language restrictions were imposed.

Data extraction and quality assessment

All articles were read in full. Data relating to sample size, study design, intervention and control, treatment duration, primary outcome measures, and results were extracted by the first author and validated by the second. The methodological quality of each trial was assessed using the Jadad scoring system,[3] which ranges from 0 (poorest) to 5 (highest). A score of 3 or above indicates reasonable methodological quality.

RESULTS

We identified 11 herbal medicinal products investigated for hypocholesterolemic properties in randomized clinical trials: guggul *(Commiphora mukul)*, artichoke (*Cynara scolymus*), garlic (*Allium sativum*), fenugreek (*Trigonella foenum-graecum*), red yeast (*Monascus purpureus*) rice, Asian ginseng (*Panax ginseng*), yarrow (*Achillea wilhelmsii*), eggplant (*Solanum melongena*), holy basil (*Ocimum sanctum*), milk thistle (*Silybum marianum*), and arjun (*Terminalia arjuna*).

The efficacy and safety of garlic has been reviewed extensively elsewhere4–6 and is therefore not discussed in this paper. Details of all identified studies are shown in Tables **1**–**5** (and **Table W1**, available online at **http://www.jfponline.com**). Guggul, fenugreek, red yeast rice, and artichoke have been studied most extensively; randomized clinical trials of these herbal medicinal products with a Jadad score of 3 or above are discussed in more depth in **Appendix B** (available online at **http://www.jfponline.com**). **Table 6** summarizes the adverse events experienced by subjects within these clinical trials and potential herb-drug interactions identified from systematic reviews.

Guggul (Commiphora mukul)

Six randomized clinical trials of guggul, involving 388 patients with different diagnoses, were identified.[7-12] Five were conducted in India and 1 in the United States; 4 were placebo-controlled; and 1 compared guggul with 2 reference compounds. The results suggest reductions in total serum cholesterol from 10% to 27% compared with baseline levels (**Tables 1** and **W1**).

High-density lipoprotein (HDL) cholesterol levels were measured in 3 of the studies.[7-9] A significant increase was seen after 8 weeks of treatment in 1 study[9]; in the others, no significant differences were seen.[7,8] A statistically significant decrease in lipid peroxide levels was reported in 1 study, with no corresponding change in the placebo-treated group.[7]

Several mild adverse events were reported during these trials, including rash, nausea, vomiting, eructation, hiccup, headache, loose stools, restlessness, and apprehension, although information regarding adverse events experienced during placebo administration was not always provided. A potential drug interaction with propranolol and diltiazem was investigated in a randomized crossover trial of 17 healthy volunteers, in which guggul was found to significantly reduce the peak plasma concentration of both drugs.[13]

Fenugreek (Trigonella foenum-graecum)

Fenugreek seeds. Five randomized clinical trials were identified, involving 140 patients; all but 1 trial was conducted in India.[14-17] Although the methodological quality of the studies was considered generally poor in 4 of the trials, statistically significant reductions in total serum cholesterol of between 15% and 33% compared with baseline were demonstrated (**Table 2**).

Fenugreek leaves. In a single-blind study of 20 healthy male volunteers, Abdel-Barry and colleagues found a nonsignificant decrease of 9% in total serum cholesterol after a single dose of an aqueous extract made from fenugreek leaves (40 mg/kg) compared with a reduction of 2.8% after dilute coffee extract (placebo) (**Table 2**). [18]

Within all the identified studies of fenugreek, patients reported mild gastrointestinal symptoms such as increased flatulence, nausea, fullness, and diarrhea during fenugreek treatment, but none was severe enough to necessitate withdrawal from the study. A 14% reduction in serum potassium was noted in healthy volunteers after a single dose of an aqueous extract of fenugreek leaves. [18]

Red yeast rice

Red yeast rice is produced by solid-state fermentation of washed and cooked rice using the fungus Monascus purpureus. It has been used in Asia as a food preservative and colorant and for its medicinal properties since the Tang Dynasty (ad 800). It is available in capsules that contain a pulverized powder of fermented rice and yeast.

Four randomized clinical trials of the lipid-lowering effects of red yeast rice conducted in patients (n=695) with hyperlipidemia were identified (**Table 3**).[19-22] In all studies, statistically significant reductions (16% to 31%) in total serum cholesterol compared with placebo or control or baseline were seen.

Adverse events experienced in clinical trials included stomachache, heartburn, dizziness, and flatulence. No changes in liver function tests were demonstrated. There was 1 case report of a 26-year-old man who used red yeast rice in preparing sausages and developed anaphylaxis due to immediate sensitivity to M purpureus.[23] Whether this is relevant to the oral administration of red yeast rice capsules is not clear.

Artichoke (*Cynara scolymus*)

The choleretic effect of the leaf extract of artichoke has been studied widely, but only 2 randomized clinical trials of its hypocholesterolemic effects, involving 187 patients, were identified (**Table 4**).[24,25] One trial (n=44 healthy volunteers), published in abstract form only, found no significant difference in lipid levels compared with placebo, although post hoc subanalyses revealed some reductions in total serum cholesterol in patients with baseline levels above 5.4 mmol/L;

these results should be interpreted with some caution. Reductions in total cholesterol of 18.5% and 8.6% were reported in the other, larger trial after artichoke and placebo treatments, respectively.

No adverse events were reported during either study. Three post-marketing surveillance studies were located: one included 417 patients and reported excellent tolerability in 95%; in the second (203 patients) no adverse reactions were reported; and the third (553 patients) described mild adverse events in 1.3% of patients (flatulence, hunger, and weakness).[24-28]

DISCUSSION

Many different herbal medicinal products have been identified with potential lipid-lowering properties (**Table 5**), but the evidence for each herb is limited. The largest amount of published literature exists for guggul, fenugreek, red yeast rice, and artichoke, with reductions in total serum cholesterol ranging from 10% to 33%.

Although HDL and low-density lipoprotein (LDL) cholesterol were not measured in all the studies, increases in HDL and decreases in LDL levels were seen with guggul, red yeast rice, and yarrow, and decreases in LDL levels were seen in studies of fenugreek, arjun, and artichoke.

Safety

Few adverse events or drug interactions were reported in clinical trials of any of the 11 herbs identified. Many are used extensively in traditional medicine and culinary practices around the world, which supports their relative safety.

However, the long-term safety for use as herbal medicinal products has not been established. Long-term exposure of large numbers of patients within a formal setting would be necessary to determine safety, although difficulties associated with all herbal medicinal products exist, such as the inability to identify active ingredients and the potential for adulteration and misbranded products. No direct or indirect evidence exists for herb-drug interactions for fenugreek, guggul, Asian ginseng, and milk thistle (**Table 6**).

Study limitations

Although differences in study design, methodological quality, statistical methods, and subject populations create problems with interpretation of these figures, they appear to compare favorably with studies of garlic; the most recent meta-analysis suggested an average effect size of 4% to 6%.[6] Studies of conventional therapeutic options for hypercholesterolemia (eg, statins) have demonstrated reductions of 20% to 30% in serum cholesterol.[29]

Several shortcomings of the review need to be addressed. First, although attempts were made to obtain data from unpublished trials by contacting authors and manufacturers, none were located. There is evidence to suggest that studies with significant positive results are more likely to be published,[30] and this may be more pronounced with unfamiliar herbal therapies.

Second, because much of this research has been conducted in India and China, our extensive search strategy may not have located all the published material.

Third, there were several weaknesses with the original trials; of the 25 randomized clinical trials of herbal medicinal products for serum cholesterol reduction identified, only 12 scored 3 or more points on the Jadad scale. The most frequent methodological flaws were conduct of single-blind or open studies and incomplete reporting of methods of randomization, blinding, and subject withdrawals.

Conclusions

Evidence suggests that physicians do not ask their patients about complementary and alternative therapies and that patients are reticent to discuss these treatments with their physicians.[31-34] Surveys indicate widespread use of

complementary and alternative therapies among patients undergoing cardiac surgery.[1,2] Although no equivalent surveys have been conducted for patients with hypercholesterolemia, in light of the relatively large number of herbal medicinal products with potential lipid-lowering properties available, it seems prudent for physicians to explore this area in their clinical decision-making process.

In conclusion, although 11 herbal medicinal products were identified with potential hypo-cholesterolemic activity, the evidence supporting individual plants is limited. In addition to lowering cholesterol, several of the herbs may exert beneficial effects in cardiovascular disease by elevating HDL levels and inhibiting lipid oxidation. The safety profiles of the products in question seems to be encouraging. Further research is therefore warranted to establish the therapeutic value of these herbs in the treatment of hypercholesterolemia.

· ACKNOWLEDGMENTS ·

The authors thank Jongbae Park, Barbara Wider, and Francesca Borelli, Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, for translation of papers from Chinese, Italian, and French, to and Esther Prati, Pharmaton, Lugano, for assistance with locating relevant articles. JTC received a research fellowship from Pharmaton SA, Lugano, Switzerland.

REFERENCES

1. Ai AL, Bolling SF. The use of complementary and alternative therapies among middle-aged and older cardiac patients. *Am J Med Qual* 2002;17:21–27.
2. Liu EH, Turner LM, Lin SX, et al. Use of alternative medicine by patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2000; 120:335–341.
3. Jadad AR, Moore A, Carroll D, et al. Assessing the quality of reports of randomised clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
4. Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol. A meta-analysis. *Arch Intern Med* 1993;119:599–605.
5. Silagy C, Neil A. Garlic as a lipid lowering agent: a meta-analysis. *J R Coll Physicians Lond* 1994;28:39–45.
6. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomised clinical trials. *Ann Intern Med* 2000;133:420–429.
7. Singh RB, Niaz MA, Ghosh S. Hypolipidemic and antioxidant effects of Commiphora mukul as an adjunct to dietary therapy in patients with hypercholesterolemia. *Cardiovasc Drugs Ther* 1994;8:659–664.
8. Szapary PO, Wolfe ML, Bloedon LT, Fair MB, Berezich DJ, Cirigliano AJ, Rader DJ. A double blind, randomised, placebo controlled clinical trial of standardized guggul extract in patients with hypercholesterolemia. Complement Ther Med 2002;10:–112.
9. Verma SK, Bordia A. Effect of *Commiphora mukul* (*gum guggulu*) in patients with hyperlipidemia with special reference to HDL cholesterol. Indian *J Med Res* 1988;87:356–360.
10. Malhotra SC, Ahuja MMS. Comparative hypolipidaemic effectiveness of gum guggulu (*Commiphora mukul*) fraction ‘A’, ethyl-P-Chlorophenoxyisobutyrate and Ciba-13437-Su. *Indian J Med Res* 1971;59:1621–1632.
11. Kuppurajan K, Rajagopalan SS, Koteswara Rao T, Sitaraman R. Effect of guggulu (Commiphora mukul–Engl) on serum, lipids in obese, hypercholesterolemic and hyperlipemic cases. *J Assoc Physicians India* 1978;26:367–373.
12. Bordia A, Chuttani SK. Effect of gum guggulu on fibrinolysis and platelet adhesiveness in coronary heart disease. *Indian J Med Res* 1979;70:992–996.
13. Dalvi SS, Nayak VK, Pohujani SM, Desai NK, Kshirsagar NA, Gupta KC. Effect of gugulipid on bioavailability of diltiazem and propranolol. *J Assoc Physicians India* 1994;42:454–455.
14. Singh RB, Niaz MA, Rastogi V, Singh N, Postiglione A, Rastogi SS. Hypolipidemic and antioxidant effects of fenugreek seeds and triphala as adjuncts to dietary therapy in patients with mild to

moderate hypercholesterolemia. *Perfusion* 1998;11:124–130.
15. Prasanna M. Hypolipidemic effect of fenugreek: a clinical study. *Indian J Pharmacol* 2000;32:34–36.
16. Sharma RD, Raghuram TC. Hypoglycaemic effect of fenugreek seeds in non-insulin dependent diabetic subjects. *Nutr Res* 1990;10:731–739.
17. Sharma RD, Raghuram TC, Rao NS. Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. *Eur J Clin Nutr* 1990;44:301–306.
18. Abdel-Barry JA, Abdel-Hassan IA, Jawad AM, Al-Hakiem MHH. Hypoglycaemic effect of aqueous extract of the leaves of *Trigonella foenum-graecum* in healthy volunteers. *East Mediterr Health J* 2000;6:83–88.
19. Keithley J, Swanson B, Sha B, Zeller J, Kessler HA, Smith KY. A pilot study of the safety and efficacy of Cholestin in treating HIV-related dyslipidemia. *Nutrition* 2002;18:201–204.
20. Heber D, Yip I, Ashley JM, Elashoff DA, Elashoff RM, Go VLW. Cholesterol lowering effects of a proprietary Chinese red yeast rice dietary supplement. *Am J Clin Nutr* 1999;69:231–236.
21. Shen Z, Yu P, Su M, et al. A prospective study of Zhitai capsules in the treatment of primary hyperlipidemia. *Natl Med J China* 1996;76:156–157.
22. Wang J, Lu Z, Chi J, et al. Multicenter clinical trial of the serum lipid-lowering effects of a Monascus purpureus (red yeast) rice preparation from traditional chinese medicine. *Curr Ther Res* 1997;58:964–978.
23. Wigger-Alberti W, Bauer A, Hipler UC, Elsner P. Anaphylaxis due to *Monascus purpureus fermented rice* (red yeast rice). *Allergy* 1999;54:1328–1336.
24. Englisch W, Beckers C, Unkauf M, Ruepp M, Zinserling V. Efficacy of artichoke dry extract in patients with hyperlipoproteinemia. *Arzneimittelforschung* 2000;50:260–265.
25. Petrowicz O, Gebhardt R, Donner M, Schwandt P, Kraft K. Effects of artichoke leaf extract (ALE) on lipoprotein metabolism in vitro and in vivo. *Atherosclerosis* 1997;129:–147.
26. Fintelmann V. Antidyspeptic and lipid lowering effect of an extract from artichoke leaves. results of clinical trials on efficacy and tolerability of Hepar SL in 553 patients. *Z Allg Med* 1996;72:3–19.
27. Fintelmann V, Wegener T. Langzeitanwendung von artischockenblattertrockenextrakt (Hepar-SL forte) bei dyspeptischem symptomkomplex. *Presented at: Phytotherapie Kongress* 1997; November 27-28, 1997; Wurzburg, Germany.
28. Held C. Von der 1. Deutsch-ungarischen Phytopharmaka-konferenz 1991; 20 November, Budapest. *Z Klin Med* 1992;47:92.
29. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389.
30. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;337:867–872.
31. Adler SR, Fosket JR. Disclosing complementary and alternative medicine use in the medical encounter: a qualitative study in women with breast cancer. *J Fam Pract* 1999;48:–453.
32. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997. Results of a follow-up national survey. *JAMA* 1998;280:1569–1575.
33. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. *N Engl J Med* 1993;328:246–252.
34. Abbot NC, Ernst E. Patients' opinions about complementary medicine. *Forsch Komplementarmed* 1997;4:164–168.
35. Guimaraes PR, Galvao AMP, Batista CM, et al. Eggplant (Solanum melongena) infusion has a modest and transitory effect on hypercholesterolemic subjects. *Braz J Med Biol Res* 2000;33:1027–1036.
36. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin dependent diabetic patients. *Diabetes Care* 1995;18:1373–1375.

37. Petronelli A, Roda E, Briganti M, Labate AMM, Barbara L. Effeto della somministrazione di silimarina sui livelli dei lipidi sierici. *Clin Ter* 1981;99:471–482.
38. Gupta R, Singhal S, Goyle A, Sharma VN. Antioxidant and hypocholesterolaemic effects of Terminalia arjuna tree bark powder: a randomised placebo controlled trial. *J Assoc Physicians India* 2001;49:231–235.
39. Agarwal P, Rai V, Singh RB. Randomised placebo-controlled, single blind trial of holy basil leaves in patients with non insulin dependent diabetes mellitus. *Int J Clin Pharmacol Ther* 1996;34:406–409.
40. Asgary S, Naderi GH, Sarrafzadegan N, Mohammadifard N, Mostafavi S, Vakili R. Antihypertensive and antihyperlipidemic effects of Achillea wilhelmsii. *Drugs Exp Clin Res* 2000;26:89–93.
41. Fugh-Berman A. Herb-drug interactions. *Lancet* 2000;355:134–138.
42. Ernst E. Possible interactions between synthetic and herbal medicinal products. Part 1: a systematic review of the indirect evidence. *Perfusion* 2000;13:4–15.
43. Ernst E. Interactions between synthetic and herbal medicinal products. Part 2: a systematic review of the direct evidence. *Perfusion* 2000;13:60–70.
44. Thompson Coon J, Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. *Drug Saf* 2002;25:323–44.