

## HERBAL THERAPEUTICS

**(4) HYPERLIPIDAEMIA**

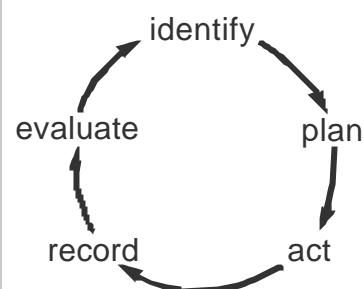
By Jo Barnes, PhD, MRPharmS

*This article considers evidence for the efficacy and safety of herbal medicines used to lower raised plasma lipid concentrations*

## identify gaps in your knowledge

1. Name two herbal products reputed to have lipid-lowering effects.
2. Can lipid-lowering herbal products be taken by pregnant or breast-feeding women?
3. Garlic products should be avoided by patients taking which medicines?

This article relates to the Royal Pharmaceutical Society's core competencies of "medicinal products" and "evidence-based practice" (see "Medicines, ethics and practice — a guide for pharmacists", number 26, July 2002, pp105–6). You should consider how it will be of value to your practice.



The prevalence of hypercholesterolaemia is rated as "very common", and the condition is clearly associated with an increased risk of atherosclerosis and ischaemic heart disease.<sup>1</sup> Research on herbal medicines used to lower raised plasma lipid concentrations has focused mainly on the effects of garlic (*Allium sativum* L.), globe artichoke (*Cynara scolymus* L.) and ispaghula (*Plantago ovata* Forsk.).<sup>2</sup> Several other herbs, such as alfalfa (*Medicago sativa* L.), milk thistle *Silybum marianum* L.), myrrh (*Commiphora molmol* Engl. and other *Commiphora* species) and turmeric (*Curcuma longa* L.), are reputed to have lipid-lowering effects, but have been subject to little scientific investigation.<sup>2,3</sup>

Hyperlipidaemia includes hypercholesterolaemia and hypertriglyceridaemia. It is beyond the scope of this article to consider the aetiology, classification, diagnosis and treatment of hyperlipidaemia, and pharmacists are advised to consult standard reference texts for this information.<sup>1</sup> Pharmacists are encouraged, where possible, discreetly to probe individuals' reasons for purchasing herbal products that could be used to lower plasma cholesterol concentrations. If the intended use is "for [lowering] cholesterol", apply usual protocols to establish why this is considered necessary (eg, as a preventive measure, or following the results of a cholesterol screening test), treatments already tried or being used, other action taken, lifestyle factors (eg, diet, exercise) and so on. Individuals using garlic or other herbal medicines listed above as a preventive measure may benefit from dietary and other lifestyle advice. Individuals with raised plasma lipid concentrations and who are not already under medical supervision may require referral to a general practitioner. Over-the-counter treatment with garlic or other herbal medicines as an adjunctive approach in hyperlipidaemia should be under medical or pharmacist supervision.

**BACKGROUND**

Garlic and, to a lesser extent, globe artichoke are widely used as foods but both also have a long history of traditional medicinal use

for a variety of conditions. The parts used pharmaceutically are garlic bulb (cloves) and globe artichoke leaf. Globe artichoke should not be confused with Jerusalem artichoke (*Helianthus tuberosus*). Ispaghula is used in food manufacture as a thickening or stabilising agent, and the seed husk is used pharmaceutically.

Other herbs reputed to have lipid-lowering properties, such as alfalfa, myrrh and turmeric, are also widely used as foods or flavourings.<sup>2</sup> Milk thistle, however, is not used in foods. The parts of these herbs used pharmaceutically for lipid-lowering are alfalfa seeds, milk thistle fruits, myrrh oleo-gum resin (which exudes from the oleoresin canals through cracks in the bark and contains a complex mixture of compounds, as well as volatile oil and gum) and turmeric rhizome (underground stem).

**MAJOR CONSTITUENTS**

Garlic is characterised by its sulphur-containing constituents, particularly alliin; other constituents include enzymes, such as alliinase and peroxidases. When formulations (eg, tablets, capsules) containing carefully dried garlic powder disintegrate in the gastrointestinal tract, alliin comes into contact with alliinase resulting in the formation of allicin. The structures of alliin and allicin are shown in Figure 1, p194. Because allicin is unstable it forms other sulphur-containing compounds, such as diallyl sulphides.<sup>2,3</sup> The particular constituents responsible for the activity of garlic have not been definitively established, but it is likely that several are important, such as S-allylcysteine and diallyl disulphides.

The active constituents of globe artichoke are also unclear, although the dicaffeoylquinic acids, particularly cynarin, are likely to be important. Ispaghula mucilage (a gum-like secretion) from the seed husk contains a mucopolysaccharide which absorbs water to form a mucilaginous mass. Constituents which may be important in other lipid-lowering herbs are alfalfa saponins, silymarin (which contains several flavolignans) in milk thistle, a ketosteroid found in myrrh, and curcumin (a diarylheptanoid) in turmeric.<sup>2,3</sup>

**PRODUCT QUALITY**

Marketed garlic products include those containing carefully dried garlic powder (thus retaining alliin and alliinase) and which are often

*Dr Barnes is a lecturer in phytopharmacy at the centre for pharmacognosy and phytotherapy at the School of Pharmacy, University of London*

standardised on content of sulphur-containing constituents, particularly alliin, or on allicin yield. One milligram of alliin is considered to be equivalent to 0.45mg allicin. Other preparations include aged garlic extracts, produced by a fermentation process, and garlic oil, a steam distillation product.<sup>2,3</sup> Most, but not all, clinical trials of garlic have investigated the effects of standardised preparations of garlic powder.

Results from studies involving preparations of garlic powder should not be extrapolated to other garlic preparations because there are differences in pharmaceutical quality.<sup>4</sup> The issue of variation between manufactured products, and the suggestion that evidence for efficacy and safety should be considered to be extract- or product-specific, were raised in the first article in this series (*PJ*, 8 June, pp804–6).

#### EVIDENCE OF EFFICACY

**Garlic** The effects of garlic preparations on raised plasma cholesterol concentrations have been explored in numerous clinical trials which have been the subject of several meta-analyses. Overall, clinical evidence indicates that garlic preparations have beneficial effects in hypercholesterolaemia, but at present the evidence is insufficient to recommend garlic as a routine treatment.

The first meta-analysis included five randomised controlled trials (RCTs) mostly involving patients with total plasma cholesterol concentrations greater than 5.17mmol/L (ideally, total cholesterol levels should be below 5mmol/L). Garlic extract 600 to 1,000mg daily for eight to 24 weeks was found to reduce total cholesterol concentrations by around 9 per cent net, compared with placebo ( $P < 0.001$ ).<sup>5</sup> Another meta-analysis included 16 trials involving patients with a range of disorders (eg, hyperlipidaemia, coronary heart disease [CHD] and hypertension), as well as healthy volunteers, who received various garlic preparations (eg, fresh garlic, garlic oil, garlic extract, dried garlic powder). The analysis reported a mean difference of  $-0.77$ mmol/L (95 per cent confidence interval [CI]:  $-0.65$  to  $-0.89$ mmol/L) in the reduction of total cholesterol concentrations between garlic recipients and participants who either received placebo or adopted a garlic-free diet.<sup>6</sup>

The most recent meta-analysis included 13 randomised, double-blind, placebo-controlled trials involving almost 800 patients with hypercholesterolaemia alone or in association with several conditions (eg, CHD, hyperlipoproteinaemia, hypertension, familial hyperlipidaemia in children), as well as healthy volunteers.<sup>7</sup> Ten trials assessed a standardised preparation of dried garlic powder

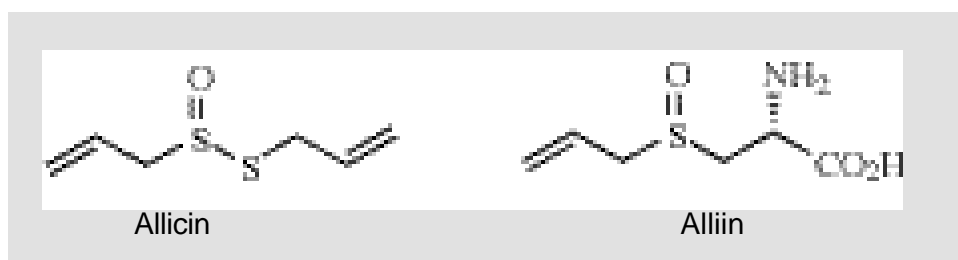


Figure 1: Chemical structures of allicin and alliin

(Kwai) at dosages of 600 to 900mg daily for eight to 24 weeks; three trials tested spray-dried powder or garlic oil. The meta-analysis indicated a significant difference in the reduction of total plasma cholesterol concentrations for garlic, compared with placebo ( $-0.41$ mmol/L, 95 per cent CI  $-0.66$  to  $-0.15$  mmol/L;  $P < 0.01$ ). This was equivalent to a net reduction in total cholesterol concentrations of 5.8 per cent, although the clinical significance of this is questionable.

A new randomised, double-blind, placebo-controlled trial which assessed the effects of garlic powder 500 and 1,000mg daily for 12 weeks in 53 patients with moderate hypercholesterolaemia (baseline low-density lipoprotein [LDL] cholesterol concentration 130 to 190mg/dL) found no statistically significant differences in the absolute mean change in LDL-cholesterol concentrations between the three groups at the end of the study.<sup>2</sup>

**Globe artichoke** Some globe artichoke preparations are standardised on cynarin content. Clinical investigation of the effects of globe artichoke leaf extract in hyperlipidaemia has reported positive results, although further rigorous studies are required to establish its benefits clearly.

A randomised, double-blind, placebo-controlled trial involving 143 patients with hyperlipoproteinaemia (baseline total cholesterol concentrations of greater than 7.3mmol/L) showed that mean total cholesterol concentrations decreased by 18.5 per cent to 6.31mmol/L and by 8.6 per cent to 7.03mmol/L in patients who received globe artichoke leaf extract (CY-450) 1,800mg daily for six weeks, and placebo, respectively ( $P < 0.0001$ ).<sup>2</sup> LDL-cholesterol concentrations also decreased significantly in the CY-450 group, compared with the placebo group ( $P = 0.0001$ ).

**Ispaghula** Ispaghula is well known for its laxative effects, but there is also substantial evidence from randomised, placebo-controlled trials and meta-analyses of such trials that consumption of ispaghula lowers total cholesterol and LDL-cholesterol concentrations.<sup>2</sup> For example, a meta-analysis of eight trials involving 656 patients with hypercholesterolaemia reported that, compared with placebo, consumption of 10.2g ispaghula daily for at least eight weeks lowered total cholesterol concentrations by 4 per cent ( $P < 0.0001$ ) and LDL-cholesterol by 7 per cent ( $P < 0.0001$ ).<sup>8</sup> The study concluded that ispaghula may be a useful adjunct to a low-fat diet in individuals with mild-to-moderate hypercholesterolaemia. The British National Formulary lists this indication for ispaghula<sup>9</sup>.

**Other herbs** There has been little clinical investigation of the reputed lipid-lowering effects of other herbs mentioned above. A small uncontrolled study involving 11 patients with hyperlipoproteinaemia who received alfalfa seeds 40g three times daily for eight weeks reported decreases in total cholesterol concentrations and LDL-cholesterol, compared with baseline values, but these effects cannot be definitively attributed to alfalfa administration.<sup>2</sup> Small and/or uncontrolled studies have reported reductions in total cholesterol concentrations following treatment with guggulipid from myrrh, turmeric extract and silymarin.<sup>2,3</sup> However, the design of these preliminary studies does not allow any conclusions on the beneficial effects of these preparations to be drawn.

#### MECHANISM OF ACTION

*In vitro* studies using cultured hepatocytes have shown that garlic, its sulphur-containing constituents and globe artichoke leaf extract

## action : practice points

1. Look at the warnings on some of the garlic products in your pharmacy. Are these adequate?
2. What specific advice and general lifestyle advice would you give on dispensing or selling Fybozest Orange? (Start by reading the appropriate section in the BNF.)
3. Use Medline ([www.ncbi.nlm.nih.gov/entrez/query.fcgi](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi)) to look at what trials on the effect of globe artichoke on lipid concentrations have been published.

## evaluate

How could your learning have been more effective?  
What will you do now and how will this be achieved?

inhibit cholesterol biosynthesis, although the precise steps in the cholesterol biosynthetic pathway that are affected by these substances have not been definitely established.<sup>2</sup> Several mechanisms have been proposed, including:

- Inhibition of hydroxymethylglutaryl-CoA reductase activity by constituents of garlic and globe artichoke leaf extract
- Inhibition of other enzymes involved in cholesterol biosynthesis, such as squalene mono-oxygenase and lanosterol-14-demethylase, by garlic constituents

Experimental studies involving several animal models of hyperlipidaemia provide supporting evidence for the cholesterol- and/or other lipid- (eg, triglyceride-) lowering effects of various garlic preparations (eg, dried powder, oil) and allicin, and for globe artichoke leaf extract, purified caffeoylquinic acids and cynarin.<sup>2</sup>

Mechanisms of action for the hypocholesterolaemic effects of alfalfa, milk thistle, myrrh and turmeric have not been clearly established.

## SAFETY ASPECTS

A meta-analysis of 13 RCTs involving mainly patients with hypercholesterolaemia, 10 of which tested the effects of a standardised preparation of dried garlic powder (Kwai) at dosages of 600 to 900mg daily for eight to 24 weeks, reported that the type and frequency of adverse events occurring with garlic were similar to those with placebo.<sup>7</sup> The most common adverse events reported were garlic breath, body odour and gastrointestinal symptoms. Other adverse effects that have been documented for garlic include a burning sensation in the mouth and gastrointestinal tract. Garlic is known to have allergenic potential, and diallyl disulphide, allyl-propyl sulphide and allicin have been identified as allergens.

Isolated reports of garlic allergy associated with ingestion of raw or cooked garlic, occupational exposure to garlic and local application of garlic have been documented.<sup>2</sup>

Post-marketing surveillance-type studies involving patients with non-specific gastrointestinal complaints or dyspepsia indicate that globe artichoke leaf extract is well-tolerated when taken at dosages of up to 1.92g daily for up to six months.<sup>2</sup> Globe artichoke contains cynaropicrin and other sesquiterpene lactones which have allergenic potential. Isolated reports of allergy following ingestion of globe artichoke and occupational exposure to globe artichoke have been documented.<sup>2</sup> Information on adverse effects, contraindications and warnings relating to ispaghula is available in standard texts.<sup>1,9</sup>

Post-marketing surveillance-type studies involving more than 3,500 patients with various types of chronic liver disorders treated with silymarin (milk thistle) 560mg daily for eight weeks indicate that the frequency of adverse effects, mainly transient, non-serious gastrointestinal effects, is around 1 per cent. Drug safety monitoring studies for alfalfa, myrrh and turmeric are lacking. Alfalfa should be avoided by individuals with a history of systemic lupus erythematosus (SLE) because there is an isolated report of exacerbation of SLE

associated with ingestion of alfalfa.<sup>2</sup>

**Interactions** Constituents of garlic have antiplatelet effects, and garlic products should be avoided or used only with caution in patients taking antiplatelet or anticoagulant agents, and in those whose blood clots slowly.<sup>2</sup> There is an isolated report of spinal haematoma in a woman who ingested excessive amounts of garlic before undergoing cosmetic surgery. It has been advised that garlic intake be discontinued 10 days before surgery.<sup>3</sup> Constituents of turmeric also have antiplatelet effects. Drug-herb interactions will be considered in detail in a later article.

**Pregnancy and lactation** Odorous components of garlic can be found in the amniotic fluid of pregnant women following garlic consumption, and the consumption of garlic by lactating women alters the odour of breast milk. The effects of *in utero* exposure to garlic odour and the neonate's behaviour towards exposure to garlic-flavoured breast milk are not known. Doses of garlic greatly exceeding amounts used in foods should not be taken during pregnancy and lactation.<sup>2</sup> Excessive use of globe artichoke, myrrh and turmeric should be avoided during pregnancy and lactation.<sup>2</sup> Alfalfa seed and milk thistle should be avoided during these periods.

## REFERENCES

1. Martindale. The complete drug reference. 33rd edition. London: Pharmaceutical Press; 2002.
2. Barnes J, Anderson LA, Phillipson JD. Herbal medicines. A guide for healthcare professionals. 2nd edition. London: Pharmaceutical Press; 2002.
3. Mills S, Bone K. Principles and practice of phytotherapy. Edinburgh: Churchill Livingstone; 2000.
4. Schulz V, Hänsel R, Tyler VE. Rational phytotherapy. A physicians' guide to herbal medicine. 4th edition. Berlin: Springer; 2000.
5. Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol. A meta-analysis. *Ann Intern Med* 1993;119:599-605.
6. Silagy C, Neil A. Garlic as a lipid lowering agent — a meta-analysis. *J R Coll Phys Lond* 1994;28:2-8.
7. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolaemia. A meta-analysis of randomized clinical trials. *Ann Intern Med* 2000;133:420-9.
8. Anderson JW, Davidson MH, Blonde L, Brown WV, Howard WJ, Ginsberg H et al. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolaemia: meta-analysis of 8 controlled trials. *Am J Clin Nut* 2000;71:472-9.
9. British National Formulary, 43. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2002.