Several herbs have a history of traditional use in enhancing cognitive performance, but have not been subject to rigorous clinical investigation. For example, withania (Withania somnifera L.) root is reputed to promote learning and memory, and old herbal texts claim that sage (Salvia officinalis L.) enhances memory. The anticholinesterase activity of several species of sage (Salvia) and their constituents has been investigated in vitro in the search for new drugs for the treatment of Alzheimer's disease, but clinical research has focused on ginkgo (Ginkgo biloba L.).

**Ginkgo**

Ginkgo, also known as the maidenhair tree, is a hardy deciduous tree that has become naturalised in Europe. The leaf is the part used pharmaceutically today, although the seeds (kernels/nuts) are used in traditional Chinese medicine.

It is beyond the scope of this article to consider the actiology, classification, diagnosis and treatment of cognitive impairment and dementia; pharmacists are advised to consult standard reference texts for this information. Pharmacists are encouraged, where possible, discreetly to probe, individuals' reasons for purchasing products containing ginkgo. If the intended use is to improve poor cognitive function, apply usual protocols to establish the possible cause, duration and type of symptoms, treatments already tried or being used, and so on. The use of ginkgo preparations in cognitive impairment and dementia may not be appropriate without medical supervision, so referral to a general practitioner may be necessary.

**Identify gaps in your knowledge**

1. What effects of ginkgo have been documented?
2. What type of outcome is used to measure the effect of a substance on cognitive deficiency?
3. Can ginkgo enhance normal cognitive function?

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.

**Evidence of efficacy**

Most clinical trials of ginkgo have tested the standardised G. biloba leaf extract EGb 761 (Schwabe, Germany) and LI 1370 (Lichtwer Pharma, Germany). The majority of studies have explored the effects of ginkgo in treating cognitive deficiency or cerebral insufficiency. The latter is an older term used (in the rest...
of Europe, not the UK) to describe symptoms thought to arise from an age-related reduction in cerebral blood flow. These include poor concentration, poor memory, forgetfulness/absentmindedness, confusion, lack of energy, tiredness, fatigue, depressed mood, headaches, and dizziness.3-5 Several other studies have investigated the effects of standardised ginkgo leaf extracts on cognitive function in patients with Alzheimer’s disease and/or multi-infarct dementia. Both these conditions share several symptoms that are characteristic of cerebral insufficiency (eg, memory impairment).

**Efficacy in cognitive deficiency/cerebral insufficiency** Evidence from controlled clinical trials indicates that standardised extracts of ginkgo leaf are more effective than placebo in relieving symptoms associated with age-related cognitive deficiency. A review of controlled clinical trials of ginkgo in patients with cerebral insufficiency identified 40 studies.6 Generally, trials tested oral doses of standardised extracts of ginkgo leaf of 120mg daily administered for at least four to six weeks. Most trials reported significant results or positive (but not statistically significant) trends in favour of ginkgo, compared with control, but many trials were of poor methodological quality. Eight studies were considered to be well-conducted randomised controlled trials (RCTs), and all of these reported statistically significant results for ginkgo, compared with placebo. Nevertheless, further randomised, double-blind, controlled trials involving larger numbers of patients were deemed necessary.7 Other randomised, double-blind, placebo-controlled trials of different ginkgo extracts have since been published, but have not provided convincing new evidence. However, it is possible that the extracts and/or the doses tested may have been inadequate.

One study, involving 60 elderly volunteers with mild to moderate age-related cognitive dysfunction reported that memory improved significantly (P = 0.016), compared with baseline values, in participants who received oral ginkgo extract (GB-8) 40mg three times daily, but no such improvement was seen in participants who received the extract 80mg three times daily or placebo.1 A methodologically more rigorous trial involving 241 patients with age-related impairment of memory and/or concentration found no statistically significant differences between participants who received undiluted alcohol:water (70:30) extract of fresh ginkgo leaves (total flavonoid glycosides 0.20mg/ml, total ginkgolides 0.34mg/ml), diluted ginkgo leaf extract, or placebo, using subjective and several objective measurements of concentration and short- and long-term memory.2

**Panel 1: Glossary**

**ADAS-Cog** The Alzheimer’s disease assessment scale cognitive sub-scale is designed to measure the severity of the major symptoms of Alzheimer’s disease. It involves assessing 11 tasks that gauge disturbances in cognitive ability (eg, memory, language, attention, orientation and the ability to perform skilled actions). Disturbances are measured on a 70-point scale that usually increases by seven to 10 points each year as cognition deteriorates. A reduction of four points indicates a clinically significant reversal of symptoms of almost six months.

**CGIC** The clinical global impression of change scale is a seven-point scale used to judge the progress (or not) of a disease when an intervention has been made. This judgement is usually made by the clinician. If the patient is deemed “very much improved”2 a score of one is given. A score of seven is given if the patient is seen to be “very much worse”.

**GERRI** The geriatric evaluation by relative’s rating instrument is a tool used to assess daily living and social behaviour. It uses 49 items to measure cognitive, social and mood characteristics. GERRI was developed because, tinnitus and dizziness are often assessed in other studies by family members who might miss subtle changes in a patient. The mood element has been shown to be least reliably estimated.

**Efficacy in dementia** There is some evidence from RCTs to support the efficacy of standardised extracts of ginkgo leaf in improving cognitive function in dementia. However, further rigorous RCTs are required to establish definitively ginkgo’s beneficial effects.

A new double-blind, controlled study explored the effects of a standardised ginkgo leaf extract (LI 1370) 50mg three times daily, or placebo, for 12 weeks in 1,121 individuals aged 18 to 70 years with tinnitus.1 At the end of the study, ginkgo leaf extract was no more effective than placebo with regard to the main outcome measure (pain severity and self-assessment of tinnitus). However, this study was also flawed methodologically. In particular, assessments were carried out via postal questionnaires and telephone calls, and not through face-to-face contact with an investigator.1
**Enhancement of normal cognitive function**

Several placebo-controlled trials involving small numbers of participants have explored the effects of standardised ginkgo leaf extracts on cognitive function in healthy (ie, cognitively intact) younger and older individuals, but have reported conflicting results. The trials tested different oral regimens of ginkgo leaf extracts (eg, 120 to 600mg in single doses, 50 or 100mg three times daily for two days, or 60mg three times daily for six weeks) and involved various assessments of memory and cognitive and psychomotor performance. Further investigation is necessary to determine whether ginkgo extracts are of value in cognitively intact individuals.

**Mechanism of action**

The precise mechanism(s) by which ginkgo leaf extracts improve impaired cognitive function is unclear. It has been suggested, following clinical investigations, that ginkgo administration may affect central cognitive function, and that effects may include decreasing the time needed for the brain to process information.

Experimental studies involving animal models designed to test aspects of learning and memory provide supporting evidence for the effects of standardised ginkgo leaf extracts,1-3,11 and following biochemical and pharmacological studies with standardised ginkgo leaf extracts (usually EGb 761) and/or its constituents, the following effects have been documented:

1. Inhibition of age-related decline in muscarinic choline receptors and promotion of choline uptake in the hippocampus
2. Anti-ischaemic activity and improvements in cerebral blood flow
3. Neuronal regeneration in certain animal models (eg, brain injury)
4. Free-radical scavenging and antioxidant activity in vitro, eg, protection of cerebellar neurons against chemically induced oxidative stress3,11

**Adverse effects**

Data from RCTs and post-marketing surveillance-type studies indicate that standardised extracts of ginkgo leaf made to pharmaceutical standards are generally well-tolerated when used at recommended doses for up to 52 weeks.1 Adverse effects reported are usually mild and include gastrointestinal symptoms (eg, diarrhoea), nausea and headache. Allergic skin reactions occur rarely. A systematic review of nine RCTs of standardised ginkgo leaf extracts in Alzheimer’s or multi-infarct dementia found that the frequency of adverse effects reported for ginkgo preparations was similar to that for placebo. A similar finding came from a systematic review/meta-analysis of trials of standardised extracts of ginkgo leaf on patients with intermittent claudication (a crippling pain in leg muscles caused by an inadequate blood supply).1

There are isolated reports of bleeding associated with ginkgo use, including a case of spontaneous hyphaema (bleeding from the iris into the anterior chamber of the eye) one week after the start of treatment with ginkgo leaf extract 80mg daily in a 70-year-old man who had been taking aspirin 325mg daily for three years, and bilateral subdural haematomas in a 33-year-old woman who had taken standardised ginkgo leaf extract for two years.1 However, a causal relationship between ginkgo ingestion and bleeding in these cases has not been definitively established. Nevertheless, because ginkgo leaf extract has been demonstrated to inhibit platelet aggregation and ginkgolide B has been shown to inhibit platelet-activating factor (important in platelet aggregation), ginkgo preparations should be avoided by patients taking antiplatelet agents and also by patients taking anticoagulants such as warfarin.1 Likewise, patients due to undergo surgery and who are taking ginkgo preparations should be advised to discontinue ginkgo before their operation.1 On the basis of what is known about the pharmacokinetics of the constituents of ginkgo leaf, treatment should be stopped at least 24 to 48 hours before surgery.

**Pregnancy and lactation**

There is a lack of information on the use of ginkgo preparations by women who are pregnant or lactating. In view of the many pharmacological actions documented for ginkgo leaf preparations, and the lack of toxicity data, the use of ginkgo during pregnancy and lactation should be avoided.1

**REFERENCES**