

# (3) COGNITIVE DEFICIENCY AND DEMENTIA

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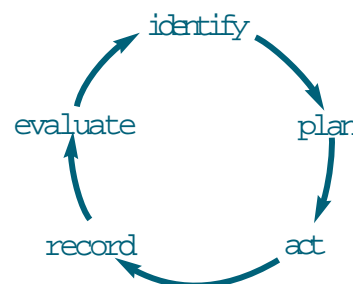
This article considers the evidence for the efficacy and safety of Ginkgo biloba



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.



Several herbs have a history of traditional use in enhancing cognitive performance,<sup>1</sup> but have not been subject to rigorous clinical investigation. For example, withania (*Withania somnifera* L.) root is reputed to promote learning and memory,<sup>2</sup> and old herbal texts claim that sage (*Salvia officinalis* L.) enhances memory.<sup>1</sup> 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,<sup>1</sup> 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.<sup>3</sup> The leaf is the part used pharmaceutically today, although the seeds (kernels/nuts) are used in traditional Chinese medicine.<sup>1</sup>

It is beyond the scope of this article to consider the aetiology, 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, other action taken, 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.

Particular consideration should be given to the potential for drug interactions with ginkgo. Information on the use of ginkgo leaf extract in conjunction with conventional medicines for Alzheimer's disease (eg, acetylcholinesterase inhibitors) is scant. Most clinical trials of ginkgo leaf extracts have excluded patients taking drugs with central nervous system activity. It has been suggested that the effects of ginkgo leaf in cognitive deficiency may involve central cholinergic systems, so the potential for interaction with other substances acting on these systems cannot be ruled out. In any case, patients taking ginkgo concomitantly with conventional medicines for Alzheimer's disease should be advised to inform their general practi-

tioner and other individuals responsible for their care of this, since it is important that the effects of ginkgo are considered when treatment outcomes are assessed.

**Major constituents** The key active constituents of ginkgo leaf are the ginkgo flavonoid glycosides, such as quercetin, kaempferol and isorhamnetin, and the terpene lactones, which include bilobalide and ginkgolides A, B, C, J and M.<sup>1</sup> Other constituents include proanthocyanidins and ginkgolic acids. The latter are allergenic.

Good quality extracts of ginkgo leaf are standardised on the content of ginkgo flavonoid glycosides (22 to 27 per cent; determined as quercetin, kaempferol and isorhamnetin), terpene lactones (5 to 7 per cent; comprising 2.8 to 3.4 per cent ginkgolides A, B and C, and 2.6 to 3.2 per cent bilobalide). The concentration of ginkgolic acids should be less than 5ppm.<sup>1</sup>

**Product quality** An analytical study which investigated 27 products containing ginkgo leaf marketed in the United States found that although most products (n = 24) claimed to contain ginkgo extracts standardised on a flavonoid glycosides and terpene lactones content within or at the upper limit of recommendations (see above), the actual content of one or both groups of these constituents was significantly greater than the stated amount in 17 products ( $P < 0.05$ , compared with specified ranges).<sup>4</sup> Furthermore, only seven products had a ginkgolic acids content of <500 ppm (the limit of quantification in this study), and in nine products, the ginkgolic acids content was >25,000ppm (overall range: <500 to 89,576, standard deviation 2,297ppm). Conclusions drawn from this study were that the pharmaceutical quality of the products tested was not comparable, and that there were important differences in dissolution profiles. Thus differences in bioavailability in humans was likely, possibly resulting in differences in efficacy and safety of some products.<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). Some products contain only dried plant material, whereas others contain concentrated standardised extracts.

**Evidence of efficacy** Most clinical trials of ginkgo have tested the standardised *G biloba* leaf extracts 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

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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, anxiety, tinnitus and dizziness.<sup>2,5</sup> 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.<sup>5</sup> 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.<sup>5</sup> 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.<sup>1</sup> 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.<sup>1</sup>

## 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.

**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 it was thought that observations made by family members were likely to be more accurate than those made by clinicians who might miss subtler changes in a patient. The mood element has been shown to be least reliably estimated.

**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" a score of one is given. A score of seven is given if the patient is seen to be "very much worse".

**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.

In a randomised, double-blind, placebo-controlled trial, 327 patients with mild to severe dementia related to Alzheimer's disease, or multi-infarct dementia, received standardised ginkgo leaf extract (EGb 761) 40mg orally three times daily ( $n = 166$ ), or placebo ( $n = 161$ ), for 52 weeks.<sup>6</sup> Participants underwent a battery of assessments at 12, 26 and 52 weeks. The primary outcome measures were the Alzheimer's disease assessment scale cognitive sub-scale (ADAS-Cog), the geriatric evaluation by relative's rating instrument (GERRI) and the clinical global impression of change (CGIC). Further definitions of these measures are given in Panel 1. In an intention to treat analysis, ginkgo recipients scored significantly better than placebo recipients on the ADAS-Cog and the GERRI ( $P = 0.04$  and  $P = 0.004$ , respectively). But a slight worsening on the CGIC was observed for both groups. The average endpoints for the intention to treat analysis were 38.6 and 34.6 weeks for the ginkgo and placebo groups, respectively.

A more recent RCT found that ginkgo was not effective in elderly people with Alzheimer's disease or vascular dementia, or age-related memory impairment. This study enrolled 214 participants who received standardised ginkgo leaf extract (EGb-761) 160 or 240mg daily, or placebo, for 24 weeks.<sup>7</sup>

A systematic review and a meta-analysis included four randomised, double-blind, placebo-controlled trials assessing the effects of standardised ginkgo leaf extracts on cognitive function in patients with Alzheimer's disease (characterised according to recognised criteria).<sup>8</sup> The trials involved oral administration of ginkgo extract 120 or 240mg daily for 12 to 26 weeks, and involved 212 patients each in the ginkgo and placebo groups. The meta-analysis of the results of the four studies indicated a significant ( $P < 0.0001$ ), but modest, difference in effect on cognitive function with ginkgo, compared with placebo (0.413, 95 per cent confidence interval: 0.22 to 0.61; corresponding to a difference of 3 per cent on the ADAS-Cog).<sup>8</sup>

Another systematic review included nine randomised, double-blind, placebo-controlled trials (including one described above<sup>6</sup>) of standardised ginkgo leaf extracts in patients with Alzheimer's disease and/or multi-infarct dementia.<sup>9</sup> Studies generally involved the administration of oral doses of ginkgo leaf extract 120 or 240mg daily for six to 12 weeks, although one study involved a 52-week administration period,<sup>6</sup> and another tested intravenous infusions of ginkgo leaf extract 200mg four times per week for four weeks. It was reported that, overall, the studies provided evidence to support the efficacy of standardised ginkgo leaf extracts in the symptomatic treatment of dementia. However, methodological limitations in several of the included studies (for example, poorly defined inclusion and exclusion criteria, and method of randomisation, as well as treatment periods less than six months and small sample sizes) were also emphasised.<sup>9</sup>

**Efficacy in tinnitus** Tinnitus is a symptom of cognitive deficiency and dementia, and several studies have assessed the effects of ginkgo preparations solely on this symptom. However, at present, there is no definitive evidence that ginkgo leaf extracts reduce tinnitus.

A systematic review of RCTs of ginkgo extracts involving patients with tinnitus included five studies; four studies compared ginkgo extracts with placebo, and one compared ginkgo extracts with conventional drugs.<sup>10</sup> Three trials tested the standardised ginkgo leaf extract EGb 761 but full details of other extracts tested in the other studies are not given in the review. The review concluded that, overall, the studies identified provided evidence to support ginkgo extract as a treatment for tinnitus, but that further investigation was required to establish the benefits fully. Typically, at least two studies had methodological flaws.<sup>10</sup>

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.<sup>1</sup> At the end of the study, ginkgo leaf extract was no more effective than placebo with regard to the main outcome measure (participants' 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.<sup>1</sup>

## action : practice points

1. Check whether or not there are sufficient warnings of interactions and cautions in or on the packaging of the *Ginkgo biloba* products in the pharmacy where you work.
2. Write a protocol for the sale of ginkgo products.
3. Browse websites like [www.mind.org.uk](http://www.mind.org.uk) (in particular the advice sheet "How to cope with memory loss") and [www.alzheimers.org.uk](http://www.alzheimers.org.uk) to see what information is available.

## evaluate

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

**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.<sup>1</sup> 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.<sup>1</sup>

**Mechanism of action** The precise mechanism(s) by which ginkgo leaf extracts improve impaired cognitive function is unclear.<sup>3</sup> 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.<sup>2</sup>

Experimental studies involving animal models designed to test aspects of learning and memory provide supporting evidence for the effects of standardised ginkgo leaf extracts,<sup>1-3,11</sup> 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
- 1 Anti-ischaemic activity and improvements in cerebral blood flow
- 1 Neuronal regeneration in certain animal models (eg, brain injury)
- 1 Free-radical scavenging and antioxidant activity *in vitro*, eg, protection of cerebellar neurons against chemically induced oxidative stress<sup>1,11</sup>

**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.<sup>1</sup> 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.<sup>8</sup> 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).<sup>1</sup>

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.<sup>1</sup> 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.<sup>1</sup> Likewise, patients due to undergo surgery and who are taking ginkgo preparations should be advised to discontinue ginkgo before their operation.<sup>1</sup> 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.<sup>1</sup>

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