

A LITERATURE REVIEW OF THE EFFICACY OF *GINKGO BILOBA* IN COGNITIVE DYSFUNCTION

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Abstract

Cognitive dysfunction and dementia are issues of concern for naturopathic practitioners in Australia. This review evaluates the evidence for the use of *Ginkgo biloba* extract in the treatment of neurological disorders, and reports on the clinical implications.

Reference

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Introduction

Degenerative neurological disease is one of the most significant health issues currently facing Western society. The rise in life expectancy over the course of the 20th century has led to a corresponding increase in cognitive disorders and mental afflictions, resulting in new challenges for health authorities, as well as complementary medicine practitioners.

In respect to dementia, the collective term for a group of diseases that includes Alzheimer's disease, Australia now faces collective annual costs of some \$6.6 billion or 1% of Gross Domestic Product. Over 162,000 people suffered with dementia in 2002, and this population was predicted to increase to 500,000 by 2040⁽¹⁾.

With a paucity of effective pharmaceutical agents for the treatment of dementia and Alzheimer's disease, various natural substances have been investigated for their potential therapeutic properties. Most significant of these is an extract of the leaves of *Ginkgo biloba*, first developed by German chemists in the 1960s and intensively studied since that time⁽²⁾. *Ginkgo biloba* extract (GBE) is a product of central importance to the practice of complementary medicine in Australia and many other countries. This review aims to evaluate the evidence available for GBE and to discuss the implications of these findings for clinical practice.

Current Management Strategies

A number of novel compounds have been developed with the aim of retarding the neural degeneration that is characteristic of dementia and its related pathologies.

Despite being promoted by their manufacturers and various Alzheimer's associations as effective⁽³⁾, it appears that their benefits are at best extremely marginal⁽⁴⁾. The authors of a five-year comparative study, recently published in *The Lancet*⁽⁵⁾, concluded that the cholinesterase inhibitors (the primary anti-Alzheimer's drug class) are a costly and relatively ineffective therapy:

Donepezil is not cost effective, with benefits below minimally relevant thresholds. More effective treatments than cholinesterase inhibitors are needed for Alzheimer's disease.

Ginkgo Biloba Extract (GBE)

In contrast to many other complementary medicines, the study of a specific extract of *Ginkgo biloba* has amassed a comprehensive body of peer reviewed scientific literature. Despite only being in common clinical usage for a relatively brief period, GBE has been intensively studied since its development some four decades ago. Early investigations were primarily pharmacological, focussing on the diverse biological activity of specific constituents of *Ginkgo*, namely the terpene lactones (terpenoids) and flavonoid glycosides (ginkgolide and bilobalide).

It is notable that modern *Ginkgo* extract is a highly concentrated substance that while having a standardised level of *Ginkgo* flavone glycosides (24%) and terpenoids (6—7%), has minimal levels of other naturally occurring components of the leaf such as the sterols⁽²⁾. In this sense, GBE cannot be considered a true galenical extract, in that it selectively emphasises specific constituents at the expense of others through phytochemical manipulation. GBE represents a contemporary form of herbal medicine; a product derived purely from pharmacological research and utilised with specific therapeutic applications in mind.

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GBE is representative of a consistently standardised product, with the vast majority of clinical trials being conducted on a specific extract known as EGb 761, first developed by the Schwabe company of Germany⁽⁶⁾. This method of product standardisation permits meaningful comparisons to be made between studies with the assurance of phytochemical consistency.

This is in marked contrast to research involving many other botanical agents, which can suffer from a lack of generalisability due to the use of poorly defined extracts with variable phytochemical profiles and consequent lack of bioequivalence. Nonetheless, it is yet to be determined which of the active constituents of GBE are responsible for its activity, if indeed such a determination is even possible. The terpenoids and flavone glycosides are currently viewed as 'marker' compounds, not necessarily those responsible for conferring therapeutic activity. According to Bone⁽⁷⁾:

...in terms of, for example, its effects in Alzheimer's disease, results did not show which are the active compounds in GBE. Even if the ginkgolides and bilobalide were found to be important...it would be unlikely that they were the only compounds important for activity.

This highlights the importance of utilising chemically-defined and high quality extracts when researching any herbal medicine. It is likely that the synergy of the herb's phytochemicals is largely responsible for its therapeutic efficacy, regardless of whether the chosen marker compounds are particularly active in themselves.

Clinical Studies

Numerous studies have been conducted on GBE over the past thirty years. The majority of these have been of poor quality and have not met current standards for high quality research ie double-blind, randomised clinical trials (RCT). Few well designed, robust trials of GBE exist. This review will focus on evaluating the RCT studies.

Early Studies

During 1970s and 1980s several small European studies examined the value of *Ginkgo* in treating a condition referred to as 'cerebral insufficiency'. This term was used in reference to the age-related cognitive decline, unrelated to pathology, commonly observed in older people. Mills and Bone define cerebral insufficiency as:

a collection of symptoms associated with mental deterioration from aging which affects many elderly people who do not necessarily have dementia or a history of strokes⁽²⁾.

It is important to note that there is no agreement in the literature on what the term 'cerebral insufficiency' represents. Consequently, the results of this earlier research lack direct application to clinical practice. Furthermore, contemporary researchers have abandoned the use of the term 'cerebral insufficiency' because of this ambiguity and lack of definition. Despite the limitations of these earlier studies, their findings did provide important direction for future research on *Ginkgo* and resulted in a general understanding of the importance of this herb in cognitive dysfunction.

Randomised Trials and GBE

A landmark study of GBE in the treatment of dementia was published in 1997 in the US. Le Bars conducted a 12 month, multicentre RCT testing the efficacy of GBE on 309 patients diagnosed with either Alzheimer's disease or multi-infarct dementia according to diagnostic criteria as outlined in the *Diagnostic and Statistical Manual of Mental Disorders (IIIr)*⁽⁸⁾. Participants were randomly assigned to a treatment group (120 mg/day of EGb 761) or placebo. This dosage (which equates to 6,000 mg dry herb equivalent of *Ginkgo*) accurately represents dosages employed in modern clinical practice, meaning the results of the study are especially relevant to practitioners.

Subject evaluations were at 12, 26 and 52 weeks, utilising three validated outcome measures: the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) (a test of memory and language), the Geriatric Evaluation by Relative's Rating Instrument (GERRI) (a caregivers evaluation) and the Clinical Global Impression of Change (CGIC). The use of validated instruments increased the reliability and accuracy of the study findings. The placebo was effectively designed, with both the intervention and inert tablets having an identical appearance. The GBE tablets were film-coated to limit the possibility of patients smelling them and undermining blinding.

The study found that:

EGb was safe and appears capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients for 6 months to 1 year.

Though the benefits were considered modest, it is worth noting that this study enrolled 'mildly to severely demented patients'. The benefits of GBE appeared to be strongest when utilised as a preventative measure against dementia⁽⁹⁾, and it is thus debatable as to the improvement that can be achieved in severely afflicted individuals.

An interesting aspect of the trial involved the decision by the researchers not to discontinue any medications being used by the participants at the commencement of the study. While understandable, given that many individuals were elderly and likely had co-existing conditions that required ongoing treatment, it raises the possibility that any of those medications may have been a confounding variable in the study.

Certain medications are known to possess cognitive side-effects and unexpected interactions with GBE then become a possibility. It is conceivable that a drug could diminish (or enhance) any observed effect of GBE, resulting in unreliable data. A possible solution to this problem would be the design of studies involving patients controlled for their pharmaceutical intake, in addition to other confounding variables. This would require individuals taking the same, or preferably no medications at the commencement of the trial.

Early studies on *Ginkgo* have been criticised for enrolling patients with differing or invalid diagnoses⁽¹⁰⁾, thereby creating uncertainty with respect to GBE's efficacy in different populations.

Enrolling patients across a spectrum of disease severity may act to reduce the import of the results, as it is unclear whether the benefits are most associated with those suffering from early or late stage disease.

This study has been noted by a number of authors for its good experimental protocol and stringent design^(2,11). According to Mills and Bone⁽²⁾:

This is a highly significant study for several reasons. Most notably, it was conducted by psychiatrists in the USA and accepted for publication in the prestigious *Journal of the American Medical Association*... This clinical trial has already had a substantial impact on the use of *Ginkgo biloba* in the USA.

Another significant RCT was conducted in Germany on patients suffering from mild to moderate Alzheimer's disease or multi-infarct dementia⁽¹²⁾. The trial enrolled 222 patients (of which 156 completed) in a double-blind, multicentre study. The dosage of GBE was relatively high (240 mg/day), equivalent to 12,000 mg of dry herb, which provides an interesting comparison to the study conducted by Le Bars⁽⁸⁾. The German study found a significant positive effect of GBE compared to placebo. The effect was more considerable than that reported for the American study, indicating a possible benefit of higher dosages. Le Bars raised the following question about the German study⁽¹³⁾:

Will doses higher than 240 mg/day further enhance the percentage of improvers? Ultimately, a control study testing the effect of multiple doses of EGb 761 would be needed to clarify the dose-response relationship and help to delineate the minimal EGb 761 regimen for an optimal response in dementia.

Another small RCT also showed positive results using GBE in patients diagnosed with Alzheimer's disease. Hofferberth found that patients (n=40) with early to moderate Alzheimer's, who received 80 mg of GBE three times daily, for 12 weeks, demonstrated improvements in 'memory and attention, psychopathology, psychomotor performance ... functional dynamics and neurophysiology'⁽¹⁴⁾. This study again highlights the importance of higher dosages of GBE for maximum therapeutic effect.

One particular RCT was designed to test the effect of GBE on cognitively-intact older adults with no pre-existing cognitive dysfunction. Mix and Crews enrolled 262 individuals aged over 60 years, and administered GBE at a dose of 180 mg over 6 weeks⁽¹⁵⁾. The study showed significant improvements in recall and recognition tasks in the treatment group at the end of the 6 week period. The authors concluded that GBE was effective in improving cognitive functioning in older adults not suffering from significant cognitive impairment.

This finding is consistent with the contemporary use of GBE by many complementary medicine practitioners, where it is given in cases of mild cognitive decline, or simply to enhance ostensibly adequate mental function. Other studies utilising GBE in older adults with sub-clinical memory impairment have reported similar results⁽¹⁶⁻¹⁸⁾.

A number of trials on GBE have shown negative or equivocal results. One 24 week, multicentre, RCT was conducted on 214 elderly participants in the Netherlands suffering from dementia or age-associated memory impairment⁽¹⁹⁾. Two treatment groups were randomly assigned to receive either 240 mg/day or 120 mg/day of GBE, alongside a placebo group. A number of methodological weaknesses limit the application of these findings. Writing in response to the trial's publication, Le Bars outlined salient criticisms⁽²⁰⁾:

- The study uses a unique source population. Unlike the earlier controlled trials by Le Bars and Kanowski, van Dongen relied on a historical case review to screen participants, rather than obtaining a diagnosis supported by full clinical and laboratory examination. Because of this, it is possible that patients were enrolled who were not suffering from the supposed condition.

- It was the intention of the trial to assess the action of GBE on patients with Alzheimer's disease, vascular dementia or a syndrome known as Age-associated Memory Impairment (AAMI). Without a comprehensive diagnostic analysis involving trained clinicians, it is not clear whether the sample contained only those individuals with these conditions. In addition, AAMI is not yet a defined clinical entity, further complicating the sample selection.

Due to the significant possibility that patients were enrolled that either did not have Alzheimer's disease, or indeed had another medical condition altogether, the results of the study must be viewed with caution. According to Le Bars:

such [a] composite population may show [an] unpredictable response to study intervention leading to a dramatic increase of the study noise.

- The choice of outcome measurements appears to have been inappropriate. None of the assessment scales measured purely memory, and given the short assessment period (12 weeks) and the absence of clearly-defined parameters for AAMI as a condition, the significance of finding no positive effect is reduced.

Another recent investigation found that GBE taken for four weeks provided no measurable benefit in memory or related cognitive function to adults with no pre-existing cognitive dysfunction⁽²¹⁾. The study itself had significant limitations, which the authors acknowledge. For example, the four-week period was probably insufficient to determine any benefit from GBE therapy; the result may represent an example of an inappropriate dosing regime, rather than an absence of clinical effect.

The Cochrane Review

Cochrane reviews are renowned for their methodological rigour and comprehensive assessment of evidence. Their 2002 review assessed 33 published studies investigating the use of GBE in dementia and cognitive impairment⁽⁶⁾. These studies represented those of higher quality, and a large number of studies were excluded on account of significant flaws in their design.

The Cochrane authors concluded:

Overall there is promising evidence of improvement in cognition and function associated with *Ginkgo*. However, the three more modern trials show inconsistent results. There is need for a large trial using modern methodology and permitting an intention-to-treat analysis to provide robust estimates of the size and mechanism of any treatment effects.

This authoritative assessment appears to support the use of GBE in cognitive dysfunction. The authors call for further research, emphasising the need to establish the appropriate dosage and length of therapy to optimise benefit.

Clinical Implications

GBE represents a herbal medicine with a considerable body of supportive research evidence and clear clinical correlations. Many practitioners utilise *Ginkgo* in a manner not dissimilar to that adopted by researchers over the past 30 years, meaning their clients are likely deriving similar benefits to those observed in the positive published studies.

On the balance of available research evidence, GBE (when taken for a sufficient period and at an appropriate dose) is likely to enhance memory and mental functioning in both those individuals with cognitive pathology and otherwise healthy persons. Evidence is currently stronger for memory enhancement in older adults than in younger age brackets.

The contention that GBE is inferior to current anti-Alzheimer's medications such as the cholinesterase inhibitors is not supported by current evidence⁽²²⁾. Important clinical considerations derived from research include:

- **Optimal Dose:** An appreciation of optimal dosage of a treatment is necessary in order to formulate efficacious treatment protocols. The problem of underdosing is one encountered frequently in complementary medicine, and may result partially from a disparity between dosages utilised by researchers and those recommended by manufacturers. In order to derive maximal benefit it must be utilised at a correct dose. This dose is between 120 mg/day (6,000 mg dry herb equivalent) for mild to moderate cognitive impairment, and 240 mg/day (12,000 mg dry herb equivalent) for more serious cognitive decline and dementia.
- **Phytoequivalence:** To obtain similar results to those observed in RCTs, practitioners should use a phytoequivalent *Ginkgo* extract to that employed by researchers ie EGb 761. Such extracts are widely available in Australia in both fluid extract and tablet form, and are consistently standardised to 24% ginkgo flavonglycosides and 6 — 7% terpenoids. Use of a non-standardised extract may result in unpredictable effects.
- **Treatment duration:** To realise full clinical benefits with GBE, treatment duration must be sufficient. In practical terms, this means 3 to 6 months for mild to moderate memory impairment, and a year or longer for individuals with dementia.

Correct application of GBE represents a formidable clinical tool for complementary medicine practitioners in the treatment of cognitive disorders.

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