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The role of *Gingko Biloba* extract in the integrative management of dementia.

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Foot line: Ginkgo in dementia
Abstract
The incidence of dementia is steadily rising in developed countries and represents a significant burden to the health care system. Given the limitations with respect to cost effectiveness of conventional pharmaceutical treatment, herbal extracts may provide a sound strategy in preventing dementias, delaying its onset, slowing progression or managing the symptoms of dementias. Gingko biloba has been widely investigated for suitability as an alternative treatment in patients with Alzheimer’s disease. While discrepancies exist in historical reviews due design limitations, this review explores more recent trials and describes the potential role for Gingko biloba in the management of dementia.

Introduction
Not unlike other degenerative disorders, the incidence of dementia increases with age; one in 15 persons aged over 65 years of age will have moderate to severe dementia which increases further to one in nine for those 80 to 84 years old and one in four in those aged over 85 years (1). These figures provide a frightening reality check for the health industry given the aging population in developed countries. With the over 65 and over 85 demographic groups increasing in both relative and absolute terms, one might expect similar relative and absolute increases in dementia cases; longer life expectancy tends to be accompanied by increased morbidity associated with aging. While people living in developed countries are living longer, the morbidity of aging may be exacerbated (including heart disease, cancer and dementia). Measures to maintain cognitive function could extend significant benefit to quality of life and health care costs.

Dementia
Dementia is a progressive reduction in cognitive function and is a broad term used to describe the symptoms of progressive decline in memory, intellect, rationality, social skills and emotional reactions (2). Disintegration of one’s personality and confusion are hallmarks of dementia (3). The difficulty confronting effective detection, differentiation and management is highlighted by 1% of the general population demonstrating a confused state which increases to 16% in the hospitalised population and to 80% in geriatric units (3). Of course, not all confused states are an indicator of dementia, even in the elderly. Confusion might result from dehydration, medication, alcohol or drug use, emotional problems, metallic disorders, sensory deprivation, nutrition deficiencies, trauma, infection and atherosclerosis to list a few (3). Simply relying on the progressive nature of cognitive decline in dementia (wait and see approach) means a delay in onset of management. Moreover, progression of cognitive deficits may well result from
escalation of other causes (e.g. co-morbidity, drug interaction). The real difficulty lies in distinguishing cognitive decline as a syndrome, symptom or mix thereof in any given patient.

The symptoms and progression of dementia can be quite variable amongst individuals based on, among other factors, the underlying aetiology, co-morbidities, part of the brain affected and individual characteristics. Nonetheless, symptoms of dementia are generally classified as (4):

- Cognitive impairment (e.g. amnesia, aphasia, apraxia and agnosia).
- Psychiatric and behavioural changes (e.g. depression, hallucinations, agitation, confusion and delusions).
- Activities of daily living dysfunction (e.g. difficulties with driving, dressing, eating).

The burden of dementia is a global issue. In developed countries, dementia affects 10% of those 65 years and older and the incidence increases exponentially with age after that (5). In the US there are more than 7 million people living with dementia with 410000 new cases annually and 50% of those living in nursing homes have dementia (5). In Australia, there are 57000 newly diagnosed cases of dementia annually in a population approximating 22 million (6). Universally these numbers are predicted to continue to increase sharply. The financial cost of dementia is significant with at least $1 in every $40 in the Australian health care system currently spent on dementia; an estimated $6.6 billion annually (4). In the US, Alzheimer’s disease alone (50-70% of dementia cases) costs more than $100 billion annually which is the third most expensive pathology (5). In the developing world, improved general health and longevity have contributed to dementia costing $73 billion annually and this burden is projected to increase dramatically (7). The aging population in both the developed and developing world will continue to put increasing pressure on health, aged care and social policies (4,8). The World Health Organisation projects that there will be 29 million people living with dementia in the developed and developing world by 2020 (9). Current estimates put the number of dementia sufferers across the globe at 24 million with a doubling rate of 20 years (10). More importantly for global health policy, the 60% of global dementia patients that live in developing countries will increase to 70% by 2040 (10) making cost effective and widely available approaches to prevention, management and treatment a priority.

Approximately 75% of the burden of disease caused by dementia arises from disability rather than premature death (8). Indeed, the lack of mortality extends the degree of morbidity. The better medicine becomes at preventing premature death (e.g. heart disease and even cancer), the
greater the impact of dementia. Nonetheless, dementia doubles the standardised death rate of individuals although the reported cause of death generally under-reports dementia as the cause of death (4).

Dementia is a broad term used that encompasses a number of unique pathologies (2). The most common causes of dementia are Alzheimer’s disease (50-70%) and vascular dementia (20-30%) (2,4,11). There are numerous other causes of dementia (eg. Lewy bodies, frontal lobe dementia, Parkinson’s disease, Pick’s disease, Wilson’s disease etc) and these may occur concomitantly with Alzheimer’s disease and vascular dementia but in some patients the aetiology remains unknown (2,4,11).

**Dementia of the Alzheimer’s type (DAT)**

DAT is the most common cause of dementia in the elderly, representing between 50% and 70% of all cases (3,12). The exact cause of DAT is unknown although researchers are investigating factors that negatively influence neuro-chemical changes in the brain that are characteristic of the disease. Specifically, a deficiency in acetylcholine (neurotransmitter) is one theory (3). Environmental factors, metabolic disturbances and immune processes are being investigated for possible causes (2). Other theories include (2,3):

- Slow infection (viral) that selectively attacks brain cells,
- Hereditary (genetic predisposition),
- Autoimmune disorder,
- Cerebral protein (amyloid) accumulation,
- Neural degeneration due to glutamate build up.

DAT is characterised by insidious onset, gradual but progressive cognitive degeneration including impaired memory, speech, orientation and cognition (3). Age and incidence of DAT is linear leading to more than 50% of people over 85 years of age having DAT and, not surprisingly then, accounts for 50% of nursing home admissions (3). Both the cause and the cure remain elusive.

Microscopically, DAT manifests as neurofibrillary tangles within neurons and senile plaques between neurons (2,13). Aggregating amyloid tissue forms as a result of disorders in processing β-amyloid and its precursor protein in selective parenchyma of the cortex and hippocampus (14,15). Subsequent inflammation degenerates nerve transmission efficiency and eventually
results in brain cell death \((13,15)\). There have been reports of an association between both high blood pressure and cholesterol with an increased risk of DAT as a result of subclinical ischaemia \((13,15)\), however, vascular dementia might also be an important consideration in these cases.

**Vascular dementia (VaD)**

VaD collectively refers to dementia that is caused by insufficient blood supply to the brain \((4)\). VaD accounts for 20% to 30% of dementia patients and results due to a number of small areas of brain damage, each functionally insignificant individually, that collectively cause a deficit. VaD can arise from several pathological processes \((3,4,11)\). Arteriosclerosis, or plaque formation in the arteries supplying blood to the brain, can result in a chronic deprivation of oxygen supply to the brain and might be characterised by chronic cerebral ischaemia \((2,4)\). Transient ischaemic attacks (TIA) tends to cause a gradual onset of multi-infarct dementia while a larger acute interruption to cerebral blood supply (stroke) is another cause of VaD \((2,4)\). The preceding causes of VaD have a tendency toward cortical regions of the brain, however, demyelination can cause VaD of sub-cortical origin (white matter) and is referred to as Binswanger’s disease \((4)\). It is also possible to have a mixed cortical and subcortical aetiology of VaD \((4)\).

**Conventional medical treatment for dementia**

Conventional interventions for dementia can be broadly described in three groups: those that disrupt its aetiology, those that interfere with the pathogenesis and those that modify its clinical manifestation \((16)\). Current first line therapy for DAT involves cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists \((16-19)\). Levels of acetylcholine drop in DAT and this is the rationale for the use of cholinergic drugs to prolong the half-life of acetylcholine in the synaptic clefts \((2,13,15,18,19)\). Cholinesterase inhibitors (ChEIs) are not curative by nature but rather aim to ameliorate symptoms of DAT by enhancing the availability of acetylcholine in the brain and acting to enhance cholinergic transmission \((16-19)\). Donepezil, galantamine and rivastigmine are examples \((18,19)\). Prolonged breakdown of ChEIs in tissue other than the brain contributes to gastrointestinal side effects such as nausea, anorexia, vomiting and diarrhoea \((13,16,18,19)\). Unwanted CNS side effects can include insomnia, confusion, agitation and headache \((18,19)\).

NMDA receptor antagonists modulate the N-methyl-D-aspartate type of glutamate receptor \((17-19)\). L-Glutamate is an excitatory neurotransmitter required for learning, memory processes and neuronal plasticity \((20)\). Glutamatergic dysfunction is implicated in the pathogenesis of ischaemic
stroke and DAT (21,22). Memantine is an amantadine derivative that acts as a non-competitive antagonist at glutamate NMDA receptors with the advantage of being able to be co-administered with ChEIs (18,19). Side effects include diarrhoea, insomnia, dizziness, headache and hallucinations (18,19).

ChEIs have been used with modest success in delaying the decline of cognitive function in approximately 40% of DAT patients, however, the delay is generally thought to only be 3-6 months (18,19). Furthermore, medication should be stopped in patients without a measurable response at 3 months (18,19). Memantine is better tolerated by patients and has shown moderate improvements in cognition (18,19). ChEIs and memantine have also been used to treat dementia symptoms in VaD (18,19). The use of anti-coagulants (eg. aspirin) for prophylactic treatment of VaD is common although not supported by evidence to benefit VaD while anti-hypertensive medications have been used to reduce the risks associated with VaD (18,19).

**Ginkgo as a complementary medicine for dementia**

Ginkgo biloba (Ginkgo) is a deciduous maidenhair tree that has survived unchanged from the Triassic period (23,24). The gingko tree can grow to a height of over 50 metres, can live for over 1000 years (23), and is highly tolerant to pollution, urbanisation and cold weather, and is extremely resistant to common environmental enemies like insects, bacteria, viruses and fungi (24,25). A highly concentrated extract from the ginkgo leaves, standardised to contain 24% gingko-flavone glycosides and 6% terpenoids, was developed by German scientists in the 1960s. The preparation is known as EGb761 (23,24). Terpenoids are naturally occurring organic chemicals (hydrocarbon) typically used for aromatic qualities while a glycoside is a molecule in which a sugar is bound to a non-carbohydrate moiety.

**Pharmacology**

The pharmacological effects of Ginkgo biloba extract include; antioxidant effects, increased microcirculatory blood flow, potent platelet-activating factor antagonist, alteration of neurotransmitter levels and other neuro-protective effects (26). It is these properties that suggest a role in dementia and DAT.

The Ginkgo flavonoids are antioxidant in nature and contribute to its free radical scavenger effects (24,27-29). Flavonoids, also known as vitamin P, are secondary metabolites in plants known for their anti-oxidant activity. Ginkgo flavonoids have been found to protect brain neurons
against peroxidation induced oxidative stress by reducing membrane fluidity; this is a major contributor of age related functional decline (30-32). Bilobalide, a potent ginkgolide, has demonstrated enhanced vasodilation via several mechanisms including; inhibition of nitric oxide (NO) release, activation of potassium/calcium channels and increased prostacyclin release (33). Ginkgolide B is widely reported to be a potent platelet-activating factor antagonist (anti-PAF) (24,27,34). Ginkgo terpenoids consisting of two classes of compounds; ginkgolides and bilobalides (terpenic lactone and terpenic trilactone respectively), have shown in several studies to minimise ischaemia induced neurotoxicity and inhibit glutamate-induced excitotoxicity (35-37).

Ginkgo biloba has been reported to alter the action of several neurotransmitters. EGb761 demonstrated monoamine oxidase (MAO) inhibition in vitro in the rat model (38,39). Sloley et al. (40) supported this finding, demonstrating that the flavanol glycoside and kaempferol from ginkgo was responsible for its potent MAO inhibition. MAO inhibitor activity alongside Ginkgo’s antioxidant and other effects is believed to contribute to its neuro-protective qualities (41). In essence, inhibition of MOA increases the action of acetylcholine which directly addresses one of the purported aetiologies of DAT and is consistent with the allopathic approach to managing DAT. Clinical studies in humans, however, employed positron emission tomography (PET) with ¹¹C clorgyline and ¹¹C L-deprenyl-D2 to quantitate MAO A and MAO B respectively (42). Ginkgo did not show evidence of significant changes to MAO A and MAO B although ginkgo doses of only 120 mg/day were used for just one month.

Direct and indirect cholinergic activity has been reported with administration of Ginkgo extract in vitro (43,44). Indirect cholinergic activity has been discussed with respect to MOA inhibition. The mechanism of action of ginkgo on the hippocampus, an area of the brain that is significantly affected in DAT, is reported to be due to its ability to normalise acetylcholine receptors (2,29). Kleijnen (45) demonstrated the ability of Ginkgo to increase cholinergic activity, while Chopin and Briley (46) found that oral administration can prevent the decline in cholinergic receptor density in the hippocampus of rats.

Ginkgo biloba is widely used for its potential neuro-protective effects (47). EGb761 proved to be effective in protecting hippocampal cultured neurons against toxicity induced by β–amyloid (Aβ) peptides, including blocking induced reactive oxygen species (ROS) accumulation and apoptosis, which are implicated in the aetiology of DAT (48,49). Mitochondrial oxidative damage is directly
related to ROS exposure and the pathogenesis of amyloid beta deposition in DAT is mediated by oxidative stress (2). EGB761 in aged mice has been shown to protect mitochondria stressed by hydrogen peroxide, antimycin and amyloid beta (50). Reduced ROS levels and ROS induced cell death in lymphocytes following short term in vivo administration of EGB761 further emphasizes its neuro-protective action (50). Tang et al. (51) confirmed these findings in cholinergic neurons in vivo. In addition, EGB761 has been shown to modulate NO-induced toxicity (49).

Colciaghi et al. (14) demonstrated EGB761 increases alpha-amyloid precursor protein (APP) and directly modulates alpha-secretase. The alpha-secretase pathway is important in the pathogenesis of AD; in particular the alpha-APPs which experimentally have been shown to exert neuro-protective effects and enhance learning and memory in the hippocampus and cortex (52). A recent investigation of the effect of dietary EGB761 supplementation on APP metabolism revealed mice transgenic for human APP protein had a 50% reduction of APP levels compared to controls in the cortex but not in the hippocampus (53). In addition, EGB761 did not seem to affect young mice; only cortex tissue from older mice showed lowered APP protein levels (53). APP is an important molecular target of EGB761 and appears to be cortex specific (53).

Clinical evidence of ginkgo on microcirculation, platelet function and anticoagulation
A meta-analysis of eight double-blind randomised controlled trials reported that Ginkgo biloba provides a modest increase in pain free walking distance compared with placebo in peripheral arterial occlusive disease (54). In the clinical setting Ginkgo was shown to enhance microcirculatory blood flow as early as an hour post administration (55). Enhanced cerebral microcirculation, in theory at least, may provide a mechanism to delay onset, slow progression and manage symptoms of dementia and DAT. In particular, improved microcirculation may play an important role in preventing and delaying progression of VaD.

Despite the purported platelet-activating factor antagonist activity, results from three recent placebo controlled studies found no significant effect for Ginkgo on platelet function or coagulation (56-58). Rare case reports of subdural haematoma associated with high doses of Ginkgo (59) and bleeding into the anterior chamber of the eye following combined Ginkgo and aspirin therapy may represent the anti PAF action of Ginkgolide B (60). Two recent randomised double-blind studies have demonstrated that Ginkgo does not affect the pharmacokinetics, pharmacodynamics, or clinical effects of warfarin (57,61). In addition, two clinical trials have shown no evidence of significant effects on bleeding (56,58). While these observations may lend
weight to an argument against a role for Ginkgo as an anti-coagulant, more recent investigations have shown that Ginkgo potentiates anti-platelet effects without actually prolonging bleeding time (62). Another laboratory based investigation demonstrated that Ginkgo had similar effects on the fibrinolytic system as streptokinase (63). Enhanced anti-thrombotic effects without the traditional side effects would extend significant advantage as prophylaxis in VaD.

Clinical evidence of ginkgo in preventing or ameliorating the effects of dementia

The bulk of the available clinical evidence has been captured in several major reviews. The 2002 Cochrane review (64) concluded that evidence to date showed cognitive improvement with ginkgo therapy with no adverse effects but recognised that only three of the reviewed articles were of satisfactory quality. The same authors undertook the 2007 Cochrane review and concluded that despite the comparable evidence of cognitive improvement, that predictability and clinical significance of ginkgo therapy was inconsistent (65). The 2009 Cochrane review (66), however, included 39 trials, most of which tested the same standardised preparation of Ginkgo (EGb761) for dementia and cognitive impairment. Only nine of these trials were of six months or greater duration, of adequate size (total of 2016 patients) and had sound methodology. Results were inconsistent for the efficacy of EGb761 to improve cognition, mood and activities of daily living. Unfortunately, all three Cochrane reviews have been confounded by very broad selection criteria. All three included studies using any strength of ginkgo, any period of treatment, any severity of cognitive decline, and populations other than those with dementia. Consequently, the findings in dementia, in particular DAT and VaD, have been largely diluted. Sub-analysis in the 2009 Cochrane review (66) of patients with DAT (925 patients) revealed similar inconsistencies in both inclusion criteria and outcomes.

A more indicative meta-analysis was undertaken to specifically assess cognitive function in patients with DAT (24). Inclusion criteria included clearly characterised patient status, exclusion of neurological co-morbidity (eg. depression), standardised ginkgo extract, randomised, placebo-controlled double blind design, and objective assessment of cognitive function. The study identified more than 50 clinical studies but most were culled due to a failure to provide a clear diagnosis of dementia or DAT (an exclusion criterion not applied in the Cochrane reviews), leaving four clinical trials with a pooled population of 424 patients. A significant (P<0.0001) improvement in objective measures of cognition in DAT patients over placebo was reported for 120 to 240mg of standardised Ginkgo biloba extract for three to six months treatment regimes (24).
A double-blind, placebo-controlled trial by Rogers and colleagues (67) demonstrated EGb761 (standardised ginkgo formulation) was comparable to donepezil, a widely prescribed acetylcholinesterase inhibitor, on cognitive function of DAT patients. The British Association for Psychopharmacology Consensus Group (68) extensively reviewed numerous anti-dementia therapies and reported that donepezil and other cholinesterase inhibitors had strong evidence from meta-analysis of randomised controlled trials supporting efficacy in dementia. Ginkgo was reported to have modest benefits to cognitive function in dementia (68). Mazza et al. (69) also compared donepezil (5mg/day) to ginkgo (160 mg/day of EGb761) in mild to moderate DAT in a 6 month randomised, placebo controlled double blind clinical trial and showed comparable efficacy between ginkgo and donepezil in DAT.

The Ginkgo Evaluation of Memory (GEM) trial is the largest randomised controlled trial in people 75 years or older with normal or mild cognitive impairment (70). More than 3000 volunteers took 240mg of EGb761 daily and were followed for an average of six years (70). The study was designed to evaluate whether EGb761 would decrease the incidence of all types of dementia including DAT (70). The end point of the study was a diagnosis of dementia confirmed on magnetic resonance imaging (MRI). The lack of functional confirmation of disease via single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging is a limitation of the GEM trial. While ginkgo was shown to be safe with no evidence of increased bleeding risk, it demonstrated no benefit for reducing dementia or DAT (70). There has been one small double blind placebo study using SPECT in 48 patients after 8 months of ginkgo therapy (versus placebo) (71). Post therapy, the ginkgo group showed improved cerebral perfusion while the control group showed a reduction in cerebral perfusion. This study provides a small insight into the potential SPECT could play in evaluating the physiological response to ginkgo therapy.

The inconsistent results of the clinical trials on the effects of ginkgo in the management and prevention of dementia may be attributed to the heterogeneity in the rating scales, functional parameters used by various investigators and the degree of training required to administer the tests ranges from minimal to significant (13,72). More importantly, the clinical trials utilise a subjective and unreliable objective measure of improved cognitive function. The clinical availability of sophisticated and sensitive functional imaging techniques now allows objective measurements in term of intra-cerebral regional perfusion and function. For example, SPECT and
PET provide sensitive physiological evaluation of regional cerebral blood flow or metabolism; enabling early detection and more sensitive characterisation of subtle physiological changes. The role of SPECT and PET in detecting pre-symptomatic cognitive decline and detection of subtle changes in response to treatment fill the void in current outcome measures. SPECT and PET may be able to reliably detected subtle changes that cannot be detected on the more subjective and less sensitive psychometric assessment tools. The heterogeneity of the various trials reviewed by the Cochrane group may represent the subjectivity of the various cognitive scales, indiscriminate population sampling (including those without dementia), inappropriate periods of treatment, non therapeutic doses, variations in disease severity and lack of characterisation of disease. Consequently, the article by Oken et al (24) provides the most reliable measure of ginkgo efficacy in dementia. Nonetheless, there remains a need for further large scale evaluation with combination of physiological and psychometric evaluation.

**Discussion**

There are numerous publications reporting positive effects for Ginkgo biloba. Those with well designed randomised controlled double blind methodology tend to have inconsistent dosage, period of evaluation and even disease characterisation (severity of cognitive decline) and the results are often confounded by the inclusion of patients without dementia. Indeed, there is a lack of adequate stratification of DAT and VaD. There are a few well designed studies that have demonstrated a significant improvement in cognition in patients with dementia (usually DAT) but they use less sensitive objective measures. A 2002 clinical trial provides a representative case example of the bias in the literature (73). While the methodology satisfied, for example, the Cochrane inclusion criteria, the reported lack of benefit of ginkgo on cognitive improvement is confounded by a sub optimal treatment period (six weeks), sampling of normal volunteers with no evidence of dementia, reliance on self, spouse, friend, and relative ratings, and low doses of ginkgo (120mg/day reflecting over the counter availability). Consequently, the data analysis does not reflect the actual influence of ginkgo on cognitive function in dementia sufferers. This factor, combined with the bias introduced by sub optimal outcome measures, treatment periods and dosage, presents a major limitation in the currently available literature in the role of ginkgo in dementia and, those, demands more robust investigation.

VaD requires stratification within clinical trials because if theory translates to practice it stands to have greater preventative, slowing of progression and symptom management than DAT. Furthermore, VaD is particularly suitable for evaluation of response to treatment using SPECT
and PET. Nonetheless, there is a paucity of evaluation of ginkgo efficacy in VaD. An evaluation of the efficacy of ginkgo in VaD and DAT patients against a placebo group using PET as the objective measure is required. Furthermore, the ability of newer PET tracers, like ‘Pittsburgh Compound B’, to detect preclinical DAT and stratify those likely to progress to symptomatic DAT (74) will afford a tool to assess prophylactic efficacy.

**Conclusion**

Dementia represents a large group of illnesses which cause a progressive decline in a person’s mental functioning. The relative and absolute population aging will see a significant increase in the number of dementia cases across the globe over the next fifty years and the associated large increase in the social and economic costs of management. The potential role of herbal medicine in delaying onset, slowing progression and managing symptoms, if definitively proven, could have an enormous effect from social and economic perspectives.

A tantalising database attests to the neuro-protective effects of Ginkgo through its multifunctional properties as a potent antioxidant, free radical scavenger, neuro- and vasoactive agent. Recent robust trials reveal variability in the efficacy of Ginkgo to manage dementia or prevent the incidence of dementia. The disparity between pharmacological data and clinical trials may lie in the subjectivity of the assessment tools used to define the presence and degree of dementia combined with inclusion of populations not reflective of those with dementia. Incorporation of less subjective assessment, including the use of functional imaging techniques, is required to inform the role of ginkgo in dementia management.

While there is a lack of current evidence for widespread adoption of Ginkgo in prophylaxis and treatment of DAT, there is sufficient evidence to encourage more robust research in the utility of Ginkgo in delaying onset and progression of dementia.
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