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Therapeutic Value of *Ginkgo biloba* in Reducing Symptoms of Decline in Mental Function

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Abstract

The Chinese tree *Ginkgo biloba* or ''maiden hair tree'' is extensively cultivated for the exploitation of the medicinal properties of its leaves. From these, a well-defined extract designated ''EGb 761'' has been developed, which was commercialized initially as Tanakan, Tebonin and Rokin; a similar product, Kaveri (LI 3170), also exists. The major therapeutic applications for these products are ''cerebral insufficiency'', other cerebral disorders, neurosensory problems and peripheral circulatory disturbances. Four primary concepts of action have been proposed to explain the pharmacotherapeutic benefits of EGb761; these are: vasoregulatory, cognition-enhancing, stress-alleviating, and gene-regulatory. These actions are believed to be realized through the principal active ingredients, flavonoids and the terpenoids ginkgolides and bilobalide acting simultaneously in concert, combination and synergy, so-called polyvalent action.

It has been proposed that EGb761 may improve the memory of healthy volunteers, and in an assessment meta-analysis of forty clinical studies, it was reported that *Ginkgo* was able to improve the twelve different symptoms comprising 'cerebral insufficiency', all of which are manifest in the elderly. These were supported in a second major study, using LI1370. However, in both instances, the evidence was largely based upon the results of self-assessment questionnaires. Latterly, in a large double blind study of men and women with the diagnosis of uncomplicated dementia who were administered *Ginkgo* for a year, a further positive outcome was claimed. In this study, patients were tested using ADAS-cog, GERRI and CGIC.

It is suggested that whilst these different outcomes are compatible with (but do not affirm) a clinical benefit resulting from the use of *Ginkgo*, the application of a more objective system of assessment would be able to provide firm proof. It is proposed, therefore, that an objective, computer-based testing system for assessment of clinical improvement in volunteers and patients administered *Ginkgo* (such as CANTAB) would provide the convincing evidence currently being sought by patients, carers, physicians, legislators and the pharmaceutical industry.

Traditionally, the plant kingdom has been recognized as an incalculably rich source of new therapeutic substances (Phillipson 1999) and many drugs in current use are extracted directly from plant material. These include analgesics like morphine and codeine, anti-malarial medicines such as quinine, cardiac anti-arrhythmic agents such as digoxin and, more recently and controversially, anti-cancer substances such as taxol (Kingston et al 1993). However in other cases, a biologically-active chemical template may serve as a springboard for the synthesis of new chemical analogues and derivatives, as in the substantial range of non-steroidal anti-inflammatory agents developed from salicin found in willow bark, and the anti-asthma prophylactic substance cromoglycate, which is based on khellin, found in the fruits of *Ammi visnaga* (O'Neill 1998). Indeed, the very great extent to which current medicines have their origins in plants is well demonstrated by Table 1. Here,

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Table 1. Top-selling medicines in 1995 (US$ billion).

*Ranitidine	3·78	Cyclosporin	1·29
Enalapril	2·31	*Nifedipine	1·27
*Omeprazole	2·30	Lovastatin	1·25
*Fluoxetine	2·07	*Amlopidine	1·24
*Simvastatin	1·96	*Nifedipine	1·14
Captopril	1·54	Pravastatin	1·12
*Acyclovir	1·45	*Diltiazem	1·10
*Ciprofloxacin	1·43	Ceftriaxone	1·09
Diclofenac	1·32	Clarithromycin	1·05
Amox-Clav Acid	1·30	*Paracetamol	1·05

*Compounds chemically related to plant-derived products

O'Neill (1998) has traced the sources of the world's twenty top selling medicines during 1995, as reported in a global market review prepared for Glaxo Wellcome at that year's end. Over half of the products listed contain an active ingredient with a structure based on a compound found in nature, and as a group they contributed £9·34 billion ($16·53 billion) to world-wide pharmaceutical sales.

Despite this evident therapeutic wealth and the enormous financial potential of natural source material, it has been suggested in a recent report that the pharmaceutical industry may have limited interest in plant-derived products (Chesney 1997). It is proposed that the reasons for this may be related to perceived difficulties connected with intellectual property rights, linked to the Convention on Biological Diversity, concerns on the quality and quantity (i.e. the supply chain) of plant raw material, or the difficulties of identifying a single, or major, putatively active component in a climate where regulatory authorities traditionally have not generally encouraged the registration of combination products. However, all these potential barriers to the ultimate widespread use of a plant-derived medicinal product, have been overcome in the case of the defined extract of the Chinese tree *Ginkgo biloba*, or the ''maiden hair tree'', which has a mutual designation among several French and German pharmaceutical companies preparing it by a common route, as EGb761.

This tree is cultivated in various parts of the world including western France, South Carolina, Japan, Korea and China, where it has been reported, quite recently, to exist in the wild in several provinces (Schmid 1997). Also, it contributes to those medicinal plants upon which up to three-quarters of the world population relies for its primary pharmaceutical care (McChesney 1997). We can see that by its widespread use and growth in different countries (there are 25 million trees cultivated in China) that the possibility exists to produce first-class quality raw material, with no problems related to the Convention on Biological Diversity. Further, the *Ginkgo* tree is grown in such substantial quantities with large harvests, that it is beyond being a victim of its own success i.e. it is not threatened by overuse. Finally, EGb761 is, today, among the top five prescription medicines in Germany. Nevertheless, across Europe, a regulatory dilemma currently exists, since in the UK, for example, *Ginkgo* is only available as a food supplement. However, as EU governments press their respective regulatory authorities towards harmonization, solutions are being sought. The European Proprietary Medicines Manufacturer Association (or Association Européenne des Specialités Pharmaceutiques Grand Public – AESGP) is carrying out a study on behalf of the European Commission on the practices of the sale and supply of herbal medicines in the different member states.

In addition, an ad-hoc committee (Working Party on Herbal Medicinal Products) has been set up within the European Medicines Evaluation Agency (EMEA) upon the initiative of the European Parliament, the European Commission and the EMEA to provide guidance on the assessment of herbal medicinal products. One proposal from the AESGP is to amend current legislation to incorporate herbal medicinal products whose efficacy is based on traditional use, subject to them meeting quality and safety requirements (AESGP 1999). This could help resolve the difficulties which currently exist where some plants are widely used in some EU member states but would be considered prescription medicines in others (Anderson 1998, personal communication).

It has been noted already that the *Ginkgo biloba* tree originates in China. De Feudis (1998) reports that it is believed to be the oldest living tree species and represents the genus *Ginkgo*. It grows to 20–30 m high, surviving up to 1,000 years and its leaves are divided into two lobes; hence the Linnean specific terminology *biloba*. The trees are dioecious. The term ''living fossil'' has been applied to *Ginkgo* because though it is fossilized in Jurassic cretaceous deposits it was, until recently, believed not to exist in the wild (Schmid 1997) and was restricted, historically, to temple and similar ornamental gardens. It is also remarkable for its fungus- and insect-resistance, and its tolerance to cold weather and urbanization.

Ginkgo was first introduced into the UK some 150 years ago. A history of the Royal Botanical Gardens, Kew, reports that the male tree at Kew was brought from the Duke of Argyll's garden in nearby Twickenham by William Aiton, a former gardener at the Chelsea Physic Garden, who was

recruited for the purpose of setting up a similar garden in Kew. Whether this is the tree referred to in De Feudis' excellent book, coming via Japan and a Dutch Botanical Garden in Utrecht, is uncertain.

Clinical and Experimental Pharmacology

Therapeutic uses of Ginkgo biloba

The first records of cultivation of *Ginkgo* appear in Chinese literature of the 11th century (Song dynasty) and treatment of asthma and bronchitis are mentioned in these ancient texts. Indeed modern Chinese pharmacopoeias introduced the leaves for treating dysfunction of heart and lungs. Also, in Malaya today, the nuts (sometimes referred to as silver apricots) are popular as desserts, particularly among children, and are highly recommended for their nutritional benefits to the brain, the eyes and the circulation (Ng 1998, personal communication).

Certainly, trees are also cultivated exclusively for their nuts. Dr Schwabe (whose company now bears his name) introduced *Ginkgo* leaves into medical practice in Germany in 1965, as a result of his personal research interests. They are now widely used mainly for ''cerebral insufficiency'' in France and Germany (but strangely not in the UK, Holland or USA). Since the leaves have been thought to improve blood circulation, benefit the brain, inhibit pain and to be astringent to the lungs, they are used also, in China, in prescriptions for atherosclerosis, angina, hypercholesterolaemia, dysentery and filariasis. It is for this reason, of alleged benefit over a wide range of disease states, that De Feudis proposes four primary concepts of action to explain the broad-ranging pharmacotherapeutic benefits of EGb761: vasoregulatory, cognition-enhancing, stress-alleviating, and gene-regulatory (De Feudis 1998).

Recognized active pharmacological principles of Ginkgo

The major therapeutic components of EGb761 are believed to be flavonoids and the terpenoids, ginkgolides and bilobalide. Over 4,000 different flavonoid chemical structures have been identified in nature. They are widely distributed in the plant kingdom and occur as pigments in flowers and fruits, as seen in tea and wine, and have been exploited as polygenetic dye-stuffs, but their precise biological roles in plants remain somewhat obscure. They comprise a benzene ring condensed with a further six-membered ring carrying a phenyl ring as a substituent in the 2-position and are usually combined with a sugar such as quercetin (so named because it was first found in oak bark, although it is now known to exist in other plant groups). In mammalian systems, they exhibit a range of biochemical and pharmacological functions including anti-oxidant, free radical scavenger, enzyme inhibitor, cation chelator, anti-allergic, anti-inflammatory, anti-proliferative, anti-viral, anti-carcinogenic, enzyme inducer and manifest benzodiazepine-like activity (De Feudis 1998).

The terpenoids comprise a group of non-saponifiable lipids, like steroids, composed of units of the five-carbon hydrocarbon isoprene. Two such units constitute a monoterpene, and higher terpenes, or polyterpenes, include natural rubber which contains hundreds of units. Also included in this group of chemical substances are menthol, camphor and fat-soluble vitamins A, E and K.

Ginkgolides are diterpene lactones containing three lactone functions and a *tert*-butyl group (which is extremely rare in plants and the cause of a bitter taste), a further *tert*-butyl group associated with a hydroxyl function characteristically attached to different carbon atoms in ginkgolides (but to the same carbon atom in bilobalide). There are four members of this group, so-called A, B, C and J. The range of biochemical and pharmacological actions includes blood platelet anti-aggregatory activity, reduction of blood viscosity, platelet-activating factor antagonism, free radical scavenging and regulation of glucocorticoid synthesis. Bilobalide is a diterpene lactone which may be involved in protecting against herbivorous insects or mammals, and also protects against low levels of oxygen in the blood.

Contemporary clinical studies with Ginkgo

There are, today, two relevant therapeutic situations where *Ginkgo* is used with the aim of enhancing cerebral function, or arresting its deterioration. One is related to the common, age-related mental decline associated with advancing years alone, and the other with neurodegenerative disorders such as Alzheimer's disease. Such clinical studies have mainly employed the recognized extract of *Ginkgo* leaves designated EGb761, containing 24% w/w flavone glycosides and 6% terpenoids, marketed under the names of Tebonin, Tanakan and Rokin. A very similar product, Kaveri (designated LI 1370) contains 25% glycosides, and has also been used.

However, it is germane at the start to mention the work in a group of sane, normal people of Subhan & Hindmarch (1984). They demonstrated a significant improvement in the memory of young, healthy, female volunteers following an acute,

single, oral dose of 600 mg *Ginkgo*, using Sternberg's memory scanning test (Sternberg 1969, 1975). The results of this randomized, double-blind cross-over design support the thesis of De Feudis (1998) in this particular example of cognitive enhancement.

The scored features assessment of Kleijnen & Knipschild (1992) is a critical review of the pooled results from forty published studies of *Ginkgo* extracts, and has been widely referenced. In these studies, divided total daily doses, normally of 120–160 mg per day, were administered over twelve weeks, and cerebral insufficiency assessed according to the twelve criteria of difficulties of concentration and memory, being absent-minded, being confused, lack of energy, tiredness, decrease of physical performance, depressive mood, anxiety, dizziness, tinnitus and headache. These symptoms have been associated with decreased cerebral circulation and may be considered early signs of impending dementia (Kleijnen & Knipschild 1992a).

Virtually all the trials showed some positive outcome, although the treatment needed to be taken for at least six weeks before benefits were discernible. In the EGb761-treated groups, 70% of patients felt ''improved'' whereas only 14% of patients felt this in the placebo-treated group. Overall, no serious side-effects were noted in any trial, and any side effects that were noted, were equally apparent in treated and placebo groups.

This supports early work of De Feudis that there is ''low incidence of risk with *Ginkgo*''. The popularity of *Ginkgo* in Germany is reflected in the fact that in 1988 there were five million prescriptions for *Ginkgo*, which cost the German taxpayer DM 370m. In a later report, Vesper & Hansgen (1994) point out that whilst the work reviewed by Kleijen & Knipschild (1992) gave some support to the efficacy of *Ginkgo* in cerebral insufficiency, there remain questions on the precise mechanism of action involved. In their more recent and double-blind study, 90 patients (spread over ten centres) were treated with a divided dose of 150 mg per day of LI 1370, for a period of twelve weeks. Medical checks were carried out before product administration began and after six and twelve weeks of dosing, including the measurement of psychometric variables (when all patients were tested at the same centre) using a computer battery called LEILA 1.0 (Hansgen 1992). It was suggested that these tests were of greater validity than the traditional methods used hitherto. However, no checks of double-blindness were repeated.

This second, major study showed that from the sixth week of treatment both attention and memory, particularly visual memory, were improved, and that this was accompanied by ''positive changes of the patients' subjective performance'' (experienced by themselves) and ''objective performance'' (observed by those around them), so demonstrating the clinical efficacy of this second variety of *Ginkgo* preparation.

It would appear, on the basis of these two studies, that *Ginkgo* is well able to ameliorate the situation of the well-recognized age-associated mental impairment in otherwise normal individuals.

More recently there have been several reports on the possible value of *Ginkgo* in cases of dementia. The earliest suggestion that *Ginkgo* may have therapeutic benefits in dementia, was indicated in an article by Warburton (1986) reviewing the clinical psychopharmacology of the product. Subsequently, short term efficacy of intravenously-administered *Ginkgo* was found in patients presenting with vascular dementia and dementia of the Alzheimer type, resulting in an improvement of psycho-pathology and cognitive performance reflected in an increased ability to cope with the demands of daily living (Hasse et al 1996).

Latterly, in a placebo-controlled, double-blind randomized trial (Le Bars et al 1997) from the North American EGb Study Group in New York, over 200 patients were treated for a year with a daily dose of 120 mg of Tebonin or placebo. They were of both sexes and with the diagnosis of mild to moderate uncomplicated dementia (according to DSM-III-R and ICD-10) of the Alzheimer or multi-infarct type. The active treatment stabilized dementia, and in many cases improved cognitive performance and social functioning, as measured by the Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog; Rosen et al 1984), the geriatric evaluation by relative's rating instrument (GERRI; Schwarz 1983) and the clinical global impression of change (CGIC; Guy 1976). Overall, this study showed *Ginkgo* (EGb761) to be efficacious in two out of three primary-outcome measures: cognitive impairment and daily living and social behaviour as judged, respectively, by ADAS-Cog and GERRI; although the benefits of *Ginkgo* treatment were unable to be detected by the clinical global impression of change (CGIC).

Scientific interpretation of the therapeutic claims for Ginkgo

The state of cerebral insufficiency referred to above, has been attributed to inadequate blood supply to the brain, resulting in a relative lack of oxygen. Under these circumstances, there is a rise in the production of free radicals which cause damage to cell membranes, leading to the characteristic twelve symptoms cited (absent mind-

edness, difficulties of concentration, memory difficulties, confusion, lack of energy, tiredness, decreased physical performance, depressive mood, anxiety, dizziness, tinnitus and headaches). However, there are obvious diagnostic concerns which arise here; not least of all the problems presented by patients responding to their physician on a self-assessment scale of 1 to 5 for each of the symptoms when, in fact, they do have unrecognized (by themselves or their carers) problems of absent-mindedness or memory difficulties, for example. Overall, these symptoms are linked to impaired cerebral blood circulation and, it is believed, may precede dementia (Kleijen & Knipschild 1992a). Also, it would be useful if, in any future studies, there was a greater importance paid to double-blindness in the study design (the contribution to *Ginkgo* preparations of a characteristic bitter taste from their ginkgolide content was noted earlier).

The key feature of neurodegenerative disorders is associated with neuronal cell loss. Since such cells are post-mitotic, there exists no possibility for cell division and so dead or damaged cells cannot be replaced. Thus, neurodegenerative disorders lead to a loss of brain tissue and, therefore, a loss of brain function, commonly known as dementia, which may manifest as loss of memory, loss of ability to pay attention or to make plans. Within this category of disorders are Alzheimer's disease, Parkinson's and Huntington's disease. Whereas in idiopathic Parkinson's disease and genetically-determined Huntington's disease, the central pathology is largely associated with a loss of neurones from discrete areas of the brain (substantia nigra and striatum, respectively), Alzheimer's disease is a relentless, progressive dementia initiated in the transentorhinal cortex (Braak et al 1997) and characterized by a wave of cell death which appears to sweep through the brain, accompanied by loss of cognitive function. Portraying Alzheimer's disease as a disease chiefly caused by a loss of cholinergic forebrain neurones is incorrect and considerably overemphasizes just one of the many features of the illness (Braak et al 1997), which occurs mainly in the over-65s. At autopsy, Alzheimer-diseased brains show cortical atrophy characterized by extensive neuronal loss and abundant neuritic plaques and neurofibrillary tangles. β-Amyloid is the main constituent of the plaques which appear central to the pathology of the disease. Because of its great economic importance, i.e. because Alzheimer's disease has become so prevalent in today's elderly populations, many pharmaceutical companies are developing products which are palliative and short-term in nature, such as inhibitors of acetylcholine esterase and synthetic acetylcholine. Naturally, these are only effective in the mild to moderate stages of the disease, but of no use once the disease has progressed further.

However, the observed, age-related, decline in mental function associated with the cell death characteristic of Alzheimer's disease (and other dementias) suggests a reduced homeostatic capacity that is believed to underlie the ageing process, resulting from damage to brain chromosomal DNA (Jesberger & Richardson 1991). This is likely to be associated with the generation of harmful free radicals, according to the free radical theory of aging first proposed nearly fifty years ago and subsequently supported by the accumulation of much data demonstrating that free-radical reactions contribute to the degradation of biological systems (Harman 1981) per-se and, indeed, may also provoke apoptosis the process by which cells are programmed to die.

Overall, therefore, the well-documented activities of *Ginkgo* in its enhancement of cerebral blood flow and in its anti-oxidant and free radical-scavenging properties (Droy-Lefaix et al 1991), together with its known antagonism of the activity of the pro-inflammatory agent, platelet-aggregating factor (Guinot et al 1989) are quite compatible with its widely reported therapeutic benefits in the treatment of both cerebral insufficiency and dementia. Further, the recent observation of a reduced incidence of Alzheimer's disease in elderly arthritic patients self-administering high doses of anti-inflammatory drugs (Eikelenboom 1996) is also compatible with the importance of *Ginkgo*'s anti-inflammatory role in ameliorating the disease process in Alzheimer's disease.

Neuropsychology

We believe that more objective methods than those employed to date, of determining clinical improvement in volunteers and patients administered *Ginkgo* are necessarily required. This will provide unequivocal proof of what is so tantalizingly perceived to be so, i.e., the pharmacotherapeutic benefits of *Ginkgo* in reducing or protecting against the symptoms of mental decline seen in age-associated memory impairment (AAMI) and dementia. One such method is the computerized system for cognitive assessment, the Cambridge Neuropsychological Test Automated Battery (CANTAB) created by Robbins et al (Robbins et al 1994, 1998) comprising three batteries of tests, related to visual memory, attention and executive function, respectively. CANTAB is an innovative collection of tests, originally developed to improve the comparative assessment of cognition from animals to man. It comprises tests which have

already proven useful in establishing the neural substrates of some types of cognitive functions (e.g., delayed matching-to-sample, spatial working memory and attentional set-shifting; Robbins et al 1998) and other tests that permit a componential analysis of the elementary steps involved. CANTAB uses only symbols, rather than words, and thus is able to transcend cultural, educational and chronological barriers. It is a simple-to-use yet highly sophisticated instrument (Curtis-Prior 1996) employing a touch-sensitive screen for options and responses in neuropsychological evaluation, and has shown great utility in a wide variety of studies, such as those proposed in the evaluation of exposure to toxicants (Fray & Robbins 1996) and occupational hazards (Maruff 1995, personal communication), the very early detection of Alzheimer's disease (Fowler et al 1995, 1997), progressive cognitive decline in Parkinson's disease (Owen et al 1997), diagnosis of Huntington's disease (Fletcher 1997), and several psychopharmacological studies related to drug-related cognitive enhancement.

Using the CANTAB system, Lange et al (1992) demonstrated that withdrawal of L-dopa from Parkinson's disease patients had a negative effect on tests for frontal lobe dysfunction but no effects on pattern and spatial recognition, whilst Sahakian et al (1993) found that tetrahydroaminoacridine improved ''attention'' but not memory, in patients with mild to moderate Alzheimer's disease, and Coull et al (1996) showed that idazoxan could improve test results of ''planning'' and ''sustained attention'' in patients with frontal lobe dysfunction; whereas in healthy young adults, Elliott et al (1997) have shown that methylphenidate (Ritalin) was more complicated in its effects: enhancing performance of ''executive'' aspects of ''spatial'' function on novel tasks yet, paradoxically, impairing previously established performance. The results of these pharmacological investigations, taken together with the conclusions drawn by Robbins et al (1994, 1998) from studies on normal subjects suggest that current notions of ''intelligence'' or ''executive'' functioning are probably too simple to account for the observed effects of drugs on human performance.

Conclusions

Overall, the three major pharmacological features of *Ginkgo* are: dilatation of blood vessels, so increasing blood supply; antagonism of platelet-aggregating factor, so reducing blood clotting and reduction of membrane damage by enhanced blood flow; and reduction in oxygen free radicals. Such therapeutic roles have great utility in disease associated with restricted blood supply, tissue damage resulting from oxygen lack and free radical production, which are the hallmarks of cerebral decline and dementia. To date, the systems of evaluation of construed cognitive enhancement have tended to be somewhat subjective. However, it is proposed that CANTAB tests coupled with strict adherence to double-blindness, would prove useful in most elucidation of the perceived effects of *Ginkgo* (and possibly other therapeutic substances) in reducing symptoms of decline in mental function.

Because of the high-incidence of dementia in Americans over 85 years old, and the current high incidence of self-medication with *Ginkgo biloba* extract, by those who fear becoming demented, without the benefit of ''. . . clear compelling evidence . . .'' as to its efficacy, the US National Institutes of Health National Center for Complimentary and Alternative Medicine and the National Institute on Aging have jointly issued a call (RFA: AT−99−01) Under the United States (US) government's Healthy People 2000 initiative. This solicits researchers to apply for funding (up to US$ 15 000 000) for a study entitled: *Ginkgo biloba* prevention trial in older individuals. This proposed two-arm, double-blind, randomized, placebo-controlled, multi-site trial is to assess whether an extract of this botanical product (*Ginkgo* prevents the occurrence of dementia and/or cognitive decline in individuals of at least 75 years of age. This unique situation may, finally facilitate the realization of the definitive study on *Ginkgo*.

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References

AESGP (1999) Deregulation 2001 – The Future Of Medicine Regulation In Europe, Section 5.8 Herbal Medicinal Products, p. 16

Braak, H., Griffing, K., Braak, E. (1997) Review Article: Neuroanatomy of Alzheimer's disease. Alzheimer's Research 3: 235–247

McChesney, J. D. (1997) The promise of plant-derived natural products for development of new pharmaceuticals. Pharmaceutical News 4: 14–19

Clinical Global Assessment Scale (CGI) (1976) In: Guy, W. (ed.) ECDEU Assessment Manual for Psychopharmacology, Rockville, MD, US Dept of Health, Education and Welfare, NIMH 218–222

Coull, J. T., Sahakian, B. J., Hodges, J. R. (1996) The α-2 antagonist idazoxan remediates certain attentional and executive dysfunction in patients with dementia of frontal type. Psychopharmacology 123: 239–249

Curtis-Prior, P. B. (1996) Computerized methods of neuropsychological assessment. Br. J. Hosp. Med. 56: 445–449

De Feudis, F. V. (1998) *Ginkgo biloba* extract (EGb 761): from chemistry to the clinic. Publr Ullstein Med. Weisbaden, Germany

Droy-Lefaix, M. T., Bonhomme, B., Doly, M. (1991) Protective effect of *Ginkgo biloba* extract (EGb 761) on free radical-induced changes in the electroretinogram of isolated rat retina. Drugs Exptl. Clin. Res. 17: 571–574

Eikelenboom, P. (1996) Inflammation et maladie d'Alzheimer. Alzheimer Actual. 107: 8–12

Elliott, R., Sahakian, B. J., Matthews, K., Bannerjee, A., Rimmer, J., Robbins, T. W. (1997) Effects of methylphenidate on spatial working memory and planning in healthy young adults. Psychopharmacology 131: 196–206

Fletcher, F. (1997) Computer ''games'' diagnose early Huntington's disease. Molec. Med. Today 3: 48–49

Fowler, K. S., Saling, M. M., Conway, E. L., Semple, J. M., Louis, W. J. (1995) Computerised delayed matching-to-sample and paired associate performance in the early detection of dementia. Applied Neuropsychol. 2: 72–78

Fowler, K. S., Saling, M. M., Conway, E. L., Semple J. M., Louis, W. J. (1997) Computerised neuropsychological tests in the early detection of dementia: prospective findings. J. Int. Neuropsychol. Soc. 3: 139–146

Fray, P. J., Robbins, T. W. (1996) CANTAB Battery: proposed utility in neurotoxicology. Neurotox. Teratol. 18: 499–504

Guinot, P., Caffrey, E., Lambe, R., Darragh, A. (1989) Tanakan inhibits platelet-activating factor induced platelet aggregation in healthy male volunteers. Haemostasis 19: 219–223

Hansgen, K-D. (1992) Psychodiagnostic software system ''Leila'' – computer diagnostics in practical application. Report Psychologie 8: 25–32

Harman, D. (1981) The aging process. Proc. Natl. Acad. Sci. USA 78: 7124–7128

Hasse, J., Halama, P., Horr, R. (1996) Wirksamkeit kurzauernder Ifusionsbehandlungen mit Ginkgo-biloba-Spezialextrakt EGb 761 bei Demenz vom vaskularen und Alzheimer-Typ. Z Gerentol. Geriat. 29: 302–309

Jesberger, J. A., Richardson, J. S. (1991) Oxygen free radicals and brain dysfunction. Intern. J. Neuroscience 57: 1–17

Kingston, D. G. I., Molinero, A. A., Rimoldi, J. D. (1993) Taxol, an exciting anti-cancer drug from *Taxus brevifolia*. In: Kinghorn, A. D., Balandrin, M. F. (eds) Human Medicinal Agents from Plants. American Chemical Society, Washington, pp 138–148

Kleijnen, J., Knipschild, P. (1992) *Ginkgo biloba* for cerebral insufficiency. Br. J. Clin. Pharmacol. 34: 352–358

Lange, K. W., Robbins, T. W., Marsden, C. D., James, M., Owen, A. M., Paul, G. M. (1992) L-Dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology 107: 394–404

Le Bars, P. L., Katz, M. M., Berman, N., Turan, M., Freedman, A. M. (1997) A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. J. Am. Med. Assoc. 278: 1327–1332

O'Carroll, R. E., Masterton, G., Dougall, N., Ebmeier, K. P., Goodwin, G. M. (1995) The neuropsychiatric sequelae of mercury poisoning: the Mad Hatter's disease revisited. Br. J. Psychiat. 167: 95–98

O'Neill, M. (1998) Screening plants for leads to novel medicines. J. Pharm. Med. 12: 211–217

Owen, A. M., Iddon, J. L., Hodges, J. R., Summers, B. A., Robbins, T. W. (1997) Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropschologia 35: 519–532

Phillipson, J. D. (1999) New drugs from nature – it could be Yew. Phytotherapy Research 13: 1–7

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., McInnes, L., Rabbit, P. M. A. (1994) Cambridge Neuropsychological Test Automated Battery (CANTAB): a Factor analytic study of a large sample of normal elderly volunteers. Dementia 5: 266–281

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., Lawrence, A. D., McInnes, L., Rabbit, P. M. A. (1998) A study performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. J. Int. Neuropsychol. Soc. 4: 474–490

Rosen, W. G., Mohs, R. C., Davis, K. L. (1984) A new rating scale for Alzheimer's disease. Am. J. Psychiat. 141: 1356–1364

Sahakian, B. J., Owen, A. M., Morant, N. J., Eagger, S. A., Boddington, S., Crayton, L., Crockford, H. A., Crooks, M., Hill, K., Levy, R. (1993) Further analysis of the cognitive effects of tetrahydroaminoacridine (THA) in Alzheimer's disease: assessment of attentional and mnemonic function using CANTAB. Psychopharmacology 110: 395–401

Schmid, W. (1997) Ginkgo thrives (correspondence). Nature 386: 755

Schwarz, G. E. (1983) Development and validation of the geriatric evaluation by relative's rating instrument (GERRI). Psychol. Rep. 53: 479–588

Sternberg, S. (1969) Memory scanning: mental processes revealed by reaction time experiments. American Scientist 57: 421

Sternberg, S. (1975) Memory scanning: new findings and current controversies. Quart. J. Exp. Psychol. 27: 1

Subhan, Z., Hindmarch, I. (1984) The psychopharmacological effects of *Ginkgo biloba* extract in normal healthy volunteers. Int. J. Clin. Pharm. Res. 4: 89–93

Vesper, J., Hansgen, K-D. (1994) Efficacy of *Ginkgo biloba* in 90 outpatients with cerebral insufficiency caused by old age. Phytomedicine 1: 9–16

Warburton, D. M. (1986) Psycho-pharmacologie clinique de l'extrait de *Ginkgo biloba*. La Presse Medicale 15: 1595–1604