International Journal of Neuropsychopharmacology (2010), **13**, 257–271. Copyright © CINP 2009
doi:10.1017/S1461145709990654

REVIEW ARTICLE

Review and meta-analysis of usage of ginkgo as an adjunct therapy in chronic schizophrenia

Vidhi Singh[1], Surendra P. Singh[2] and Kelvin Chan[3]

[1] *MediWare Computer Software Engineering, Wolverhampton, West Midlands, UK*
[2] *Mental Health Directorate, Wolverhampton City Primary Care Trust and University of Wolverhampton, Wolverhampton, West Midlands, UK*
[3] *University of Wolverhampton, Wolverhampton, West Midlands, UK*

Abstract

This study aimed to review the roles of antioxidants in the pathophysiology of schizophrenia, whether the properties of ginkgo can ameliorate symptoms of this illness, and evaluate available literature to test this assumption. This review is based upon published works on antioxidants and ginkgo. A primary electronic search for meta-analysis on the usage of ginkgo or its derived products in schizophrenia was conducted using Pubmed, Cochrane Library, EMBASE, CINAHL, PsycINFO and AMED. Inclusion criteria were: criteria-based diagnosis of schizophrenia, randomized case assignment, use of ginkgo as an add-on therapy, and assessment using standardized rating scales to measure the state of psychopathology for negative and total symptoms of schizophrenia. Additionally, a detailed review was undertaken to investigate if antioxidants are involved in development of psychotic symptoms in schizophrenia. The six studies that fulfilled the selection criteria were constituted of 466 cases on ginkgo and 362 cases on placebo. They all used the Scale for the Assessment of Negative Symptoms (SANS) to measure negative symptoms, and the Scale for the Assessment of Positive Symptoms (SAPS) or the Brief Psychiatric Rating Scale (BPRS) to measure total symptoms. Difference between ginkgo and control groups from their pre- and post-trial scores and its pooled standard deviation were used to compute standardized mean difference (SMD). Ginkgo as an add-on therapy to antipsychotic medication produced statistically significant moderate improvement (SMD = −0.50) in total and negative symptoms of chronic schizophrenia. Ginkgo as add-on therapy ameliorates the symptoms of chronic schizophrenia. The role of antioxidants in pathogenesis of schizophrenia has also been explored.

Received 11 June 2009; Reviewed 22 July 2009; Revised 30 July 2009; Accepted 17 August 2009; First published online 24 September 2009

Key words: Antioxidants, chronic schizophrenia, EGb, ginkgo, meta-analysis.

Background and hypothesis

It is interesting to note that since ancient times traditional Chinese medicine has used ginkgo leaves and its fruit to treat brain disorders. *Ginkgo biloba* L. (family Ginkgoaceae) known as living fossil has grown in China for more than 150 million yr (McKenna *et al*. 2002). Similarly, usage of medicinal plants has been well documented in the Ayurvedic text of Rig-veda and Atharv-veda around 5000 B.C. (Mukherjee & Wahile, 2006) and further expanded in the early works by Attreya, Dhanwantary, Charak and Sushrut among many others in the first millennium B.C. Use of herbal preparations in the West also has its roots in ancient civilizations of the Middle East, Egypt, Greece and Rome (Wicke, 1998). In the East, there are a number of established medical institutes training physicians in these methods of treatment. Ayurvedic and Chinese medicines are part of their public and private healthcare systems, and are well accepted and appreciated by the local population; sometimes this is the only form of treatment available through traditional family trained practitioners. In the West, over the past 20 yr ginkgo has gained popularity for treatment to improve peripheral and cerebral circulatory disturbances, including claudication and memory impairment (Hopfenmüller, 1994; Kleijnen & Knipschild, 1992). Ginkgo tops the list of herbal medicine sales in the USA (Koerner, 2007; O'Hara *et al*. 1998).

Address for correspondence: Dr S. P. Singh, Steps to Health, Mental Health Directorate, Wolverhampton City Primary Care Trust, Wolverhampton, West Midlands WV10 9TH, UK.
Tel.: +44 1902 445852 *Fax*: +44 1902 444 514,
Email: Dr.S.Singh@wlv.ac.uk

Ginkgo – as an antioxidant and immunostimulatory agent

Chemical compounds (e.g. hydrogen peroxide), which can oxidize other molecules or promote the formation

of other oxidizing agents are named pro-oxidants. Pro-oxidants with unpaired electrons are named free radicals and these unstable electrons make the compound highly reactive. Pro-oxidants without unpaired electrons are known as non-radical pro-oxidants. Free radicals are produced during the aerobic phase of metabolic cycles; their half-life can last from a nanosecond to few seconds and have damaging effects on living cells. The presence of antioxidants prevents or delays such an oxidation process. The antioxidant defence system in living cells is comprised of enzymes removing free radicals, e.g. superoxide dismutase (SOD), catalase, or glutathione peroxidase; proteins that minimize the availability of pro-oxidants such as transferrin and hepatoglobulins; heat-shock proteins produced within cells as a result of stress and then influence the functions of other regulatory proteins; and scavenger molecules such as α-tocopherol, ascorbic acid, or glutathione acting on reactive oxygen species (ROS) and reactive nitrogen species (RNS).

The term oxidant stress refers to an imbalance when production of pro-oxidant activity exceeds the capability of the anti-oxidant defence system. This oxidant stress has been implicated in the pathogenesis of several disorders (Halliwell & Gutteridge, 1990). Antioxidants are chemicals that reduce this oxidative stress (Dabiri *et al*. 1994) and can be classified into hydrophilic and lipophilic types depending on their solubility. It is uncertain if the ratio or quantity of these two types of antioxidants and their interaction with gallic acid in plant-derived products (USDA, 2007) can account for their estimated differential properties, if any.

In experimental situations on rat brains, there are reports that up-regulation of SOD plays a protective role in hippocampal ischaemia (Chandrasekaran *et al*. 2001; Wengenack *et al*. 1997) and glutamate neurotoxicity (Schwartz *et al*. 1998). Ginkgo has been found to be effective in the treatment of cerebral insufficiency (Kleijnen & Knipschild, 1992) and Alzheimer's disease (Andrieu *et al*. 2008; Knapp *et al*. 1994; Le Bars *et al*. 1997). Antioxidant agents are reported to have a mediating role in the prevention of cell damage in the ageing brain (Oyama *et al*. 1994). There are animal studies to support its protective role on cardiomyocytes (Schneider *et al*. 2008), intestinal inflammation (Kotakadi *et al*. 2008), liver carcinogenesis (Dias *et al*. 2008), intermittent claudication (Pittler & Ernst, 2000), hippocampal loss (Takuma *et al*. 2007) and other neuronal damage (Augustin *et al*. 2009; Rojas *et al*. 2008; Saleem *et al*. 2008). Ginkgo has antioxidant properties (Maclennan *et al*. 2002) and has been found to improve brain circulation at the microvascular level (Kubota *et al*. 2001; Sun *et al*. 2003; Yan *et al*. 2008). Negative symptoms in schizophrenia seem to have underlying cognitive deficits (Rector *et al*. 2005; Spoletini *et al*. 2009) and it is logical to assume that ginkgo as an antioxidant may positively contribute to treatment of this disorder.

There are reports of raised levels of SOD in schizophrenia (Abdalla *et al*. 1986; Reddy *et al*. 1991; Zhang *et al*. 2001*a*, *b*) and a reduction after treatment with ginkgo as an add-on therapy (Zhou *et al*. 1999). Increased SOD may appear to be a compensatory mechanism in response to increased oxidative stress (Lohr *et al*. 2003; Yao *et al*. 2001). Vitamin E, a potent antioxidant, can also reduce the severity of positive symptoms in schizophrenia (Lohr & Browning, 1995). These corollaries have led to speculation that oxidative stress may have a pathophysiological role (Herken *et al*. 2001) and its defence mechanisms are impaired in schizophrenia (Ranjekar *et al*. 2003).

Dopamine and norepinephrine activities are associated with an increase in the production of free radicals (Lohr, 1991; Lohr & Browning, 1995). This, in turn, can result in destruction of phospholipids and an alteration in the viscosity of cell membranes causing further impairment of serotonergic and catecholaminergic receptor functions. Typical antipsychotic medications mediate their therapeutic effect by blocking dopamine hyperactivity to treat positive symptoms of schizophrenia. The actions of atypical antipsychotic drugs are probably mediated through different and more than one neuroregulatory system (Butini *et al*. 2009; Meltzer, 2002), and may be slightly superior in the treatment of schizophrenia (Kronig *et al*. 1995; Leucht *et al*. 1999; Möller, 1993). Ginkgo can increase synaptosomal uptake of 5-HT (Ramassamy *et al*. 1992) similar to some of the atypical antipsychotic medications (Philibin *et al*. 2009). Antioxidant treatment of schizophrenia can reduce the damaging effects of free radicals (Zhang *et al*. 2005). Pre-treatment with ginkgo also reduces amphetamine-induced hyperactivity (Trovero *et al*. 1999). Antipsychotic medications may possess D_2- and D_4-mediated neuroprotection dependent on cysteine-aspartic acid proteases (caspase) rather than ROS-dependent mechanisms (Bastianetto *et al*. 2006). It is possible that the introduction of ROS-dependent neuroprotective intervention may bring additional benefits to schizophrenia patients.

Schizophrenia may also be associated with changes in the immune system (Chittiprol *et al*. 2009; Müller *et al*. 1999, 2000). Some of the important immunoprotective mechanisms are mediated through CD+ in human T cells, CD4+ in TH1 and TH2 cells and IL-2 as the T-cell growth factor activated by CD4+ present

in TH1. All of these immunostimulatory components (T cells, CD3+, CD4+, CD4+/CD8+ ratio and IL-2) have been found to be lower and the SOD level higher in chronic schizophrenia when compared to a healthy control group (Sperner-Unterweger *et al*. 1999; Zhang *et al*. 2006*a*). Treatment with ginkgo increases CD3+, CD4+, IL-2 secreting cells, CD4+/CD8+ ratio, and decreases SOD levels (Zhang *et al*. 2006*a*). These findings indicate that ginkgo may possess immunostimulatory properties. There are also studies that report differential effects on T-cell proliferation (Tang *et al*. 2006).

As indicated above, antioxidants may have mechanisms of action through more than one target, and there may exist an interaction between excess free-radical production and a decrease in immune function in schizophrenia. Ginkgo as a potent antioxidant and immunostimulator should have beneficial effects in the treatment of schizophrenia (Zhang *et al*. 2006*b*). This study examines the biological properties of ginkgo in relation to known and assumed aetiopathogenesis of schizophrenia and hence negative results are not the focus of this review. Whether or not these modes of action are general or specific is also far from certain.

A study conducted in the UK found up to 50-fold variability in antioxidant activities of ginkgo preparations available from different manufacturers (Mantle *et al*. 2003). So far, only a limited number of randomized blind trials testing the efficacy of antioxidants in the treatment of schizophrenia have been carried out. It is unlikely that necessary research grants on this subject will be forthcoming from profit-making organizations, especially for a product which is essentially classified as a nutritional supplement. Research on herbal products is further hampered by complexities arising from various national and international biodiversity rules and regulations. There are also inherent limitations in standardizing the formulation, production and identification of active ingredients from plant products (Ganzera *et al*. 2001).

EGb is a compound derived from dried ginkgo leaves and is manufactured through the adaptation of standardized techniques. In general the chemical constituents of ginkgo leaves and seeds are essentially the same, but proportions of its constituents vary slightly. Both contain flavonoids such as ginkgetin, bilobetin, quercetin, kaempferol and isohamnetin. Other constituents are terpene, flavoglycosides (ginkgo heterosides), anthocyanins, lactones, procanthocyanins and ginkgolic acid. Flavanoids are supposed to have antioxidant activity (Köse & Doğan, 1995; Marcocci *et al*. 1994), whilst terpenoids are an antagonist to platelet-activating factor (Braquet, 1986). The extract is claimed to contain approximately 24% flavone glycosides and 6% terpene lactones. Ginkgolide B and bilobalide from the lactones group respectively constitute 0.8% and 3% of the total EGb extract. Proanthocyanadins, glucose, rhamnose, organic acids, D-glucaric and ginkgolic acids are some of the other constituents (Diamond *et al*. 2000). In the USA it is available as a dietary supplement as Gingold Nature's Way, in France as Tankan, and in Germany as Tebonin and Rökan. It is difficult to synthesize, but can be produced as a standardized mixture from the natural plant product with reliable quality control. Thus the product can be used for efficacy testing in clinical trials. Interestingly, all the trials included in this meta-analysis used EGb.

The interest in the use of medicinal herbs has increased scientific scrutiny and debate of their potential therapeutic use and safety concerns. This has necessitated updates of knowledge on herbal products to enable clinicians and patients to make informed decisions (Chan, 2005). It is well known that treatment with antipsychotics alone fail to bring adequate control of symptoms in schizophrenia. The pathophysiology of negative symptoms, which is commonly associated with cognitive deficits (Dickinson & Harvey, 2009) continues to remain an unexplained mystery. It is imperative to summarize the usefulness of ginkgo in the treatment of schizophrenia as an add-on therapy, especially in view of the fact that it is safe, its side-effects are comparable to a placebo (Birks & Evans, 2007), it is not expensive and is available as a food supplement. There is a growing trend of promoting alternative and complementary therapies to expand the list of choices available to users and practitioners.

Objectives

Schizophrenia is a syndrome with five main subtypes (APA, 2000). Most of these categories, except catatonic subtypes, are chronic in nature. The residual subtype is chronic in nature and mainly characterized by the presence of persistent and refractory negative symptoms. Disorganized and undifferentiated subtypes have a mixture of persistent positive symptoms and predominance of negative symptoms and are typically resistant to treatment. Paranoid subtype is less likely to be characterized by the presence of negative symptoms. In addition to general psychopathology, delusions, hallucinations, altered psychomotor activity and thought disorders are grouped under positive symptoms; and withdrawn behaviour, impaired abstract

thinking, lack of spontaneity and flow of conversations and stereotyped thinking are grouped under negative symptoms. Since studies on specific diagnostic categories may be very few, the decision was taken to focus on trials that included cases with chronic symptoms of schizophrenia despite adequate intervention with antipsychotic medications. An earlier review was conducted by the Cochrane Group (Rathbone *et al*. 2005) in 2005 and then republished in 2007 (Rathbone *et al*. 2007).

Clinicians tend to use polypharmacy in 50% or more of their cases (Faries *et al*. 2005; Pandurangi & Dalkilic, 2008) in a desperate attempt to treat chronic and/or resistant symptoms of schizophrenia. This practice is prevalent despite lack of conclusive evidence and against the best practice guidelines (Patrick *et al*. 2006). The present study also aimed to explore the association of responsiveness of add-on therapies with age of onset, duration of illness, age when entered into trials, dose of antipsychotic medications and ginkgo, baseline severity of symptoms, duration of intervention and gender differences.

Data source

The first stage of the strategy was: (1) electronic search of relevant databases, (2) tracing the references of PubMed web pages linked to individual abstracts of previously searched articles, and (3) checking cross-references for additional relevant studies. All randomized, controlled trials on schizophrenia using drug interventions were searched in title and abstract in databases from PubMed, Cochrane Library, EMBASE, CINAHL, PsycINFO and AMED. Other databases which were also searched included Chinese Clinical Trials Register (ChiCTR), ilib, Traditional Chinese Medicine Literature Analysis and Retrieval System, the China National Knowledge Infrastructure database, and the Chinese Biomedical database.

Study selection

The syntax for the PubMed search was '(Schizophrenia[MeSH]) AND (Ginkgo biloba[MeSH]) Limits: Humans, Clinical Trial, Randomized Controlled Trial, Controlled Clinical Trial)'. Out of 14 search results, eight (Atmaca *et al*. 2005; Doruk *et al*. 2008; Lin *et al*. 2007; Luo *et al*. 1997; Zhang *et al*. 2001*a*, *b*, 2006*b*; Zhou *et al*. 1999) came from the PubMed database, three (Knable, 2002; Werneke, 2008; Werneke *et al*. 2006) from other electronic databases, and three (Chen *et al*. 1997; Meng *et al*. 1996; Xu *et al*. 2002) from cross-referencing of the electronically searched articles. Out of these, one was a case report (Lin *et al*. 2007), one (Zhang *et al*. 2006*b*) was unrelated to the subject matter, and three (Knable, 2002; Werneke, 2008; Werneke *et al*. 2006) were review publications. There were three publications by the same group of authors at the same centre with very similar methodologies and an overlapping dataset. The main author had been successfully contacted earlier regarding his publications with positive feedback. During the stage of analysis, doubt arose if their subsequent publications included part of data from their previous studies. Attempts to contact the author for further clarification did not materialize and hence therefore only one (Zhang *et al*. 2001*b*) of those three publications (Zhang *et al*. 2001*a*, *b*; Zhou *et al*. 1999) was included. Accordingly a final list of seven studies were deemed suitable for further evaluation (Atmaca *et al*. 2005; Chen *et al*. 1997; Doruk *et al*. 2008; Luo *et al*. 1997; Meng *et al*. 1996; Xu *et al*. 2002; Zhang *et al*. 2001*b*). From this list of seven articles, four were in Chinese language and were translated by one of the authors (K.C.) who is fully conversant in written and spoken Chinese. One of the articles (Chen *et al*. 1997) included a mixture of more than one active herbal ingredient and hence was excluded from the analysis. The process of selection is displayed in the Table 1. There were six studies (Atmaca *et al*. 2005; Doruk *et al*. 2008; Luo *et al*. 1997; Meng *et al*. 1996; Xu *et al*. 2002; Zhang *et al*. 2001*b*) that fulfilled the inclusion and exclusion criteria, and were therefore selected for this review and analysis.

Table 1. Study selection process

	Publications
Electronic search using specified search criteria	11
Manual search	3
Not relevant to the subject	−2
Excluded as studies were not of primary type, e.g. reviews	−3
Excluded as studies were suspected of using duplicate data	−2
Studies selected for detailed evaluation	7
Studies that met inclusion and exclusion criteria	6

Inclusion criteria were use of ginkgo as add-on therapy in schizophrenia where response of treatment was monitored using standardized negative and total symptom rating scales, e.g. Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS; Andreasen,

1990), Positive and Negative Symptom Scale (PANSS; Kay *et al*. 1987), and Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Abstracts of all selected articles were further screened, first, by two authors to ascertain inclusion criteria for robustness of structured diagnostic methods or application of diagnostic criteria, use of valid rating scales before and after the trial, randomization and presence of a control group. For negative symptoms, order of preference for scale was SANS, PANSS negative subscale, and BPRS negative subscale; and for scores of total psychopathology PANSS, BPRS, and SAPS. Total scores on BPRS and SAPS may not cover the same domains but they still have modest correlation, $r=0.61$ (Gur *et al*. 1991), and hence in the absence of BPRS scores the total score was treated as equivalent to the score on SAPS. Exclusion criteria were the use of ECT and transcranial magnetic stimulation, studies on rapid tranquillization as a method of research intervention, and duration of treatment limited to <2 wk.

Data extraction

Difference of means and standard deviation from baseline to end of intervention scores on both total and negative symptom rating scales individually in each arm of the experimental and control groups were the minimum dataset necessary for statistical analysis. In absence of fixed dosing schedules, mean or median of titrated or flexible dose regimens were used to calculate the baseline dose of antipsychotic medication. This dose was converted to chlorpromazine equivalent daily defined dose (DDD) applying WHO DDD criteria (WHO, 2009). The remaining incomplete values were obtained using imputation techniques.

The dataset extracted for each study is as follows – dose of baseline antipsychotic medications, dose of add-on ginkgo preparation, standardized weighted mean (SWM) of baseline score for total and negative symptoms, mean age of onset in years, mean duration of illness in years, mean age of patients in study, duration of trial in weeks, proportion of males in sample, number of patients in add-on drug group, number of patients in placebo group, and standardized mean difference (SMD) of scores on negative and total symptom rating scales from baseline to end of trial in ginkgo and placebo groups and their standard deviations.

All studies finally selected for analysis had their scores rated on SANS for negative symptoms, and BPRS or SAPS for scores on total psychopathology. Severity of baseline symptoms was calculated as the ratio between overall baseline mean symptom score of the total sample with its standard deviation. In the absence of overall baseline mean in the published results, it was determined as ratio between weighted mean of combined experimental and control group [equation (1), Supplementary Appendix, available online] with their pooled standard deviation [equation (2), Supplementary Appendix]. A default value of Pearson's correlation coefficient of $r=0.5$ was used to calculate pooled standard deviation of repeated measures for control and experimental groups [equation (3), Supplementary Appendix], similar to the approach adopted by others (e.g. Winkley *et al*. 2006). For the non-dependent dataset, the process is defined in equation (6) of the Supplementary Appendix. The SMD was computed to reflect the difference between baseline and end of trial scores for both control and experimental groups.

R statistical software (version 2.7.2; R Development Core Team, 2009) and its meta-package were used for statistical analysis, and its GLM package to explore the regression model. The MICE imputation package (van Buuren & Oudshoorn, 2007) available in R programming language was used to obtain incomplete data. The programming codes for enhanced and structured graphic output were written in R language by one of the authors (V.S.).

Data synthesis

Summary attributes of the studies are given in Table 2 displaying their essential details and quality rating (Jadad *et al*. 1996).

As depicted in Table 3, all studies used standardized extract of ginkgo as EGb and its dose varied between 120 and 360 mg/d. There was preponderance of males over females, and average age of onset and duration of the illness in the studies was 27 yr and 11 yr, respectively. Minimum duration of trials among all studies was 8 wk. Four of the six trials were conducted in East Asia and the remainder in Eastern Europe. The overall sample size of 828 cases from all six studies is made up of 466 cases in the experimental group using EGb and 362 cases in the control group. The equivalent DDD (WHO, 2009) of baseline antipsychotic doses ranged between 0.73 and 2.08 among the studies.

As shown in the Table 4, the second study (Luo *et al*. 1997) has the largest sample size and has contributed the maximum weight of 26% for the random-effects model for negative symptoms and 61% for the fixed-effect model for total symptoms (Table 5) of schizophrenia. In each experimental and control group, the SMD between post-trial and pre-trial scores

Table 2. Studies summary

Study attributes	Meng *et al*. (1996)	Luo *et al*. (1997)	Zhang *et al*. (2001*b*)	Xu *et al*. (2002)	Atmaca *et al*. (2005)	Doruk *et al*. (2008)
Randomized	Yes	Yes	Yes	Yes	Yes	Yes
Blinding	Double blind	Double blind	Double blind	Open label	Single blind	Single blind
Antipsychotics group	Mixed	Mixed	Haloperidol	Chlorpromazine	Olanzapine	Clozapine
Ginkgo compared with …	Placebo	Placebo	Placebo	Placebo	None	Placebo
Total symptoms scale	BPRS	BPRS	BPRS	SAPS	SAPS	BPRS
Negative symptoms scale	SANS	SANS	SANS	SANS	SANS	SANS
Diagnostic criteria	ICD-10	ICD-10	DSM-IIIR	CCMD-2-R	DSM-IV	DSM-IV
Diagnosis	Schizophrenia of duration >3 years, in stable state, SANS >50, two patients relapsed during trial	Chronic schizophrenia, SANS >50, BPRS >30, duration >5 yr	Treatment resistant (not responding to two antipsychotics, each for 3 months) schizophrenia of duration >5 yr	Chronic schizophrenia, duration >5 years, stable for 6 months before trial	Schizophrenia, stable for 1 month	Treatment-resistant schizophrenia first treated with clozapine and then entered the trial
Score (Jadad *et al*. 1996)	3	3	3	2	2	2

BPRS, Brief Psychiatric Rating Scale; CCMD-2-R, Chinese Classification of Mental Disorders – Second Edition, Revised; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD-10, International Classification of Diseases – 10th Revision; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

Table 3. Study attributes

Author/year	Base drug	Male (%)	Age (yr)	Onset (yr)	Duration (yr)	Trial (wk)
Meng *et al*. (1996)	Chlorpromazine	50	35	24	11	8
Luo *et al*. (1997)	Antipsychotic	82	37	29	9	16
Zhang *et al*. (2001*b*)	Haloperidol	53	44	23	21	12
Xu *et al*. (2002)	Chlorpromazine	79	46	24	11	8
Atmaca *et al*. (2005)	Olanzapine	48	28	22	6	8
Doruk *et al*. (2008)	Clozapine	64	31	21	9	12
Summary (average)		74	39	27	11	14

Table 4. Results for EGb as an adjunct therapy for negative symptoms of chronic schizophrenia

Author/year	Base drug	Severity	SMD	S.E.	95% CI	Wt%	OR
Meng *et al*. (1996)	Chlorpromazine	4.34	−1.01	0.36	−1.72 to −0.31	11	6.3
Luo *et al*. (1997)	Antipsychotic	3.89	−0.50	0.09	−0.68 to −0.32	26	2.5
Zhang *et al*. (2001*b*)	Haloperidol	3.46	−0.12	0.19	−0.50 to 0.25	20	1.2
Xu *et al*. (2002)	Chlorpromazine	3.08	−0.67	0.21	−1.07 to −0.27	19	3.4
Atmaca *et al*. (2005)	Olanzapine	6.40	0.37	0.38	−0.37 to 1.10	11	1.9
Doruk *et al*. (2008)	Clozapine	3.42	−1.10	0.33	−1.75 to −0.44	13	7.3
Random-effects model	($Q=15.11$, d.f. = 5, $p<0.05$)	3.82	−0.50	0.16	−0.81 to −0.18	100	2.7

CI, Confidence interval; OR, odds ratio; SMD, standardized mean difference, S.E., standard error of SMD; Wt, weight in percentage.

Table 5. Results for EGb as an adjunct therapy for total symptoms of chronic schizophrenia

Author/year	Base drug	Severity	SMD	S.E.	95% CI	Wt%	OR
Meng *et al*. (1996)	Chlorpromazine	1.12	−0.15	0.34	−0.81 to 0.52	4	1.3
Luo *et al*. (1997)	Antipsychotic	4.82	−0.57	0.09	−0.75 to −0.39	61	2.8
Zhang *et al*. (2001*b*)	Haloperidol	3.03	−0.25	0.19	−0.62 to 0.13	14	1.6
Xu *et al*. (2002)	Chlorpromazine	2.66	−0.64	0.21	−1.04 to −0.24	12	3.2
Atmaca *et al*. (2005)	Olanzapine	4.52	−0.76	0.39	−1.51 to 0.00	3	3.9
Doruk *et al*. (2008)	Clozapine	6.66	−0.20	0.31	−0.80 to 0.41	5	1.4
Fixed-effects model	($Q=5.35$, d.f. = 5, $p>0.05$)	4.25	−0.50	0.07	−0.64 to −0.36	100	2.5

CI, Confidence interval; OR, odds ratio; SMD, standardized mean difference, S.E., standard error of SMD; Wt, weight in percentage.

were computed. Subsequently, differences between experimental and control groups were obtained in terms of SMD. Based on 13 parameters for each of six studies, out of the 78 required parameters, data were missing for six parameters which required imputation. None of missing data belonged to scores on rating scales.

The studies were heterogeneous ($Q=15.11$, d.f. = 5, $p<0.05$) for negative symptoms and so using the random-effects model, EGb was found to have moderate effect size in the treatment of negative symptoms of chronic schizophrenia (Fig. 1).

For total symptoms, the heterogeneity test ($Q=5.35$, d.f. = 5, $p>0.05$) was negative and the fixed-effects model demonstrated moderate effect size in favour of add-on treatment for total symptoms (Fig. 2). These effect sizes are marginally superior to the effect of antidepressant medications in the primary treatment

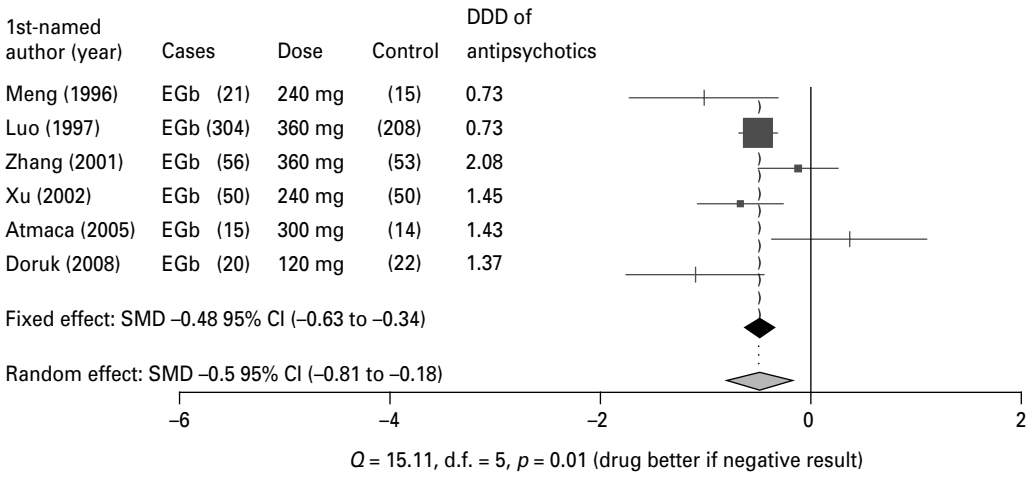

Fig. 1. EGb as adjunct therapy for negative symptoms of chronic schizophrenia. DDD, Daily defined dose chlorpromazine equivalent.

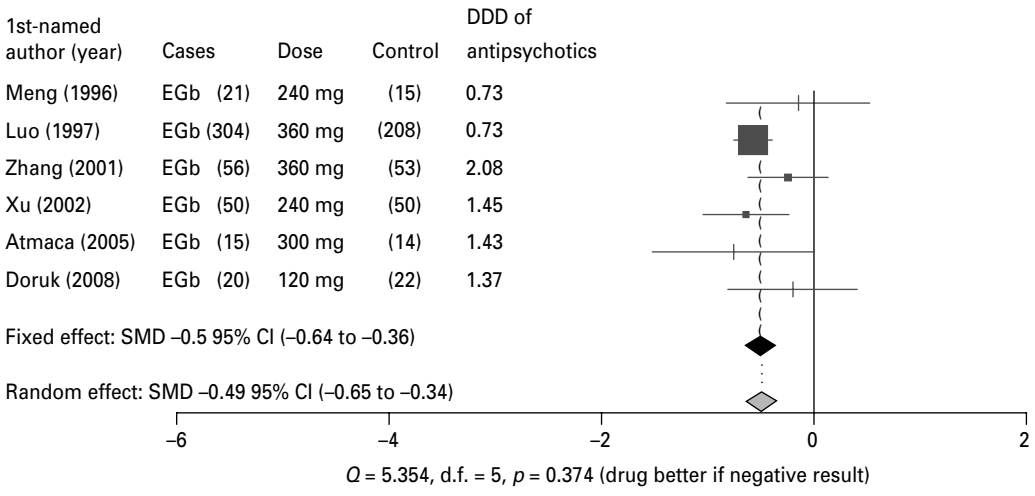

Fig. 2. EGb as adjunct therapy for total symptoms of chronic schizophrenia. DDD, Daily defined dose chlorpromazine equivalent.

of depressive illness (Kirsch *et al*. 2008) and within the range of effect sizes reported for second-generation antipsychotics for treatment of schizophrenia (Davis *et al*. 2003).

Stepwise regression using a generalized linear model (GLM) adopting Gaussian distribution between SMDs for negative symptoms with other numerical parameters did not reveal significant association. The same is also applicable for total symptoms.

Subgroup analysis for atypical (clozapine and olanzapine) and typical (chlorpromazine and haloperidol) antipsychotic groups is shown in Table 6. Since clozapine became available in China for clinical use in 1976 (Zhu & Yang, 2008), studies using mixed antipsychotic medications (Luo *et al*. 1997; Meng *et al*. 1996) might have used clozapine as a part of their treatment regimen and hence they were not assigned to either typical or atypical groups for the purpose of this analysis.

Studies included in this meta-analysis originated either from China or Turkey and a subgroup analysis was performed to test regional differences and is displayed in Table 7.

Sensitivity analysis

Out of the six studies, EGb was effective in four for negative symptoms and in two for negative symptoms in the treatment of chronic schizophrenia. The estimated effect size of 0.5, assuming 10% spontaneous improvement, yielded an odd ratio of 2.5 (Table 4) and number needed to treat (NNT) of 9 (Schünemann *et al*.

Table 6. Typical and atypical subgroup analysis

	Q	d.f.	*p*	Model	SMD	95% CI	*p*
Chlorpromazine and haloperidol							
Negative symptoms	3.79	1	>0.05	FEM	−0.38	−0.66 to −0.10	<0.05
Total symptoms	1.97	1	>0.05	FEM	−0.43	−0.71 to −0.16	<0.05
Clozapine and olanzapine							
Negative symptoms	8.52	1	<0.05	REM	−0.38	−1.81 to 1.06	>0.05
Total symptoms	1.28	1	>0.05	FEM	−0.42	−0.89 to 0.06	>0.05

CI, confidence interval; FEM, fixed-effects model; REM, random-effects model; SMD, standardized mean difference.

Table 7. Regional variation

	Q	d.f.	*p*	Model	SMD	95% CI	*p*
Studies conducted in Turkey							
Negative symptoms	8.52	1	<0.05	REM	−0.38	−1.81 to 1.06	>0.05
Total symptoms	1.28	1	>0.5	FEM	−0.42	−0.89 to 0.06	>0.05
Studies conducted in China							
Negative symptoms	6.57	3	>0.05	FEM	−0.49	−0.63 to −0.34	<0.05
Total symptoms	3.93	3	>0.05	FEM	−0.51	−0.66 to −0.37	<0.05

CI, confidence interval; FEM, fixed-effects model; REM, random-effects model; SMD, standardized mean difference.

2008), anticipating 13% improvement from baseline severity score. Using alternative *r* values did produce different effect size and heterogeneity, but did not have impact on statistical significance for negative symptoms ($r=0.1$, SMD $=-0.43$, NNT $=11$; and $r=0.9$, SMD $=-0.71$, NNT $=6$) and total symptoms ($r=0.1$, SMD $=-0.38$, NNT $=13$; and $r=0.9$, SMD $=-0.84$, NNT $=5$). We tested for publication bias with the assumption that non-significant studies were not published. The 'trim and fill' method revealed no publication bias for negative symptoms or change in its effect size; and two publication bias (Doruk *et al*. 2008; Meng *et al*. 1996), for total symptoms with slight increase in effect size to −0.54. We also analysed the results assuming that there might be bias in cross-cultural publication even for negative outcomes and found the same result for total symptoms with the same two filled studies; and for negative symptoms, there was a marginal reduction in SMD to −0.45 with one filled study (Doruk *et al*. 2008).

Conclusion

One of the required standards in clinical trials on the efficacy of treatment is the assurance of the quality of the products being investigated. All trials included in the analysis used standardized ginkgo preparation EGb as an add-on therapy and were compared against a placebo except in one study (Atmaca *et al*. 2005). Sample selection criteria were consistent with diagnosis of chronic schizophrenia using established criteria. Assessment of change in clinical symptomatology was performed using established rating scales for total and negative symptoms. All trials lasted ⩾8 wk. Three of studies were double blind, two single blind and one was open label. Baseline DDD among these studies varied between a range of about 0.7–2. The overall effect size for treatment of total and negative symptoms are medium (Cohen, 1988) perceived as 'visible to the naked eye' (Coe, 2002). Association of underlying variables with therapeutic outcome could not be established applying regression analysis probably because of the small number of studies in this analysis. The finding of this study is at variance with the previously published meta-analysis for negative symptoms scores on SANS (Rathbone *et al*. 2005, 2007). Some caution should be taken to interpret the result on total score as scores of two studies on SAPS were treated as equivalent to scores on total psychopathology on the ground of high correlation (Gur *et al*. 1991).

Effect sizes for negative symptoms, individually for chlorpromazine and clozapine studies, were statistically significant while those of olanzapine and

haloperidol were not. For the total symptoms, it was only chlorpromazine group which responded to the add-on therapy. Efficacy of the add-on therapy was also analysed if difference emerged for typical *vs*. atypical subgroups (Table 6). This showed that EGb is effective only when added to typical antipsychotic medications. This finding should be treated only as indicator due to sample size limitation in the atypical subgroup.

Around 90% of the total sample belonged to the Chinese population with the remainder coming from Turkey. Further analysis of data revealed statistically significant moderate effect size for both negative and total symptoms for studies conducted in China (Table 7). One of the explanations for lack of significant effect size for studies conducted in Turkey might be attributed to the small sample size in this subgroup.

The interpretation of results should take account of heterogeneity among the trials. For example, one of the studies (Luo *et al*. 1997) with a relatively large sample size did not account for drop-outs of 22 cases in the ginkgo group and 11 in the placebo group and it is uncertain if cases fulfilled the criteria for the treatment of resistant schizophrenia, i.e. failing to respond to two antipsychotics. The severity of total symptoms in one of the six studies (Meng *et al*. 1996) was noticeably lower than the other studies in this review. Another study (Doruk *et al*. 2008) does not give information about duration of treatment with clozapine before inclusion in the trial and progressive improvement in negative symptoms could be attributed to the continuing treatment with clozapine. Two of the studies (Meng *et al*. 1996; Xu *et al*. 2002) did not carry the observation forward despite the drop-outs. Due to limited number of trials, we adopted the modified criteria to include the studies which were not double blind.

Although there are several reviews using ginkgo on various conditions, none applies the meta-analysis technique about its usage in schizophrenia. Despite some limitations as described above, this review appears to be first of its kind to summarize the results of randomized control trials. All included trials were conducted in the Eastern hemisphere where ginkgo is more likely to be used as a traditional medicine. Lack of interest by pharmaceutical companies and various regulations governing biodiversity law may impede initiation of a project on herbal medicines.

Although ginkgo may have therapeutic potential, it is uncertain which of its chemical ingredients or its combinations are ultimately responsible for its therapeutic response. Without further research it will remain uncertain as to whether or not antioxidant properties alone play a specific role in the aetiopathogenesis of schizophrenia. The unit of the antioxidant properties of a compound is described in terms of oxygen radical absorbance capacity (ORAC), which is equal to units of micromoles of trolox equivalents per 100 g substance in question. A widely used dose of ginkgo of 360 mg from its most potent preparation will give 5000 ORAC a day (Mantle *et al*. 2003). If only ginkgo's antioxidant activity is of exclusive significance then there are other products which can provide similar or better ORAC values. For example, fruit consumption of 'five a day' can give up to 1750 ORAC units, or alternatively, a huge amount of ORAC units can be obtained simply by consuming spiced foods like Indian curries (48504 ORAC) with usual ingredients like clove (314446 ORAC), cinnamon (267536 ORAC), turmeric (159277 ORAC), cumin seeds (76800 ORAC) and kidney beans (8459 ORAC) (USDA, 2007). Further research work is needed to tackle these questions.

This study aimed to assess the effectiveness of ginkgo as an add-on therapy for chronic schizophrenia patients who are already receiving adequate doses of licensed antipsychotic medication of proven efficacy as a main line of treatment. For an add-on product to be of therapeutic relevance it should have an effect size that can be clinically observed and appreciated. Production and marketing of such preparations should have economical and commercial viability similar to that of antidepressants. The role of antipsychotic medication as polypharmacy is far from clear in a sizable proportion of symptomatic patients of chronic schizophrenia. Accordingly, even marginal improvement with add-on treatments has merit parallel to observed effect size from usage of antidepressant medications.

Generally speaking ginkgo appears safe (Birks & Evans, 2007) and whilst its use is justified on the grounds mentioned above; precaution should be taken to monitor side-effects, adverse effects and toxicity. Side-effects are similar to those found in common drugs like nausea, gastric irritation, diarrhoea, headache, dizziness and allergic rashes. Ginkgo acts as an anti-platelet factor and exerts a synergistic effect with the monoamine oxidase inhibitor group of drugs (Diamond *et al*. 2000). Its use should be avoided with warfarin and should be discontinued before surgical procedures. A chemical called gingotoxin is found in uncooked ginkgo seeds and if consumed in large quantities can induce seizure activity (NIH, 2008). The average monthly drug cost for each diagnosed case of schizophrenia varies between £8 for typical antipsychotics to £280 for atypical antipsychotics like

clozapine (Lewis *et al*. 2006) and the cost of 360 mg/d EGb will be £30 to £40. Usage of EGb in clinical practice may also broaden the choice for patients, physicians, psychiatrist and other mental health professionals.

The findings of this review have limitations due to the limited number of studies and relatively small sample sizes. The role of antioxidants in the pathophysiology of schizophrenia warrants further clinical trials as well as laboratory-based research work. There is a need to exploit the expertise of native users and traditional practitioners. Currently, we are some distance from achieving these objectives; however, people and cultures who have belief in and evidence of experience from usage of ginkgo will continue to use this for the foreseeable future.

Main learning points

(1) EGb has statistically significant moderate therapeutic benefit with acceptable safety limits as an add-on therapy for treatment of total and negative symptoms of chronic schizophrenia.
(2) Available evidence indicates that, with some precautions, ginkgo is safe to use.
(3) Inclusion of this drug in local and national formularies will expand the choice available to patients and practitioners.

Suggestions

(1) More randomized, double-blind trials in chronic schizophrenia with control on confounders that may influence antioxidant properties of ginkgo.
(2) Further research in the area of drug interactions with psychotropic medications.
(3) Further research is needed in the area of phytochemistry and the development of alternative cost-effective formulations.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/pnp).

Acknowledgements

The authors gratefully acknowledge the assistance of Dr N. Kar, and the support provided by the Quality of Life Research and Development Foundation in preparation of the manuscript.

Statement of Interest

None.

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