GINGKO BILOBA ROLE IN PATIENTS WITH ALZHEIMER'S

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ABSTRACT

In the treatment of central nervous system and cardiovascular illnesses, Ginkgo biloba extract (GBE) has been extensively employed. A total of 17 preclinical studies and 20 clinical trials examining the therapeutic efficacy of GBE against Alzheimer's disease (AD) were retrieved from electronic sources; however, no systematic review has been undertaken. Meta-analysis of the AD-related pathological characteristics or symptoms was carried out by extracting the data from the reports and conducting Morri's water maze cognitive function evaluations on 45 animals treated with GBE in six studies. In multiple experiments involving rats and mice, GBE was shown to minimize escape latencies (I2 > 70%, p 0.005). There were eight clinical studies with a total of 2100 participants. GBE increased the SKT and ADAS-Cog scores in early-stage Alzheimer's patients following long-term administration of high dosages and long-term administration. The research has two evident limitations: a lack of sample size calculations and low procedure quality. Preclinical and clinical findings, however, point to the necessity for future large-scale clinical studies in order to explore the effects of long-term GEB treatment on early-stage Alzheimer's disease (AD).

KEYWORDS: Ginkgo biloba extract; Alzheimer's disease; clinical trial; meta-analysis

INTRODUCTION

AD, or Alzheimer's disease, is a debilitating, age-related, and ultimately fatal illness of the nervous system. As of 2019, the Alzheimer's Disease International (ADI) estimates that more than 50 million people globally have dementia, and they project that the number will climb to 152 million by 2050, which would have a significant impact on both society and the economy. There are no viable therapies for Alzheimer's disease at this time. Developing a treatment for Alzheimer's disease that works will benefit millions of individuals in two ways: directly by enhancing their health, and indirectly by lessening the strain on health systems.

When it comes to Alzheimer's disease pathogenesis, the two primary structural alterations in the brain are amyloid plaques and neurofibrillary tangles. Amyloid hypothesis and tau hypothesis are the two most widely recognized explanations for the onset of Alzheimer's disease. "Secretase" is the mem-brane protease that cleaves the amyloid- precursor protein (A PP), and A aggregation is the primary component of amyloid plaques in Alzheimer's disease patients. Another important cause of neurofibrillary tangles in Alzheimer's disease is hyperphosphorylated tau aggregation. However, at this point in time, there is no treatment for AD that can reverse the pathological alterations or disease progression. A disease-modifying medication is urgently needed to halt the course of Alzheimer's disease, according to current studies.

Ginkgo biloba, a well-known Chinese herbal remedy, has been used for centuries. Dr. Willmar Schwabe created a standardized ginkgo biloba leaf extract (GBE) in the 1970s that included various pharmacologically active components (Karlsruhe, Germany). The extraction solvent is acetone (60 percent w/w), and the dry extract comes from G. biloba leaves (35–67:1). More than 20 percent of the extract is made up of ginkgo flavonoids (such as quercetin, kaempferol, and isorhamnetin), 5–7 percent terpene lactones (ginkgolides A, B, and C), and less than 5 PPM of the acid ginkgoid acid. Flavonoids and terpenoids are the primary components in standardized gingko biloba extract. It's possible that these components are responsible for GBE's antioxidative, anti-inflammatory, and antiapoptotic effects in the treatment of Alzheimer's disease, which include: protection against mitochondrial dysfunction, amyloid genesis, and A aggregation; modulation of ion homeostasis and phosphorylation of the tau protein; and even the induction of growth factors. According to a number of studies, GBE dramatically enhanced the Morris water maze test performance of mice with Alzheimer's disease (AD). GBE's anti-AD effectiveness has been studied in clinical studies since 1985. However, due to the small sample sizes and problems in the methodology, these findings are questioned as to their usefulness, correctness, and dependability. There is a pressing need for a

comprehensive evaluation of the scientific literature on the effectiveness of GBE in treating Alzheimer's disease.

The findings of our comprehensive meta-analysis of literature on preclinical and clinical research on GBE for AD therapy are summarized in this review. We also discuss the possible pathways of GBE's neuroprotection in AD based on animal studies. To get to the bottom of these discrepancies, we looked at both successful and unsuccessful clinical studies. A reference for the evaluation of the methodological quality of AD preclinical and clinical trials is also provided in this review.

LITERATURE REVIEW

Masayuki Hashiguchi, et al (2015) Ginkgo biloba's efficacy in the treatment of dementia is still debatable. Using meta-analysis, researchers set out to determine if Ginkgo biloba was effective and safe for use in individuals with dementia. We looked for controlled studies of Ginkgo biloba for dementia therapy in MEDLINE, Embase, the Cochrane databases, and Ichushi. Extracts of clinical data and outcomes were made. One hundred and eighty-one trials including 2381 patients using EGb761 extract fulfilled our inclusion criteria, which were 12 to 52 weeks and a daily dosage of more than 120 mg. To treat dementia, Ginkgo biloba extract may be taken in 240-mg daily doses, which are both safe and effective.

Tao Wang et al (2018) Due to its high starch content and functional component ginkgo biloba extracts, ginkgo is a potential culinary substance and herbal medication (GBEs). International research suggests that GBEs may successfully alleviate moderate cognitive impairment and Alzheimer's symptoms. However, the GBEs' limited bioavailability prevents them from being used in vivo, which is a major limitation. Ginkgo and corn starch-based nano-carriers have been produced, and GBEs have been loaded onto starch nano-spheres (SNPs) via nanoprecipitation.

Bruno Vellas et al (2012) Alzheimer's disease is on the rise, and we must act quickly to stem the tide. To see whether long-term usage of standardised Ginkgo biloba extract may reduce the occurrence of Alzheimer's disease in senior persons with memory problems, our goal was to conduct this study. GuidAge clinical trial participants aged 70 and older who reported memory problems to their primary care physician in France were randomised into two groups and given placebos in the double-blind, placebo-controlled GuidAge clinical trial. Using a computer-generated randomization sequence, we assigned individuals in a 1:1 ratio to receive either 120 mg of standardised ginkgo biloba extract (EGb761) twice day or a matching placebo. Participants, researchers, and other members of the study team were all kept in the dark about which group they belonged to. For the duration of the study, participants were monitored by primary care doctors and experts in memory centres. The log-rank test was used to compare individuals who got at least one dosage of the study medicine or placebo with those who received a placebo. On average, we administered 1406 doses of Ginkgo biloba extract to individuals between March 2002 and November 2004, while on average, we administered 1414 doses of placebo to participants throughout same time period. The risk of developing probable Alzheimer's disease was not proportional over the course of the study's five-year follow-up period, with 61 of the ginkgo group's participants diagnosed (12 cases per 100 person-years), while only 73 of the placebo group's participants were diagnosed (14 cases per 100 person-years; HR 084, 95 percent CI 060-118; p=0306) Alzheimer's disease progression was unaffected by long-term usage of standardized ginkgo biloba extract in this study.

Masayuki Hashiguchi, et al (2015) Ginkgo biloba's efficacy in the treatment of dementia is still debatable. Using meta-analysis, researchers set out to determine if Ginkgo biloba was effective and safe for use in individuals with dementia. We looked for controlled studies of Ginkgo biloba for dementia therapy in MEDLINE, Embase, the Cochrane databases, and Ichushi. Extracts of clinical data and outcomes were made. Standard mean differences (SMDs) in scores of the Syndrome Kurztest (SKT), Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) for cognitive efficacy, or odds ratios (ORs) for dropout and adverse medication responses were used in the meta-analysis findings. One hundred and eighty-one trials including 2381 patients using EGb761 extract fulfilled our inclusion criteria, which were 12 to 52 weeks and a daily dosage of more than 120 mg. 9 of 13 trials were analysed, 7 of which employed the SKT and 2 ADAS-Cog (dose 120 mg, 26 weeks) scores as effectiveness criteria. There was a statistically significant difference between Ginkgo biloba and placebo in the change in SKT scores (SMD = –0.90 [–1.46, –0.34]), but two studies using ADAS-Cog did not show a statistically significant difference between ADAS-Cog and placebo (–0.06 [–0.41, 0.30]) in the meta-analysis of all patients. SMDs [95 percent CI] in SKT in the

combined AD and VaD subgroup (–1.07 [–1.66, –0.47]) and AD subgroup (–1.36 [–2.27, –0.46]) favoured Ginkgo biloba over placebo for the Alzheimer's disease (AD) and vascular dementia (VaD) subgroups. In the combined AD and VAD subgroup, the SMD in SKT score in 240-mg daily Ginkgo biloba groups was significantly bigger than with placebo (–0.71 [–1.28, –0.14]) Dropout rates weren't different between the two groups, although the Ginkgo biloba groups had considerably reduced side effect dropout rates than the placebo groups (OR = 1.72 [1.06, 2.80]).) groups. To treat dementia, Ginkgo biloba extract may be taken in 240-mg daily doses, which are both safe and effective.

MATERIALS AND METHODS

First, a search of the electronic databases, Web of Science and PubMed, was conducted to discover studies concentrating on the effectiveness of Gingko biloba extract on AD animal models published between 2000 and 2019. There were two key terms utilised in the article search: “Alzheimer” and “Ginkgo Biloba”. In addition, we used Google Scholar to get the top 200 results, which were then ordered by importance. Using the inclusion criteria, two reviewers (Liming Xie and Qi Zhu) independently screened the abstracts of all eligible publications (Table 1). When we couldn't agree, a third reviewer was brought in to look at the paper (Erjin Wang). For the ClinicalTrials.gov website, the clinical trial results were searched using three key terms, "Alzheimer disease" OR "Dementia" AND "Gingko biloba," as well as four key phrases, "clinical trial," "Alzheimer disease" OR "Dementia" AND "Gingko biloba," in Google Scholar.

Table 1. Inclusion and exclusion criteria for selecting preclinical articles.

Inclusion Criteria:
Parallel experiments were conducted to evaluate the effects of EGB761 on AD protection in vivo.
Laboratory animals of any species, age, sex, or strain to induce AD models were included.
Any kind of EGB761 intervention compared with a control group was included. Dosages, methods of treatment, and curative times were not limited.
Exclusion Criteria:
Duplicated references; articles with incorrect and incomplete data; no access to the databases; review articles, comments, letters, and case reports.

Selection Criteria

Preclinical studies are chosen based on a set of inclusion and exclusion criteria laid forth in Clinical trial selection criteria are described in Table 2 in Table 1.

Table 2. Inclusion and exclusion criteria for selecting clinical articles.

Inclusion Criteria:
The clinical trials were designed as double-blind randomized placebo-controlled trials.
The patients, by age, sex, administration route and duration, dosage, were included in the trials.
Specific and reliable criteria for the AD assessment, such as the SKT and MMSE, were included.
Exclusion Criteria:
Duplicated references; repetitive clinical data; articles with incorrect and incomplete data; no access to the databases; review articles, comments, letters, and case reports.

DATA EXTRACTION AND ANALYSIS

Two researchers independently retrieved and tallied the data from the chosen papers once the screening was complete. Table 3 lists the details of the preclinical publications, including the following: This includes the first author's name and publication date, as well as the AD animal model; the types of animals utilised; the dose of treatment; the length of treatment; the method of administration; and the outcomes of the tests. List of clinical research papers' specific information is shown in Table 4: (1) Subject, author(s), and year of publication; (2) Location; (3) Criteria for inclusion; (3) Setting; (4) Duration; (5) Treatment; (6) Conclusions (7) sub-categories of interest; Participant demographics: (9) Age; (10) Withdrawal rate. Numerical values were derived from the graphs using Image J programme.

Review Manager 5.3 was used to perform a meta-analysis. We used a fixed effects model to analyse the data using a Q test and I2 statistics to determine the degree of heterogeneity. An I2 > 75 percent indicates substantial levels of heterogeneity, whereas I2 less than 25 percent indicates mild heterogeneity. Heterogeneity was determined to exist when the P value was less than 0.01.

Quality Assessment

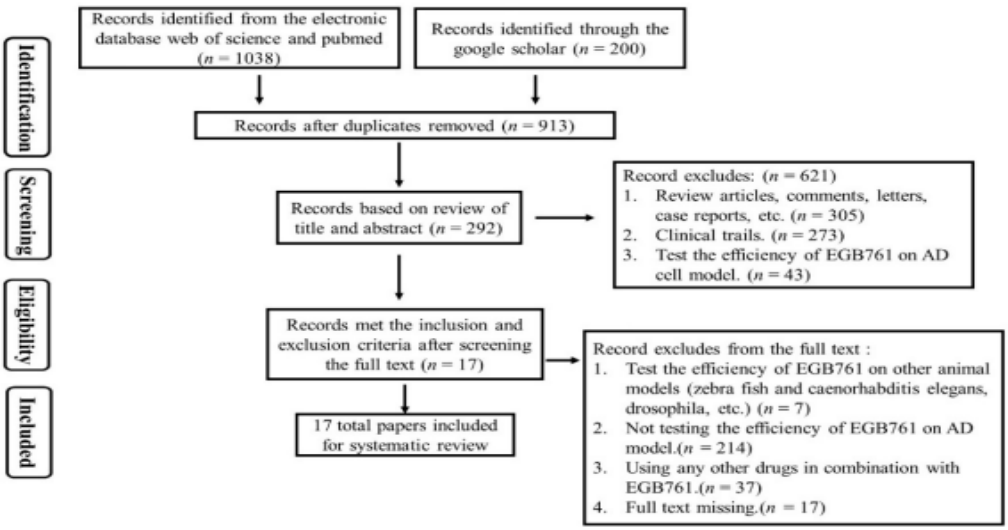
The CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Stroke) list was used to rate the methodological quality of the included papers. These qualities were also taken into consideration while developing the preclinical research assessment criteria. The following was the list of requirements:

For the study to be considered valid, it must meet the following criteria: (1) peer-reviewed journal publication; (2) random allocation of animals; (3) blind evaluation of outcomes (dose–response relationship); and (4) appropriate animal model, sample size calculation, and compliance with all applicable animal welfare regulations. A maximum of eight quality points might be awarded to each article. Another criterion, an ITT analysis, was added to the evaluation of the clinical trials (intent-to-treat analysis).

Study Selection

Screening of Preclinical Studies

More than 1000 publications were found in electronic databases such as Web of Science, PubMed and Google Scholar using a simple search. According on the following criteria, we eliminated 200 items from consideration: (3) The efficacy of the GBE was assessed in AD cell models (n = 43) and in reviews, comments, letters, and case reports (n = 305). Following that, 275 articles were omitted for the following reasons after thorough screening of the remaining 292 articles: First, the GBE was evaluated on non-human animal models (zebra fish, Caenorhabditis elegans, etc.), and the GBE was not tested on an AD model; second, other medications were utilized in conjunction with GBE; and third, the whole text was lacking. Lastly, we compiled a total of 17 papers.



The screening flow chart of the preclinical studies.

Recruitment Status of GBE Clinical Trials

Using the ClinicalTrials.gov website or Google Scholar, 98 clinical studies including G. biloba were found, as shown in Figure 2. 57 clinical studies have been completed, which is more than half of the total number. Unknown (n = 13), active but not recruiting (n = 2), terminated (3), withdrawn (3), enrolled by invitation (n = 1), recruiting (n = 14), and not yet recruiting (n = 5) were the statuses of the remaining. A meta-analysis and an evaluation of the methodological quality of 20 clinical trial-related papers were included in this systematic review.

Article Characteristics

An evaluation of the preclinical studies that were included Six mice and eleven rats were utilised in the preclinical investigations mentioned in the 17 papers. C57BL/6 mice, Tg2576 mice, TgAPP/PS1 mice, and TgCRND8 APP-transgenic mice were all employed in this study. There were five Wistar rats and six Sprague–Dawley rats utilised in the study. Research using just male animals were found in twelve of the articles, whereas studies using only female animals were found in four. For each article, the number of animals and their age ranged from 8 to 36. Table 3 provides the specifics. AlCl3 (n = 4), scopolamine (n = 1), hyperhomo cysteinemia (n = 1), and A 25–35 (n = 3) were used in half of the research to create their AD models. A unifying aspect of all toxin-induced AD models is that they resemble the clinical abnormalities and cognitive impairment of Alzheimer's disease, although each has its own limitations. AlCl3 (aluminium) has a large impact on enzyme activity, which in turn affects protein synthesis and neurotransmitter function. This approach also spends a significant amount of time simulating this effect.

Recruitment status of GBE clinical trials.

CONCLUSIONS

GBE's anti-AD characteristics in animal models were shown to be mostly due to numerous pathways, as demonstrated by a meta-analysis of preclinical investigations. GBE may enhance cognitive performance in the early stages of Alzheimer's disease by providing a high dosage (240 mg/day) and long-term treatment (over 24 weeks). However, these findings should be interpreted with care in light of the many methodological issues raised in the peer-reviewed papers. Clinical studies concentrating on individuals with early-stage Alzheimer's disease (AD), or a healthy elderly population with long-term GBE administration over 24 weeks at a high dose (>240 mg/day) may help determine if GBE may alleviate or prevent AD.

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