Ginkgo Biloba's Neuroprotective Potential in Alzheimer's Dementia

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Abstract:

Alzheimer's disease (AD), which is characterized by increasing cognitive impairment and neuroinflammation, is a growing global health concern. Ginkgo biloba extract (standardized as EGb 761) has attracted a lot of interest among botanical therapies because to its many neuroprotective qualities. The main reason for its effectiveness is the combination of terpene lactones and flavonoid glycosides, which work in concert to tackle the underlying pathophysiology of dementia via multiple different pathways. Ginkgo biloba's strong antioxidant capability is the primary basis of its neuroprotective potential. The extract reduces the oxidative stress that usually precedes neuronal death in AD patients by scavenging reactive oxygen species (ROS) and increasing the activity of superoxide dismutase. Additionally, Ginkgo biloba exhibits a special capacity to maintain mitochondrial integrity, which stabilizes cellular energy production and prevents pro-apoptotic signals from being activated. In addition to protecting cells, the extract modifies the amyloid cascade by preventing peptides from aggregating into harmful oligomers, hence lowering the "plaque load" that interferes with synaptic transmission.

According to clinical studies, ginkgo biloba is especially useful for stabilizing or delaying the deterioration of cognitive abilities and enhancing the ability of people with mild-to-moderate dementia to perform activities of daily living (ADL). The clinical data is still a little inconsistent because of variations in extract concentrations and patient demographics, even though it also improves cerebral microcirculation and lowers blood viscosity, offering a secondary vascular advantage. Ginkgo biloba ultimately functions as a clinically useful, well-tolerated adjunct therapy that tackles the complexity of neurodegeneration through a multi-target pharmacological approach, even though it is not a disease-modifying solution.

Keywords: Alzheimer disease, Ginko biloba: EGb761

Introduction:

Many people are curious about the differences between Alzheimer's disease and dementia. The general term "dementia" refers to a specific collection of symptoms. Symptoms of dementia include issues with language, memory, and problem-solving skills; trouble focusing; and finding it difficult to comprehend and communicate ideas [3]. Confusion is another symptom. impulsive behaviour and poor judgment, among others. The outcome is dementia symptoms of modifications to the brain[3]. Numerous distinct Dementia symptoms can be brought on by certain conditions.

Alzheimer's disease (AD) is currently the third most common cause of death in the US and one of the biggest global health issues. About 60–70% of cases of dementia are caused by Alzheimer's disease (AD), a neurodegenerative illness[8]. In 2018, the anticipated cost of treatment in the United States alone was $1 trillion.

The pathophysiology and processes of AD remain poorly known, despite the disease's high prevalence, the immense suffering it causes, and the strain it places on the patient's family. Therefore, it appears vital to look for solutions regarding the pathophysiology and management of AD[2]. Atypical metabolism of apolipoprotein E and

hyperphosphorylation of Tau protein, which manifests as senile plaques in the cerebral parenchyma, are the primary pathogenetic factors identified in the literature.

Numerous potential explanations for the pathogenic alterations seen in AD brains include neuronal death, excitotoxicity, inflammation, and oxidative stress[4]. Antioxidants, anti-inflammatory medications, cholinergic agents, estrogens, neurotrophic factors, and calcium ion channel antagonists are among the preventive medicines that have been suggested for the prevention and treatment of AD[1], but none of them have been shown to have a clear therapeutic impact.

On the other hand, EGb761 has long been believed to be "multivalent" and has been shown to have distinct profiles of action from a number of widely prescribed medications for AD[30,31]. Thus, EGb761 may be able to prevent or treat AD.

Signs of mild Alzheimer's disease:

A person with mild Alzheimer's disease may appear healthy, but they are increasingly having difficulty understanding their surroundings. The individual and their family frequently come to the realization that something is amiss gradually[32]. Issues may consist of:

1. Memory loss that disrupts daily life[32].
2. Loss of spontaneity and sense of initiative.
3. Planning or problem-solving difficulties.
4. Getting lost and wandering.
5. Changes in personality and mood.
6. An increase in hostility and/or anxiety.

At this point, Alzheimer's is frequently diagnosed.

Signs of severe Alzheimer's disease:

1. Not being able to communicate.
2. Lack of awareness of the environment or recent experiences.
3. Losing weight while having little desire to eat seizures[32].
4. overall physical deterioration, including issues with the skin, teeth, and feet.
5. Having trouble swallowing.
6. Groaning, moaning, or grunting.
7. An increase in sleeping.
8. loss of control over the bowels and bladder[32].

History:

The ginkgo biloba that is still present in the botanical garden of Utrecht was likely among the first to be brought to Europe in the 18th century (around 1730). Gothenburg wrote a poem in Heidelberg on September 27,1815, attributing the tree's glory to the fact that it was "Entrusted by Orient to his garden" and that it could be united into single entity (Gothe,1819).

A ginkgo (Ginkgo biloba) is regarded as a living fossil; did you know that? Of a group of trees that existed before dinosaurs roamed the planet, it is the only species still in existence. Over the past 180 million years, its genetic makeup has not changed.

15-million-year-old Gingko beckii fossilized logs embedded in the basalt cliffs can be seen if you ever get the chance to visit the Ginkgo Petrified Forest State Park in Washington state, which is close to the Columbia River Gorge and Wanapum Lake[7].

The trees, which were believed to be extinct, were found in Japan in 1691 by German physician and scientist Engelbert Kaempfer while he was employed by the Dutch East India Company.

***Figure* 1: Ginkgo biloba (Salisburia adiantifolia)**

Ginkgos endured in China's mountainous areas, where Buddhist monks revered them as sacred trees. After that, the monks brought trees to Japan to plant in the gardens of temples and palaces. In 1785, Philadelphia resident William Hamilton introduced the first three ginkgos to Philadelphia, Pennsylvania.

He planted two in his garden and gave one to his friend, William Bartram, Hamilton's trees no longer exist, but the one he gave to Bartram can still be seen today in Bartram's Garden in Philadelphia.

Plant Profile:

***Figure* 2: Ginkgo fruit plant**

The fan-shaped, bilobed leaves of the ginkgo biloba tree, which is prized for its beauty and longevity, change from green to golden yellow in the fall. *G. biloba* leaves are used in traditional Chinese medicine to treat neurological problems, circulatory disorders, and respiratory diseases. *G. biloba* leaves are also used as insecticides and fertilizer.

Extracts from G. biloba leaves are utilized as dietary supplements because of their possible health benefits[28], which have captured the attention of the global market since they have the ability to enhance health.

Glycosides and ginkgolides are among the pharmaceutically active compounds found in the leaves of G. biloba extracts[5].

Taxonomy:

Kingdom: Plantae

Clade: Tracheophytes

Clade: Gymnospermae

Division: Ginkgophyta

Class: Ginkgopsida

Order: Ginkgoales

Family: Ginkgoaceae

Genus: Ginkgo

Species: G.Biloba

Morphological features of Ginkgo biloba :

Ginkgo biloba's plant body is sporophytic, and the sporophyte's overall habit is similar to that of several conifers. The trees grow up to 30 meters in height and have a noticeable ex-current growth habit. Ginkgo tree exhibit an extremely erratic branching structure. The branches are dimorphic, meaning they consist of dwarf shoots, which are short branches with limited growth, and long shoots, which are of infinite growth with dispersed leaves. Long shoots can grow up to 50 cm in length in a year.

Dwarf shoots grow rather slowly. A dwarf shoot that is two to three centimeters long could be several years old. Sometimes it is difficult to distinguish between the two sorts of shoots; for example, a dwarf shoot may change into a long shoot, while a long shoot may occasionally change into a dwarf shoot for a year or two before returning to its previous state. The long shoots have deeply lobed foliage leaves, whilst the dwarf shoots have fewer lobed leaves that are occasionally nearly whole . According to Bierhorst (1971), the amounts of auxin generated in the apical meristems may be the cause of variations in the growth patterns of long and dwarf shoots.

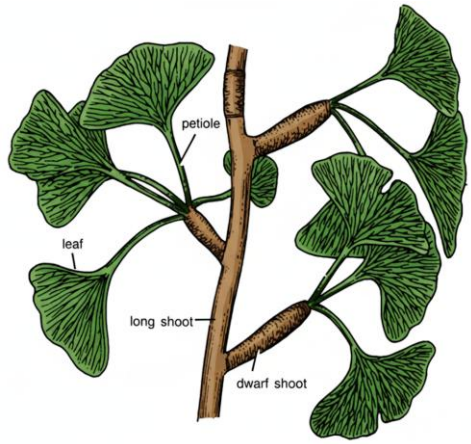

***Figure* 3: Ginkgo plant morphology**

Ginkgo biloba has a lengthy system of tap roots. Deep in the ground, the roots have several branches. The leaves are big, simple, petiolate, wedge-shaped or fan-shaped, with a narrow base and an enlarged apex. Their resemblance to the Maiden-hair fern (Adiantum) allows them to be identified as gymnosperms. The species was given the name "biloba" by Linnaeus (1771) because the leaves are typically bilobed. nevertheless, the tree also consistently has leaves with several lobes.

In contrast to the dwarf shoot, which may have sinuate or even whole leaves, the long shoot and seedlings have strongly bilobed leaves. They may be pale yellow, bright yellow or dark green in hue. The leaves have a typical dichotomous form of venation Ginkgo biloba's foliar epidermis also displays a few distinctive traits. The outline of epidermal cells is polygonal in the spaces between the veins and rectangular above them. The leaves only have stomata on their lower surface, making them hypostomatic.

Microscopical Description:

Table 1: Microscopy of Ginkgo biloba

PARTS	DESCRIPTION
Upper Epidermis	The upper epidermis is composed of one layer of cells that are subsquare or subrounded and have a thin, distinct cuticle covering them.
Collenchyma	Found only in mature and old leaves, it is arranged on the inner sides of the midrib's upper and lower epidermises.
Palisade Tissue	Located directly beneath the topmost layer of skin, this tissue is extended at right angles to the surface and frequently has an uneven appearance.
Spoongy Tissue	Mesophyll cells are smaller than palisade cells and have wide intercellular gaps between them.
Vascular Bundles	These are found at regular intervals throughout the lamina's width; they are collateral, with xylem dorsal and phloem ventral, encircled by fibers, and adjacent clusters of calcium oxalate.
Clusters Of Calcium Oxalate	spread across parenchyma cells.
Secretary Canals	Found in the mesophyll between vascular bundles, which are large and distinct.
Fiber Bundles	Vascular bundles are encircled by walls that have somewhat thickened.
Lower Epidermis	One layer of thin cuticle-covered cells that are subrounded or subsquare.

Phytochemistry and Phytoconstituent of Ginkgo biloba:

Biosynthesis and the resulting output are influenced by climatic, seasonal, and diurnal influences. The ginkgo plant's aerial portions and actively growing tissues are where the biosynthesis takes place[5]. The generation of flavonoid content throughout the entire annual vegetative cycle, from the early bud stage to the leaf fall, has not been impacted by these circumstances.

biloba leaves produce secondary metabolites in response to elevated ozone (O3); raised O3 was found to decrease isorhamnetin, condensed tannin, and phenolic contents while increasing quercetin and terpene concentrations 23% higher than control due to the level of reactive oxygen species (ROS). While the concentration of bilobalide grew by 220%, ginkgolide C by 69.6%, ginkgolide A by 34.1%, and ginkgolide B by 34.3%, the rise in terpene concentration is season-dependent, with the largest increase taking place in September.

Protocatechuic acid, p-hydroxybenzoic acid, vanillic acid, caffeic acid, p-coumaric acid, ferulic, chlorogenic acid, 6-hydroxykynurenic acid, ginkgolic acid, cardanols, cardol, and urushiol are among the phenolics and nonphenolics found in G. biloba leaves, along with ascorbic acid, D-glucaric acid, quinic acid, quinic acid, and

shikimic acid . 3.1% ginkgolides, 2.9% bilobalides, and 24% flavonoids are present in concentrated ginkgo leaf extract made from dried leaves[38].

The extract also contains high proanthocyanidins, polyisoprenoid-derived betulaprenols, flavan-3-ols, coumaroyl flavonol glycoside, 2-hexenal, ginnol, ginnon, ginkgolic, and organic acids (both nonphenolics and phenolics)[38], as well as anthocyanidins and organic acids that are crucial to its water solubility[13,5]. Monoterpenes and sesquiterpenes are found in ginkgo heartwood, while bilobol, ginkgolic acid, 4-methoxy-pyridoxine, and ginkbilobin are found in the seeds.

The phytochemistry, pharmacological activity, and applications of G. biloba have been the subject of more published publications in recent decades, and the tree is considered a paradigm for the study of plant ageing. Pharmacology, toxicology, and clinical studies of the neuroprotective value of ginkgo leaf extract are currently of interest.

Regulatory bodies in these nations help standardize the extract into dosage for safe human use as a herbal medication, and safety precautions are implemented. It is believed that the issues with clinical treatment of neurodegenerative illnesses may be resolved by the new and expanding research on the neuroprotective function of ginkgolides.

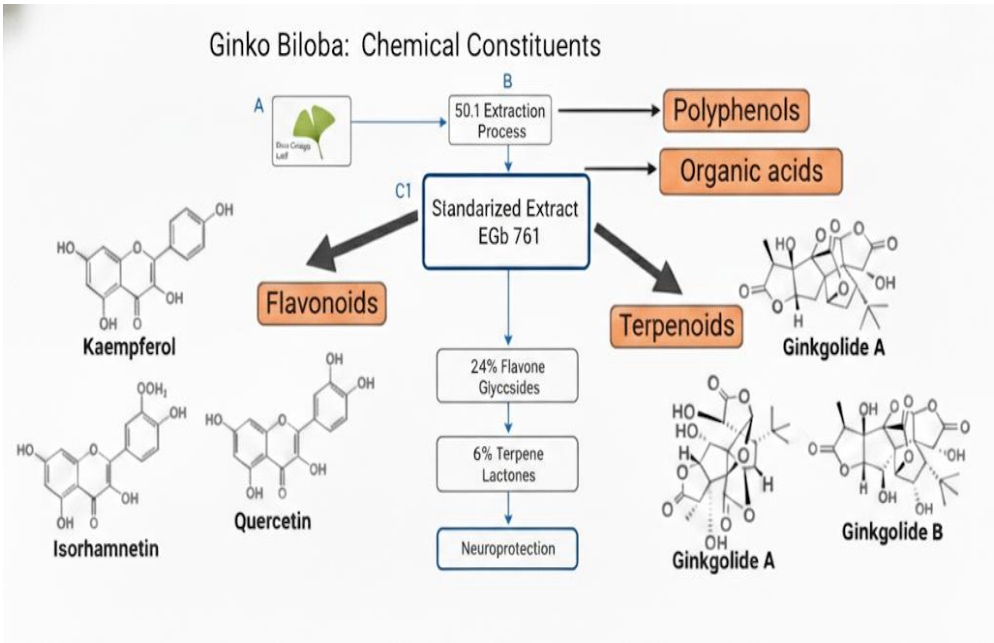

Figure 4: chemical constituents of Ginkgo biloba

Mechanism of Neuroprotection by EGb761:

Anti-inflammatory effect:

The neurological mechanism of AD has been linked to inflammation [9]. It has been discovered that pathologically sensitive areas of AD brains contain elevated levels of cytokines, acute phase reactants, and other inflammatory mediators[9]. It has been shown that EGb761 has anti-inflammatory properties[10,11]. The combined action of its flavonoid and ginkgolide constituents may be responsible for these effect[11].

Ginkgolides' ability to inhibit platelet-activating factor (PAF) may be linked to their anti-inflammatory properties. There is strong evidence that PAF regulates cytokines in inflammatory reactions. Rats given PAF intracerebroventrally may produce more leukotriene, especially leukotriene C4[12-14], a pro-inflammatory mediator[12,13]. PAF has a variety of roles in neuronal processes and brain development and can be generated in neurons after being stimulated by neurotransmitters like glutamic acid and N-methyl-D-aspartic acid (NMDA)[15].

In rats, intracerebroventrical injection of BN-52021 (ginkgolide B) considerably reduced the increase in cerebral fluid peptidoleukotriene levels caused by PAF[13,14]. In a fetal rat brain[33], BN-52021 may also lessen PAF-induced thromboxane B and eicosanoid synthesis. Our previous investigation demonstrated that ginkgolide B could totally prevent PAF-induced reduction of cell viability in SH-SY5Y cells[34], which supports these conclusions. Ginkgolides A and B were found to have PAF-antagonistic activity as well as to decrease the production of pro-inflammatory cytokines such as interleukin-1 and tumor necrosis factor-alpha in lipopolysaccharide-stimulated rat cell lines.

However, lipooxygenase, which is involved in the production of leukotrienes, is said to be inhibited by the flavonoid portion of EGb761. Furthermore, we have shown in a recent study that quercetin, a flavonoid component of EGb761, may also contribute to the PAF-antagonist effect of EGb761.

Antioxidant activity:

It has long been believed that oxidative stress is a key factor in the pathophysiology of AD. The idea that EGb761's beneficial effects are mostly caused by its ability to scavenge free radicals is backed by a large number of in vivo and in vitro investigations. Pretreating cerebellar granules, for instance EGb761-treated cells successfully reduced oxidative damage caused by H2O2/FeSO4.

As an alternative Neuroblastoma cell line N2a that expresses Aβ and transgenic Caenorhabditis elegans, EGb761, was found to be able to considerably lessen the induced Reactive oxygen species (ROS) concentrations associated with In addition to directly reducing ROS, EGb761 may also stabilize the cellular redox state by enhanced antioxidant enzyme activity and protein content[20]. As an example, EGb761 was found to be able to increase the activity of superoxide dismutase (SOD), catalase, and protein levels.

In the rat hippocampus and ileum. Additionally, glutathione (GSH) reductase activity and Two enzymes essential for the synthesis and reduction of GSH, gamma-glutamyl cysteinyl synthetase, were additionally improved by EGb761 It is proposed that the flavonoid fraction is primarily in charge of the antioxidant qualities of EGb761. It is suggested that the flavonoid fraction uses direct scavenging to produce antioxidant effects[20].

Increases in antioxidant proteins like SOD, prooxidant transitional metal ion chelation, and ROS and GSH. It is believed that flavonoids' antioxidant properties are due to their polyphenol composition[21]. Two flavonoid components with this structure, quercetin and myricetin, particularly successfully prevent tertbutyl hydroperoxide from oxidizing[37].

On the other hand, there is ongoing debate over terpene lactones' antioxidant capacity. The ability of bilobalide and ginkgolides B, C, and J to scavenge superoxide has been shown to be inconsistent, whereas ginkgolide A has been shown to be incapable of doing so.

It is possible to attribute the variation in the terpene lactones' antioxidant activity to variations in the experimental models and the kind of oxidative stress that was employed[36,37].

Figure 5: mechanism and effects shown by Ginkgo biloba

Extraction of Ginkgo Oil:

As it influences recovery efficacy, extraction is a crucial downstream process in ginkgols fraction microheterogeneity from GB. The connection between a solvent's capacity to dissolve ginkgols and their solubility. impacts the extraction of ginkgols and the distribution coefficient.

Therefore, selecting a proper solvent for extraction is crucial[16]. Additionally, when choosing solvents, solubility, safety, selectivity, and cost should be taken into account[19,20].

According to the analogies and intermiscibility rule, the polarization of the solvent is important since it affects the partition system's selectivity, allowing for the distribution of several bioactive ingredients in the extract[16,17]. First, the GB (dry, 100 g) was extracted to produce petroleum ether (PE, 10.5 g) extract, which was separated using column chromatography (45 to 75 μm) and eluted with EtO2-.To create a GA fraction (5.6 g), use HCO2H-PE (11: 1: 89, v/v/v).

A combination of GA homologs (purity >90%) was obtained following two iterations of the separation process[19]. Before evaluating the ginkgol's potential for medicinal use, the ginkgol must be extracted. Therefore, selecting the right solvent will aid in obtaining the desired analyte.

petroleum ether was utilized in the initial step of ginkgol extraction, however, alternative solvents can be examined and compared with increasing the extraction yield[18]. Deep eutectic solvents (DES) have been proposed as sustainable alternatives for standard organic extractants for the extraction of bioactive substances. DES was utilized to extract GA.

Before extracting GA from GB leaves or sarcotesta, sample pretreatments including milling and drying are frequently used to minimize particle size. The extraction kinetics and, thus, the yield of ginkgols can be improved by increasing the active surface[22].

It should be mentioned that ginkgols' extractability and permeability (solubilization and mass transfer) can be improved by enzymatic pretreatment (amylase, cellulases, pectinases, hemicellulases, etc.) or various

combinations of enzymes, ultrasonic, and ball milling, which breaks down the cell wall and releases the network of wall-bound biomolecules. While extracting ginkgols, temperature plays an essential role.

Theoretically, rising temperatures increase the solubility of lipids by reducing the cohesiveness and adhesion between oil-matrix molecules and oil molecules, speeding up lipid transport. However, the disintegration of thermolabile compounds and the loss of extractants at high temperatures could result in the extraction of unwanted compounds.

The next step will be the decarboxylation of GA, which will be heated for two hours (135–) after being combined with Ca(OH)2 at a ratio of 0.02:1 (g/g). 140°C). The mixture will be filtered, condensed, then extracted with PE (60–90 C) to create brown oil (ginkgol) after it reaches room temperature.

A mixture of ginkgol homologs will be produced by further refining this oil using column chromatography (250 ~ 21.2 mm, 10 μm). Two pumps (WK500LC-500P) linked to an injector (1 mL loop) and an ultraviolet detector were used to separate the ginkgol[18,16]. The ginkgols were then separated using preparative HPLC. An ideal separation procedure on a Welch Ultimate AQ-C18 HPLC column was attained at a flow rate of 24 mL/min using MeOH-H2O (86:14, v/v) as the eluent.

Consequently, in ideal conditions, the five main ginkgol peaks were almost separated by baseline, and the separation took 68 minutes. Because the variables affecting ginkgol's retention can vary widely, it is typically difficult to examine the chromatographic behavior of complicated combinations. Because of this, it is challenging to decide which of the several combinations will yield the best outcomes.

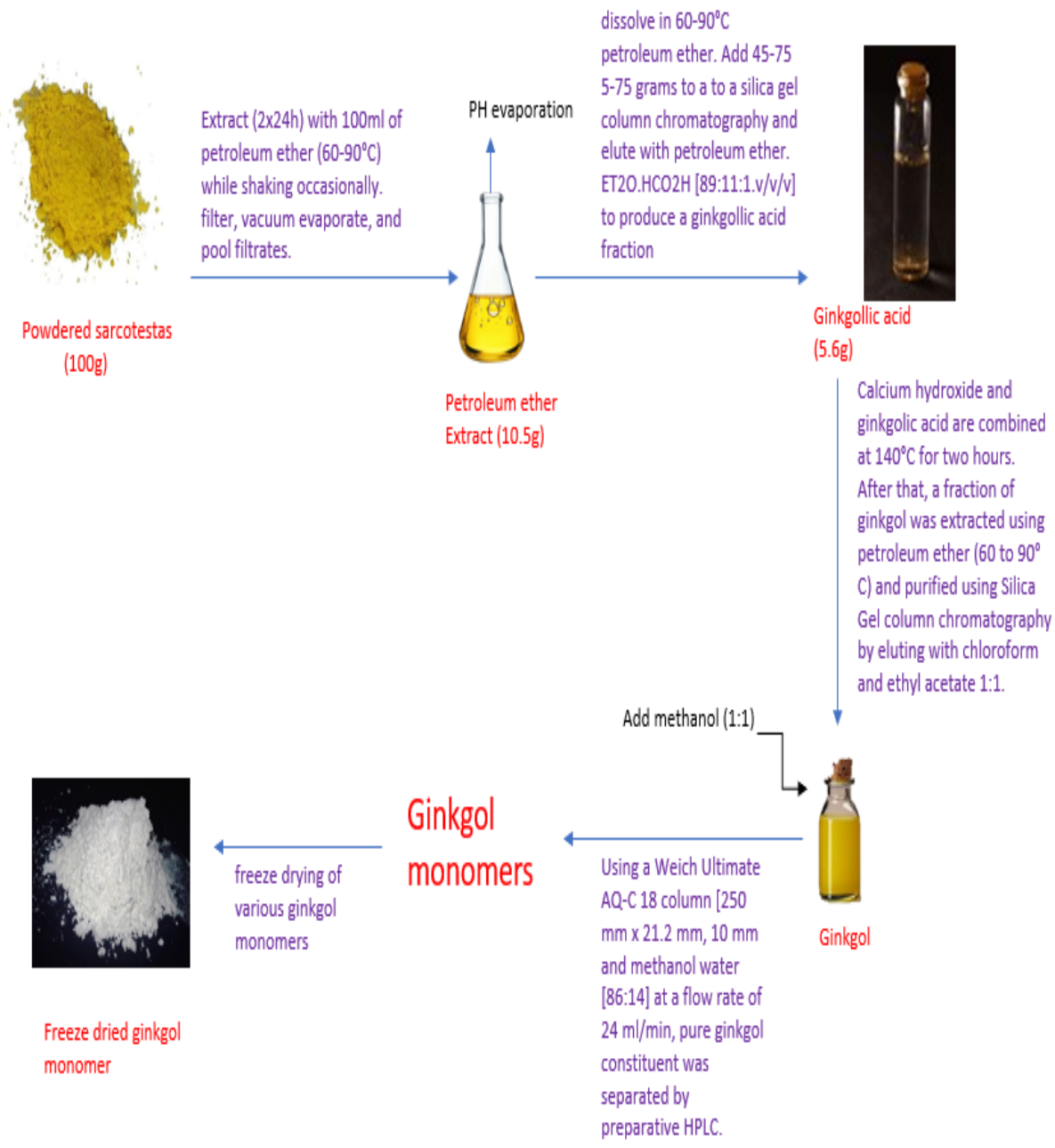

Figure 6: Extraction process of Ginkgol

Ginkgo Biloba and Alzheimer Disease and Dementia: Clinical Trials

Table 2: The negative results of clinical trials of AD with EGb.

Study	Patient gender [male/female]	Age	Ginkgo biloba dose mg/day	Duration	Inclusion criteria	Outcome measures
Subhan & Hindmarch [1984]	8M	32	120; 240; 600	one dose	Healthy volunteers	CFF; CRT; LARS
Schaffler & Reeh [1985]	8 F	27.3	80	2 weeks	Healthy volunteers	Complex choice test battery of oculomotor and cardiorepiratory test
Stough et al. [2001]	26F; 24M	30.4	120	30d	Healthy volunteers exclude head injury, intellctual developmental disability, current use of any other medications.[35,30]	Digit Symbol Substitution Test; Speed of Comprehension Test; Symbol Digit Modalities Test; Digit Span ;Trail Making Test[25]
Mattes and Pawlik[2004]	EGb : 11F, 10M	24.1	184.5	13 w	Healthy volunteers of 18-40 yrs of age body weight of 45.5 -91 kg no known medical condition, no chemosensory abnormalities[35].	Affect grid ;POMS
Burns et al.[2010]	EGb;54M	31.1	120	12w	Healthy volunteers exclude taking cardiovascular , anticoagulant, antidepressant and antianxiety medication exclude any injury impaired cognitive tests[23].	____

Table 3: The Positive results of clinical trials of AD with EGb.

Study	Paitents Gender [Male/Female]	Age	Ginkgo Biloba Dose Mg/Day	Duration	Inclusion Criteria	Outcome Measures
Wesnus et al.[1987]	EGb: 8F ; 19M	70.7, 71.3	120	8w ; 12w	Elderly paitents have mild signs of imapiairment in everyday function on the Crichton Geriatric Rating Scale.	Benton visual retention test ; Digit span test; psychometric test battery.
Rai et al [1991]	Egb: 8F, 4M	73.4, 78.3	120	12w; 24w	Age >50 yrs have signs of mild to moderate memory impairment classified by NINCDS - ADRDA	Folstein Mini-mental state examination; Kendrick battery; Digit recall task[27].
Kanowski et al. [1997]	EGb: 52F 27M	EGb: male: 69.7 Female : 70.2	240	24w	Age ≥ 55 years SKT score of 6 to 18 MMSE score of 13 to 25.	CGI (p<0.05);SKT(p
Rigney et al.[1999]	14F;22M	43.6	120;150; 240;300	2d	Asymptomatic volunteers Good physical and mental health Free from concomitant medication[23,24].	Short-term memory test (p<0.05) & reation times [p<0.05]
Le bars et al.[2000]	EGb:65F; 55M	68	120	26w	Age≥45yearsAdiagnosisofuncomplicated AD or multi-infarct dementia MMSE score of 9 to 26 Global Deterioration Scale score of 3 to 6	ADAS cog [p<0.05]; GERRI [p<0.01].
Kanowski et al. [2003]	EGb: 72 F 34M	72	240	24w	Age≥55yearsSufferedfromdementiaof the Alzheimer's type or multi-infarct dementia SKT score of 6to 18 MMSE sore of 13 to 25	SKT[p<0.01] CGI[p<0.01] ADAS-cog [p<0.01]
Hoerr & Nacu [2016]	EGb: 139 F 61 M	65.1 64.9	240	24w	Scored ≤35 in the Test for the Early Detection of Dementia with Differentiation from Depression SKT score of 9to23 NPI score ≥ 6.	NPI [p<0.01]; SKT[p,0.01]

Conclusion:

In modern pharmacology, ginkgo biloba—specifically, the standardized extract EGb 761 represents an individual "living fossil" that provides a multifaceted strategy for Alzheimer's disease treatment. Ginkgo's therapeutic strength, in contrast to single-target synthetic drugs, is found in its diverse chemical profile. Ginkgolides, particularly Ginkgolide B, act as strong anti-inflammatory agents by opposing the Platelet-Activating Factor (PAF), while flavonoid glycosides offer strong antioxidant defense.

According to the research, ginkgo biloba actively disrupts the underlying pathophysiology of neurodegeneration rather than merely masking dementia symptoms like memory loss and personality abnormalities. It provides a strong defense for aging neurons by improving cerebral blood flow, regulating mitochondrial activity, and reducing the harmful effects of amyloid-beta plaques. The extract exhibits great promise in enhancing the quality of life and cognitive stability for those in the mild-to-moderate stages of Alzheimer's disease, even if severe Alzheimer's poses difficulties that no single botanical can now overcome.

In order to guarantee a high concentration of advantageous terpenes while reducing unfavorable ginkgolic acids, complex extraction techniques—using sophisticated solvents and decarboxylation techniques—are ultimately necessary for the successful integration of Ginkgo biloba into therapeutic practice. Ginkgo biloba is an essential link between ancient herbal knowledge and contemporary neuroprotective medicine as a well-tolerated supplementary medication.

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