

## A COMPREHENSIVE REVIEW OF GINKGO BILOBA EXTRACT'S NEUROPROTECTIVE EFFECTS IN PARKINSON'S DISEASE

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### ABSTRACT

A progressive neurodegenerative condition, Parkinson's disease (PD) involves the gradual loss of dopaminergic neurons in the substantia nigra, located in the midbrain and basal ganglia. This degeneration leads to a decline in dopamine levels. Initially, PD impacts areas such as the dorsal motor nucleus of the vagus nerve and the olfactory bulbs, later progressing to the locus coeruleus and substantia nigra. In advanced stages, cortical regions also become involved, complicating the disease's pathophysiology. Ginkgo biloba extract, derived from the ancient Ginkgo biloba tree, has shown promise in addressing neurodegenerative conditions, including Alzheimer's and Parkinson's disease. Key compounds in GBE, such as EGb761 and Ginkgetin, possess notable antioxidant, anti-apoptotic, and neuroprotective properties. This review explores the bioactive components and their role in neuroprotection and other

activities demonstrated by ginkgo biloba extract.

**KEYWORDS:** Ginkgo biloba extract, EGb761 & Ginkgetin, basal ganglia, Nigro-striatal pathway.

### INTRODUCTION

James Parkinson provided the first description of Parkinson's disease in the year 1817 and 200 years later the study revealed PD is mainly seen in elderly people in the age group above 50. Neurotoxins and gene mutations are the underlying cause of PD. Underlying symptoms of

Parkinson's disease are, Hypokinesia or Akinesia (partial or complete loss of muscle movement), Bradykinesia (suppression of voluntary movements), muscle rigidity, it becomes difficult to start and stop a voluntary movement, persons with muscle rigidity walk with shuffling gait. Tremors start at rest; they begin in the hands (pill-rolling tremors) and later on, diminish during voluntary movements. PD is also associated with dementia, depression, hallucinations, and autonomic dysfunction due to the degeneration of non-motor parts. Patients also have a variable degree of cognitive impairment problems remembering things and solving problems.

### **GINKGO BILOBA EXTRACT**

The Ginkgo biloba plant has many medicinal uses mainly the leaves of the ginkgo biloba have many medicinal values, Preparation and standardisation methods of ginkgo biloba leaves have already been told by Dr Willmar Schwabe Pharmaceuticals (Germany). Ginkgo biloba is considered a relic species since it is the sole surviving species in the Ginkgoales order (class Gymnospermae). Originating over 200 million years ago, this dates back to the era of the dinosaurs.<sup>[1]</sup> Moreover, Ginkgo biloba has been a key component of Chinese medicine for 5,000 years, primarily used to treat conditions like asthma and bronchitis.

Ginkgo Biloba has been found to inhibit the activity of Platelet-activating factor (PAF), a phospholipid came out from cell membranes. PAF is responsible for inducing platelet aggregation, thrombus formation, neutrophil degranulation, as well as the production of reactive oxygen species (ROS).It also increases micro-vessel permeability and causes bronchoconstriction. These effects are countered by Ginkgolide B, which prevents erythrocyte aggregation and blocks PAF from binding with platelets. Additionally, Ginkgolide B hinders PAF's influence on eosinophils, such as chemotaxis, degranulation, adhesion, and cytotoxicity, all of which contribute to inflammatory responses. GBLE (Ginkgo Biloba Leaf Extract) is known for its various pharmacological properties, attributed to one or more active components. Reported effects of GBLE include antioxidant activity as a free radical scavenger, relaxation of vascular walls, improved blood flow or microcirculation, and stimulation of neurotransmitters, with benefits for cerebrovascular disorder symptoms.<sup>[2]</sup>

The Ginkgo biloba leaf extract contains comprising of 24% flavonoid glycosides (quercetin, kaempferol and isorhamnetin), 6% terpenoids, 3.1% ginkgolides(A, B, C, and J) and 5 -10% organic acids including hydroxy kynurenic, kynurenic, protocatechuic, p-hydroxybenzoic, and vanillic acids and 2.9% bilobalide, some of which are less commonly found. These

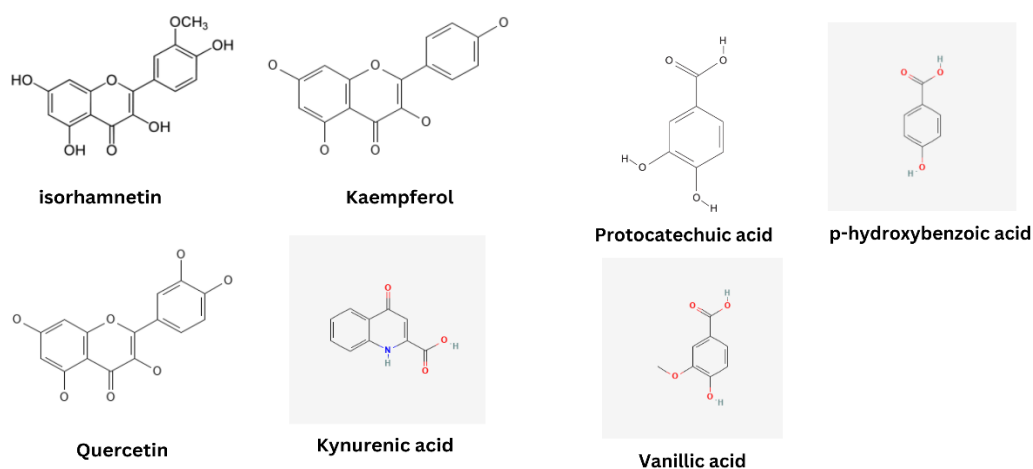
compounds contribute to the extract's acidic nature and aid in its water solubility. Despite this, key components such as flavonoids, terpenes, and other active ingredients are not inherently water-soluble, but their chemical environment in the Ginkgo biloba extract allows for solubility.<sup>[4]</sup> The pharmacologically active compounds in GBE are recognized as flavonoids and terpenoids. Oxidative stress leads to the damage of dopaminergic cells in PD, triggered by the action of specific toxins. An example is 6-hydroxydopamine, which generates reactive oxygen species that damage catecholaminergic neurons. Dopaminergic cell death is associated with toxins such as MPTP/(MPP+), rotenone and paraquit. Both rotenone and MPP+ disrupt the function of complex I in the electron transport chain of mitochondria. These toxins, when used in experimental models, highlight the role of oxidative stress as a key contributor in neurodegenerative processes.<sup>[5]</sup> It has been proposed that MPTP contributes to the initiation of Parkinson's disease and is employed to study how EGb 761 might affect the disease. The oxidative metabolism of MPTP into MPP+ is regarded as a crucial factor in its neurotoxic effects. Studies on rat brains have found that monoamine oxidase inhibitors, particularly MAO-B, prevent the conversion of MPTP into MPP+, whereas selective inhibition of MAO-A has no effect, indicating that MAO-B is essential to MPTP's oxidative metabolism.<sup>[6]</sup> Ginkgo biloba leaf extract functions as a powerful antioxidant and free radical scavenger. Pre-treatment of cerebellar granule cells with GBE has demonstrated a reduction in oxidative damage induced by H<sub>2</sub>O<sub>2</sub>/Fe<sub>2</sub>SO<sub>4</sub>. Research on Parkinson's disease models in rodents suggests that EGb 761 may help in treating PD by reducing the depletion of striatal dopamine levels, preventing neurodegeneration in the nigrostriatal pathway, and diminishing levodopa toxicity.<sup>[7]</sup> Toxins in the striatum and substantia nigra have been demonstrated to be adversely affected by the EGb 761 extract. Studies show that in rats, EGb 761 can improve the activity of antioxidant enzymes in the striatum, substantia nigra, and hippocampal region. Recent studies have accumulated substantial evidence suggesting that the individuals with Parkinson's diseases experience elevated oxidative stress, which is likely to contribute to neuronal degeneration and cell death associated with these conditions.<sup>[8]</sup>

Alzheimer's disease, dementia, and several other neurodegenerative diseases are also treated with the "EGB761 extract".<sup>[9]</sup> GBE is also used for protection against ischemia death, it also improves memory, preserves brain receptors and suspects age-related loss and enhances neuronal plasticity.<sup>[10]</sup>

Research models of Parkinson's disease have demonstrated the involvement of apoptosis in the disease's progression. Various experimental mouse models have been utilized, including those where Parkinson's was induced by administering MPTP or 6-OHDA into one side of the ventral tegmental area.” In mitochondria, rotenone and various other inhibitors targeting complex-I have been found to decrease ATP synthesis and increase the levels of reactive oxygen species.”<sup>[11]</sup> EGb 761 has demonstrated antiapoptotic effects across various tissues, attributed to its multifaceted and synergistic actions. It prevents apoptosis primarily through its antioxidant properties, which enhance the expression of specific genes and boost intracellular levels of certain enzymatic antioxidants. The flavonoids within EGb 761 prevent lipid peroxidation by interacting with lipid bilayer molecules, thereby maintaining membrane stability and functionality. Pretreatment with EGb 761 also helps preserve mitochondrial membrane potential in PC12 cells, leading to increased ATP production and reduced oxidative stress damage. Moreover, EGb 761 administration lowers the activation of proteins involved in the intrinsic apoptotic signalling pathway.

### Major components of Ginkgo biloba leaves

| Plant extract        | Major Components           | Constituents   |
|----------------------|----------------------------|--|
| Ginkgo biloba leaves | Terpenoids (6%)            | Ginkgolides A, B, C, and J account for 3.1%<br>Bilobalide makes up 2.9%  |
|                      | Flavonoid glycosides (24%) | Quercetin, Kaempferol, isorhamnetin  |
|                      | Organic acids              | Hydroxy kynurenic acid, kynurenic acid, protocatechuic acid, p-Hydroxybenzoic acid, and vanillic acid, among others. |



**Figure 1: Structures of active components of EGb761 extract.**

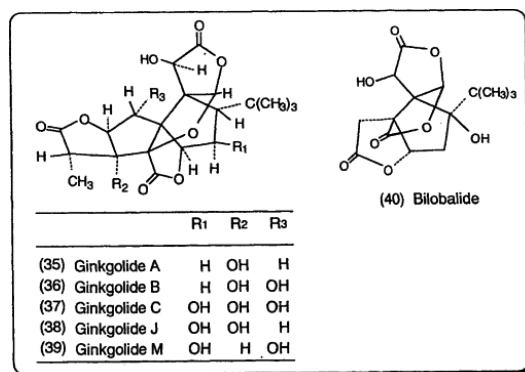


Figure 2: Ginkgolides A, B, C, J & bilobalide (13).

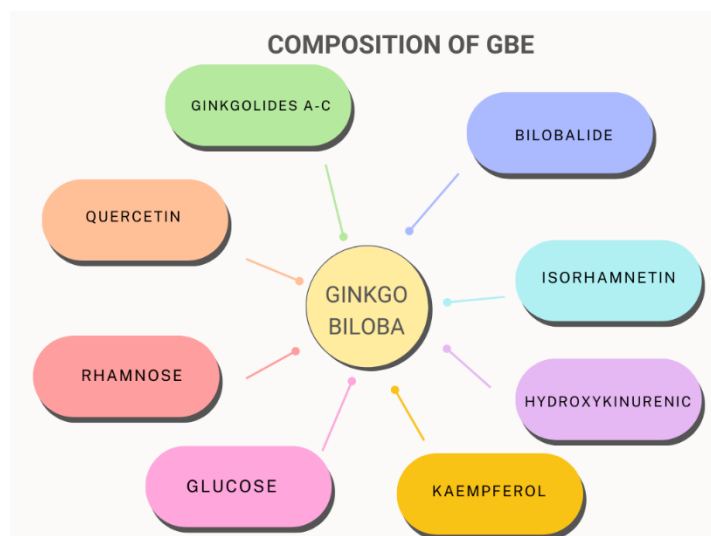


Figure 3.A: Visual representation of the active constituents found in GBE, highlighting the various categories of bioactive compounds.

## CONCLUSION

The degeneration of the nigrostriatal pathway initiates a decline in dopamine levels and impaired oxidative phosphorylation. EGb761, a compound containing flavonoids and terpenoids, has shown various pharmacological effects on the central nervous system. Both EGb761 and ginkgetin have demonstrated neuroprotective and antioxidative properties in this context. Notably, EGb761 is known for its ability to scavenge free radicals and provide anti-apoptotic effects. Studies further support this, showing that pre-treatment with GBE in cerebellar granules reduces oxidative damage.

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