**Ginkgo Biloba and Curcuma Longa Root’s Synergistic Potency on Neurobehaviour of Streptozotocin-Induced Neurodegenerative Disorders**

**Abstract**

Neurodegenerative conditions like anxiety, depression, and Alzheimer's disease can result from prolonged exposure to stress. Herbal supplements like Ginkgo biloba and Curcuma longa (turmeric) are being investigated as a result of the search for natural neuroprotective agents. In order to mitigate streptozotocin-induced neurodegeneration, this study examined the effects of combining ginkgo biloba supplements with Curcuma longa root extract. Twenty-five rats weighing between 90 and 120 grammes were split into five groups of five animals each. Group A was the control group; Group B was the negative control group (STZ alone); and Groups C–E were given extracts orally for 21 days at doses of 50, 100, and 150 mg/kg of Ginkgo biloba supplement and 200, 400, and 500 mg/kg of turmeric root extract. Following daily extract administration, a neurobehavioral test was performed. After 21 days, the animals were sacrificed and blood was extracted via ocular puncture into an EDTA container, and the serum was separated for oxidative biomarker analysis by centrifugation. The brain hippocampus was extracted and homogenized to measure the hippocampus absorbance level. Ginkgo biloba supplement and Curcuma longa root extract, at the doses tested on the Group C-E, significantly decreased p≤0.05 MDA, while GSH and SOD significantly increased p≤0.05 compared to group B. The hippocampus absorbance level increased non-significantly when compared to B. When comparing the test group to group B, there was a notable improvement in spatial memory and cognitive function, as evidenced by the significant decrease in escape latency and the number of errors (p≤0.05) and the significant increase in path efficiency. This study implies that some neurodegenerative diseases in diabetic rats may be lessened by the combined application of Curcuma longa roots and Ginkgo biloba supplements.

**Keywords:** Ginkgo Biloba, Curcuma Longa, Streptozotocin, Neurodegenerative Disorders.

**Introduction**

 Stress is a common occurrence that can seriously harm both the body and the brain. Neurodegenerative diseases like anxiety, depression, and Alzheimer's disease (AD) can result from prolonged exposure to stress. Research on treating AD with ingredients derived from natural substances is expanding as the disease's incidence rises and its importance grows. This is because natural substances have a variety of aetiologies that could be used as therapeutic strategies to slow the progression of AD (1). Herbalists claim that ginkgo biloba and curcuma longa, or turmeric, are two natural substances with a wide range of therapeutic potential.

Fossil tree, kew tree, and maidenhair tree are some common names for ginkgo, which is derived from the Chinese and Japanese names for the plant, meaning "silver apricot" or "silver fruit" (2). For centuries, traditional medicine has utilized the ancient plant ginkgo biloba, whose extract has been demonstrated to possess neuroprotective and antioxidant qualities. Early-stage Alzheimer's disease, vascular dementia, peripheral claudication, and tinnitus of vascular origin are all conditions that are frequently treated with ginkgo biloba. Numerous studies have examined the effectiveness of ginkgo in treating dementia and cerebrovascular disease, and systematic reviews indicate that the herb may help with dementia symptoms (3).For many years, ginkgo biloba extract has been used medicinally to treat dementia and to improve cerebral and peripheral blood flow. Numerous substances found in the extract, including terpenoids and flavonoids, are believed to support its vasotropic and neuroprotective properties (4, 3). Ginkgo has a long history in traditional Chinese medicine and is among the oldest living tree species in the world, according to an ethnomedical review. Ginkgo nuts were given to royal court members as a senility remedy. Ginkgo was also used in traditional medicine to treat kidney and bladder issues, bronchitis, and asthma (5). In Chinese culture, ginkgo has enormous medicinal, spiritual, and horticultural significance. The supplements are best-selling herbal medicines that have been used for many years in traditional medicine to treat blood disorders, enhance memory, and provide the most well-known method of maintaining mental acuity (6).



B

A

**Fig .1** A. Curcuma longa (Monya & Nature magazine,2017), B. Ginkgo biloba leaf (Bio-Botanico,2023)

Curcuma longa, a polyphenol-rich spice, has also been traditionally used to alleviate various ailments, including stress-related disorders. Its active compound, curcumin, has potent antioxidant and anti-inflammatory effects. Turmeric originates from the Indian subcontinent and South East Asian countries. Turmeric has been used in various traditional systems of medicine like Ayurveda, Siddha, and Chinese medicine for the treatment of various diseases (7).

In India, it is traditionally used for disorders of the skin, upper respiratory tract, joints, and digestive system (8).Turmeric has been used to treat dysentery, and anecdotal reports show that it has been quite successful. Turmeric may also prevent heart disease and stroke by preventing the blood clots. Also, it has been shown to lower cholesterol.

Even though these herbs have been the subject of numerous studies, there aren't many that compare their neuroprotective effects to stress exposure. Investigating the relative neuroprotective effects of Curcuma longa and Ginkgo biloba supplements on stress exposure in Wistar rats is the goal of this study.

**Materials & Methods**

**Experimental Animals**

We bought 25 male wistar rats from an animal vendor in the state of Nnewi, Anambra. They were separated into five groups, Groups A through E, each consisting of five rats, and weighed between 90 and 129 grammes. In the Animal House of Chukwuemeka Odumegwu Ojukwu University in Nigeria, the rats in each group were housed in individual cages with natural daylight and darkness cycles. The rats had unrestricted access to tap water and standard rat food. They were given two weeks to get used to their surroundings.

**Collection and Preparation of Tumeric Extract**

2400g of fresh turmeric was bought from the market and scrubbed thoroughly to remove dirt and contaminants. Ethanol was selected as the solvent for the effective extraction of phytochemicals. Eighty grammes of powdered plant material were soaked in 200 millilitres of ethanol for several days at room temperature, shaking occasionally to mix. Following extraction, the mixture was filtered to separate the liquid extract from solid residue using filter paper, and the ethanol was evaporated. To preserve its quality and effectiveness over time, the finished extract was kept in airtight containers away from heat and light (32,35,36,37,38).

**Ginkgo biloba supplement:**

We bought a can of Ginkgo biloba supplement from Headbridge Market in Onitsha, which contained 120 mg of 100 capsules. Since one supplement capsule contains 120 mg, 6 ml of water was added to it to bring the concentration down to 2000 mg/ml.

**Acute Toxicity**

The two-stage method of (10), modified by (11, 12), was used to calculate the median lethal dose (LD50). The Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, COOU, Uli, is where this study was carried out. Ultimately, neither extract showed any signs of mortality.

**Induction of Diabetes/Neurogenerative Disorder**

Using the method described in (13, 14, 15, 16), the test group rats were given an intraperitoneal injection of Streptozotocin at a dose of 65 mg/kg to induce diabetic neurodegenerative disorders before the extract was administered. Group E, on the other hand, received their induction 48 hours before the last day of the experiment before the sacrifice, after receiving the extract (a supplement of turmeric and ginkgo biloba) for 21 days. To verify that the rats had the disorders, a traction test was performed on them.

**Experimental Animal Groupings**

**Group A (**Control group): Rats in this group were given feed and water only.

**Group B (**Negative control group): Rats in this group received 65mg/kg of Streptozotocin drug

**Group C:** Rats in this group received 65mg/kg of Streptozotocin + 200mg/kg tumeric and 50mg/kg of Ginkgo biloba

**Group D:** Rats in this group received 65mg/kg of Streptozotocin + 400mg/kg tumeric extract and 100mg/kg wt of,Ginkgo biloba

**Group E:** Rats in this received 500mg/kg tumeric extract and 150mg/kg of Ginkgo biloba and were later induced with 65mg /kg after 48 hours prior to the sacrifice.

The administration lasted for 21 days through oral gavage. All experimental protocols were observed under strict supervision following the administration of the drugs.

**NEUROBEHAVIOURAL TEST**

The following neurobehavioural test was carried out using the procedures of (17, 18, 19):

**Procedure for Hippocampus absorbance**

The brain was harvested and washed in ice cold normal saline and sectioned. It hippocampus was removed and was weighed. It was then put into mortar and was mixed with normal saline and was homogenized. Then the homogenate was centrifuge and the supernatant was retrieved and was placed in the spectrophotometer and read at absorbance of 450nm and the value was taken.

**Determination of Oxidative Stress Parameters**

Each group's hippocampal tissues were removed and mixed with assay buffer. After centrifuging the tissues for 10 minutes at 4°C at 14,000 × g, the supernatants were gathered for examination. Assay kits were used to measure the SOD and CAT activities. As directed by the manufacturer, a Sigma-Aldrich® assay was used to measure the MDA levels (1, 33,34).

**Barnes Maze Test:**

It is a rat-specific visual-spatial learning and memory exercise. The object consists of a raised circular surface with holes all around it. Principles: This behavioral paradigm evaluates rodents' memory and spatial learning in arid environments. During each trial, the animal is placed in the center of the platform and given a set amount of time to reach the Target Escape Hole. The experiment is over if an animal enters the Target Escape Hole before the timer goes off. The experimenter leads the animals to the Target Hole, where they are given a brief period of time to live inside the tube before being returned to their original cage if they are unable to enter in time. While the other components remain constant, the Target Escape Hole is moved daily. Four trials in all are given to the participants. To get out of the open space and bright light and into a dark box underneath the maze, the rats use visual cues from outside the labyrinth to find an exit. Notably, it takes a long time to find the exit into the dark box beneath the maze.

**Collection of Samples**

The animal was anaesthetized and placed in a covered bucket filled with chloroform.A capillary tube was used to obtain a blood sample via occular puncture in a tube containing EDTA. The tube was centrifuged for 30 minutes, and the serum was extracted using a micropipette and placed in a plain tube for the assay.

**Statistical Analysis of Results**

The data from the study were analyzed using Statistical Packages for Social Sciences (SPSS), version 25. The brain weight data were examined using ANOVA, multiple comparison and post hoc LSD. The data were considered significant at p<0.05.

**Results and Discussion:**

**Table 1: Effect of Gingko biloba supplements and *Cucuma longa* on body weight following STZ-induced toxicity**

|  |  |  |  |
| --- | --- | --- | --- |
| **Group (N=5)** | **Initial body weight (g)** | **Final body weight (g)** | **Percent (%) Diff**  |
|  | **MEAN±SEM** | **MEAN±SEM** |  |
| Group A (control) | 91.40±0.67 | 96.20±0.58 | 4.8 |
| Group B (STZ only) |  97.20±1.24 | 101.40±1.44 | 4.2 |
| Group C  | 108.80±1.56 | 107.00±1.64 | -1.8 |
| Group D  | 115.20±0.86 | 112.60±0.81 | -2.6 |
| Group E  | 125.20±1.77 | 121.00±1.80 | -4.2 |

STZ: Streptozotocin, SEM: standard error of mean, \*: significant, #: not significant

**Table 2: Effect of Gingko biloba supplements and *Cucuma longa* on MDA levels following STZ-induced toxicity**

|  |  |
| --- | --- |
| **Group (N=5)** | **MDA level (Umol/L)** |
|  | **MEAN±SEM** |
| Group A (control) | 1.61±0.06 |
| Group B (STZ only) | 3.52±0.02\* |
| Group C  | 2.93±0.06\*@ |
| Group D  | 1.75±0.03#@ |
| Group E  | 2.03±0.04\*@ |

STZ: Streptozotocin, SEM: standard error of mean, \*: significant, #: not significant compared to group A, @: significant, $: not significant comparison made with group B.

**Table 3: Effect of Gingko biloba supplements and *Cucuma longa* on SOD and GSH levels following STZ-induced toxicity**

|  |  |  |
| --- | --- | --- |
| **Group (N=5)** | **SOD level (U/mg protein)** | **GSH level (U/mg protein)** |
|  | **MEAN±SEM** | **MEAN±SEM** |
| Group A (control) | 1.54±0.05 | 1.19±0.06 |
| Group B (STZ only) | 0.75±0.05\* | 0.55±0.04\* |
| Group C  | 1.03±0.02\*@ | 1.12±0.02#@ |
| Group D  | 1.45±0.04#@ | 1.45±0.07\*@ |
| Group E  | 1.16±0.02\*@ | 1.34±0.03#@ |

STZ: Streptozotocin, SEM: standard error of mean, \*: significant, #: not significant compared to group A, @: significant, $: not significant comparison made with group B.

**Table 4: Effect of Gingko biloba supplements and *Cucuma longa* on hippocampus absorbance level following STZ-induced toxicity**

|  |  |
| --- | --- |
| **Group (N=5)** | **Hippocampus absorbance level (%)** |
|  | **MEAN±SEM** |
| Group A (control) | 68.70±1.32 |
| Group B (STZ only) | 64.50±0.69# |
| Group C  | 67.90±0.63#$ |
| Group D  | 65.45±6.14#$ |
| Group E  | 65.15±0.14\*$ |

STZ: Streptozotocin, SEM: standard error of mean, \*: significant, #: not significant compared to group A, @: significant, $: not significant comparison made with group B.

**Table 5: Effect of Gingko biloba supplements and *Cucuma longa* on escape latency, errors, and path efficiency following STZ-induced toxicity**

|  |  |  |  |
| --- | --- | --- | --- |
| **Group (N=5)** | **Escape latency (secs)** | **No. of errors** | **Path efficiency (%)** |
|  | **MEAN±SEM** | **MEAN±SEM** | **MEAN±SEM** |
| Group A (control) | 46.00±0.57 | 3.33±0.33 | 79.00±0.06 |
| Group B (STZ only) | 51.00±0.58\* | 4.67±0.33\* | 70.00±0.04\* |
| Group C  | 39.00±0.57\*@ | 1.32±0.33\*@ | 86.33±0.02\*@ |
| Group D  | 37.00±0.58\*@ | 1.00±0.00\*@ | 91.00±0.07\*@ |
| Group E  | 35.00±0.58\*@ | 1.00±0.00\*@ | 92.000±0.03\*@ |

STZ: Streptozotocin, SEM: standard error of mean, \*: significant, #: not significant compared to group A, @: significant, $: not significant comparison made with group B.



Oxidative stress occurs when there are more reactive oxygen species (ROS) than antioxidants that can scavenge them, which may have negative effects. Oxidative stress is defined as an imbalance between the systemic manifestation of reactive oxygen species and the ability of a biological system to promptly detoxify the reactive intermediates or repair the damage they cause (20). Peroxides and free radicals are created when a cell's normal redox state is disrupted. These substances damage DNA, lipids, proteins, and other components of the cell and can have harmful consequences.

DNA strands are harmed by oxidative stress brought on by oxidative metabolism in addition to base damage. Most base damage occurs indirectly and is caused by reactive oxygen species like hydrogen peroxide (H2O2), hydroxyl radical (OH), and superoxide radical (O2 −). Oxidative stress is believed to contribute to the development of Alzheimer's disease, cancer, Parkinson's disease, Lafora disease, Alzheimer's disease, atherosclerosis, heart failure, myocardial infarction, autism, vitiligo, lichen planus, sickle-cell disease, fragile X syndrome, autism, infection, chronic fatigue syndrome, and depression, according to study (21). The body system can prevent this oxidative stress by producing antioxidant enzymes (22).
Our results show that, in comparison to the other test groups, STZ considerably raised the MDA level in group B rats. This result is consistent with that of (23, 24), who found that rats' MDA levels increased after receiving STZ. This result implies that polyunsaturated fatty acids, which ROS degrade, may undergo lipid peroxidation due to STZ. Significantly, the test groups' levels of glutathione reductase (GSH), superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) were higher than those of the negative control group B. These were in line with the reduction in MDA activity that tumeric root extract and ginkgo biloba caused in these animals, which improved ROS. These are consistent with research by (25,13) that showed an increase in antioxidant enzymes after rats were given plant extract.
This study also looked into the remedial effects and mechanism of ginkgo biloba and tumeric root extract in rats with STZ-induced learning and memory impairment.
Behavioural experiments first showed that the learning and memory impairments caused by STZ were restored by ginkgo biloba and tumeric root extract. ROS-induced cognitive and memory impairments in diabetes are frequently assessed using the STZ-induced animal model (26). According to recent reports, oxidative stress-related memory loss is caused by STZ administration (27). In this study, STZ was used to impair rats' memory and cognitive function. Furthermore, numerous studies have explicitly examined the effects of STZ given half an hour prior to behavioural tests, indicating its influence on memory acquisition impairment.

The results of earlier research were used to calculate the right dosage of STZ supplementation for the behavioural tests (28).
Since our study's goal was to compare the various concentrations of tumeric root extract and ginkgo biloba extract and ascertain whether their synergistic effect could improve STZ-induced impairment, we concentrated on varying doses.
Ginkgo biloba and tumeric root extract treatment enhanced short- and long-term memory in the behavioural tests, which is consistent with the results of other studies (29).

Furthermore, in the navigation-maze test, which assessed memory consolidation and exploratory behaviour, the results showed that the extract enhanced spontaneous behaviour. In addition, there was a variation in the escape latency between the groups in the MWM test from the second training day. According to the test day results, extract enhanced both spatial memory and memory acquisition.
Moreover, earlier research in diabetic rats has demonstrated that oxidative stress is a key factor in the development of AD. In general, the brain needs high oxygen levels to perform synaptic functions, and oxidative stress is especially harmful to the hippocampus and cortex (30).

 The main way that antioxidant enzymes work is by eliminating or neutralising oxidative materials like reactive oxygen species (ROS), commonly referred to as free radicals. Synapses can produce free radicals, which can alter their composition and functionality. Free radicals, for example, can damage receptors, degrade neurotransmitters, disrupt signal transduction pathways, and cause synaptic loss (30). The administration of STZ to rats in this study resulted in a marked increase in MDA levels, indicating the induction of oxidative stress, by inhibiting the defensive activities of the antioxidant enzymes SOD and CAT. On the other hand, by boosting SOD and CAT activity and preventing STZ-induced oxidative stress, the extract treatment preserved the antioxidant system while lowering the MDA content. These findings demonstrated that in rats given STZ, etract may help restore the antioxidant enzyme defence system.
One such pharmacological agent that has been shown to interfere with LTP induction is STZ (31). The results of this study are in line with earlier research demonstrating that STZ reduces LTP in the hippocampus's CA1 region. Furthermore, the results of this study indicated that the extract treatment might have caused a dose-dependent increase in the normalised fEPSP slope (%) of the LTP, which was recorded in the CA1 region following TBS induction.

**CONCLUSION**

According to this study, the extract prevented neuronal damage, decreased oxidative stress in the hippocampus, and mitigated learning and memory impairments brought on by STZ. These results provide a fresh viewpoint on the protective effects of ginkgo biloba and tumeric root extract, as well as learning and memory impairments, and may be used to treat neurodegenerative diseases.

**Ethical Approval**

The Faculty of Basic Medical Science at Chukwuemeka Odumegwu Ojukwu University's Uli campus granted ethical approval. Rats are handled and treated in accordance with the National Institutes of Health's guidelines for the care and management of laboratory animals

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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