INVESTIGATING THE EFFECTS OF ETHANOL LEAF EXTRACT OF *FICUS EXASPERATA* ON THE CEREBRUM OF ADULT WISTAR RATS.

BY

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BMS2004973

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BENIN CITY, EDO STATE.

FEBRUARY, 2025.

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A PROJECT SUBMITTED TO THE DEPARTMENT OF ANATOMY, IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF BACHELOR OF SCIENCE (B.Sc) IN ANATOMY, IN THE UNIVERSITY OF BENIN, BENIN CITY, EDO STATE.

FEBRUARY, 2025.

DECLARATION

I ONYENUE PRAISES OLUWAPELUMI declare that:

1. This research is based on the experimental work which I undertook in the Department of Anatomy, University of Benin, under the supervision of Dr. Edwin E. Ighalo.

2. Hitherto, this research has not been submitted for the award of a degree anywhere else.

3. All ideas, perspective and notions are based solely on this research, with due credit accorded to all external insights and contributions referenced in the course of this work.

ONYENUE PRAISES OLUWAPELUMI

CERTIFICATION ON PLAGIARISM

We the undersigned, attest and declare that the project undertaken by:

ONYENUE PRAISES OLUWAPELUMI

Titled:

INVESTIGATING THE EFFECTS OF ETHANOL LEAF EXTRACT OF *FICUS EXASPERATA* ON THE CEREBRUM OF ADULT WISTAR RATS.

Has successfully passed the anti-plagiarism test and does not violate any copyright regulations.

___________________________ __________________________

DR. EDWIN E. IGHALO **DATE**

(SUPERVISOR)

__________________________ __________________________

ADAZE B. ENOGIERU (Ph.D) **DATE**

(Ag. HEAD OF DEPARTMENT)

CERTIFICATION

This is to certify that this research work with the title **"INVESTIGATING THE EFFECTS OF ETHANOL LEAF EXTRACT OF *Ficus exasperata* ON THE CEREBRUM OF ADULT WISTAR RATS"** was carried out and submitted by **PRAISES OLUWAPELUMI ONYENUE (Mat. No: BMS2004973)** to the department of Anatomy, University of Benin, under the supervision of **DR. E. E. IGHALO,** in partial fulfillment of the requirement for the award of Bachelor of Science Degree (B.Sc) in anatomy.

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DR. E. E. IGHALO	**DATE**
(SUPERVISOR)	
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ADAZE B. ENOGIERU (Ph.D)	**DATE**
(HEAD OF DEPARTMENT)	
________________________	________________________
EXTERNAL EXAMINER	**DATE**

DEDICATION

This research is dedicated to the source of all things, whose providence sustains life, to the one by whose hands I've been nurtured, to all the rats and other animals that have been used in scientific research, whose contributions have been instrumental in the advancement of several discoveries and therapeutic innovations, and to the continuity of scientific breakthroughs in medicine and health technology.

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ABSTRACT

Ficus exasperata is a deciduous, dioecious medicinal plant of the Mulberry family, which is widely employed in traditional medicine due to its therapeutic and pharmacological properties. Despite its extensive medicinal application, there are very limited research on the effects of its ethanol leaf extract on the cerebrum. This study therefore, investigates the potential effects of the ethanol leaf extract on the structure and function of the cerebrum of adult Wistar rats. Thirty-five (35) adult Wistar rats, divided into: control, low-dose, medium-dose, and high-dose treatment groups. were treated with graded concentration of sand paper leaf extract (200mg, 400mg, 600mg, 800mg, 1000mg/kg body weight respectively), for a period of 30 days. Biochemical and histological analyses were then conducted to assess cerebral functions and structural changes. The result revealed administration of the ethanol leaf extract of *Ficus exasperata,* induced a dose-dependent increase in the body weight of Wistar rats, with higher doses producing a more significant effect. In addition, the extract exhibited minimal impact ($p< 0.05$) on cerebral oxidative stress markers e.g. Superoxide Dismutase (SOD), Catalase (CAT), Glutathione peroxidase GPX and Malondialdehyde (MDA). The extract also induced beneficial vasoactive changes including vasodilatation and increased blood circulation (active congestion), which decreased with increasing concentration of the sand paper leaf extract. The 200mg/kg body weight leaf extract had the most potent vasoactive effect, while the 1000mg/kg body weight extract had the least effect. However, the structural integrity of the neurons and neuroglia cells were sustained. Further studies are recommended to properly understand the mechanisms involved in its actions so as to ensure safe therapeutic use in humans.

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF STUDY

Plants and herbs have played an inevitable, fundamental role in human existence for a long time, by providing resources for food, medicine, and environmental sustainability (Gurib-Fakim, 2006). Over centuries, medicinal herbs and plants have been proven to be essential to the sustainability of human life, by providing remedies for various ailments, thereby playing an integral role in several traditional healing practices and forming the foundation of modern medicine and pharmacology (Bamola *et al.,* 2018). Today, the exploration of several bioactive compounds found in plants, has helped to drive groundbreaking discoveries in therapeutic interventions, particularly for very complex diseases (Majeed *et al.,* 2023). Although certain therapeutic claims that have been associated with plants have been shown to be inaccurate, the practice of medicinal plant therapy still remain rooted in the many evidence-based findings accumulated over the years (Gurib-Fakim, 2006) and the increase in global interest in plant-based treatments is fueled by their accessibility, perceived safety, and the potential to yield positive results regarding drug development (Pal and Shukla, 2002).

One of such plants is *Ficus exasperata*, commonly known as the sandpaper tree, forest sandpaper fig or white fig (Ahmed *et al.,* 2012). This deciduous and dioecious species belongs to the *Moraceae* family and is widely distributed across tropical Africa and parts of Southern Asia, including India, Sri Lanka, and Yemen (Bafor *et al.,* 2009; Wahua *et al.,* 2021). Traditionally, different parts of this plant have been utilized for managing wounds, skin infections, gastrointestinal disorders, and respiratory ailments (Salehi *et al.,* 2021). The leaves, in particular, are crushed for topical applications or brewed into decoctions for therapeutic use (Enogieru *et al.,* 2015). Scientific studies have further identified a range of pharmacological activities, including anti-ulcer, anti-inflammatory, anti-diabetic, anti-fungal properties etc. (Sirisha et al., 2010). Despite these findings, there remains limited understanding of its effects on the central nervous system.

The cerebrum, which is the largest, most superior and anterior part of the brain, plays a critical role in sensory perception, cognition, decision-making, and motor control amongst other functions (Purves *et al.,* 2001). Structurally, it comprises of two hemispheres separated by the falx cerebri and is divided into four lobes: frontal, parietal, temporal, and occipital (Kandel *et al.,* 2013). The outer layer, known as the cerebral cortex, is made up of grey matter and is profoundly involved in higher-order brain functions (Irshad, 2015). Damages to the cerebrum, whether structural or functional, can lead to significant neurological disorders.

Despite the growing reliance on traditional herbal medicine and the established pharmacological properties of *Ficus exasperata*, there is insufficient understanding on how the potential effects of its bioactive compounds can influence the activities of the central nervous system. This study is being carried out in an attempt to explore the possible impacts of the ethanol leaf extract of *Ficus exasperata* on cerebral structure and function.

1.2 STATEMENT OF RESEARCH PROBLEM

Medicinal herbs are widely employed in traditional medicine, due to their therapeutic potential however, many of these herbs are yet to be sufficiently examined, especially regarding their effects on specific organ systems, particularly the central nervous system (Majeed *et al.,* 2023). The leaves of *Ficus exasperata* have been recognized for their anti-inflammatory, anti-diabetic, and other pharmacological properties but their influence on brain function and structure is yet to be fully known (Jagetia and Rao, 2006). This presents a significant knowledge gap, as the plant is frequently used in traditional medicine, including for conditions that could involve the brain.

The cerebrum is known to govern higher-order functions such as cognition, sensory processing, and motor control, making it very vulnerable to damage from oxidative stress, inflammation, and neurodegenerative conditions (Kim *et al.,* 2024). Although *Ficus exasperata* is known to contain bioactive compounds with antioxidant and anti-inflammatory effects, there is no substantial evidence to determine whether these compounds benefit or harm the cerebrum (Ibrahim *et al.,* 2012).

To address this gap, this study will evaluate the effects of the ethanol leaf extract of *Ficus exasperata* on the cerebrum of adult Wistar rats in order to provide critical insights into the neuroprotective or neurotoxic potential of the plant, offering evidence-based conclusions about its safety and efficacy in traditional medicine.

1.3 AIM OF THE STUDY

This research is aimed at evaluating the potential effects of the ethanol leaf extract of *Ficus exasperata* on the structural and functional integrity of the cerebrum in adult Wistar rats.

1.4 OBJECTIVES OF THE STUDY

- To conduct a histological analysis of the cerebrum and assess possible changes in following administration of the extract.
- To investigate the biochemical effect of the extract on oxidative stress markers in the cerebrum such as Glutathione Peroxidase, Superoxide Dismutase, Malondialdehyde, Catalase etc.
- To identify the phytochemical composition of the ethanol leaf extract of *Ficus exasperata.*

- To examine any possible changes in the weight of the cerebrum and general body weight of the adult Wistar rat.

1.5 RESEARCH QUESTIONS

- What effect does the ethanol leaf extract of *Ficus exasperata* exert on the Cerebrum structure and function of adult Wistar rat?
- Does the leaf extract of *Ficus exasperata* cause any significant change in the organ and body weight of the Wistar rats?
- How does the extract influence the activities of oxidative stress markers in the cerebrum such as Glutathione Peroxidase, Superoxide Dismutase, Malondialdehyde, Catalase?
- What are the active phytochemical constituents of the ethanol leaf extract of *Ficus exasperata*?
- Does the administration of the extract induce histological changes in the cerebrum of adult Wistar rats?

1.6 SIGNIFICANCE OF THE STUDY

The major significance of this study is in its ability to provide insight into the neuropharmacological and histological effects of *Ficus exasperata*, contributing to evidence-based validation of its medicinal use. The findings from this study, could help in guiding the safe application of the plant extract in traditional medicine and therapy, and provide a foundation for future drug development targeting neurological disorders. In rural regions around the world where there is limited access to sophisticated, modern medicine, *Ficus exasperata* could prove a more affordable and potentially safer and effective alternative, thereby maintaining the health and well-being of the general population.

CHAPTER TWO

LITERATURE REVIEW

2.1 PLANT OF STUDY *(Ficus exasperata)*

Fig. 2.1: *Ficus exasperata plant* (Rujuta Vinod, 2019).

Ficus exasperata, commonly known as the Sandpaper Fig, is a tree which belongs to the genus, Ficus. It contains about 850 species of woody trees, shrubs, vines, epiphytes and hemi-epiphytes in the mulberry family *Moraceae* (Wahua *et al.,* 2021). It is a fast-growing species which is widely distributed in tropical and subtropical regions, particularly in Africa, Southern Asia (including India, Sri Lanka, and Yemen), and parts of Central and South America. The species thrives in secondary forests, riverbanks, and disturbed areas due to its adaptability and is often seen to grow up to a height of about 20m (Burkill, 1997). It is identified by several common and native names which include “sand paper tree”, “Papier de verre” in French, “Kharpatra” in India, “Msasa Mkuyu” in Swahili, “Anyanrin” or “Asesa” in Igbo, “Ewe ipin” in Yoruba, “Baure” in

Hausa, “onyankyerɛn” (Akans), “Nyadɛlɛ‟ (Nzema) and “Nyadkese‟ (Ga) in Ghana, Kawusa (Nupe), Ameme (Edo), (Bafor *et al.,* 2009; Irvin, 1961). The whole plant is known to have several medicinal properties in African traditional medicine (Woode *et al.,* 2020).

2.1.1 TAXONOMY OF *Ficus exasperata*

Taxonomic classification of *Ficus exasperata*

Kingdom: Plantae

Subkingdom: *Viridaeplantae*

Phylum: *Tracheophyta*

Subphylum: *Euphyllophytina*

Infraphylum: *Radiatopses*

Class: *Magnoliopsida*

Subclass: *Dilleniidae*

Superorder: *Urticanae*

Order: *Rosales*

Family: *Moraceae*

Tribe: *Ficeae*

Genus: *Ficus*

Species: *exasperata*

Scientific name: *Ficus exasperata Vahl*

Common names: sandpaper tree, forest sandpaper fig.

Synonyms: *Ficus asperrima, Ficus hispidisssima, Ficus politoria, Ficus silicea etc.* (Ahmed *et al.,* 2012).

2.1.2 BOTANICAL DESCRIPTION.

Ficus exasperata is scabrous, ovate-leaved and is a terrestrial afro-tropical shrub or small tree that preferably grows in evergreen and secondary forest environments (Ahmed *et al.,* 2012). It usually starts it growth process as an epiphyte, by growing in the limb of another tree. As it ages, it sends down aerial roots and buttresses, which quickly become much thicker and more vigorous roots, supporting the heavy branches and anchoring them to the ground. The slightly curved trunk, which can be grooved usually reaches 50 cm in diameter (Bissanti, 2023).

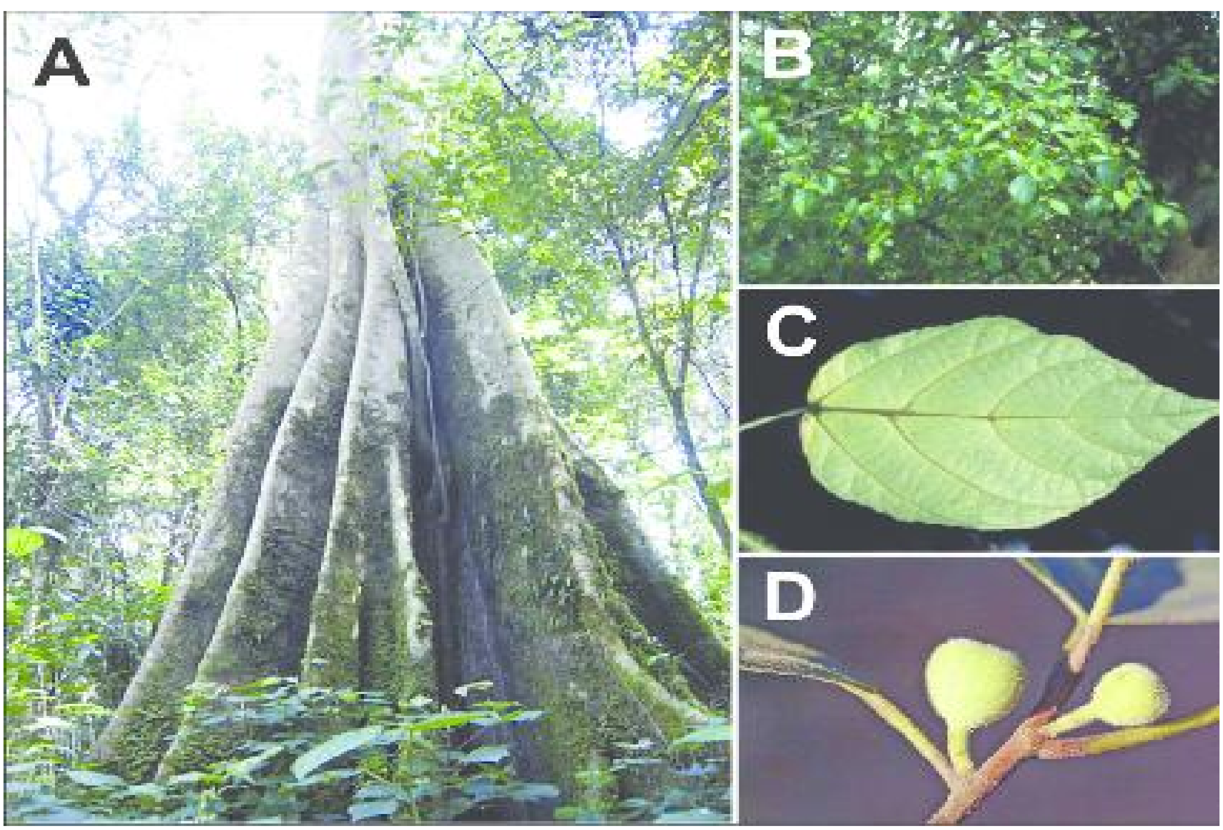

Fig. 2.2: Image showing parts of *Ficus exasperata* plant (Ahmed *et al.,* 2012). (A) *Ficus exasperata* tree trunk, (B) Foliage, (C) Leaf, (D) Fruits

2.1.2.1 LEAVES AND FIG.

The leaves of *F. exasperata,* are usually rough and sandpapery when felt, giving the tree its name "Sandpaper fig tree" (Green institute, 2023). They are said to be distichous in appearance i.e. arranged in two rows, alternate, and range in size from 3–20 cm long to 2–12 cm wide. The leaves are ovate to elliptic in shape, with a subcoriaceous to coriaceous texture. Their tips are shortly pointed, and their bases may be sharp or blunt. Each leaf typically has 3–5 pairs of lateral veins, with the basal pair reaching up to the the leaf margins at or above the middle (Niangadouma, 2010). The upper surface is very rough due to tiny hairs, which help protect the plant from herbivores and reduce water loss through transpiration (Green institute, 2023).

The petioles are 0.5–4 cm long, and the stipules, which are 0.2–0.5 cm long, are covered with stiff hairs and caducous in nature. The tree produces figs that are either single or found in pairs in the leaf axils, and occasionally, they grow on older wood. These figs are small, nearly round and measure 1–2.5 cm in diameter. They are covered with fine hairs and have a peduncle (fruit stalk) that is about 0.5–1 cm long. Tiny basal bracts, about 1 mm long, are scattered on the peduncle (van Noort *et al.,* 2024).

2.1.2.2 BARK.

The outer bark of the tree is smooth and ranges in color from pale grey or green to a brownish colour, while the inner bark varies from creamy white to pale brown in color. Unlike some species e.g. *Ficus sycomorus, Ficus elastica etc., Ficus exasperata* does not produce latex; however, when cut, it releases a clear, viscous, non-milky sap. Its crown is broad and spreading, and the young branches are hispidulous in texture i.e. covered in short, stiff hairs (Niangadouma, 2010; Ahmed *et al.,* 2012).

2.1.2.3 FRUITS.

The fruits of *F. exasperata* are small, round, and green when unripe, turning yellow or purple when ripe and contains the syconium, obvoid seeds (Yakubu *et al.,* 2019). Although these fruits are edible, they are not commonly consumed by humans due to their small size and limited availability (Green institute, 2023).

2.1.2.4 FLOWERING SYSTEM.

Ficus exasperata has a unique flowering system commonly seen in figs. The flowers are tiny and grow within a specialized structure known as "a syconium", which is often mistaken for a fruit. Initially, this syconium appears green and hard but gradually ripens to become yellow or orange in color. The flowers of *F. exasperata* are typically unisexual, i.e. they have separate male and female flowers within the syconium. The syconium contains three types of flowers:

1. Male flowers: These type produces pollen.
2. Female flowers: These type develop into seeds.
3. Gall flowers: These are specialized female flowers, short styled and provide food and shelter for the fig wasp, a tiny insect that pollinates the fig. (Ken Fern, 2024; Niangadouma, 2010).

2.1.3 ORIGIN AND DISTRIBUTION

The term *"Ficus"* refers to the classical Latin name for the fig tree, which was already recognised at the time and was most likely derived from *Hebrew*. The specific epithet *"exasperata"* originates from the word *"exaspero",* which means harsh, scabrous or irritating, roughened (Bissanti, 2023).

Ficus exasperata thrives in tropical climates with warm temperatures and adequate rainfall. It is well-adapted to both wet and dry seasons and can grow in a variety of soil types, such as sandy, loamy, and clay soils (Botanical realm, 2024). It is native to the tropical regions of Africa, including Nigeria, Cameroon, Ghana, and the Democratic Republic of Congo. It also extends from Senegal in the west to Djibouti (Africa) and Yemen (Asia) in the east, and further south to countries like Mozambique, Zambia, Angola, and Zimbabwe (Africa) (Ahmed *et al.,* 2012; Fern, 2010). Additionally, this species grows in the southern part of the Arabian Peninsula and is cultivated in several other areas with climates suitable for its growth, such as in India and Sri Lanka and in parts of Central and South America. (Niangadouma, 2010; Green Institute, 2023).

2.1.5 ETHNO-MEDICINAL AND TRADITIONAL USES OF THE PARTS OF *Ficus exasperata*

There have been previous studies and observations on the traditional uses and medicinal applications of *F. exasperata.* It has been observed that the root, bark, fruit, seed and leaf are used extensively in traditional medicine in Africa, Yemen, and India for various treatments including analgesic, antiarthritic, diuretic vermifuge, febrifuge, abortifacient, ecbolic, wound healing, animal fodder, general debility, malnutrition, parasitic infections (cutaneous and subcutaneous), leprosy, ophthalmic and oral infections, nasopharyngeal afflictions, arthritis, rheumatism, gout, oedema, kidney disorders, diarrhoea, dysentery, haemorrhoids, and sexually transmitted diseases (Singh and Sharma, 2023; Ahmed *et al.,* 2012; Sasidharan *et al.,* 2023).

2.1.5.1 ROOTS.

Decoctions prepared from the root of the plant are commonly administered in the treatment of urinary tract infections, gonorrhea, asthma, tuberculosis and in cases of persistent cough, the root may be chewed directly to provide relief (Chhabra *et al.,* 1990; Niangadouma, 2010) The root bark has also been traditionally used to manage eye-related ailments, while the root scrapings are applied externally as a body tonic. Additionally, the root exhibits anthelmintic properties, making it effective in expelling intestinal worms (Uzama *et al.,* 2018).

2.1.5.2 STEM BARK.

The stem bark of *Ficus exasperata* is also traditionally utilized as an infusion to treat coughs, intestinal worms, hemorrhoids, and spleen enlargement, and is also incorporated into remedies for heart conditions. Cold extracts of the bark are consumed to alleviate dizziness (Bissanti, 2023; Ahmed *et al.,* 2012). A maceration of the bark of *F. exasperata* combined with Senna occidentalis and Setaria megaphylla, is administered to facilitate childbirth or treat gonorrhea (Niangadouma, 2010; Osawaru *et al.,* 2024). The sap from the stem bark is applied to stop bleeding and manage wounds, sores, abscesses, eye ailments, and stomachaches (Bafor and Igbinuwen, 2009; Chhabra *et al.,* 1984) while ash from the burnt bark is sprinkled on wounds, and bark scrapings are prepared into embrocations with stimulant and tonic properties (Hasnat *et al.,* 2024). Furthermore, Enogieru *et al.* (2015), confirmed that the aqueous stem bark extract of *F. exasperata* demonstrated hepatoprotective effects, when they induced liver damage in experimental rats via high doses of paracetamol.

2.1.5.3 FRUIT.

The fruit is consumed to relieve coughs and venereal diseases while the dried and powdered form of the fruit is added to porridge for the treatment of infertility in women (Niangadouma, 2010). When mixed with water, it is usually taken against the case of fever. According to a study by Bello *et al.* (2014), the fruit of *F, exasperata* is a good dietary source of protein, fibre and nutraceutical elements.

2.1.5.4 LEAVES

In Nigeria, the fresh leaves are traditionally incorporated during the milling or pounding of oil palm fruits to enhance the quality and stability of the extracted oil. In addition, the rough texture of the leaves is quite useful as a natural sandpaper for polishing a variety of wooden, metal, and ivory objects, including kitchen utensils, gourds, sticks, bows, spear shafts, chairs, boards, and bracelets (Fern, 2010; Niangadouma, 2010). Decoctions of the leaf are employed as an antipyretic agent (Haxaire, 1979), to treat diarrhoea (Noumi and Yomi, 2001), to treat coughs, epilepsy, high blood pressure, rheumatism, arthritis, intestinal pains, and wounds (Dalziel, 1948), and to treat insomnia (Kerharo, 1974).

Hutchinson (1985) noted that the dried leaf decoction when taken orally and rubbed on the abdomen, can induce uterine contractions during childbirth and in like manner, infusions of the dried leaves are employed as therapy against stomach-ache (Akah *et al.,* 1997). Additionally, as a treatment for ulcers, some of the leaves of *Ficus exasperata* are chewed and consumed three times over the course of one to two months (Berg, 1989), and according to Bafor and Igbinuwen (2009), the leaf juice combined with lemon juice and eaten twice daily may be effective in treating emphysema, bronchitis, asthma, and Tuberculosis.

Furthermore, the leaves can be boiled in water and the steam inhaled to relieve chest pain (Assi, 1990), an aqueous extract of the leaves is administered in the treatment of haemorrhoids (Focho *et al.,* 2009), and a maceration of the leaves in water, taken orally is used as a medication to treat malaria (Titanji *et al.,* 2008).

2.1.6 REVIEW ON THE PHARMACOLOGICAL AND THERAPEUTIC PROPERTIES OF THE LEAVES OF *Ficus exasperata*

The Leaves of *F. exasperata,* being the most studied component of the plant, has been observed to possess a wide range of ethno-medicinal, pharmacological and therapeutic properties and applications including antioxidant, anti-inflammatory, antiarthritic, antiulcer, antipyretic, antidiabetic, hypotensive, anticonvulsant, antinociceptive, antimicrobial activities etc. (Ahmed *et al.,* 2012).

2.1.6.1 ANTIARTHRITIC AND ANTIOXIDANT PROPERTIES

The ethanol leaf extract was observed for its antioxidant and antiarthritic activities. The oral administration of the leaf extract (30-300 mg/kg) in Freund's adjuvant-induced arthritis model in rats exhibited antiarthritic effects and the analysis of the extract in in-vitro experimental models showed its antioxidant potential (Abotsi *et al.,* 2010).

2.1.6.2 ANTIMICROBIAL IMPACT AND PHYTOCHEMICAL CONSTITUENTS

Adebayo *et al.* (2009), examined the methanol extracts of *F. exasperata* stem bark, leaf, and root for the presence of significant phytochemicals and compounds, coupled with their effects against the growth of certain micro-organisms. While phytochemicals like alkaloids and terpenoids were absent, other reducing sugars, flavonoids, saponins, and tannins were identified. In addition, the leaf extract particularly demonstrated notable antimicrobial activities against various pathogenic organisms found in humans (e.g. P. aeruginosa, S. typhi, S. aureus, and E. coli.), by inhibiting their growth at concentrations of 5.0, 1.0, 1.5 and 1.25 mg/ml respectively, suggesting their potential as natural antimicrobial agents.

2.1.6.3 HYPOTENSIVE EFFECT

The leaf extract of *F. exasperata* exhibited a dose-dependent hypotensive effect, when Ayinde *et al,* (2007) tested them on rabbits. A decrease in mean arterial blood pressure was seen with the water extract when the mean arterial pressure decreased by 16.6 ± 1.1 mmHg at 10 mg/kg and by 38.3 ± 0.6 mmHg at 30 mg/kg. This significant fall in blood pressure at various dosages is attributed to its stimulation of muscarinic receptors in the heart or histamine release into systemic circulation leading to the substantial drop in blood pressure.

2.1.6.4 ANTI-INFLAMMATORY ACTIVITY.

The anti-inflammatory activity of the leaves and stem bark of *F. exasperata* was evaluated by Amponsah (2012), using carrageen-induced foot oedema model in 7-day old chicks. This test was carried out by measuring the ability of the extracts to inhibit protein denaturation, which is a common cause of inflammation, along with the inhibitory effects of the extracts on enzymes like cyclooxygenase (COX) involved in the inflammatory pathway. The findings supported the therapeutic potential of *F. exasperata* in managing inflammatory diseases by showing a dose-dependent reduction in oedema. (However, the stem bark showed the highest anti-inflammatory potency, with an ED50 of 50.65 ± 0.012 mg/kg, the dose required to achieve 50% of the maximal effect).

2.1.6.5 ANTINOCICEPTIVE AND ANTI-PYRETIC PROPERTIES

The hydro alcoholic leaf extract of *F. exasperata* was studied by Woode *et al.* (2009), for its antinociceptive and anti-pyretic capabilities in animal models. The extract indicated antinociceptive actions that were dosage dependent, as well as minimal efficiency in treating pyrexia induced by baker's yeast. However, the antinociceptive action of the extract was totally repressed by theophylline, a non-selective adenosine receptor antagonist and mildly repressed by naloxone, an opioid antagonist.

2.1.6.6 ANTIDIABETIC POTENTIAL

Various leaf extracts of *Ficus exasperata* were analyzed for their ability to suppress diabetes mellitus. Phytochemical screening was conducted on the extracts, and their inhibitory effects on the activities of α-amylase and α-glucosidase were evaluated in vitro. The findings revealed that the aqueous extract of *F. exasperata* demonstrated significant inhibitory activity, with low IC50 values of 3.70 mg/mL for α-amylase and 1.70 mg/mL for α-glucosidase, indicating the antidiabetic potential of the leaf (Kazeem *et al.,* 2013).

2.1.6.7 ANTIULCER ACTIVITIES

The gastroprotective activities of aqueous leaf extracts of *Ficus exasperata,* along with *Spondias mombin* against indomethacin-induced (30 mg/kg) gastric ulcer in Wistar rats, were investigated by Sabiu *et al.* (2015). The result indicated a significant decrease in the ulcer index of the rats, following a daily administration of 200 mg/kg b.w. of *F. exasperata* thereby, attesting to the ulcer-repressing capability of the plant.

2.1.6.7 ANTICONVULSANT CHARACTERISTICS

An hydroalcoholic leaf extract of *F. exasperata*, yielded positive results against seizures induced by pentylenetetrazole and picrotoxin in mice. The extract (30-300 mg kg (-1), p.o.) effectively prolonged the onset and reduced the duration of pentylenetetrazole- and picrotoxin-induced convulsions, thereby affirming the seizure-inhibiting characteristic of the leaf of *Ficus exasperata (*Woode *et al.,* 2011).

2.1.7 TOXICITY OF *Ficus exasperata*

A number of toxicity tests on different leaf extracts of *F. exasperata* have been carried out. Some of the results have shown the extracts to be somewhat harmless, while others revealed some possible negative impacts (Ahmed *et al.,* 2012).

In a previous study, the acute toxicity of the aqueous leaf extract of *F. exasperata* on haematological parameters, body weight, and body temperature in mice was observed over a 24-hour and 14-day period. Although the extract did not cause mortality or significant behavioral changes during the oral administration tests, the 14-day daily dosage trial revealed a substantial reduction in the red blood cell count, haemoglobin count, and hemocrit values ($p < 0.05$) and an abrupt rise in body temperature ($p < 0.05$). In some groups, deaths were recorded following intraperitoneal injection of the aqueous leaf extract. These findings suggested that the short-term oral administration of the extract may be relatively harmless however, long-term toxicity research should be carried out, so as to verify the ethical application of the plant extract (Bafor and Igbinuwen, 2009).

In another research, the acute toxicity of crude methanol leaf extract from *F. exasperata Vahl* was conducted on male Wistar albino rats to evaluate its safe dosage and potential effects on the liver. The methodology involved administering various doses to determine the LD50, which was found to be above 5000 mg/kg. Although some signs of toxicity, such as sluggishness and elevated liver enzyme levels, were noted at higher doses, no deaths occurred during the observation period. Malondialdehyde levels (a marker of lipid peroxidation) increased significantly with doses of 3000 mg/kg and 5000 mg/kg, suggesting oxidative stress (Shemishere *et al.,* 2020).

2.2 ORGAN OF STUDY (Cerebrum)

2.2.1 Introduction

The cerebrum, often referred to as the forebrain, is the largest region of the human brain and is in charge of the most complex and advanced intellectual, emotional, social and psychological features of mankind. It also forms the highest component of the brain, consisting of two hemispheres that are almost symmetrical and are divided by a deep longitudinal cerebral fissure that houses the corpus callosum. Each hemisphere controls the opposite side of the body, by sending motor commands to, and receiving sensory information from the contralateral half of the body. (Knapp, 2020; Moore *et al.,* 2017).

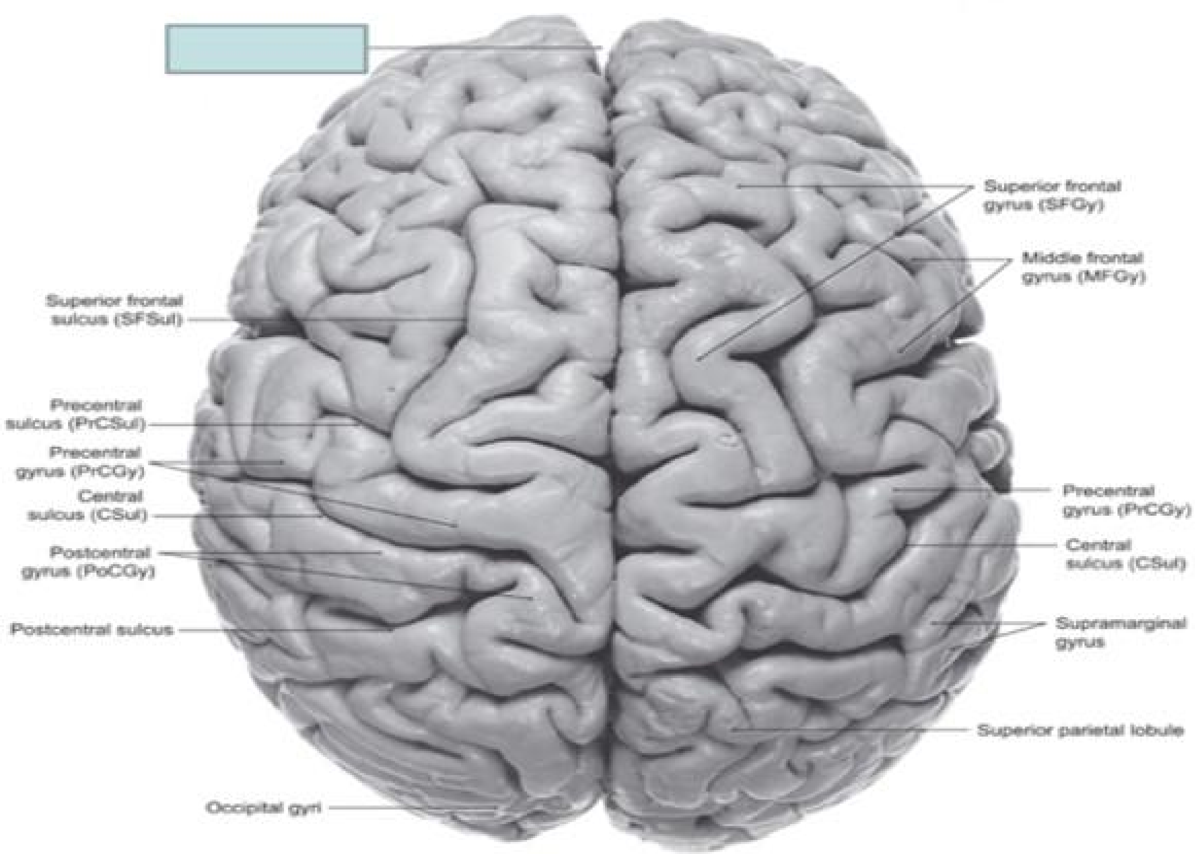

Fig. 2.3: Image showing the superior view of the Cerebral hemispheres (Quizlet, 2024).

The cerebral cortex is the outer grey matter layer of the cerebrum and is composed of nerve fibres (axons of neurons) that make up the white matter and grey matter (Venkat, 2022). It is mostly composed of the cell bodies, dendrites, and axons of neurons. While the superficial gray matter is responsible for processing information, the deeper white matter act as channels for communicating between the grey matter and other regions of the body (LaDouceur, 2023). The outer surface of the cerebral cortex is covered in numerous folds and grooves, known as gyri and sulci (Ocran, 2024).

The cerebrum is divided into six lobes: frontal, parietal, temporal, occipital, insula, and limbic lobes, each responsible for specific functions (Lewis, 2018). The frontal lobe manages mental activities, planning, and voluntary movement; the temporal lobe handles emotions and memories; the parietal lobe contains primary somatosensory areas that important for navigation and spatial orientation; and the occipital lobe houses the visual cortex for processing sight (Guy-Evans, 2018). The cerebrum also contains functional areas which are categorized into motor areas (voluntary muscle control), sensory areas (receiving sensory information), and association areas (complex functions such as learning, reasoning, and communication) (Ocran, 2015; Javed *et al.,* 2019).

2.2.2 Embryology of the Cerebrum.

The development of the cerebrum begins during neurulation in the third week of gestation, when the notochord appears in the mesoderm. The notochord secretes growth factors that signals the superficial ectoderm to differentiate into neuroectoderm. This neuroectoderm then forms a thickened structure called the neural plate which deepens to create a neural groove, while the lateral margins of the neural plate rise to form the neural folds (Barnes, 2018).

As development progresses, the neural folds continue to elevate and later fuse in the dorsal midline of the embryo, transforming the neural groove into a neural tube. The open ends of the tube are called the cranial and caudal neuropores and they are connected to the amniotic cavity. The cranial neuropore close on day 25, while the caudal close on day 28. The formation of the neural tube is completed by the end of the fourth week of development (Sadler *et al.,* 2019).

The cephalic end of the neural tube presents three dilations which gives rise to the primary brain vesicles: the prosencephalon (forebrain), the Mesencephalon (midbrain) and the rhombencephalon (hindbrain). At the 5^{th} week of development, the primary brain vesicles have differentiated into five secondary vesicles in total. The prosencephalon (forebrain) divides into the telencephalon and diencephalon, the Mesencephalon (midbrain) persists and the rhombencephalon (hindbrain) forms the metencephalon and myelencephalon. The Cerebrum is the adult derivative of the Telencephalon.

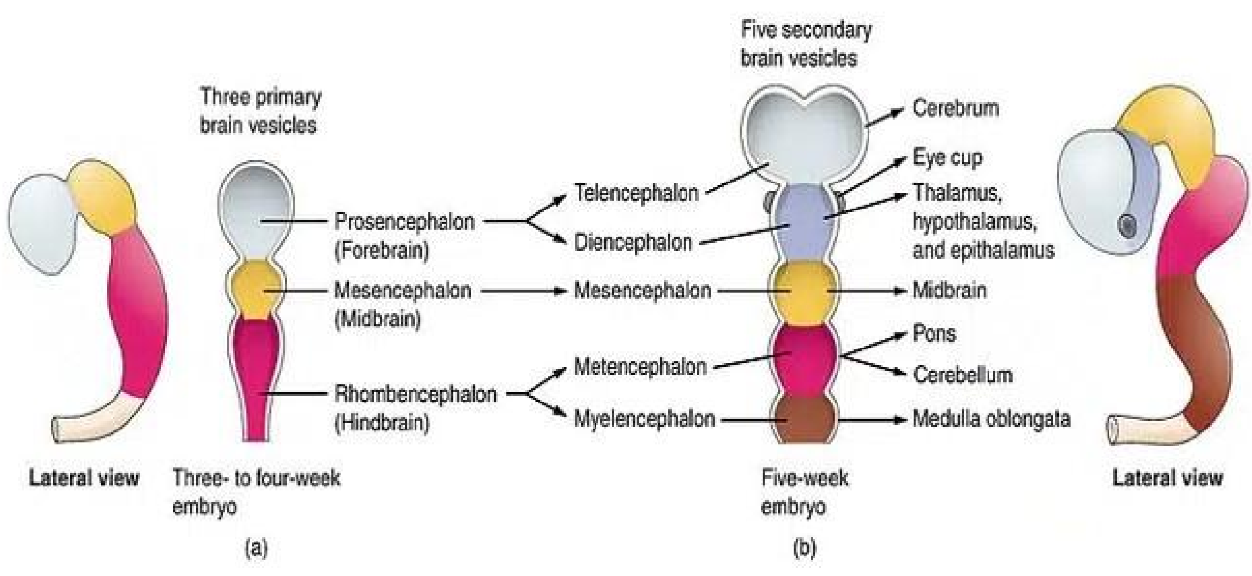

Fig. 2.4: The formation of the primary and secondary brain vesicles and their derivatives (OpenStax College, *TM Anatomy,* 2018).

2.2.3 Gross Anatomy

The cerebrum is a heavily convoluted, bilobed structure that occupies most of the cranial cavity. When viewed from above, the two cerebral hemispheres form an ovoid mass which is broader posteriorly than it is, anteriorly. They are separated by the longitudinal cerebral fissure, a deep median cleft (Singh V., 2014). The greater part of each hemisphere consists of white matter, which houses important masses of grey matter. The outer layer, known as the cerebral cortex, is essential for various functions, including perception, movement, adaptation, and advanced mental activities such as memory, learning, and creativity (Jawabri and Sharma, 2023). Phylogenetically, the cortex is classified into three types: **archicortex** (the oldest, represented by the hippocampus in man), **paleocortex** (intermediate in development, represented by cingulate gyrus), and **neocortex** (most recent in man, forming 90% of the cortex) (Ocran, 2015).

2.2.3.1 External Features of the Cerebral Hemispheres.

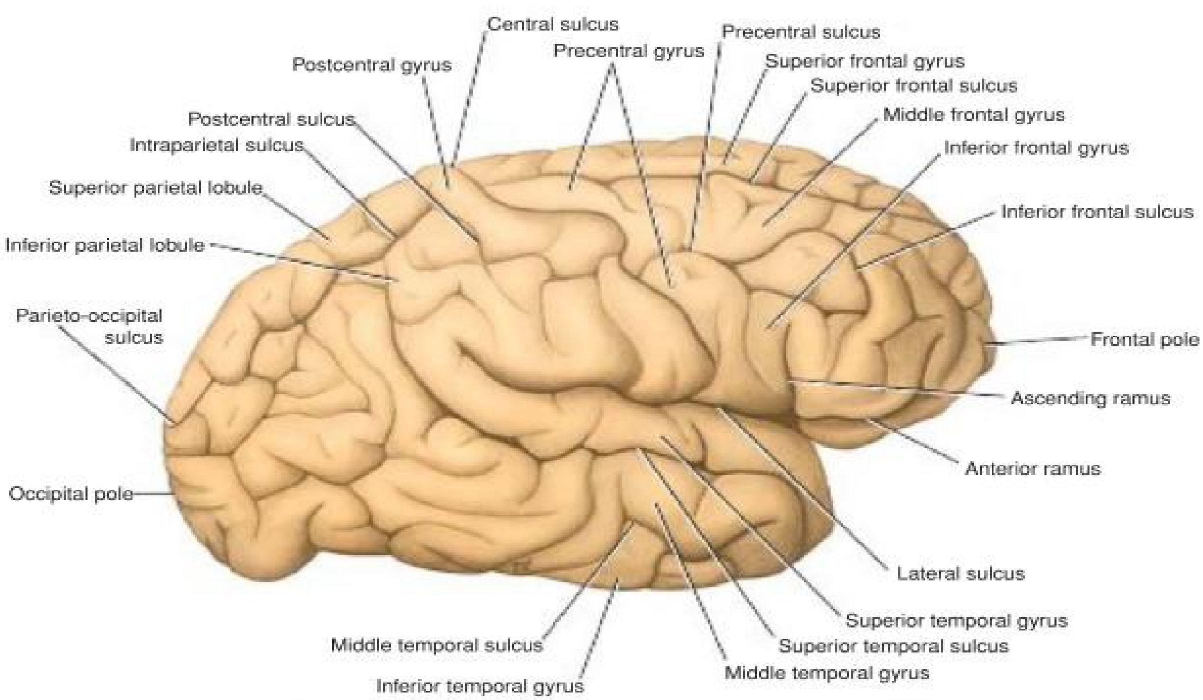

Fig. 2.5: Lateral view of the right cerebral hemisphere (Splittgerber and Snell, 2019).

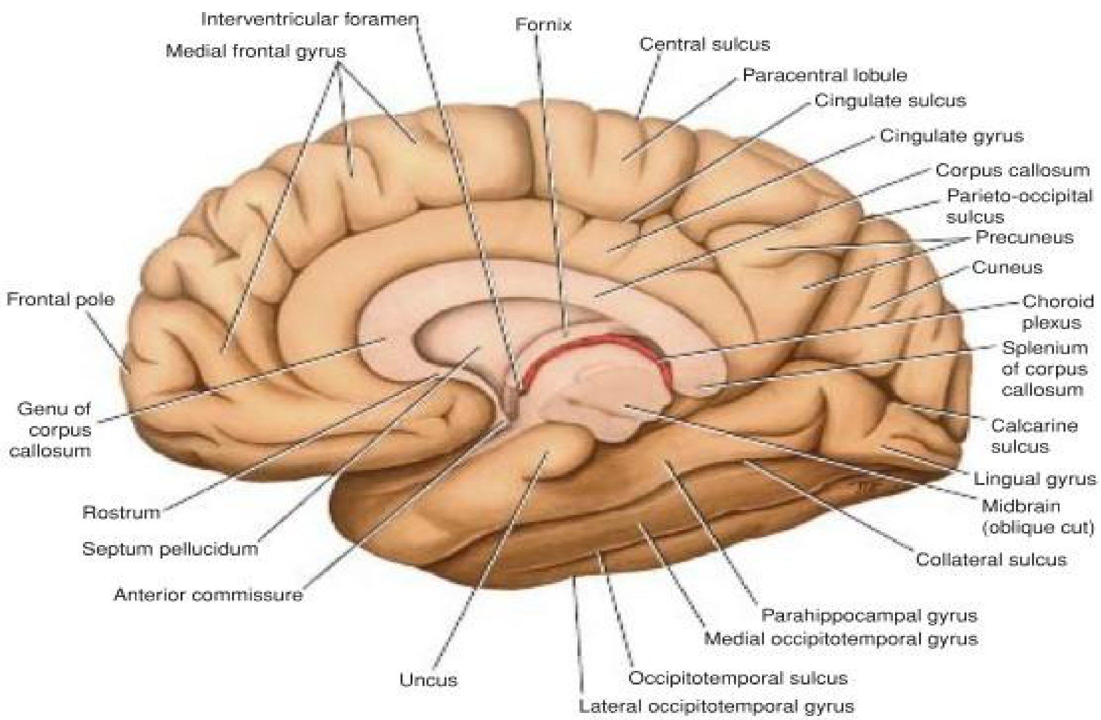

Fig. 2.6: Medial view of the right cerebral hemisphere (Splittgerber and Snell, 2019).

The cerebral hemispheres present the following external features: poles, surfaces, borders, sulci, and gyri.

Poles

Located on each cerebral hemispheres are three poles; frontal, occipital, and temporal. The frontal pole occupies the anterior end of the hemisphere and lies opposite the medial end of the superciliary arch. The occipital pole is located posteriorly, on the hemisphere lying at a close distance superolateral to the external occipital protuberance. The temporal pole is situated in between the frontal and occipital poles and is directed forwards and slightly inferiorly (Chauhan *et al.,* 2021; Singh V., 2014).

Surfaces

Each hemisphere of the cerebrum has three surfaces: superolateral, medial, and inferior. **The superolateral surface** includes the convex C-shaped area that extends around the sylvian fissure from the frontal pole anteriorly to the occipital pole posteriorly and the temporal pole inferiorly. **The medial surface** borders the midline, extending into the posterior temporal lobe and surrounding the corpus callosum, from the frontal pole to the occipital pole. **The inferior surface** faces downward towards the base of the cranium, containing portions of the frontal, temporal, and occipital lobes, and extends from the frontal to the occipital pole, bordered laterally by the lateral (sylvian) fissure. (Naidich *et al.,* 2016, Chauhan *et al.,* 2021).

Borders

A coronal section across the cerebral hemispheres reveals the three borders of each hemisphere: The **superomedial border**, which partitions the superolateral surface from the medial surface, the **inferolateral border** which separates the superolateral surface from the tentorial surface and the **inferomedial border** that surrounds the cerebral peduncle and separates the medial surface from the inferior surface. (Singh I., 2018; Singh V., 2014).

Sulci and Gyri

The cerebral cortex is folded into bumps called gyri and intervening fissures called sulci, in order for it to fit within the rigid cranial cavity thereby, increasing the surface area of the hemispheres. These structures act as landmarks for identifying different regions of the brain and separate the lobes of the cerebrum (Lakna, 2018; Guy-Evans, 2021). The four main sulci include: **The central sulcus (of Rolando) (**which runs antero-inferiorly, ending just above the posterior ramus of the lateral sulcus to separate the frontal and parietal lobes), **Lateral sulcus of Sylvius** (which arises on the inferior surface of each hemisphere, divides into three rami and separates the temporal lobe from the frontal and parietal lobes), **Parieto-occipital sulcus** (which marks the boundary between the parietal and occipital lobes, as well as between the cuneus and precuneus on the lateral and medial surfaces of the hemisphere) and **Calcarine Sulcus** (which extends from the occipital lobe to the parieto-occipital sulcus on the caudal end of the medial surface of the occipital lobe). (Splittgerber and Snell, 2019; Singh V., 2014; Lakna, 2018; Loukopoulou, 2024).

2.2.3.2 Lobes of the Cerebrum

Frontal Lobe

The frontal lobe is the largest lobe of the brain, positioned anterior to the central sulcus and superior to the lateral sulcus, occupying about one-third of the cerebral hemisphere. It is made up of three surfaces: Supero-lateral, medial, and inferior. The lateral surface contains four principal gyri: **the precentral gyrus,** (that is partitioned by the precentral sulcus and the Central sulcus) **superior frontal, middle frontal,** and **inferior frontal gyri** (which are partitioned by the Superior and inferior frontal sulci). The frontal lobe, is divided into several significant areas: prefrontal cortex, premotor cortex, and primary motor cortex, which control motor tasks and higher functions. In the dominant hemisphere (which is usually the left side), the expressive language area (Broca area, Brodmann areas 44 and 45) is present. Damage to these areas can cause contralateral motor weakness, expressive aphasia in the Broca's area, disinhibition, poor judgment, and emotional/social regulation deficits. (Sendic, 2022; Jawabri and Sharma, 2023; Singh I., 2018; Javed *et al.,* 2019).

Parietal Lobe

The parietal lobe lies in between the frontal and occipital lobes, and superior to the temporal lobe. It also has three surfaces: supero-lateral, medial, and inferior. Its lateral surface features the **postcentral gyrus**, partitioned by the central and postcentral sulci and contains the somatosensory cortex, which is responsible for processing sensory input. Other important landmarks of the parietal lobe include the Superior and inferior Parietal lobules (which are divided by the intraparietal sulcus), supramarginal and angular gyri. The parietal lobe plays a crucial role in perception, sensation, and sensory integration with vision. Lesions in the dominant (usually left) parietal lobe can cause Gerstmann's syndrome, which is characterized by agraphia, acalculia, finger agnosia, and left-right disorientation. Damage to the non-dominant parietal lobe may result in hemi-spatial neglect syndrome, affecting the ability to recognize the contralateral side. Bilateral damage to the lateral parietal lobe can lead to Balint's syndrome, which includes ocular apraxia and simultagnosia (Shahid, 2022; Splittgerber and Snell, 2019; Javed *et al.,* 2019; Jawabri and Sharma, 2023).

Temporal Lobe

The temporal lobe is the second largest brain lobe, making up about 20% of the neocortical volume. It is located in the middle cranial fossa, inferior to the lateral sulcus, and extends to the occipital lobe. It has three surfaces: lateral, basal, and medial. The lateral surface contains the superior, middle, and inferior temporal gyri, the medial surface contains the para-hippocampal gyrus and the occipitotemporal gyrus, separated by the collateral sulcus and the inferior surface contains the fusiform gyrus and the inferior temporal gyrus. The temporal lobe is vital for processing sensory input related to emotions, memory, and language comprehension, housing the primary auditory cortex and Wernicke's area. Lesions can lead to receptive aphasia, characterized by unintelligible speech (Irshad, 2015; Singh V., 2014; Ferreira, 2023; Javed *et al.,* 2019).

Occipital Lobe

The occipital lobe is the smallest and most posterior lobe of the cerebrum, located beneath the occipital bone and behind the parieto-occipital sulcus. It has three surfaces: lateral, medial, and inferior. The lateral surface features lateral occipital gyri, while the medial surface is marked by the calcarine sulcus, which divides the lobe into the cuneus (above) and the lingual gyrus (below). The inferior surface connects with the fusiform gyrus. The primary function of the occipital lobe is visual processing, with the primary visual cortex situated in Brodmann Area 17 within the calcarine sulcus. Damage to one occipital lobe can lead to homonymous hemianopsia and visual hallucinations, while bilateral damage results in cortical blindness, where vision is lost despite intact light reflexes (Irshad, 2015; Stewart, 2023; Singh I., 2018; Javed *et al.,* 2019; Jawabri and Sharma, 2023).

Insular Lobe (Insula)

The insula, or island of Reil, is a triangular lobe which lies hidden, deep within the lateral sulcus, making it invisible from the surface of the brain, without retracting the frontal and temporal lobes. At the point where both lobes which are referred to as the opercula (singular: operculum). It includes the short gyri of the insula at the front and the long gyrus at the back, separated by the central sulcus of the insula. The insular cortex is bordered by a limiting sulcus, distinguishing it from the opercular regions of the frontal, parietal, and temporal lobes (Vaković, 2018).

Limbic Lobe

The limbic lobe is a C-shaped group of brain structures located on the medial surface of the cerebral hemisphere, forming a ring around the corpus callosum. It includes the cingulate gyrus, which arches over the corpus callosum, and the parahippocampal gyrus in the medial temporal lobe. The cingulate sulcus separates the cingulate gyrus from the superior frontal and parietal lobules, while the collateral sulcus distinguishes the parahippocampal gyrus from the fusiform gyrus. At the anterior end of the parahippocampal gyrus is the uncus, a hook-like structure (Crumbie, 2023).

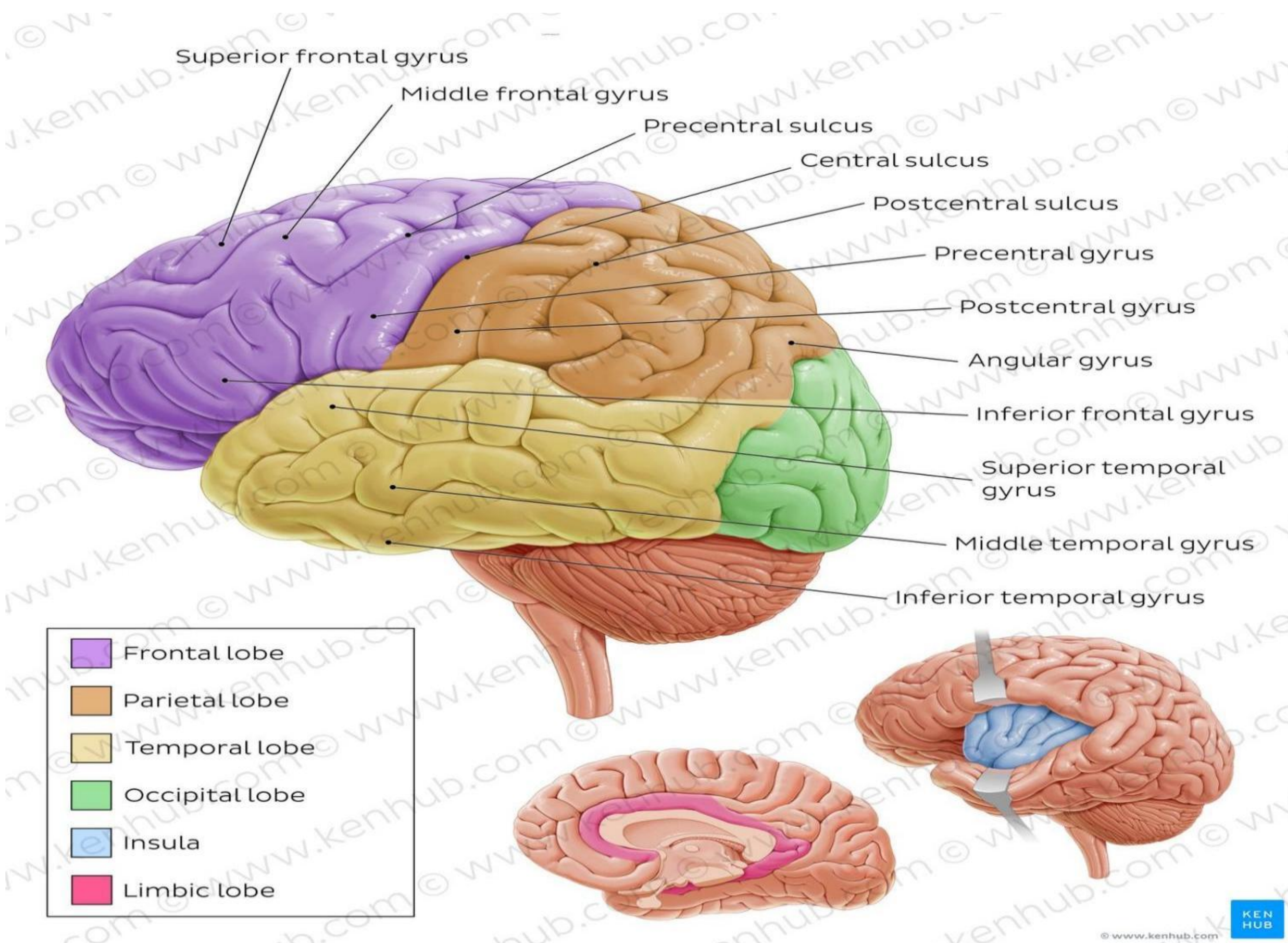

Fig. 2.7: Image showing the lobes of the brain and their associated sulci and gyri (kenhub.com, 2023).

2.2.3.3 An overview of the Internal Features of the Cerebrum.

The interior of the cerebrum consists of large masses of gray matter, lying beneath the white matter along with cavities (ventricles) filled with cerebrospinal fluid (CSF). Immediately lateral to the third ventricle, there lies the thalamus and hypothalamus (and certain smaller masses) derived from the diencephalon. More laterally, there is the corpus striatum, which is derived from the telencephalon. It consists of two masses of grey matter, the caudate nucleus and the lentiform nucleus, which consists of two functionally distinct parts, the putamen and the globus pallidus (Figure 13.2). A little lateral to the lentiform nucleus, is the cerebral cortex in the region of the insula. Between the lentiform nucleus and the insula, there is a thin layer of grey matter called the claustrum. The caudate nucleus, the lentiform nucleus, the claustrum, and some other masses of grey matter (all of telencephalic origin) are referred to as basal nuclei or basal ganglia (Singh I., 2018; Schmahmann *et al.,* 2008).

The white matter of the cerebral hemispheres is composed of commissural, association, and projection fibers. Commissural fibers primarily connect the cortices of both hemispheres, with dense concentrations in the corpus callosum. Association fibers connect various cortical regions within the same hemisphere, while projection fibers link the gray matter to subcortical structures, the brainstem, and the spinal cord. A significant group of projection fibers forms the internal capsule, located lateral to the thalamus and the head of the caudate nucleus. From the internal capsule, fibers spread in a fan-like arrangement known as the corona radiata to reach the cortex, with some descending to the capsule, while fibers from the corpus callosum intersect with the corona radiata. (Sinnatamby, 2011; Emos *et al.,* 2023; Grujičić, 2023).

The corpus callosum is composed of approximately 100 million commissural fibers that connect symmetrical regions of the two hemispheres. It begins at the anterior commissure near the lamina terminalis and thickens as it extends, consisting of four parts: rostrum (extending upwards and forwards), genu (bending backwards), body (arched convexly upwards), and splenium (thick, rounded posterior end). In horizontal sections, the fibers of the genu form the forceps minor as they arch forward to the frontal cortex, while the fibers of the splenium curve backward to the occipital cortex, forming the forceps major. Between these, fibers spread laterally, creating the roof of the lateral ventricle and, in the temporal lobe, the tapetum along the lateral wall of the inferior and posterior horns. (Sinnatamby, 2011; Goldstein *et al.,* 2019; Singh I., 2018).

2.2.3.4 Arterial supply of the Cerebrum

The brain requires a continuous supply of oxygen and glucose therefore, it receives about 20% of the total cardiac output despite being just 2% of body weight. The blood supply of the Cerebrum is divided into anterior and posterior circulations (Jones, 2022; Bui and Das, 2023).

Anterior Circulation

This circulation is supplied by branches of the internal carotid arteries (ICA) and accounts for 80% of blood flow to the cerebrum. This artery branches into the anterior cerebral artery (ACA), which supplies the frontal and superior medial parietal lobes, and the middle cerebral artery (MCA), which supplies the lateral hemispheres. The Middle cerebral artery is the most common site for ischemic strokes, which majorly affects the language areas (Luxgrant, 2020; Javed *et al.,* 2019).

Posterior Circulation

It is supplied by the vertebral arteries and accounts for 20% of cerebral blood flow, covering the occipital lobes, brainstem, and cerebellum. The basilar artery which is formed by the merging of the vertebral arteries, provides posterior supply of blood and contributes to the circle of Willis.

Terminal branches of this circulation include the posterior cerebral arteries (PCA), which supply most of the occipital lobe and connect to the Middle cerebral artery via the posterior communicating artery (Purves *et al.,* 2001; Konan *et al.,* 2020).

2.2.3.5 Venous Drainage of the Cerebrum

The venous drainage of the cerebrum efficiently returns deoxygenated blood and metabolic waste to systemic circulation through an organized system of superficial and deep cerebral veins, which drain into dural venous sinuses before emptying into the internal jugular veins (Barnes, 2016; Safadi and Tadi, 2022).

Superficial Cerebral Veins

These group of veins drain the cortex and subcortical white matter. They are categorized into superior, middle, and inferior groups. The superior group drains the superolateral surface into the superior sagittal sinus, the middle (or superficial Sylvian vein) drains the lateral surface into the cavernous sinus, and the inferior group drains the inferior surfaces into the transverse and cavernous sinuses (Standring, 2020; Safadi and Tadi, 2022).

Deep Cerebral Veins

These veins drain deep brain structures like the basal ganglia and thalamus. They include the internal cerebral veins, which unite to form the great cerebral vein (of Galen), and basal veins (of Rosenthal), which drain the orbitofrontal cortex and mesencephalon. The great cerebral vein drains into the straight sinus (Snell, 2019; Moore *et al.,* 2018).

Dural Venous Sinuses

The dural venous sinuses, located between the dura mater layers, collect blood from cerebral veins and cerebrospinal fluid (CSF). Major sinuses include the superior sagittal sinus, inferior sagittal sinus, straight sinus (formed by the union of the inferior sagittal sinus and great cerebral vein), and the transverse and sigmoid sinuses, which drain to the internal jugular veins (Barnes, 2016; Bajzer, 2004).

2.2.4 Histology of the Cerebrum

The cerebral cortex is made up of axons of neurons (supported by neuroglia), that transit to and fro several cortical and subcortical regions of the CNS. These neurons are histologically classified into five different morphological types, arranged in layers. They include the **Pyramidal cells** (pyramid-shaped cells with varying sizes and a single axon that projects inferiorly to other cortical areas), **Stellate (granular) cells (**small, rounded star-shaped cells, with multiple short dendrites and a short vertical axon), **Cells of Martinotti** (short, polygonal, multipolar cells with a few short dendrites and a vertically projected axon,), **Fusiform cells** (spindle-shaped, elongated cells with bipolar dendrites) and **Horizontal cells of Cajal** (small, spindle shaped, horizontally oriented cells, running parallel to the surface of the cortex) (Singh, 2014).

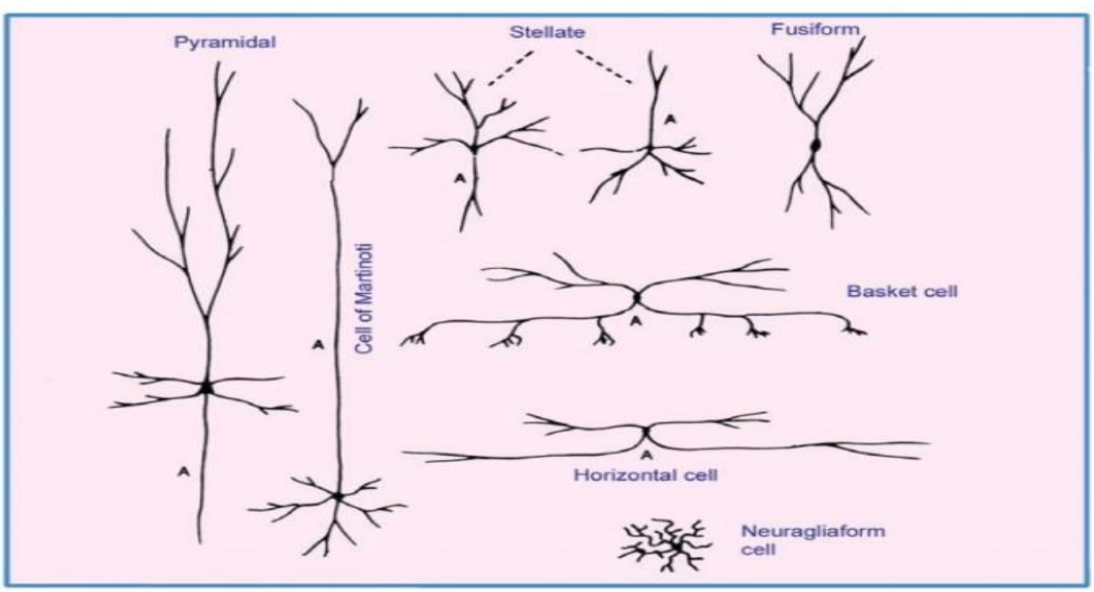

Fig. 2.8: Cell types found in the Cerebrum (*brainkart,* 2023)

The neocortex is arranged into six layers or laminae, each differing in morphology, size and types of neurons. The layers from the surface downwards are **Flexiform (Molecular) Layer 1 (**most superficial layer, comprising of sparse neurons, dendrites and axons of cells from the deeper layer), **External granular layer II** (contains a dense population of small pyramidal cells and stellate (granular) cells), **Pyramidal cell Layer III** (contains medium-sized pyramidal cells along with the cells of Martinotti), **Inner Granular Layer IV** (composed of densely packed stellate neurons), **Ganglionic Layer V** (consists mainly of large pyramidal cells and less stellate and Martinotti cells) and **Multiform Layer VI** (heterogenous, containing wide variety of cells with differing morphology e.g. pyramidal cells, martinotti cells, stellate cells (superficially) and fusiform cells (in the deeper layers) (Singh I., 2018).

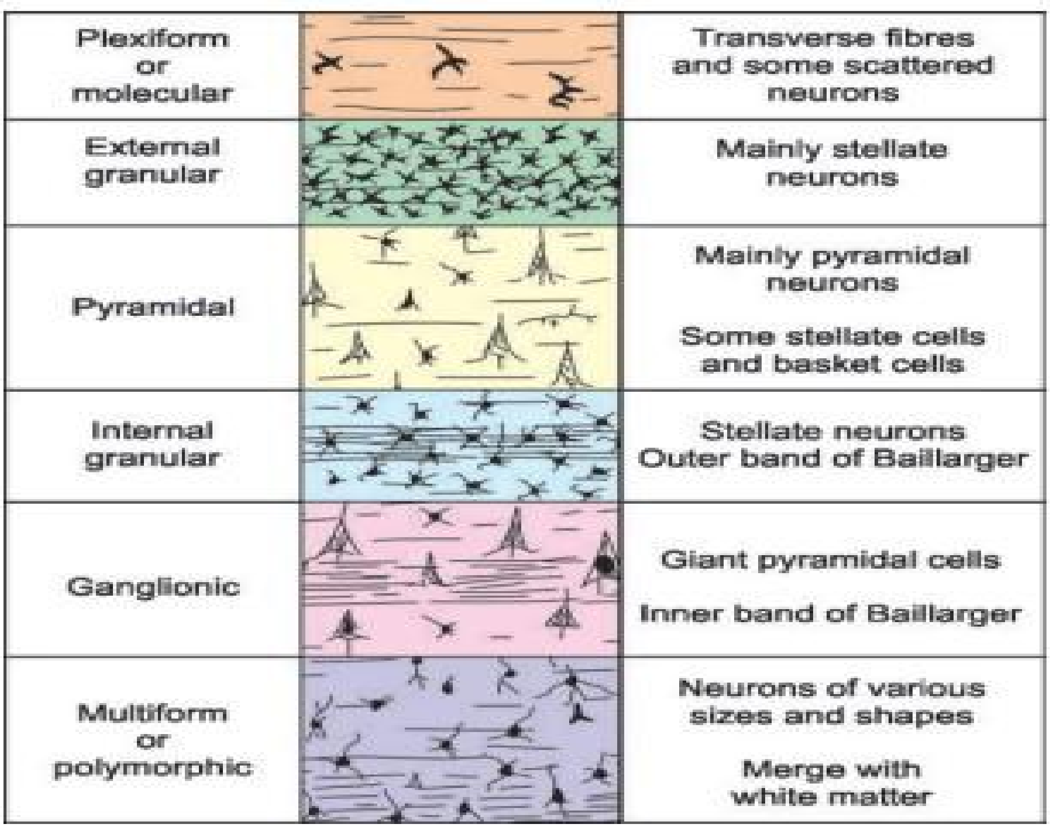

Fig. 2.9: Layers of the Cerebral neocortex (Singh, 2018).

The cerebral cortex is also composed of a mass of supporting cells called Neuroglia, which provide mechanical and metabolic support to the nerve cells of the cerebrum. They include **Astrocytes** (star-shaped cells, providing structural support and maintaining blood-brain barrier) (Abbott *et al.,* 2006), **Oligodendrocytes** (responsible for myelination of axons) (Fields, 2008), **Microglia** (involved in immune defense and phagocytosis) (Kettenmann et al., 2011) and **Ependymal cells** (involved in cerebrospinal fluid (CSF) production and circulation).

2.2.5. Functional Areas of the Cerebrum

The cerebral cortex is composed of numerous functional regions and units that process several signals and impulses. These areas are equally in charge of several distinct brain processes, such as higher intellectual, motor, and sensory capabilities. These functional areas are situated within the lobes of the cerebral cortex.

The frontal lobe is made up of the prefrontal cortex, premotor cortex, primary motor cortex (Brodmann area 6), Broca's area (Brodmann areas 44 and 45) which are responsible for voluntary movement, language and communication, short-term memory tasks, motivation, planning, making decisions, behavioural characteristics etc.

The parietal lobe plays a crucial role in processing proprioceptive and mechanoreceptive stimuli, including sensations of touch, position, vibration, pressure, pain, and temperature. Additionally, it is involved in learning, language comprehension, spatial awareness, and stereognosis—the ability to identify objects based on their size, shape, weight, and other distinguishing features. The primary somatosensory cortex (Brodmann areas 3,2,1), somatosensory association cortex (Brodmann areas 5, 7), and the secondary somatosensory cortex (Brodmann areas 40, 39) which forms part of the Wernicke's area, are all located here.

The occipital lobe contains the primary visual cortex (Brodmann Area 17) and is the center for the reception, processing and interpretation of visual information.

The temporal lobe houses the primary auditory cortex and Wernicke's area. It is responsible for interpreting sensory information and deriving meanings, which aids in the retention of visual memories and understanding language. It also plays a key role in translating and processing various sounds and tones.

The insular cortex is involved in processing and integrating taste, visceral and pain sensations, as well as vestibular functions.

The limbic lobe comprises of regions involved in emotional modulation, regulation of visceral and autonomic functions, as well as learning and memory processes (Ocran, 2024; Jawabri and Sharma, 2023).

CHAPTER THREE

MATERIALS AND METHOD

3.1 MATERIALS

Animals: Thirty-five (35) Adult Wistar rats

Extract: Ethanol leaf extract of *Ficus exasperata*

Feed: Growers Mash

Instrument: Plastic cages, ceramic plates, cotton wool, disposable gloves, specimen bottles, forceps, surgical blade, orogastric tube, 5ml syringe, masking tape, weighing balance, microtome, slide tray, tissue embedding station, light microscope, measuring cylinder.

Reagent: 10% formal saline, chloroform, distilled water, eosin, haematoxylin, paraffin wax, xylene.

3.2 METHOD

3.2.1 PROCUREMENT AND PREPARATION OF PLANT EXTRACT

Procurement of Plant

The leaves of *Ficus exasperata* were collected in Ehor town, Uhumwonde local government area of Edo State, Nigeria. The Plant was identified by a botanist in the department of Plant Biology and Biotechnology, Faculty of Life Sciences, University of Benin, Benin city, Edo State.

Preparation of plant extract

A tubular filter made of stainless-steel and having high filtration precision was employed. After maceration, the extraction was performed using basic extraction and fractionation procedures to determine the quality and quantity of bioactive compounds. Ethanol was used for solvent extraction.

The phytochemicals were purified through several chromatographic techniques including paper chromatography and thin-layer chromatography. Finally, UV spectroscopy was used to characterize the compounds. The plants were collected accurately and timely, and their authenticity was confirmed through expert drying and proper grinding.

Bioactive compounds were isolated through extraction and fractionation, and their quantity and quality were determined. The following tests were used to identify the bioactive substances:

Dragendorff test for alkaloids.

Liebermann-Burchard's test for steroids.

Gold becter's test for tannins.

Shinoda's test for flavonoids.

Ferric chloride test for phenolic compounds.

Biuret test for protein.

3.2.2 ANIMAL CARE AND EXPERIMENTATION

In this research, thirty-five (35) adult Wistar rats, weighing about 110g – 200g were experimented upon. The animals were bought and tended for at the animal care center of the department of anatomy, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin city, Edo State. The animals were then kept in carefully cleaned and disinfected cages, where they underwent acclimatization over a period of two weeks. During this period, they were adequately fed with livestock's growers mash, produced by Top Feed limited, Sapele, Delta State, Nigeria, along with daily access to clean water. To ensure adequate ventilation, the plastic cages used were fitted on the lid with wire gauze. Regular cleaning of the cage was carried out at intervals to prevent infections due to unhygienic environment.

The procedures for the maintenance of the experimental animals, were carried out according to the international guidelines for the care and use of laboratory animals in scientific researches (Russell and Burch, 1959).

3.2.3 EXPERIMENTAL DESIGN

After two weeks of acclimatization to animal house settings, the thirty-five rats were randomly distributed to Six (6) groups; A, B, C, D, E, F, of six (6) rats each, except the control group (A) which had five (5) rats. They were administered daily, with oral doses of the ethanol leaf-extract of *Ficus exasperata*, over a period of 4 weeks, using an orogastric tube. The table below shows the volume of extract administered to each group.

GROUPS	**DOSAGES**
Group A	Served as the control group.
Group B	Treated with 200 mg/kg of *Ficus exasperata*
Group C	Treated with 400 mg/kg of *Ficus exasperata.*
Group D	Treated with 600 mg/kg of *Ficus exasperata*
Group E	Treated with 800 mg/kg of *Ficus exasperata*
Group F	Treated with 1000 mg/kg of *Ficus exasperata*

Table 3.1 Showing experimental design

3.2.4 METHOD OF SACRIFICE AND TISSUE COLLECTION

At the end of the experimental period, the final weight of the rats was taken using compact electric weighing scale calibrated in grams. The rats were then placed in an enclosed container containing Cotton wool, soaked with 50ml chloroform, for about 30-50 sec for anaesthetization, after which the Rats were placed on the dissection table, in a supine position.

A cranial incision was made to expose the brain tissue and the cerebrum was harvested, weighed and fixed in 10% formal saline in a universal bottle for histological analysis. In turn, blood samples were collected through the inferior vena cava and the heart, via venous and cardiac puncture respectively, using 5ml syringes and were transferred into an EDTA bottle for biochemical analysis.

3.2.5 HISTOLOGICAL TECHNIQUE

1. The cerebrum was excised and promptly transferred into 10% formal saline for fixation. The tissue was dehydrated by passing through an ascending grade of alcohol (70%, 90%, 96%, and absolute alcohol 100%) respectively.
2. Alcohol was cleared from the tissue using xylene for an hour, to completely remove any traces of it.
3. The tissue was infiltrated with molten paraffin wax for 22 hours at a temperature range of 30°C-60°C.
4. Embedding of the tissue was carried out with the use of an embedding mold. The molten paraffin wax was poured into the embedding mold and then the infiltrated tissue was placed into it, such that the sections can be easily cut both longitudinally and then transversely. It was then put in the cold chamber to solidify in a plastic cassette.

5. This is allowed to cool and form a block; afterwards, it is separated (this is also called De-blocking). The tissue is ready for sectioning.
6. The sectioning was carried out on a rotary microtome and sectioned at a thickness of 5 microns.
7. Sections came out in ribbons and were placed in 20% alcohol for spreading of the tissue, and it was allowed to float in a water bath at a temperature of 30°C.
8. The sectioned tissues were picked from the water bath using a microscope slide and placed on the hotplate to melt excess wax and dry the tissue on the slide.
9. The sectioned tissues were placed in xylene for 5 minutes to remove paraffin wax from the tissues.
10. Hydration was carried out by passing the tissues through descending grades of alcohol (100%, 96%, 90%, and 70%) and water for 5 minutes each.
11. Staining was done using haematoxylin and eosin dyes. The tissues were stained in haematoxylin for 10 minutes and rinsed in water. After that, they were differentiated in 1% acid alcohol briefly and blued to develop the color.
12. They were subsequently counterstained with eosin and rinsed in 90% alcohol. Dehydration was done in 90% alcohol and two changes of absolute alcohol at 5 minutes each.
13. The sections were thereafter cleared in xylene for 5 minutes.
14. Finally, the slides were mounted with a cover slip, ready to be viewed under a microscope.

3.2.6 BIOCHEMICAL ANALYSIS

The biochemical analysis of the sample was carried out to determine the effect of the extract on the activities of oxidative stress/antioxidant markers, which include Catalase, Superoxide Dismutase (SOD), Glutathione peroxidase (GPx) and Malondialdehyde (MDA).

3.2.6.1 DETERMINATION OF CATALASE (CAT) ACTIVITY

Catalase (CAT) activity was estimated by the method described by Cohen et al., (1970).

REAGENTS

Hydrogen peroxidase (H2O2), Sulphuric acid (6M) H2SO4

PREPARATION OF REAGENT

0.01M KMnO4 was prepared by distilling 0.158g of KMnO4 in 100ml of distilled water. Phosphate buffer (pH 7.4) 0.426g of NaHPO4 and 0.240g of NaH2PO4 was weighed and dissolved in 100ml of distilled water. 6M H2SO4 and 32.3ml of conc. H2SO4 was added to 66.7ml of distilled water.

PROCEDURE

To an unknown volume of plasma (0.5ml), 5.0ml of H2O2 was added. This was mixed by inversion and allowed to stand for 30min. The reaction was stopped by adding 1.5ml of 6M H2SO4 and 7ml of 0.01M KMnO4. These were mixed by inversion and allowed to stand for 10min. The absorbance was read at 480nm within 30-60 seconds against distilled water. The enzyme blank was run simultaneously with 1.0ml of distilled water instead of hydrogen peroxide. The enzyme activity was expressed as μmoles of H2O2 decomposed/min/mg/protein.

CALCULATION

$$\text{Activity} = \frac{\text{OD/min} \times V}{M \times V \times L \times Y}$$

Where OD = Absorbance, L= Light path, V= Total volume of reaction sample, M= Molar coefficient of H_2O_2 (40/m/cm), V= Volume of sample, Y= mg protein in the sample.

3.2.6.2 ESTIMATION OF SUPEROXIDE DISMUTASE ACTVITY (SOD)

This was determined according to the methods of Masra and Fridorich (1972)

PRINCIPLE

Adrenaline undergoes auto oxidation rapidly to adrenochrome whose concentration can be determined at 420nm with the aid of a spectrophotometer. The auto oxidation of adrenaline depends on the presence of super-anions. Superoxide dismutase inhibits the auto-oxidation of adrenaline by catalyzing the breakdown of superoxide anion. The degree of inhibition reflects the activity of SOD which is determined at 420nm.

REAGENT AND PREPARATION

Carbonate buffer (0.05M) pH 10.2: This was prepared by dissolving 0.2014g of Na_2CO_3, 0.2604g $NaHCO_3$ and 0.0372g of EDTA in 100ml of distilled water. The pH was adjusted to 10.2 using Sodium hydroxide.

Hydrochloric acid (0.005M): This was prepared by adding 0.044 concentration of HCL to 99.96mls of distilled water.

Adrenaline solution (0.3mM): This was prepared by dissolving 0.01098g of adrenaline in 100mls of 0.005M HCL solution.

Plasma volume of 100ml was mixed with 125ml of carbonate buffer and 150ml of adrenaline solution. 100ml of distilled water was mixed with 1.25ml of carbonate buffer as reference sample. These were mixed and absorbance read at 420nm.

These were mixed and read at 420nm

$$\%\text{inhibition} = \frac{(\text{O.D test} - \text{ODref}) \times 100}{\text{OD test}}$$

Enzyme concentration can thus be calculated: $\text{unit/mg protein} = \frac{\%\ \text{inhibition}}{50 \times Y}$

Where Y = mg of protein in the volume of sample used.

3.2.6.3 ESTIMATION OF GLUTHATHIONE PEROXIDASE (GPx)

This was determined according to Nyman (1959)

PRINCIPLE

This is based on the oxidation of pyrogallol to purpurogallin by peroxidase activity, resulting in a deep brown color disposition, read at 420nm.

REAGENT AND PREPARATION

Pyrogallol (20mM): 0.2552g of pyrogallol was dissolved in 100mls of distilled water.

PROCEDURES

To an aliquot of plasma (0.2ml), 2.5ml of phosphate buffer, 2.5ml of H2O2, 1.5ml of distilled water and 2.5ml of pyrogallol was added. The reaction was allowed to stand for 30mins at room temperature. A deep brown color was formed which was read at 480nm.

CALCULATIONS

$$\text{Activity} = \frac{\text{OD/min x vt x Df}}{\text{E x Vs x Y}}$$

OD= Absorbance of test, Vt= Total volume of reaction mixture, Df= Dilution factor = 1, E= Molar extinction co-efficient (12/m/cm), Vs= Volume of sample, Y= mg of protein used.

3.2.6.4 DETERMINATION OF MALONDIALDEHYDE (MDA)

Malonaldehyde activity was determined using the thiobarbituric acid assay (Buege and Aust, 1978).

PRINCIPLE

Malonaldehyde, a product of lipid peroxidation reacts with thiobabituric acid (TBA) to give a red species.

PROCEDURES

A volume of plasma (1.0ml) was added to 2.0ml of TCA-TBA-HCL and mixed thoroughly. The solution was heated for 15mins in a boiling water bath. After cooling, the flocculent precipitate was removed by centrifuged at 1000g for 10min. The absorbance was determined using the formula;

$$\text{MDA (mol/mg protein)} = \frac{\text{A x V x 100}}{\text{M x V x Y}}$$

A= Absorbance, V= Total volume of reaction mixture, M= Molar extinction coefficient, V= volume of the sample, Y= mg protein.

3.2.7 STATISTICAL ANALYSIS

Results obtained were expressed as Mean ± SEM (standard error of mean). Differences among the means were determined by one-way analysis of variance (ANOVA). Values were considered statistically significant if P value is less than 0.05 ($p < 0.05$). LSD Post Hoc test was used to determine where the significance lay. Statistical package Graphpad Prism version 9 for Windows was used to analyze the data obtained in the study.

CHAPTER FOUR

RESULTS

4.1 PHYTOCHEMICAL ANALYSIS

The Phytochemical screening of the ethanol leaf extract of *Ficus exasperata*, revealed the presence of several phytochemicals which are presented in the table below.

Table 4.1 showing the active phytochemicals contained in the leaf extract of *Ficus exasperata*

PHYTOCHEMICALS	**RESULTS**
Flavonoids	++
Tannins	+
Saponins	+
Phlobatannins	-
Glycosides	-
Alkaloids	++
Terpenoides	-
Sterols	-

KEY:

-	ABSENT
+	PRESENT
++	LARGELY PRESENT

4.2 STATISTICAL ANALYSIS

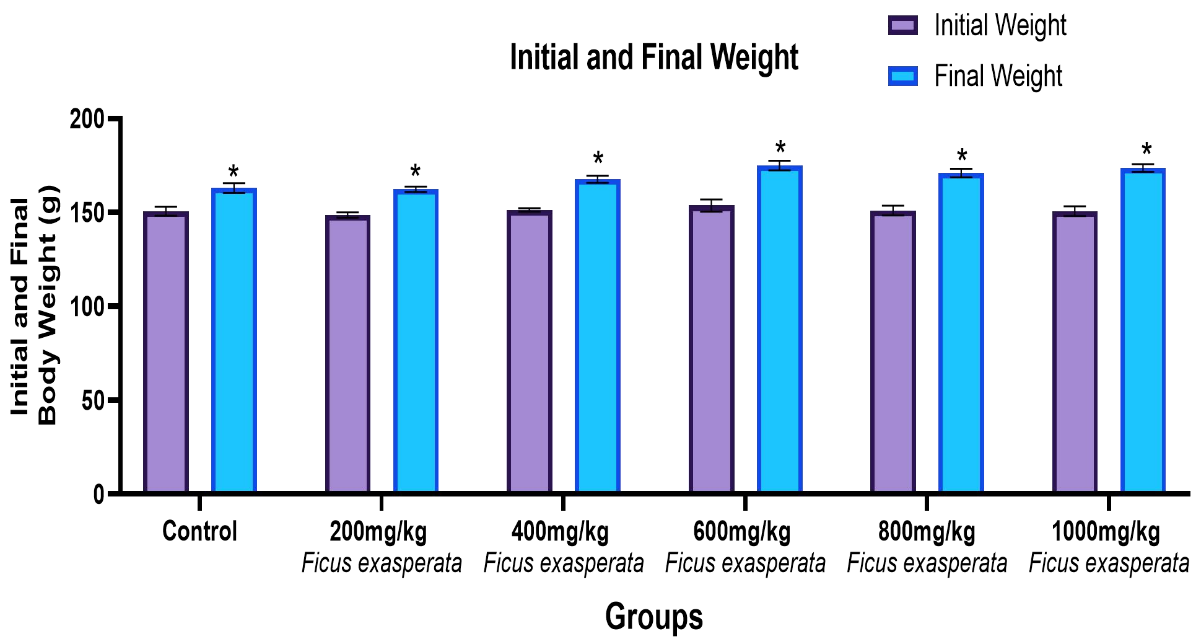

Chart 4.1: Showing Initial and Final Body weight after administration.

Values are given as mean ± SEM.

There was a statistically significant increase (*$p < 0.05$) in the final weight across within and across all experimental groups when compared with their respective initial weights.

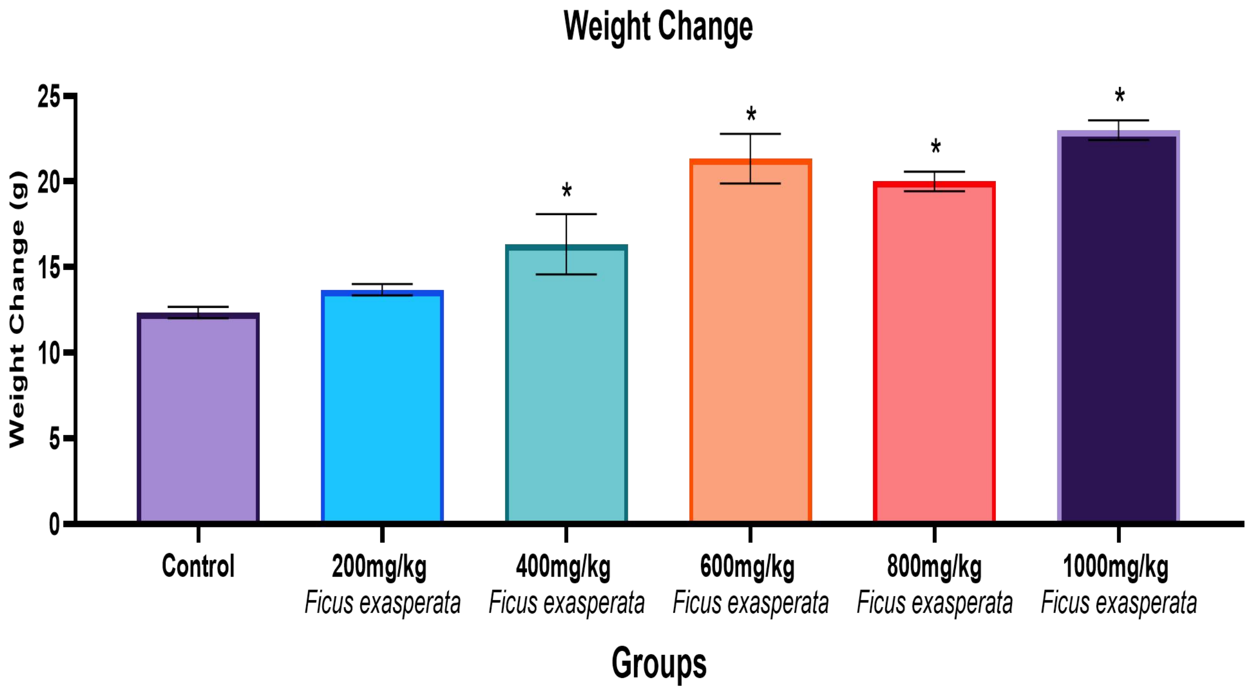

Chart 4.2: Showing weight change after administration. Values are given as mean ± SEM. *represents statistically significant difference ($p < 0.05$).

There was a statistically significant increase ($p < 0.05$) in rats treated with 400mg/kg, 600mg/kg, 800mg/kg and 1000mg/kg of *Ficus exasperata leaf extract*, compared with the control group.

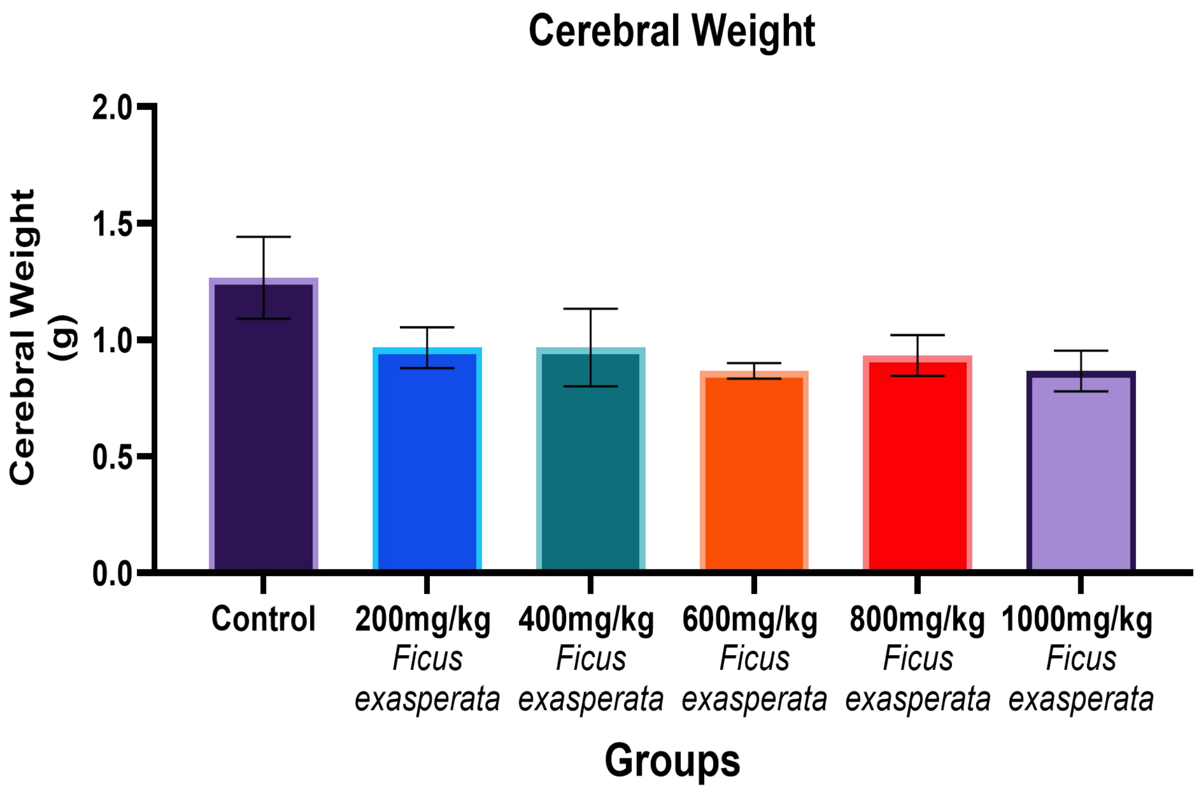

Chart 4.3: Cerebral weight after administration.

Values are given as mean ± SEM.

There was no statistically significant difference ($p < 0.05$) in Cerebral weight of rats treated across the groups, when compared with the control group.

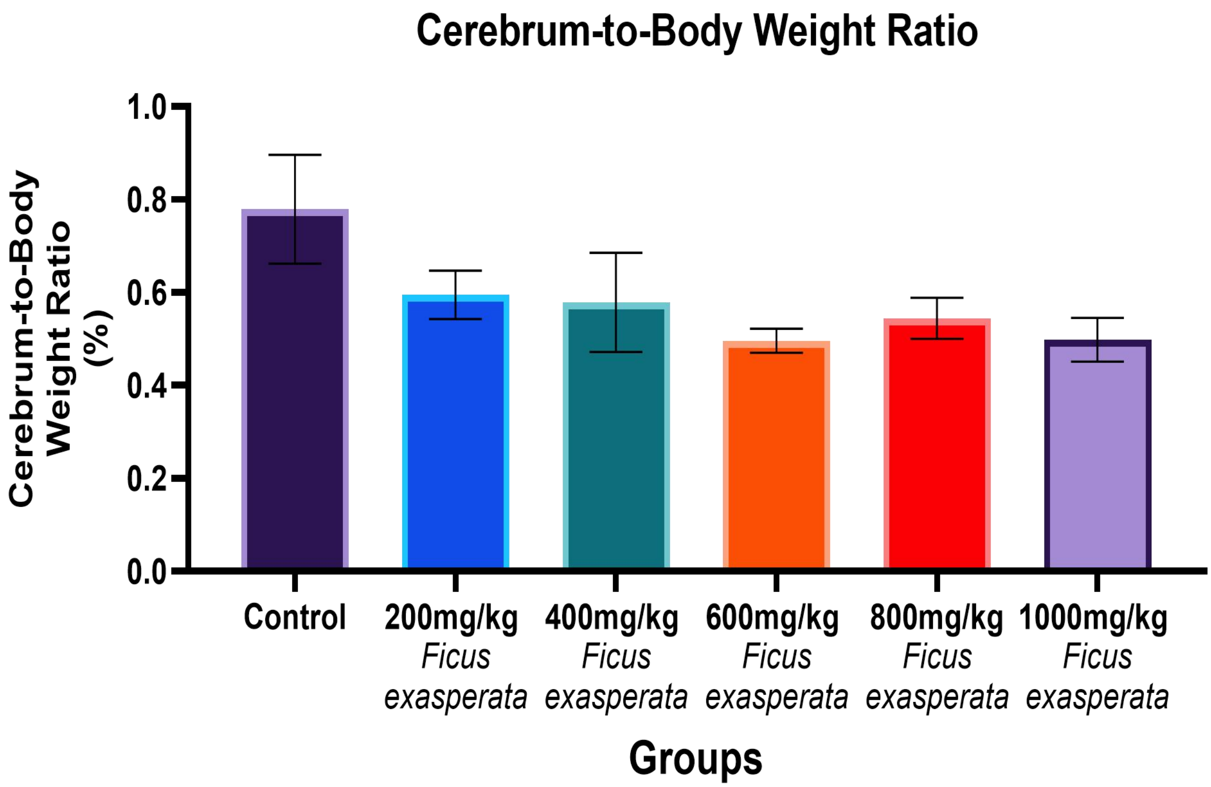

Chart 4.4: Showing Cerebrum to Body weight ratio after administration.

Values are given as mean ± SEM.

There was no statistically significant difference ($p < 0.05$) in Cerebral to body weight ratio (%) for rats treated across the groups, when compared with control group.

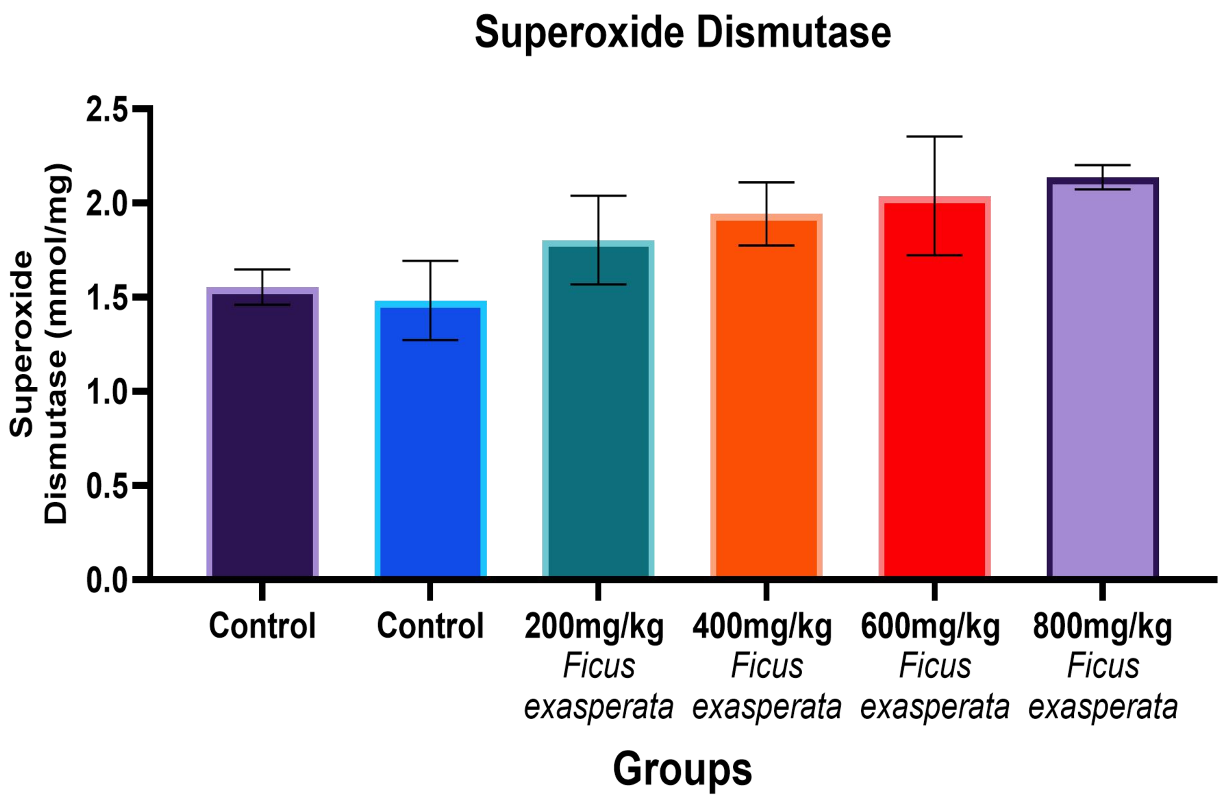

Chart 4.5: Showing superoxide dismutase activity in the Cerebrum of control and treatment groups after administration.

There was no statistically significant difference ($p < 0.05$) in Superoxide dismutase activity across the groups, when compared with the control group.

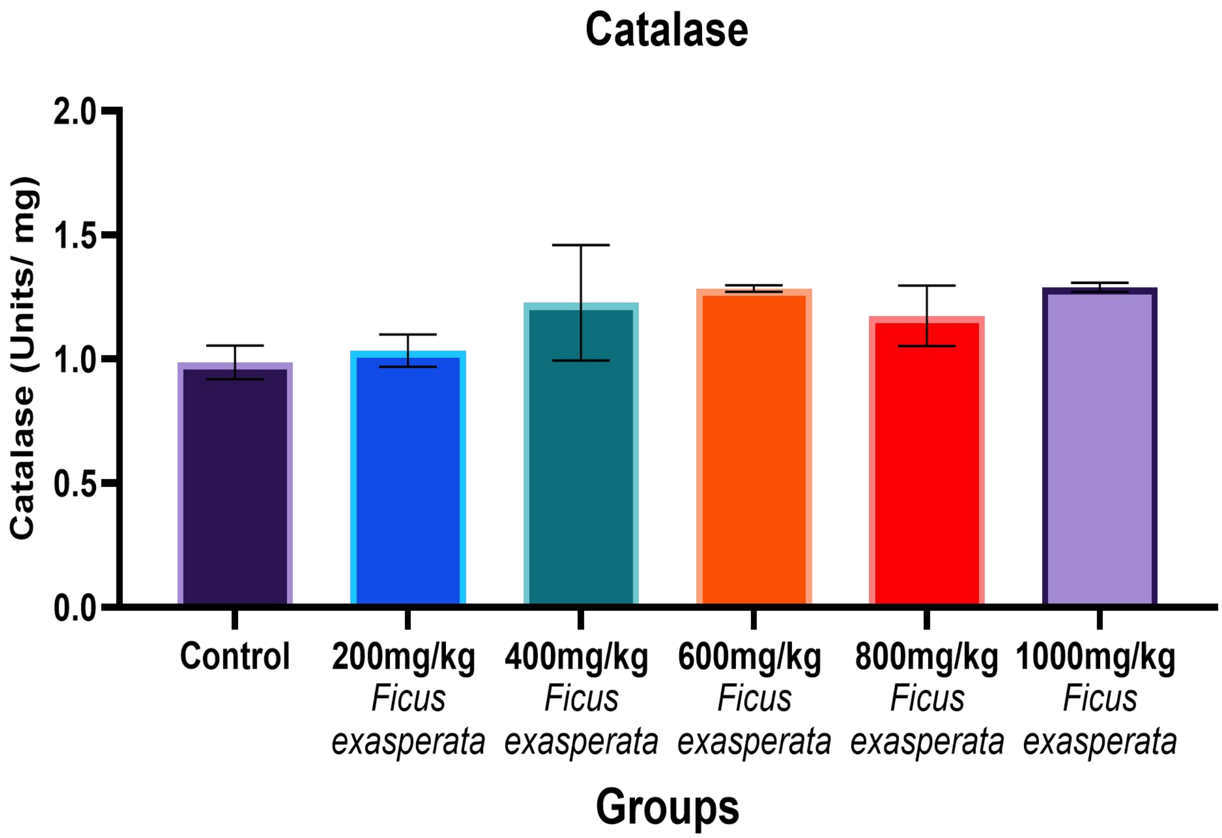

Chart 4.6: Showing catalase activity in the Cerebrum of control and treatment groups after administration.

Values are given as mean ± SEM.

There was no statistically significant difference ($p < 0.05$) in Catalase activity across the groups, compared with the control group.

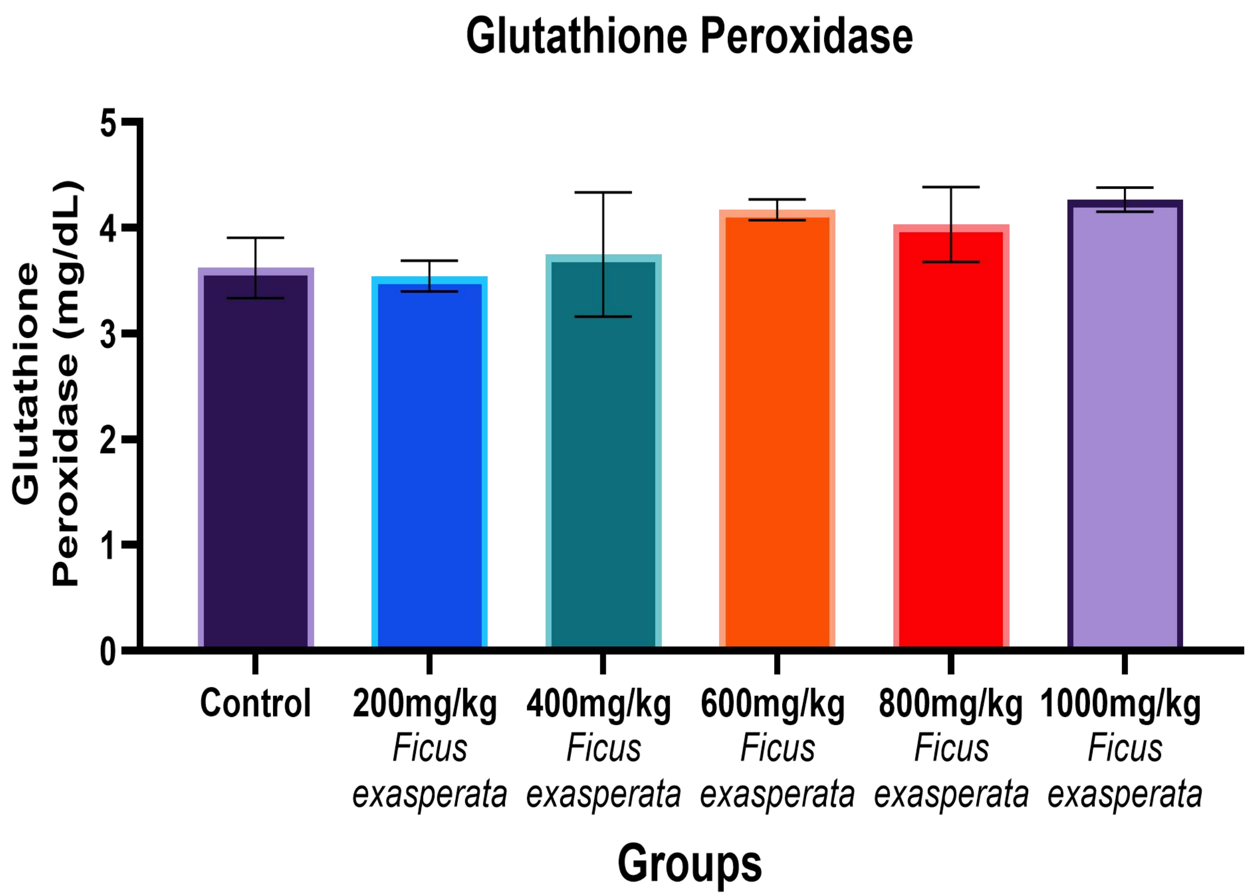

Chart 4.7: Showing glutathione Peroxidase activity in the Cerebrum of control and treatment groups after administration.

Values are given as mean ± SEM.

There was no statistically significant difference ($p < 0.05$) in Glutathione peroxidase activity across the groups, compared with the control group.

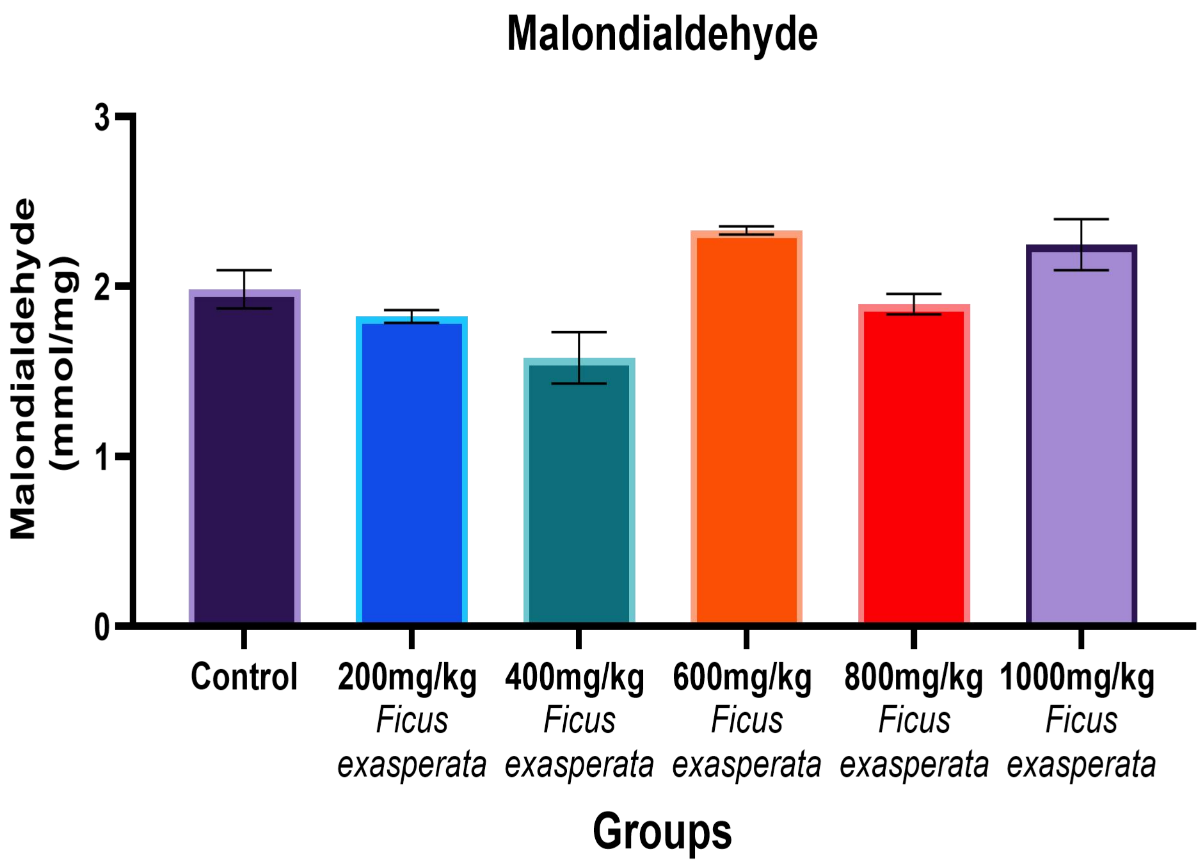

Chart 4.8: Showing lipid peroxidation activity in the Cerebrum of control and treatment groups after administration.

Values are given as mean ± SEM.

There was no statistically significant difference ($p < 0.05$) in Glutathione peroxidase activity across the groups, compared with the control group.

4.3 HISTOLOGICAL ANALYSIS OF CEREBRUM.

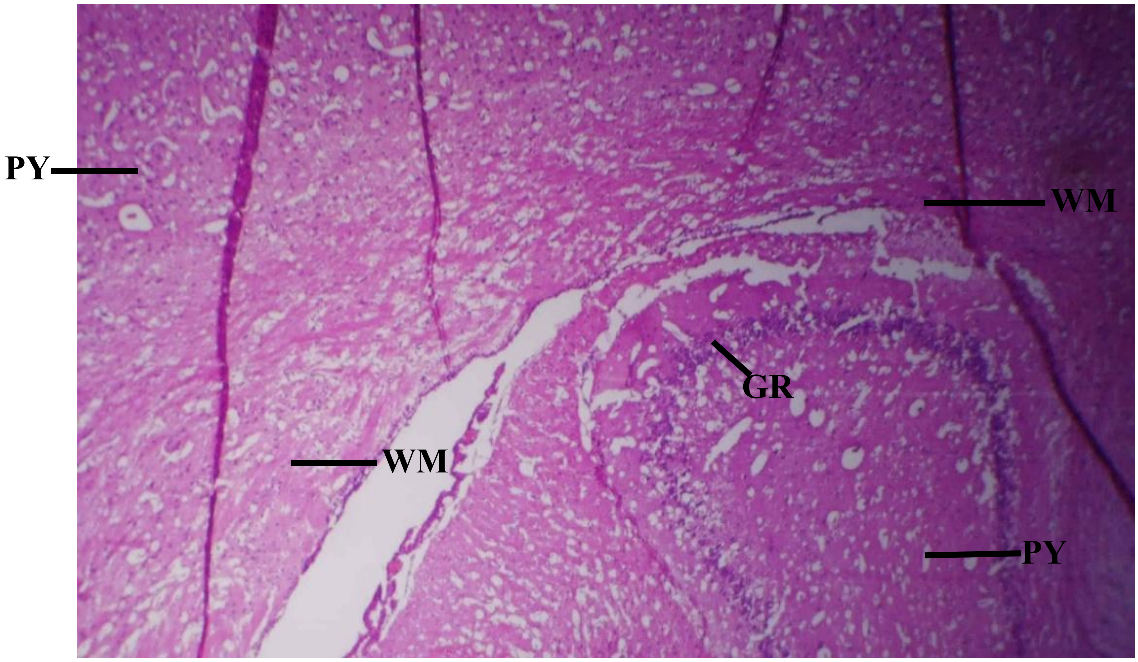

Plate 1: Showing normal architecture of rat (group A) cerebrum: white matter (WM), granular layer (GR), pyramidal layer (PY): HandE 40 X.

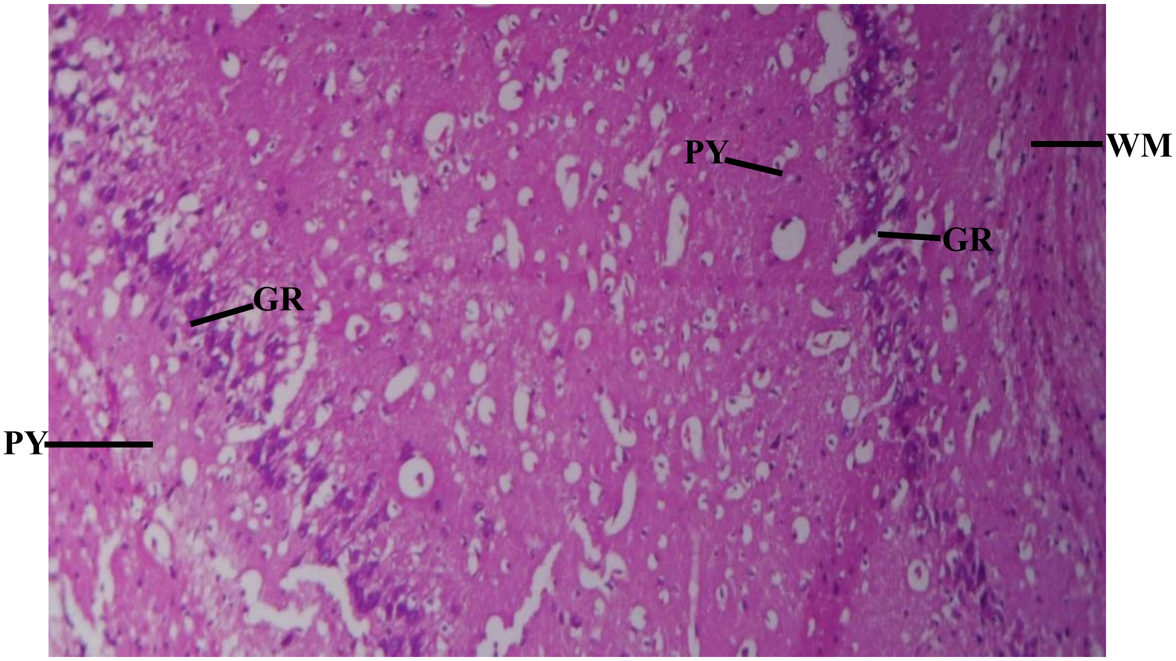

Plate 2. Showing normal architecture of rat (group A) cerebrum: white matter (WM), granular layer (GR), pyramidal layer (PY): HandE 100 X.

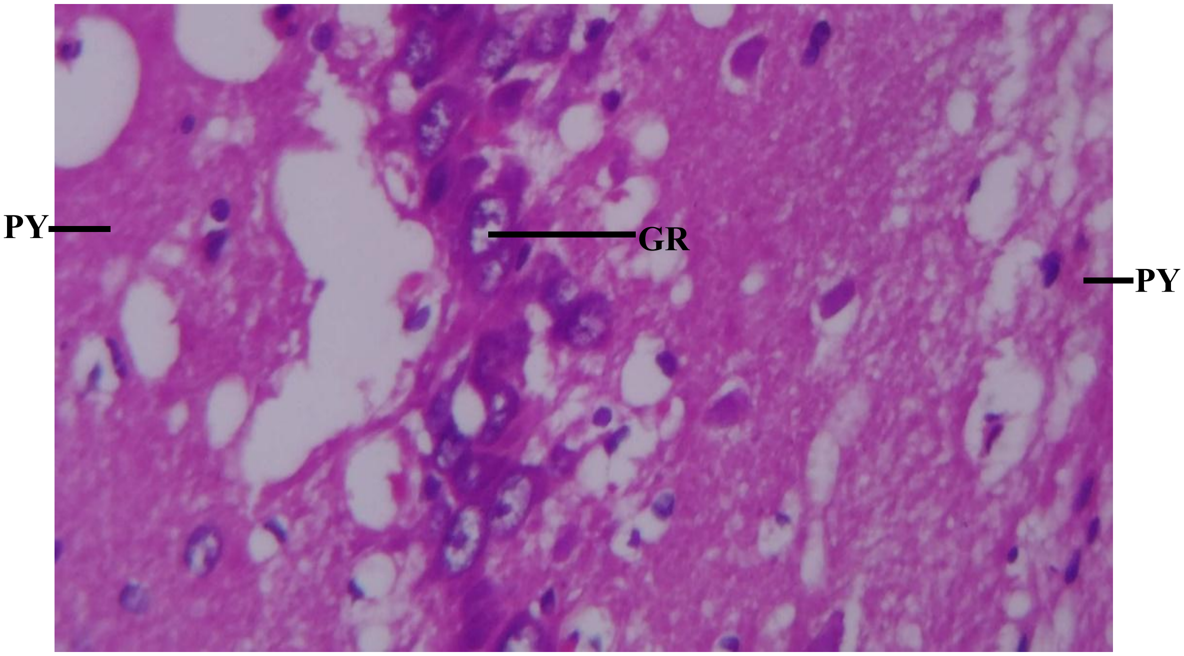

Plate 3. Showing normal architecture of rat (group A) cerebrum: white matter (WM), granular layer (GR), pyramidal layer (PY): HandE 400 X.

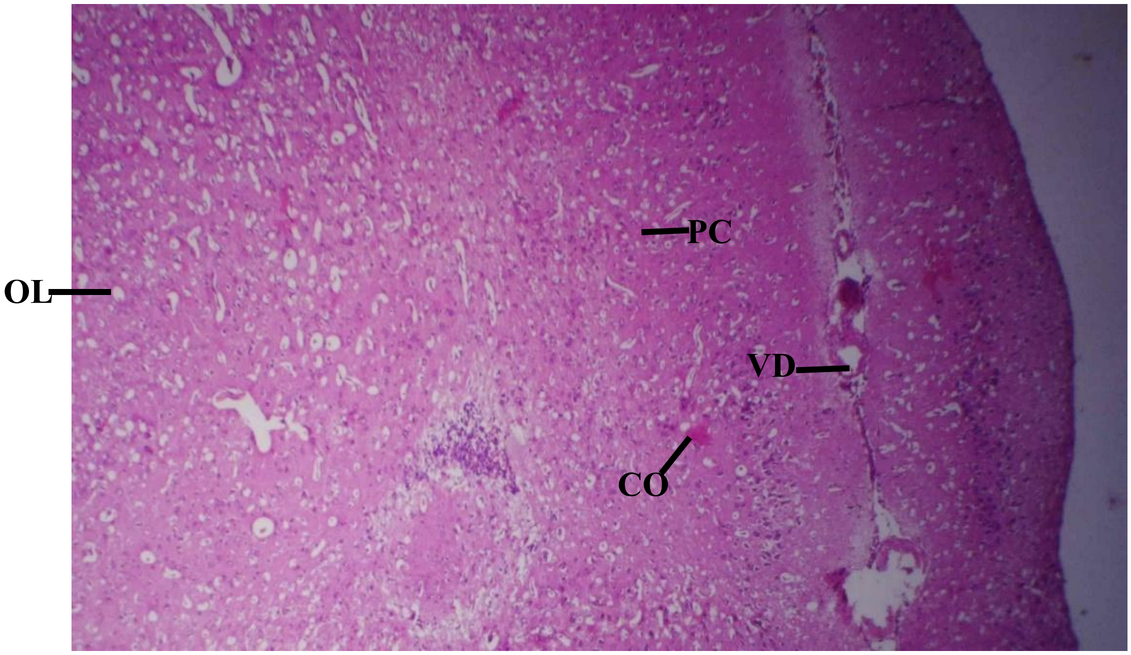

Plate 4. Rat cerebrum given 200mg Extract show: cerebral vasodilatation (VD) and congestion (CO), normal pyramidal cells (PC) and oligodendrocytes (OL): HandE 40 X.

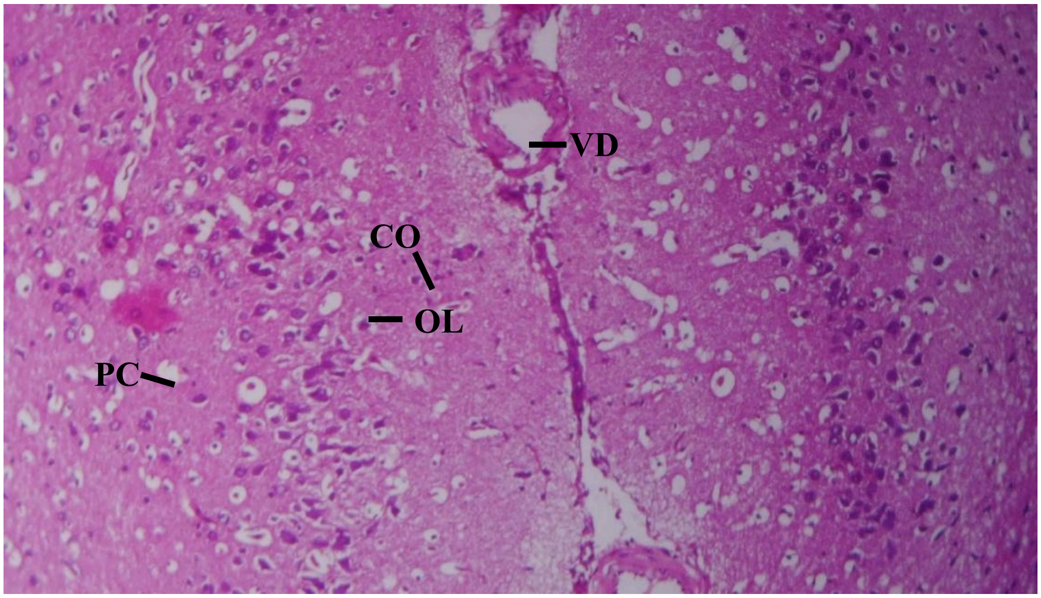

Plate 5. Rat cerebrum given 200mg Extract show: cerebral vasodilation (VD) and congestion (CO), normal pyramidal cells (PC) and oligodendrocytes (OL): HandE 100 X.

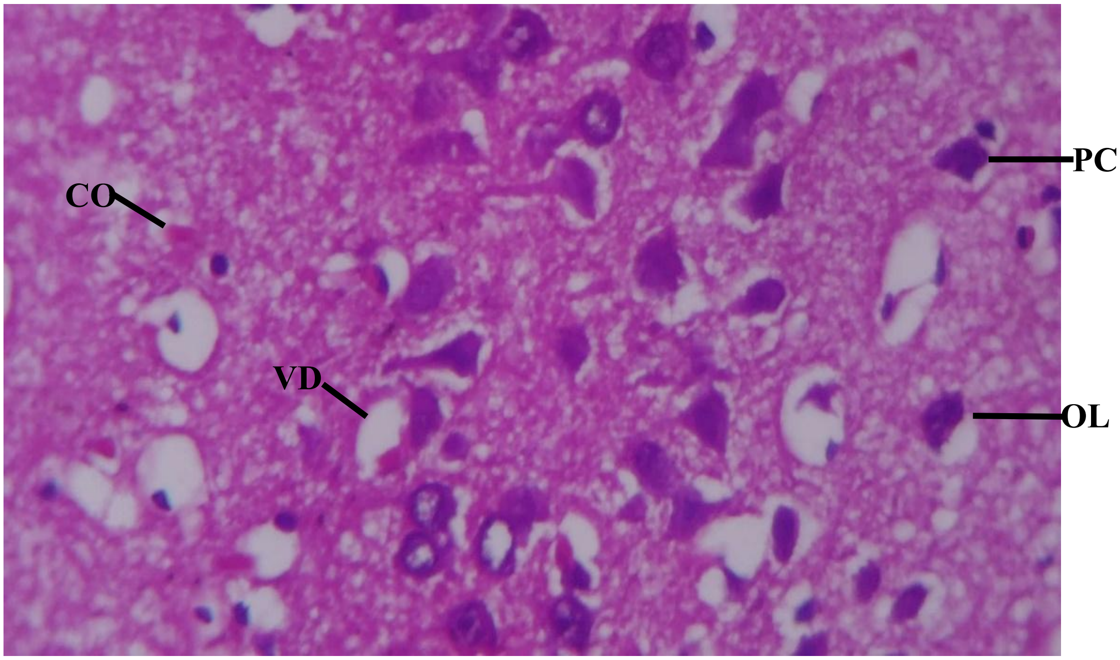

Plate 6. Rat cerebrum given 200mg Extract show: cerebral vasodilatation (VD) and congestion (CO), normal pyramidal cells (PC) and oligodendrocytes (OL): HandE 400 X.

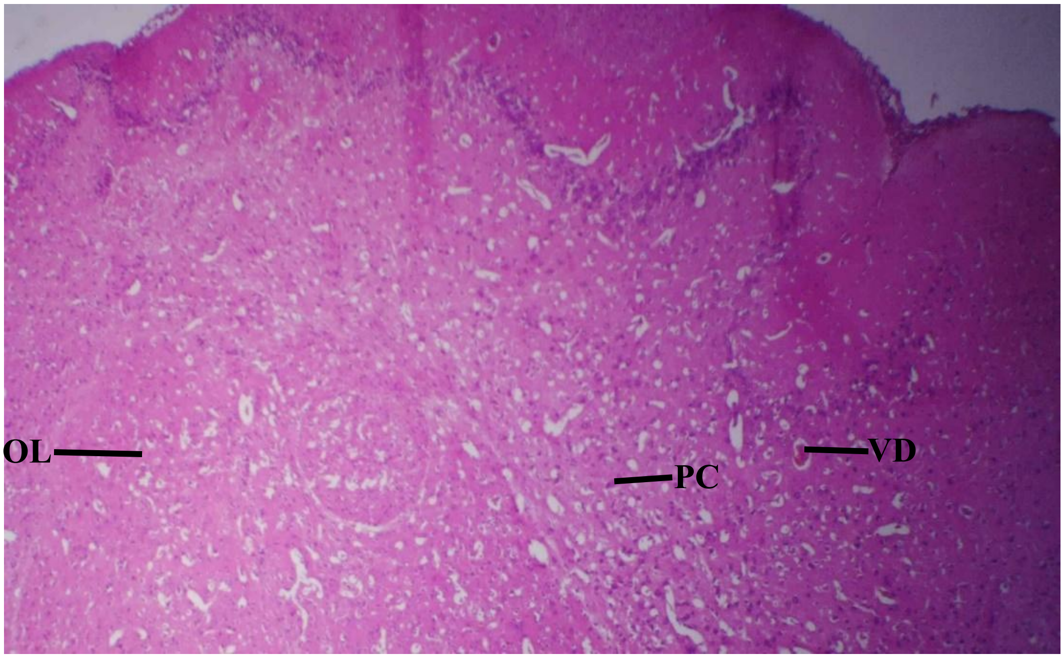

Plate 7. Rat cerebrum given 400mg Extract show: cerebral vasodilatation (VD), normal oligodendrocytes (OL) and pyramidal cells (PC): HandE 40 X.

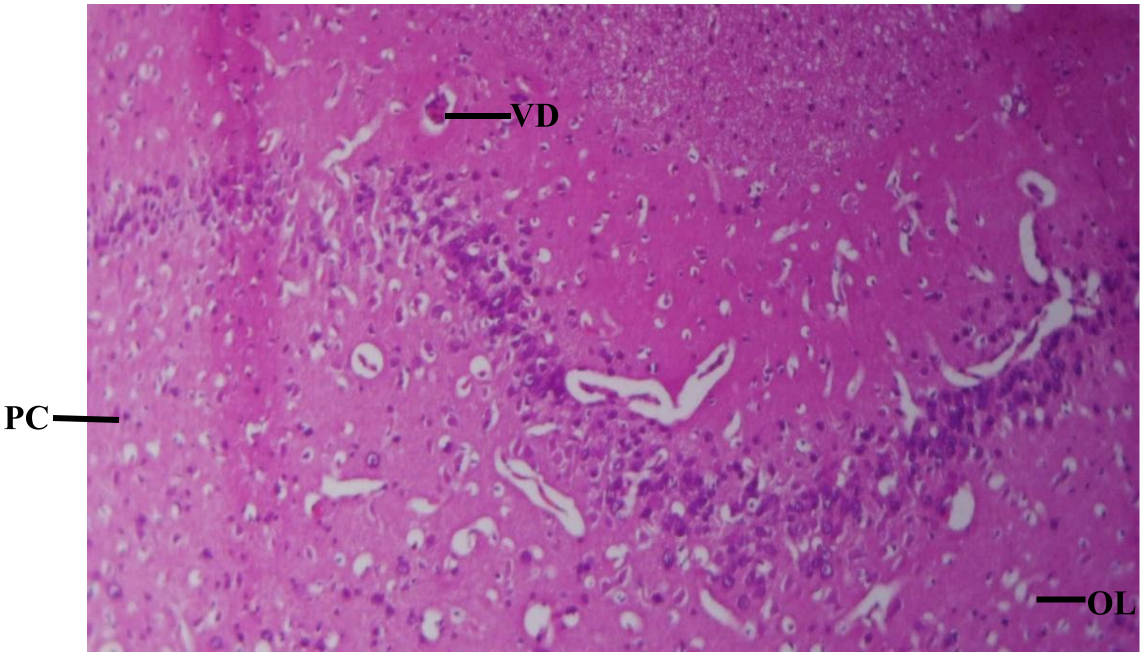

Plate 8. Rat cerebrum given 400mg Extract show: cerebral vasodilatation (VD), normal oligodendrocytes (OL) and pyramidal cells (PC): HandE 100 X

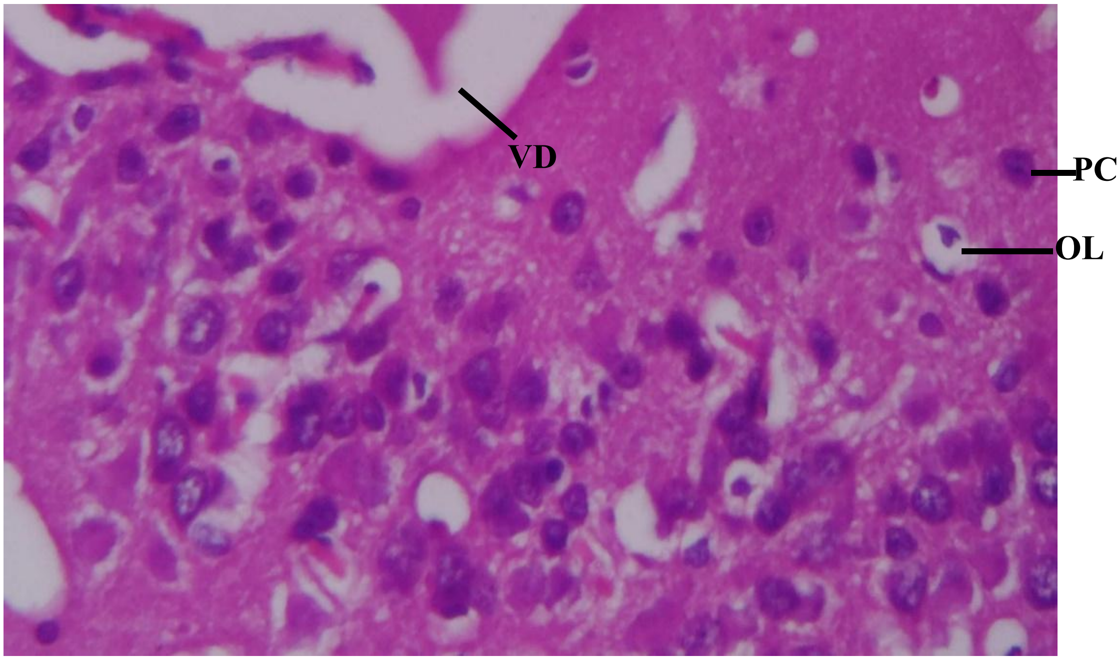

Plate 9. Rat cerebrum given 400mg Extract show: cerebral vasodilatation (VD), normal oligodendrocytes (OL) and pyramidal cells (PC): HandE 400

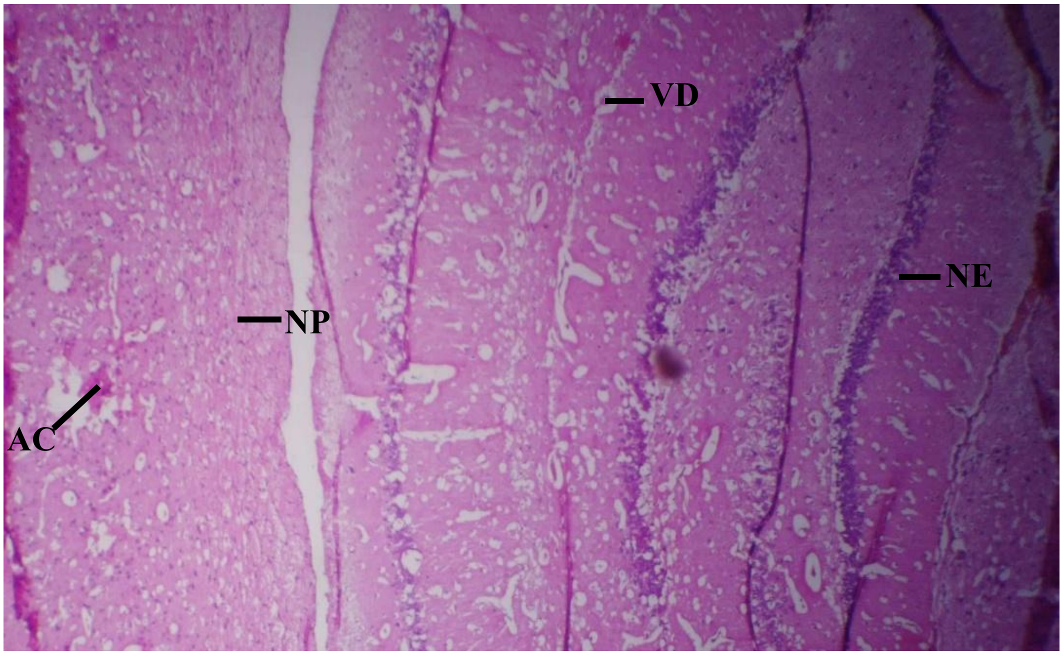

Plate 10. Rat cerebrum given 600mg extract show: cerebral vasodilatation (VD) and congestion (AC), normal granular layer neurons (NE) and neuropil (NP): HandE 40 X.

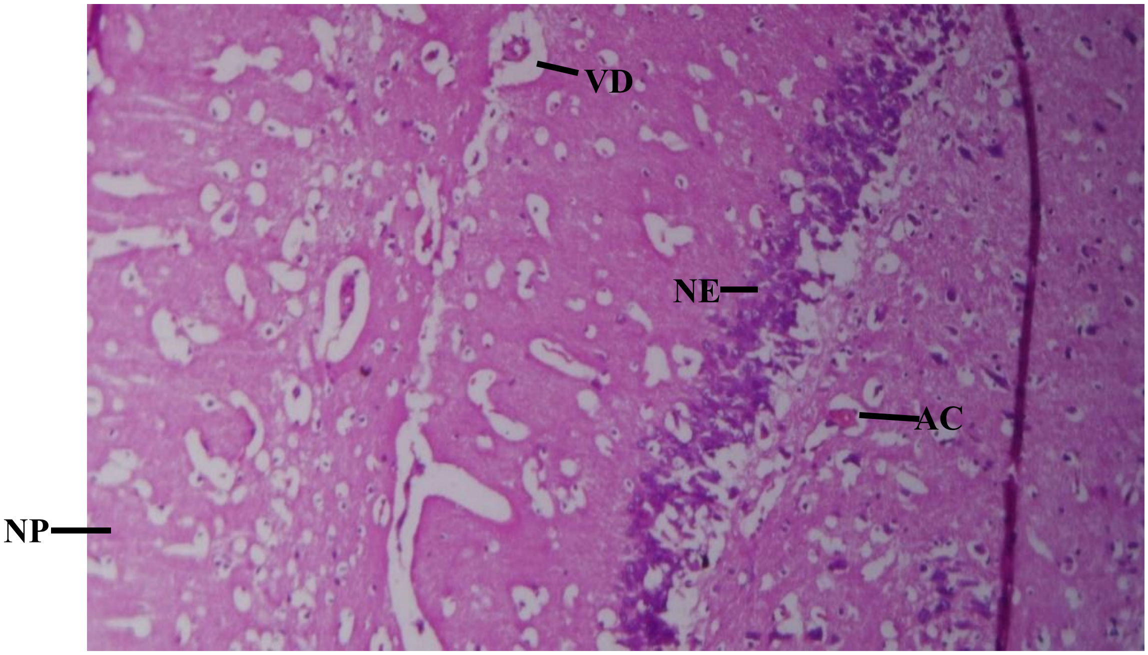

Plate 11. Rat cerebrum given 600mg extract show: cerebral vasodilatation (VD) and congestion (AC), normal granular layer neurons (NE) and neuropil (NP): HandE 100 X.

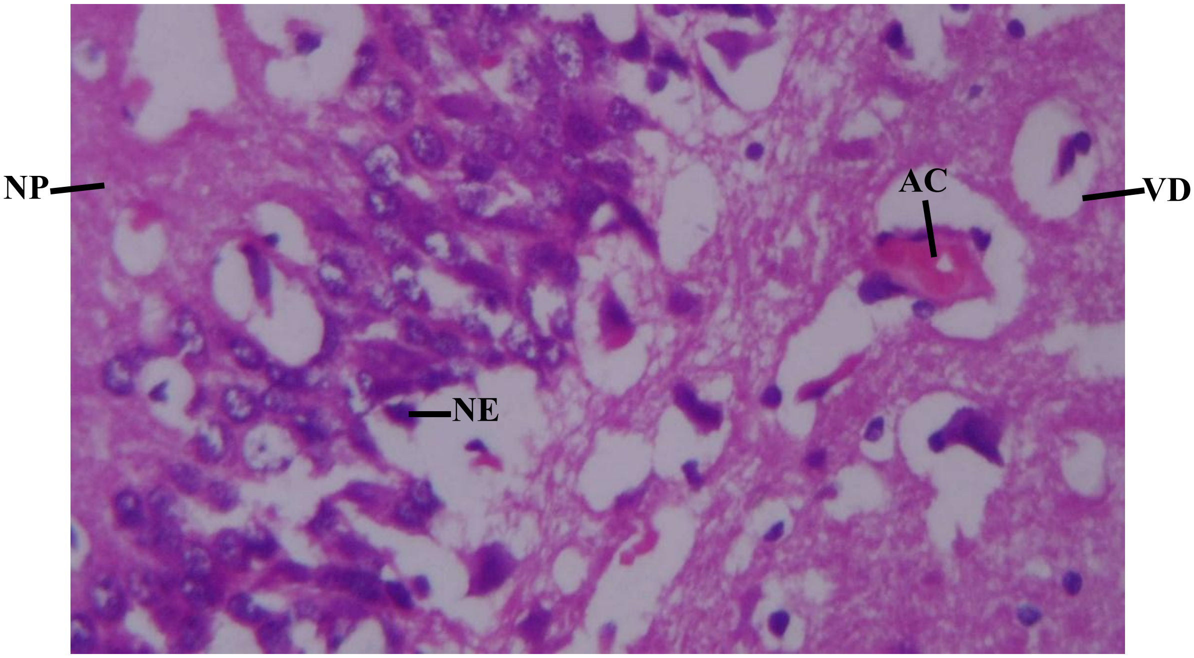

Plate 12. Rat cerebrum given 600mg extract show: cerebral vasodilatation (VD) and congestion (AC), normal granular layer neurons (NE) and neuropil (NP): HandE 400 X.

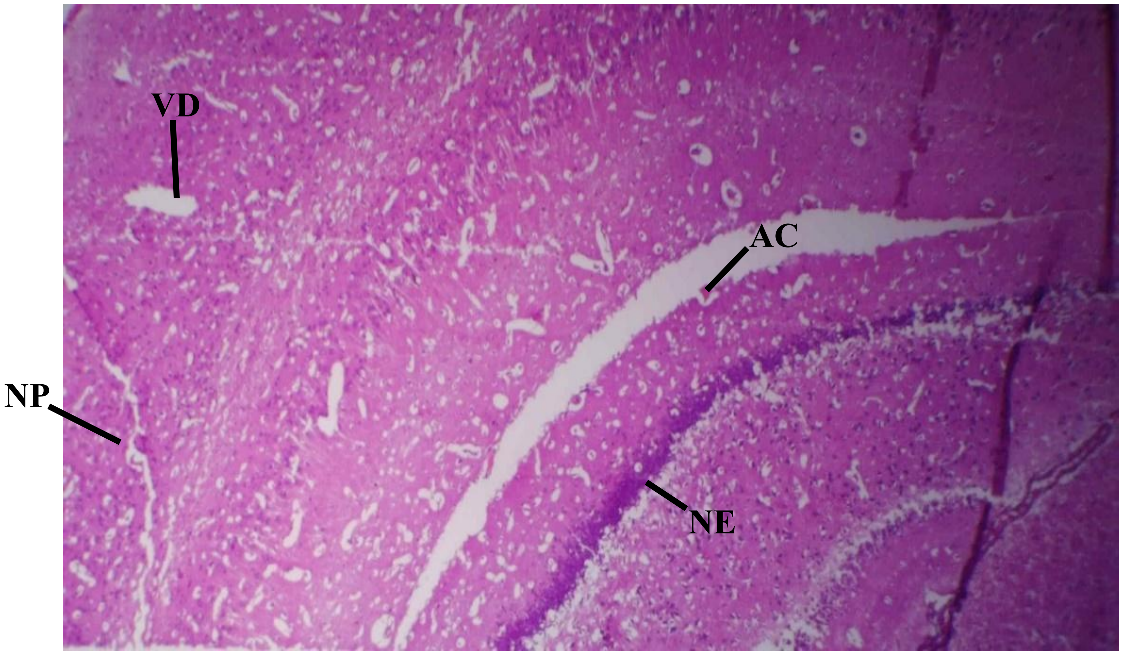

Plate 13. Rat cerebrum given 800mg extract show: vasodilatation (VD), active congestion (AC), normal granular layer neurons (NE) and neuropil (NP): HandE 40 X

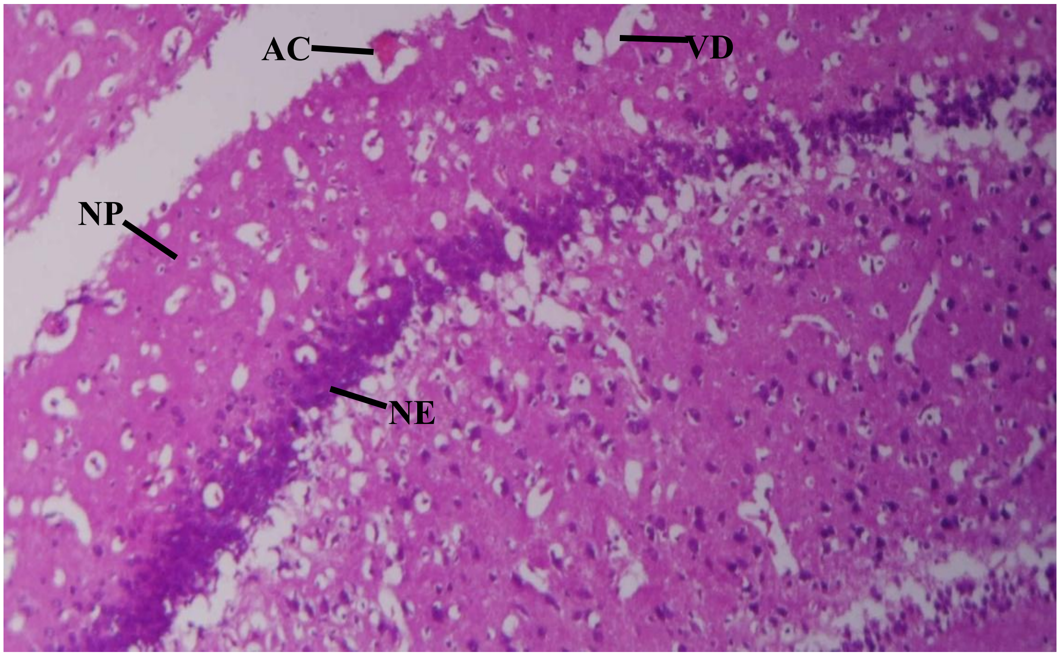

Plate 14. Rat cerebrum given 800mg extract show: vasodilatation (VD), active congestion (AC), normal granular layer neurons (NE) and neuropil (NP): HandE 100 X.

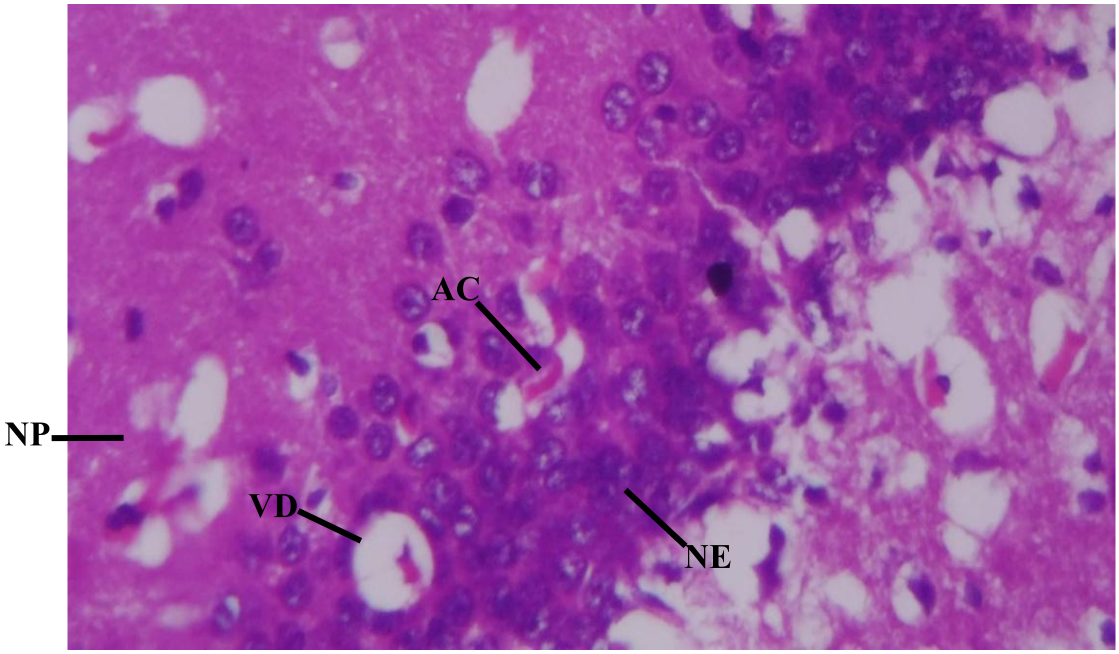

Plate 15. Rat cerebrum given 800mg extract show: vasodilatation (VD), active congestion (AC), normal granular layer neurons (NE) and neuropil (NP): HandE 400 X.

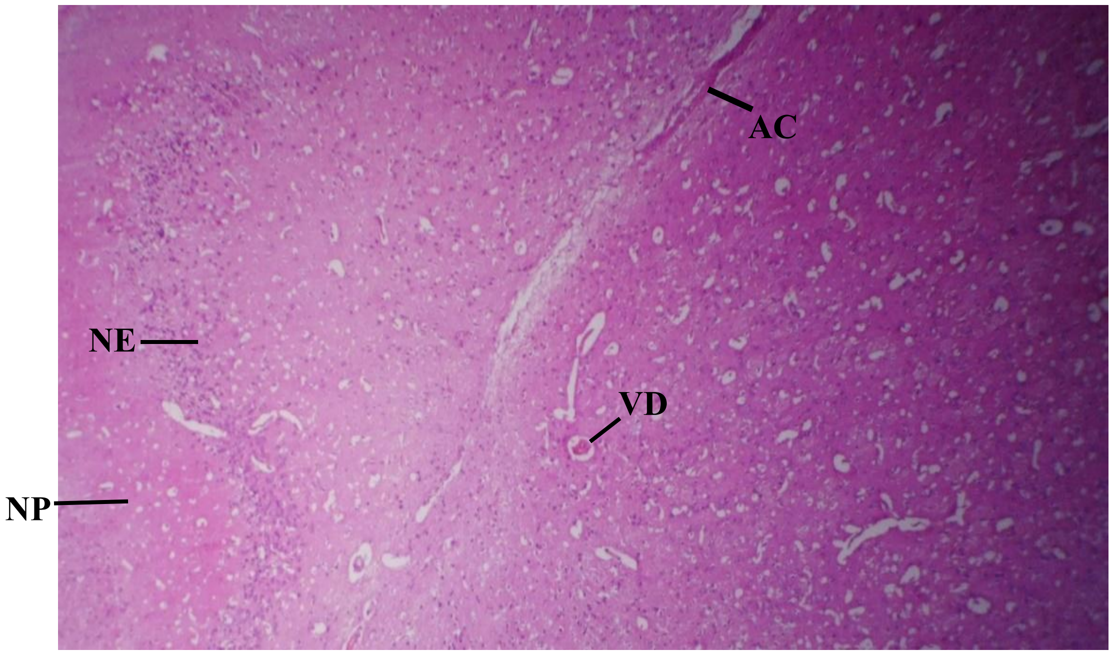

Plate 16. Rat cerebrum given 1000mg Extract show: active vascular congestion (AC), vasodilatation (VD), normal granular layer neuron (NE) and neuropil (NP): HandE 40 X.

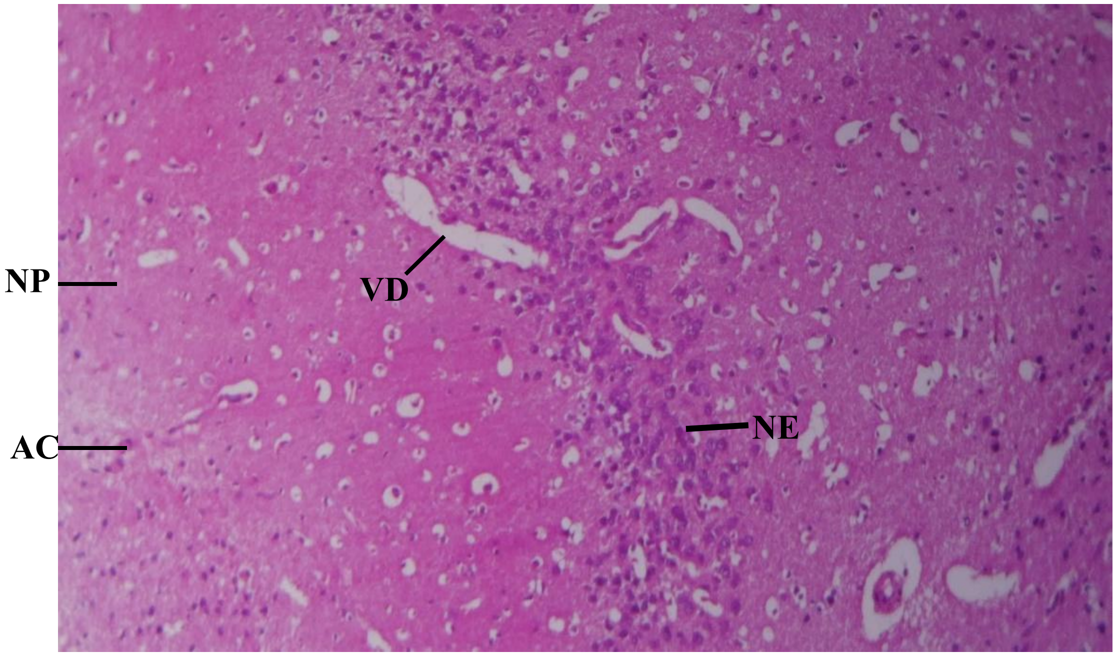

Plate 17. Rat cerebrum given 1000mg Extract show: active vascular congestion (AC), vasodilatation (VD), normal granular layer neuron (NE) and neuropil (NP): HandE 100 X.

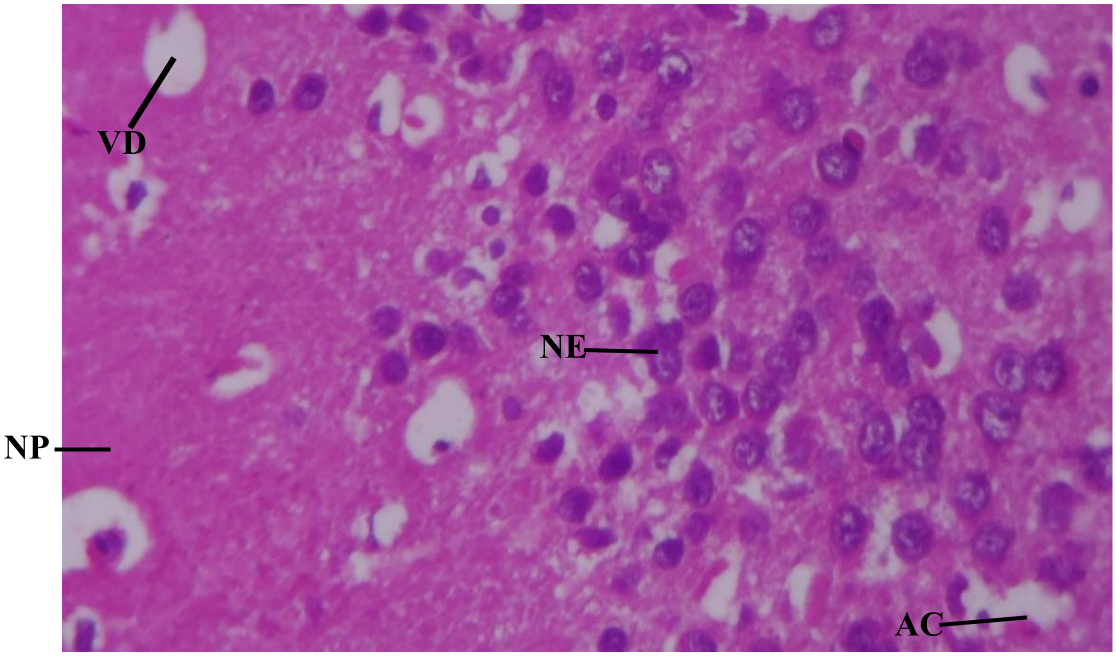

Plate 18. Rat cerebrum given 1000mg Extract show: active vascular congestion (AC), vasodilatation (VD), normal granular layer neuron (NE) and neuropil (NP): HandE 400 X.

CHAPTER FIVE

DISCUSSION, CONCLUSION AND RECOMMENDATION

5.1 DISCUSSION.

Ficus exasperata, (or sandpaper leaf tree) which is a tropical plant of the mulberry family, is well known for its numerous traditional medicinal uses, including its application in the treatment of hypertension, inflammation, wounds, and gastrointestinal disorders. It was earlier stated that various parts of the plant, such as the leaves, bark, roots and stems, can and have been employed in ethnomedicine due to their rich phytochemical composition and pharmacological properties. It was also earlier observed there has not been a broad understanding or examination of the activities and effects of the plant on the central nervous system. Hence, the whole essence of this research was to investigate any possible effect that the ethanol leaf extract of *Ficus exasperata* would exert on the structure and function of the cerebrum, in the hope that whatever results generated from the study will positively contribute to the development of much safer, affordable and effective drugs against neurodegenerative diseases and neurological disorders prevalent nowadays.

5.1.1 Phytochemical Analysis

The phytochemical analysis of the ethanol leaf extract of *Ficus exasperata* was carried out and the results revealed the presence of flavonoids, tannins, saponins, and alkaloids, which are known to exhibit very significant pharmacological properties in living systems. Flavonoids, for instance, have been noted to possess strong antioxidant and anti-inflammatory effects (Wang *et al.,* 2006) while alkaloids, according to Moskowitz (1992), were observed to exhibit neuroactive and vaso-modulatory properties.

5.1.2 Effects of *Ficus exasperata* on Body and Cerebral Weight

The final body weight of the groups treated with the ethanol leaf extract of *Ficus exasperata* were compared against their initial body weight before administration began. The result from this comparison demonstrated a statistically significant increase ($p<0.05$) in the final body weight across all the experimental groups that were administered the leaf extract. This suggests definitely that the extract does not cause weight loss and may even contribute to an increase in the metabolic activities that lead to proper food digestion and weight gain. These findings agree with the conclusion of a previous study carried out by Irene and Chukwunonso (2006), when they examined the change in organ and body weight changes of white albino rats administered with aqueous extract of *Ficus exasperata* at different doses.

The weight of the cerebrum from the treated groups was equally analyzed. Result from this study showed no statistically significant difference ($P<0.05$), between the Cerebral weight of the treated groups, compared to the control group. This suggests that the extract does not cause any potential negative effect on brain tissue growth.

5.1.3 Biochemical Analysis of Oxidative Stress and Antioxidant Markers

Oxidative stress is known to play a critical role in causing neurodegenerative disorders, making the activity of antioxidant enzymes an important marker for evaluating the safety of medicinal herbs. Therefore, the biochemical analysis of the oxidative stress and antioxidant markers was carried out to investigate if there was any effect on their activity level by the extract.

The results obtained from the present study revealed that the extract had minimal statistically significant ($p>0.05$) effect on superoxide dismutase (SOD) activity level across all the treated group, compared to the control group. The result equally revealed an insignificant increase ($p>0.05$) in the activity level of catalase (CAT) across all the treated groups, compared to the control group. This was also confirmed for the effect of the extract on the activity of glutathione peroxidase (GPx), which was also found to be statistically insignificant ($p>0.05$) across all the treated groups, compared to the control group.

This observed minimal effect of the leaf extract of *F. exasperata*, a well-known plant with confirmed antioxidant potentials, on the investigated antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), raises very interesting questions about its antioxidative mechanism of action, since it seems unable to significantly enhance the activities of these enzymatic antioxidant defenses. A possible explanation for the reason behind this outcome is that, *Ficus exasperata* may exert its antioxidant effects through non-enzymatic pathways rather than by engaging endogenous antioxidant enzymatic defenses. Previous research has shown that some plant extracts including *Ficus exasperata* and *Persea americana*, can directly scavenge for Free-radicals, by neutralizing the reactive oxygen species (ROS) without necessarily increasing the activities of antioxidant enzymes (Awala *et al.,* 2017). Since the extract contains flavonoids, a phenolic phytochemical known for its ability to expel free radicals directly (Pietta, 2000), there may be no need for any significant upregulation of the antioxidant enzymes activity level. Another possible explanation is that *Ficus exasperata* helps to maintain redox homeostasis in tissues (Alli Smith *et al.,* 2018), without disrupting the natural activity of enzymes. Several tissues in the body have a balanced quantity of pro-oxidants and antioxidants, and since not all extracts with antioxidative potentials utilize enzymes in exerting their antioxidant effect. Some substances may prevent the excess production of reactive oxygen species by counteracting the activities of the pro-oxidants (Teixeira *et al.,* 2003). These would certainly explain the reason behind the unremarkable increase in the activity level of the Cerebral antioxidant markers in the treated groups.

The results from the study equally revealed that, lipid peroxidation levels were found to remained unchanged, due to the insignificant increase ($p>0.05$) in malondialdehyde (MDA) levels in the cerebrum of the treated groups, compared to the control group.

5.1.4 Histological Analysis of the Cerebrum

The histological evaluation of the cerebrum following the administration of graded concentrations of *Ficus exasperata* leaf extract, was carried out in order to investigate any structural or functional change in the cerebral tissue architecture.

Histological sections of group A (control), which were fed only baseline feed and water, exhibited normal cerebral microanatomy, with the pyramidal and granular cell layers being intact, along with neurons and neuroglial cells, including oligodendrocytes, within the white matter.

The histological section of all the groups that were treated with graded concentrations of *Ficus exasperata* leaf extract (200 mg/kg, 400 mg/kg, 600 mg/kg, 800 mg/kg, and 1000 mg/kg body weight), equally showed normal cerebral tissue structure with the presence of well-defined neurons (pyramidal and granular cells) and neuroglia (oligodendrocytes). These findings suggest that the extract neither induce neuronal degeneration/damage nor disrupt normal brain histological architecture, within the studied dose range.

Furthermore, some beneficial vasoactive changes including vasodilatation and increased blood circulation (active congestion), affecting the veins and capillaries were observed across all the treated groups. These vascular effects were more pronounced in the groups that were administered lower doses of the extract but diminished as the concentration of the extract increased. The 200 mg/kg body weight extract exhibited the most potent vasoactive effect, while the 1000 mg/kg body weight extract exhibited the least effect. This suggests a dose-dependent response, implying that lower concentrations of the leaf extract of *Ficus exasperata* may optimize vascular function by inducing vasodilatation, while the higher concentrations of the extract may induce a protective/inhibitory response to prevent excessive vasodilation. This observed dose-related vasodilatation and enhanced cerebral blood flow may be attributed to the presence of flavonoids in the leaf of *Ficus exasperata.*

Flavonoids (and tannins) have been widely reported to exert vaso-protective effects, by modulating endothelial function via endothelial-dependent relaxation pathways (Chalderone *et al.,* 2004). They also enhance the activity of endothelial nitric oxide synthase (eNOS), an enzyme that produces nitric oxide (a potent vasodilator), and further increase the bioavailability of nitric oxide (NO), promoting vasodilatation (Woodman, 2010). Furthermore, García-Lafuente *et al.* (2009) studied the ability of flavonoids to influence vascular permeability and microcirculation, leading to increased capillary dilatation and improved blood flow. Similar vasoactive properties have been reported in medicinal plants with high flavonoid content. For instance, *Ginkgo biloba* extract has been shown to induce cerebrovascular dilation and improve microcirculation, supporting its use in neurovascular disorders (Smith and Luo, 2003). Also, extracts from *Cymbopogon citratus* (lemongrass) and *Citrus medica* have demonstrated vasodilatory effects in experimental models (Dzeufiet *et al.,* 2014). The presence of alkaloids in the leaf extract could further contribute to vascular modulation due to their influence on adrenergic receptor signaling (Amssayef and Eddouks, 2023). Other plant extracts containing bioactive phytochemicals have been observed to mediate similar vasodilatory effects (Ozolua *et al.,* 2009).

5.2 CONCLUSION

This study therefore provides considerable evidence that the ethanol leaf extract of *Ficus exasperata* possesses the ability to modulate positive cerebrovascular functions, which is characterized by vasodilatation and increased blood circulation while also exerting negligible effects on the activity of antioxidant enzymes of the cerebrum. The extract equally maintained the structural integrity of the neurons and neuroglial cells across all treatment groups, confirming its neuroprotective potential.

5.3 RECOMMENDATION

Further studies are recommended to properly elucidate the underlying mechanisms involved in the vasoactive properties of *Ficus exasperata* leaf extract, its long-term safety and potential therapeutic applications in cerebrovascular health.

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