**EFFECTS OF CO-EXPOSURE TO A HIGH-FAT DIET AND BISPHENOL A ON THE CEREBELLAR HISTOLOGY AND MICROGLIA EXPRESSION OF MALE WISTAR RATS**

**BY**

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**CERTIFICATION**

This is to certify that the project titled **Effects Of Co-Exposure To A High-Fat Diet And Bisphenol A On The Cerebellar Histology And Microglia Expression Of Male Wistar Rats** was carried out by Okoudu Blessing with the registration number Ebsu/2020/105067 in partial fulfilment of the award of Bachelors of Science (B.Sc.) under the direct supervision of Mr. EMEKA CHIKA IGWE and presented to the Anatomy Department of Ebonyi State University Abakaliki, Ebonyi State.

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**DEDICATION**

I dedicate this work to the Almighty God for His guidance, wisdom, and strength throughout this journey. To my beloved family, whose unwavering support, love, and prayers have been my constant source of encouragement. To my academic mentors, whose guidance and belief in my potential have inspired me to strive for excellence. Lastly, to the pursuit of knowledge and scientific advancement, may this research contribute meaningfully to the understanding of dietary exposure.

**ACKNOWLEDGEMENTS**

My deepest gratitude goes to my supervisor, Mr. Emeka Chika Igwe for their invaluable guidance, patience, and mentorship, which were instrumental in the successful completion of this work. I am deeply indebted to the Dean of the Faculty of Basic Medical Sciences, my supervisor, for his visionary leadership and support, and to our lecturers, for their dedication and encouragement throughout this academic journey. I also extend my appreciation to the entire faculty and staff of the Anatomy Department led by Dr. Njoku Clinton for their support and provision of resources that facilitated this research.

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**ABSTRACT**

The cerebellum, critical for motor coordination and cognitive functions, is vulnerable to environmental and dietary insults such as Bisphenol A (BPA) and high-fat diets (HFD). Despite growing evidence of their individual neurotoxic effects, the combined impact of HFD and BPA on the cerebellum remains poorly understood. This study aimed to investigate the effects of co-exposure to HFD and BPA on the cerebellar cortex histology and microglia expression. Sixteen male Wistar rats were divided into four groups: control, BPA only, HFD only, and HFD and BPA. The study duration was 12 weeks. These cerebellar tissues were collected on day 85th, fixed in 10% neutral buffer, and processed for haematoxylin and eosin (H&E) staining and AIF-1 immunohistochemistry. Histological changes and nuclear areas expressing microglia (NAEM) were analyzed using a compound microscope, YW500 camera, Image View software and Image J. The control group showed normal cerebellar cortex layers, while BPA-exposed rats exhibited enlarged and degenerating glial cells, distorted Purkinje cells, and severe granular cell layer (GCL) distortion. HFD-exposed rats displayed similar glial and Purkinje cell changes with severe GCL distortion, whereas the HFD + BPA group showed milder GCL distortion. NAEM quantification revealed no significant differences across groups. The combination of BPA and HFD distorted the histological architecture of the cerebellar cortex. This damaging observation may not depend on microglia activities.

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**CHAPTER ONE**

**INTRODUCTION**

**1.1 Background to the Study**

The cerebellum is a crucial part of the brain being among the three (3) major areas (Aleman, 2022) responsible for coordinating motor control, balance, posture, and cognitive functions such as attention and language (B. M. Carlson, 2019; Martí-Clua, 2022). Although traditionally known for its role in movement coordination, recent studies have highlighted its involvement in non-motor functions, including emotion regulation and higher cognitive processing (Ciapponi *et al*., 2023; Zhang *et al*., 2023; Prati *et al*., 2024). Due to its extensive neural connections with other parts of the central nervous system, the cerebellum is highly vulnerable to damage from metabolic disturbances and environmental toxins (Ruggles & Benakis, 2024), which can lead to motor dysfunction and cognitive impairments (McCann & Maguire-Zeiss, 2021). The cerebellum’s sensitivity to oxidative stress and inflammation makes it a key area of interest in neurotoxicity research (Nishimura *et al*., 2021; Omotoso *et al*., 2022), especially in the context of dietary and environmental exposures (Chen *et al*., 2024a).

One major dietary concern is the consumption of a high-fat diet (HFD), which has become increasingly prevalent in modern society due to shifts toward processed and fast foods (Clemente-Suárez *et al*., 2023; Qi & Wang, 2023). A high-fat diet, particularly rich in saturated fats and trans fats (Navarro-Tapia *et al*., 2022), has been linked to the development of numerous health problems (Wali *et al*., 2020), including obesity (Sood *et al*., 2023), insulin resistance (Ye *et al*., 2021), and cardiovascular disease (X. Tian *et al*., 2022). Beyond these systemic effects, there is increasing evidence that an HFD can significantly impact brain function, including the cerebellum (Sharma, 2021; Chen *et al*., 2022). In the brain, a high-fat diet has been shown to promote oxidative stress, inflammation, and lipid peroxidation (Jiang *et al*., 2021; Adedeji *et al*., 2022), leading to cellular damage and impaired neuronal signalling (Li *et al*., 2023; Berdún *et al*., 2024). Studies have demonstrated that long-term intake of HFD can disrupt the blood-brain barrier, increase the production of inflammatory cytokines, and alter neurotransmitter metabolism, contributing to cognitive deficits and neurodegenerative changes (Amelianchik *et al*., 2022; Delle *et al*., 2023; Gladding *et al*., 2024). The cerebellum, being rich in lipid content, is particularly susceptible to these changes, as excessive dietary fats can accumulate in its tissues, impairing normal function (Tan & Norhaizan, 2019; Jelinek *et al*., 2021; Olufunmilayo *et al*., 2023). These effects are concerning because they contribute to both motor deficits and cognitive impairments, which can severely impact quality of life (Nantachai *et al*., 2022; Butterfield, 2023).

Compounding the detrimental effects of a high-fat diet is the widespread exposure to environmental toxins such as Bisphenol A (BPA) (Manzoor *et al*., 2022a). BPA is an industrial chemical used to produce polycarbonate plastics and epoxy resins, which are found in a wide range of consumer products, including water bottles, food containers, and the lining of metal cans (Chen *et al*., 2024b). BPA is an endocrine disruptor, meaning it can interfere with the body's hormonal systems by mimicking oestrogen, a vital hormone in various biological processes (Hafezi & Abdel-Rahman, 2019; Rizzo *et al*., 2023). The widespread use of BPA has raised significant concerns due to its ability to leach into food and beverages, leading to chronic exposure in humans and animals (Adeyi & Babalola, 2019; Ohore & Zhang, 2019). BPA has been implicated in several health issues, including reproductive disorders, obesity, and cancer (Molina-López *et al*., 2023; Dalamaga *et al*., 2024). However, its effects on the brain, particularly the cerebellum, have also attracted growing attention (Hyun & Ka, 2024).

Research on BPA exposure has shown that it can cross the blood-brain barrier and accumulate in brain tissues, where it induces oxidative stress and inflammation, particularly affecting areas involved in motor control and cognition (Vom Saal & Vandenberg, 2021). The cerebellum, due to its sensitivity to hormonal fluctuations and metabolic disturbances, is highly vulnerable to BPA's toxic effects (Costa & Cairrao, 2024). Studies have indicated that BPA exposure can lead to the activation of inflammatory pathways in the brain, causing microglial activation and neuronal damage (Al-Shami *et al*., 2024; Costa & Cairrao, 2024). Additionally, BPA has been shown to disrupt neurogenesis, impair synaptic plasticity, and increase the risk of neurodegenerative diseases (X. Wu *et al*., 2023). The combined exposure to BPA and a high-fat diet may thus create a synergistic effect, amplifying the damage to the cerebellum and accelerating the onset of neurodegenerative changes (Liu *et al*., 2022; Lee *et al*., 2023a).

Given the harmful impact of both HFD and BPA on the cerebellum, there is a growing need to explore markers that can help detect and quantify neuroinflammation in this context (Costa & Cairrao, 2024). One such marker is Allograft Inflammatory Factor-1 (AIF-1), a calcium-binding protein primarily expressed by activated microglia, the immune cells of the central nervous system (Jurga *et al*., 2020). AIF-1 regulates immune responses, particularly in inflammatory and neurodegenerative conditions. When microglia are activated in response to injury, toxins, or metabolic disturbances, they release pro-inflammatory cytokines and other factors that can lead to neuronal damage (Donovan *et al*., 2018). AIF-1 is upregulated in microglia during these inflammatory processes, making it a valuable marker for assessing the extent of neuroinflammation in the brain (Lee *et al*., 2023b).

AIF-1 has been widely studied in the context of neurodegenerative diseases, such as Alzheimer's and Parkinson's, where it has been shown to correlate with the severity of microglial activation and neuroinflammation (Bosco *et al*., 2023; Pathak & Sriram, 2023). In the brain, AIF-1 can be used to track the progression of inflammation caused by metabolic or environmental insults (Postler *et al*., 2000; Schwab *et al*., 2001) like HFD and BPA exposure. By detecting increased levels of AIF-1 in cerebellar tissue, researchers can assess the extent of microglial activation and gauge the potential for neuronal damage (Lai *et al*., 2024). In addition to being a marker for inflammation, AIF-1 has also been implicated in cell proliferation and migration, further highlighting its importance in understanding the neuroinflammatory processes that occur in response to toxic exposures (De Leon-Oliva *et al*., 2023).

**1.2 Statement of Problem**

The increasing consumption of HFD and widespread exposure to environmental toxins like BPA pose significant risks to public health, particularly affecting metabolic and neurological systems (Lambré *et al*., 2023; Kamaludin *et al*., 2024; Lința *et al*., 2024). The cerebellum, responsible for motor coordination and cognitive functions, is particularly vulnerable to damage from oxidative stress and inflammation caused by these factors (Olufunmilayo *et al*., 2023). High-fat diets have been linked to neuroinflammation, lipid accumulation, and cognitive decline (Liang *et al*., 2023; Mackey-Alfonso *et al*., 2024), while BPA, a known endocrine disruptor, has been associated with neurotoxicity, oxidative damage, and hormonal disruption in the brain (Costa & Cairrao, 2024; Hyun & Ka, 2024). Despite growing concerns, the combined impact of HFD and BPA on cerebellar health remains poorly understood, and there is a lack of specific markers to accurately assess the resulting neuroinflammation and damage. There is also a lack of reliable biomarkers, such as Allograft Inflammatory Factor-1 (AIF-1), to measure the extent of neuroinflammation and damage. This study aims to fill this gap by investigating cerebellar changes in male rats co-exposed to a high-fat diet and BPA.

**1.3 Aim of the Study**

The study investigates the effects of co-exposure to a high-fat diet and Bisphenol A on the cerebellum of male rats, focusing on neuroinflammation and structural changes using Allograft Inflammatory Factor-1 and routine staining techniques

**1.4 Objectives of the Study**

The objectives of the study include;

* To assess the histological changes in the cerebellum of male rats exposed to a high-fat diet and BPA using routine staining techniques.
* To evaluate the expression of Allograft Inflammatory Factor-1 (AIF-1) as a marker of neuroinflammation in the cerebellum of rats co-exposed to a high-fat diet and BPA.
* To compare the cerebellar structural alterations between rats exposed to only a high-fat diet, only BPA, and the combination of both.
* To determine the extent of microglial activation and inflammatory response in the cerebellum due to the combined exposure to a high-fat diet and BPA.
* To explore the potential relationship between cerebellar neuroinflammation and functional impairment caused by the combined exposure.

**1.5 Significance of the Study**

This study will provide valuable insights into the combined effects of a high-fat diet and Bisphenol A (BPA) on cerebellar health, specifically neuroinflammation and structural changes. Identifying Allograft Inflammatory Factor-1 (AIF-1) as a potential marker for cerebellar inflammation will contribute to a deeper understanding of neurotoxic impacts from diet and environmental toxins. The findings will serve as a reference point for future studies and help guide further research on mitigating the neurotoxic effects of such exposures.

**1.6 Scope of the Study**

This study will focus on examining the histological changes and neuroinflammation in the cerebellum of male rats co-exposed to a high-fat diet and Bisphenol A (BPA), utilising Allograft Inflammatory Factor-1 (AIF-1) as a marker, and will limit its analysis to structural and inflammatory alterations.

**CHAPTER TWO**

**LITERATURE REVIEW**

**2.1 Cerebellum**

**2.1.1 Overview**

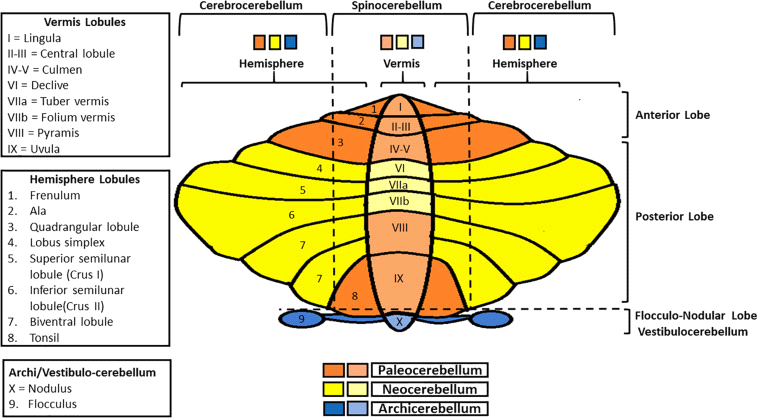
The cerebellum is a structure of the central nervous system that is located on the dorsal hindbrain on top of the fourth ventricle (Laumonnerie & Solecki, 2020). The cerebellum is a vital component in the human brain as it plays a role in motor movement regulation and balance control (Van Essen *et al*., 2018). The cerebellum coordinates gait and maintains posture, controls muscle tone and voluntary muscle activity but is unable to initiate muscle contraction (Witter & De Zeeuw, 2015). Damage to this area in humans results in a loss in the ability to control fine movements, maintain posture, and motor learning (Manto *et al*., 2012; Roostaei *et al*., 2014). The cerebellum is composed of various cell types exhibiting a wide range of morphology that reflects tightly regulated ontological processes. The neuroscientist Santiago Ramón y Cajal, through his microscopic studies at the end of the 19th century, was the first to highlight the diversity of cellular morphology in the cerebellum (Laumonnerie & Solecki, 2020).

Morphologically, the cerebellum is a foliated structure consisting of a laminated cortex, white matter, and paired sets of four cerebellar nuclei. The cerebellar cortex organizes itself with a central region called the vermis and two lateral hemispheres (Hawkes, 2018). The vermis has three main lobes that are distributed along the rostrocaudal axis and further subdivide into 10 lobules (Hodos, 2009). This organization is well conserved in avian and mammalian species, with some variation in the size and number of the lobules. The cortex includes three laminae: the molecular layer is the most superficial of these, followed by the Purkinje layer, and then the internal granular layer (IGL) (Wolf *et al*., 2009). The laminae are each composed of a well-characterized set of neurons. Stellate and basket cells are GABAergic inhibitory interneurons that populate the molecular layer, which otherwise consists mostly of parallel fibre axons (Schmahmann, 2019). Candelabrum cells and Purkinje cells (PCs) are also GABAergic neurons and reside in the Purkinje layer. The granular layer is more diverse and contains two types of GABAergic inhibitory interneurons, Golgi and Lugaro neurons, as well as cerebellar granule neurons (CGNs) and unipolar brush cells (UBCs), which are glutamatergic excitatory neurons (Fine *et al*., 2002). Except for Purkinje cells, all cortical neurons project locally. In addition to the cerebellar cortex, deep cerebellar nuclei (CNs) are located in the deep white matter of the cerebellum adjacent to the roof of the fourth ventricle (Yang & Lisberger, 2014). The CNs consist of several neuronal cell types: large glutamatergic projection neurons, midsized GABAergic inhibitory projection neurons and small GABAergic and glycinergic interneurons (Uusisaari *et al*., 2007).

**2.1.2 Gross Anatomy of the Cerebellum**

The cerebellum is located in the posterior cranial fossa. The fourth ventricle, pons and medulla are in front of the cerebellum (Standring, 2016). It is separated from the overlying cerebrum by a layer of leathery dura mater, the cerebellar tentorium; all of its connections with other parts of the brain travel through the pons. Anatomists classify the cerebellum as part of the metencephalon, which also includes the pons; the metencephalon is the upper part of the rhombencephalon or hindbrain (Hawkes, 2018). Like the cerebral cortex, the cerebellum is divided into two cerebellar hemispheres; it also contains a narrow midline zone (the vermis). A set of large folds is, by convention, used to divide the overall structure into 10 smaller lobules (Van Essen *et al*., 2018). Because of its large number of tiny granule cells, the cerebellum contains more neurons than the total from the rest of the brain, but takes up only 10% of the total brain volume (Roostaei *et al*., 2014). The number of neurons in the cerebellum is related to the number of neurons in the neocortex. There are about 3.6 times as many neurons in the cerebellum as in the neocortex, a ratio that is conserved across many different mammalian species (Herculano-Houzel, 2010).

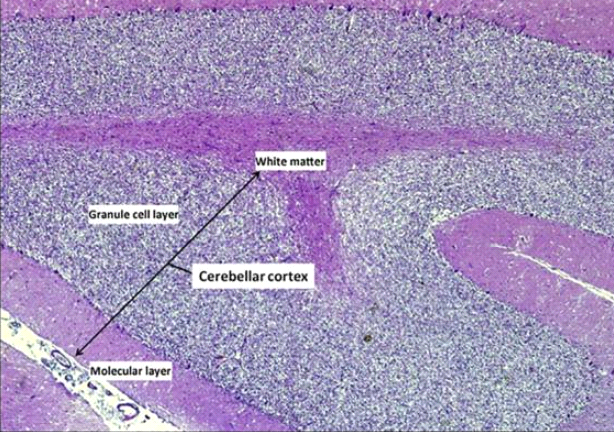
The unusual surface appearance of the cerebellum conceals the fact that most of its volume is made up of a very tightly folded layer of gray matter: the cerebellar cortex. Each ridge or gyrus in this layer is called a folium. Highresolution MRI finds the adult human cerebellar cortex has an area of 730 square cm (Lyu *et al*., 2024), packed within a volume of dimensions 6 cm × 5 cm × 10 cm (Roostaei *et al*., 2014). Underneath the gray matter of the cortex lies white matter, made up largely of myelinated nerve fibers running to and from the cortex. Embedded within the white matter—which is sometimes called the arbor vitae (tree of life) because of its branched, tree-like appearance in cross-section—are four deep cerebellar nuclei, composed of gray matter (Amore *et al*., 2021). Connecting the cerebellum to different parts of the nervous system are three paired cerebellar peduncles. These are the superior cerebellar peduncle, the middle cerebellar peduncle and the inferior cerebellar peduncle, named by their position relative to the vermis (Purves *et al*., 2013). The Schematic representation of cerebellar gross anatomy is shown in the Figure 1.



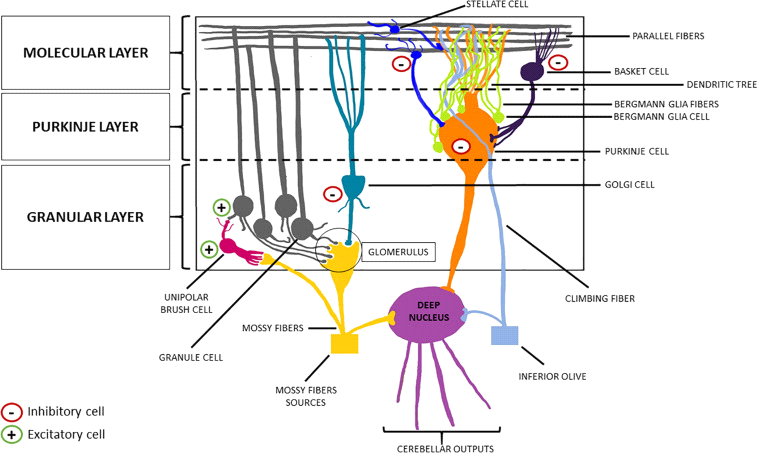
**Figure 1: Schematic representation of cerebellar gross anatomy (Amore *et al*., 2021).**

**2.1.3 Cerebellar Microanatomy and Circuitry**

The cerebellum presents an outer gray matter layer (namely the cerebellar cortex), a deeper cerebellar white matter the so-called arbor vitae, and, within this latter, the deep cerebellar nuclei, dentate, globose, emboliform, and fastigial nuclei (Voogd, 2003). The cerebellar cortex is composed of three layers (from the deepest to the most superficial: the granular layer, the Purkinje layer, and the molecular layer), four inhibitory cell types like stellate cells, basket cells, Purkinje cells (PCs), and Golgi cells, two excitatory cell populations; granule cells and unipolar brush cells (UBCs), and glial cells among which Bergman glia (Buffo & Rossi, 2013; Roostaei *et al*., 2014) as shown in Figures 2 and 3.



**Figure 2: The cerebellar cortex (Buffo & Rossi, 2013).**



**Figure 3: Schematic representation of the cerebellar cortex (Buffo & Rossi, 2013; Roostaei *et al*., 2014).**

The granular layer contains a large number of granular cells (excitatory). Each of them presents few descending dendrites, and a single ascending axon reaches the molecular layer, where it splits in a T-shaped way, generating the parallel fibers (Mugnaini *et al*., 2011). This layer also contains interneurons, such as the UBCs and the Golgi cells, whose descending dendrites, together with the granule cells dendrites, and the mossy fibers (a major afferent cerebellar pathway originating from the brainstem nuclei, the spinal cord, and the reticular formation) form the synaptic structure known as glomerulus (Voogd & Glickstein, 1998; Mugnaini *et al*., 2011). Specifically, UBCs present one short dendrite whose brush engages in synaptic contact with a single mossy fiber terminal (the term brush indicates the fact that the tip of the UBC dendrite forms a paint brush-like tuft of dendrioles); while their axons branch locally within the granular layer, making contact with the granule cells (Mugnaini *et al*., 2011). Finally, the axons of the PCs whose main body is located in the homonym middle layer, surrounded by multiple Bergman glia cells that, in turn, modulate their activity) cross this layer to reach the deep cerebellar nuclei, thus generating the cerebellar efferences (Buffo and Rossi, 2013). Conversely, the PCs send their dendrites to the molecular layer wherein Bergmann glia (BG) fibres extend], forming a dendritic tree, making synapses both with the parallel fibres, and with the axons of the outer stellate cells (Voogd and Glickstein, 1998). These inhibitory interneurons are placed in the upper part of the molecular layer, as opposed to the internal stellate cells, which are below them and send an axon in the middle layer, making synapsis with the PCs (Sudarov *et al*., 2011; De Luca *et al*., 2016). Lastly, the molecular layer hosts the basket cells, another inhibitory interneuron type, and the climbing fibers. These latter represent the other major afferent pathway of the cerebellum, generating from the contralateral inferior olivary complex and making synapsis with the dendrites of PCs (Buffo and Rossi, 2013; Roostaei *et al*., 2014).

Cerebellar circuitry appears to be a complex network of excitatory and inhibitory inputs and outputs with recurrent and interconnected loops involving the cerebellum and different brain regions. Notably, evidence deriving from anatomical, clinical, and neuroimaging data allowed us to point out the mutual connection between the cerebellum and basal ganglia, multiple cerebral cortex areas (particularly primary and associative ones), as well as thalamus and hypothalamus (Bostan *et al*., 2013; Benagiano *et al*., 2018). Two types of neuron play dominant roles in the cerebellar circuit: Purkinje cells and granule cells. Three types of axons also play dominant roles: mossy fibres and climbing fibres which enter the cerebellum from outside, and parallel fibres which are the axons of granule cells. There are two main pathways through the cerebellar circuit, originating from mossy fibres and climbing fibres, both eventually terminating in the deep cerebellar nuclei (Amore *et al*., 2021).

**2.1.4 Embryology of the Cerebellum**

Cerebellar development is a process that starts early during the first trimester of pregnancy 30 days post-conception and lasts until 2 years of postnatal age (van Essen *et al*., 2020). There is very little literature data regarding human cerebellar development before the 8th gestational week (Haldipur *et al*., 2018) and most of our knowledge about cellular and molecular maturation is derived from animal-based studies on fish, birds and rodents, especially mice. The cerebellum originates from the dorsal portion of the hindbrain that gives rise to the posterior part of the alar plates of the metencephalon. Its development can be summarized in four steps: organization of the cerebellar territory, establishment of cerebellar progenitors GABAergic and glutamatergic ones, migration of the granule cells, and formation of the cerebellar nuclei and circuitry (ten Donkelaar *et al*., 2003).

The cerebellar hemisphere and vermis form by the 12th week. Accordion-like folds gradually start developing from about the fourth month. Neurons of the cerebellar cortex form by the neuroblast derived from the matrix cells in the ventricular zone (Yuskaitis & Pomeroy, 2017). Other neuroblasts from the ventricular surface differentiate into cerebellar nuclei, whose axons grow towards the mesencephalon (midbrain) and create the superior cerebellar peduncle (Moreno-Rius, 2019). Later, projections of the axons of the cortico-pontine and the pontocerebellar fibres will develop the middle cerebellar peduncle and connect the cerebral cortex with the cerebellum. The inferior cerebellar peduncle will form mainly by the growth of sensory axons from the spinal cord, the olivary and vestibular nuclei (Haldipur *et al*., 2018).

**2.1.5 Blood Supply, Lymphatics and Nerve Supply**

The cerebellum is provided with blood from three paired major arteries: the superior cerebellar artery (SCA), the anterior inferior cerebellar artery (AICA), and the posterior inferior cerebellar artery (PICA). The SCA supplies the upper region of the cerebellum. It divides at the upper surface and branches into the pia mater where the branches anastomose with those of the anterior and posterior inferior cerebellar arteries. The AICA supplies the front part of the under- surface of the cerebellum. The PICA arrives at the under-surface, where it divides into a medial branch and a lateral branch. The medial branch continues backwards to the cerebellar notch between the two hemispheres of the cerebellum; while the lateral branch supplies the under-surface of the cerebellum, as far as its lateral border, where it anastomoses with the AICA and the SCA (Matsushima *et al*., 2016; Delion *et al*., 2017).

The cerebellum attaches to the brainstem by three groups of nerve fibres called the superior, middle, and inferior cerebellar peduncles, through which efferent and afferent fibres pass to connect with the rest of the nervous system (Manto *et al*., 2012; Roostaei *et al*., 2014).

**2.1.6 Functions of the Cerebellum**

The strongest clues to the function of the cerebellum have come from examining the consequences of damage to it. Animals and humans with cerebellar dysfunction show, above all, problems with motor control, on the same side of the body as the damaged part of the cerebellum (Manto *et al*., 2012; Roostaei *et al*., 2014; Witter & De Zeeuw, 2015; Van Essen *et al*., 2018). They continue to be able to generate motor activity but lose precision, producing erratic, uncoordinated, or incorrectly timed movements. A standard test of cerebellar function is to reach with the tip of the finger for a target at arm's length: A healthy person will move the fingertip in a rapid straight trajectory, whereas a person with cerebellar damage will reach slowly and erratically, with many mid-course corrections. Deficits in non-motor functions are more difficult to detect (Lyu *et al*., 2024). Before the 1990s the function of the cerebellum was almost universally believed to be purely motor-related, but findings have brought that view into question (Manto & Mariën, 2015).

Although a full understanding of cerebellar function has remained elusive, at least four principles have been identified as important: (1) feedforward processing, (2) divergence and convergence, (3) modularity, and (4) plasticity.

* **Feedforward processing**: The cerebellum differs from most other parts of the brain (especially the cerebral cortex) in that the signal processing is almost entirely feedforward— that is, signals move unidirectionally through the system from input to output, with very little recurrent internal transmission (Pisotta & Molinari, 2014).
* **Divergence and convergence**: In the human cerebellum, information from 200 million mossy fiber inputs is expanded to 40 billion granule cells, whose parallel fiber outputs then converge onto 15 million Purkinje cells (Amore *et al*., 2021). Because of the way that they are lined up longitudinally, the 1000 or so Purkinje cells belonging to a microzone may receive input from as many as 100 million parallel fibres, and focus their output down to a group of less than 50 deep nuclear cells (Apps & Garwicz, 2005).
* **Modularity**: The cerebellar system is functionally divided into more or less independent modules, which probably number in the hundreds to thousands. All modules have a similar internal structure, but different inputs and outputs (Apps & Garwicz, 2005).
* **Plasticity**: The synapses between parallel fibres and Purkinje cells, and the synapses between mossy fibres and deep nuclear cells, are both susceptible to modification of their strength (Boyden *et al*., 2004).

The cortex of the vermis coordinates the movements of the trunk, including the neck, shoulders, thorax, abdomen, and hips. Control of the distal extremity muscles is by the intermediate zone of the cerebellar hemispheres, located adjacent to the vermis. The remaining lateral area of each cerebellar hemisphere provides the planning of sequential movements of the entire body along with involvement in the conscious assessment of movement errors (Manto *et al*., 2012; Guell *et al*., 2018).

**2.1.7 Clinical Significance**

Damage to the cerebellum often causes motor-related symptoms, the details of which depend on the part of the cerebellum involved and how it is damaged. Damage to the flocculonodular lobe may show up as a loss of equilibrium and in particular an altered, irregular walking gait, with a wide stance caused by difficulty in balancing (Amore *et al*., 2021). Damage to the lateral zone typically causes problems in skilled voluntary and planned movements which can cause errors in the force, direction, speed and amplitude of movements. Other manifestations include hypotonia (decreased muscle tone), dysarthria (problems with speech articulation), dysmetria (problems judging distances or ranges of movement), dysdiadochokinesia (inability to perform rapid alternating movements such as walking), impaired check reflex or rebound phenomenon, and intention tremor (involuntary movement caused by alternating contractions of opposing muscle groups) (Tamada *et al*., 2020). Damage to the midline portion may disrupt whole-body movements, whereas damage localized more laterally is more likely to disrupt fine movements of the hands or limbs. Damage to the upper part of the cerebellum tends to cause gait impairments and other problems with leg coordination; damage to the lower part is more likely to cause uncoordinated or poorly aimed movements of the arms and hands, as well as difficulties in speed. This complex of motor symptoms is called ataxia (Gupta, 2017; Webb, 2017).

The list of medical problems that can produce cerebellar damage is long, including stroke, haemorrhage, swelling of the brain (cerebral oedema), tumours, alcoholism, physical trauma such as gunshot wounds or explosives, and chronic degenerative conditions such as olivopontocerebellar atrophy. Some forms of migraine headache may also produce temporary dysfunction of the cerebellum, of variable severity. Infection can result in cerebellar damage in such conditions as prion diseases and Miller-Fisher syndrome, a variant of Guillain–Barré syndrome (Severino & Huisman, 2019; Shen *et al*., 2019; Sun *et al*., 2019).

**2.2 High-fat diets (HFDs)**

**2.2.1 Overview**

High-fat diets (HFDs) refer to dietary patterns in which a significant proportion of total caloric intake comes from fats (Han *et al*., 2023). While there is no universally accepted threshold for defining an HFD, most studies classify diets containing more than 35-40% of total daily energy from fat as high-fat (Bastías-Pérez *et al*., 2020). The composition of fats in an HFD can vary widely, including saturated fats, unsaturated fats (monounsaturated and polyunsaturated), and trans fats, each having distinct metabolic effects (DiNicolantonio & O’Keefe, 2022).

HFDs are commonly contrasted with low-fat diets, which typically contain less than 30% of total energy from fat, and balanced diets that maintain a moderate fat intake while incorporating adequate carbohydrates and proteins (Osterberg *et al*., 2015). HFDs can be further categorized based on their fat sources, such as Western diets (rich in saturated and trans fats), ketogenic diets (low in carbohydrates and high in healthy fats), and Mediterranean high-fat diets (predominantly unsaturated fats from plant-based sources like olive oil and nuts) (Bellissimo & Hundley, 2024).

Despite the negative connotations associated with high-fat diets due to their link with obesity and cardiovascular diseases, infertility (Hohos & Skaznik-Wikiel, 2017), certain HFDs, like the ketogenic diet, have gained recognition for their therapeutic benefits in epilepsy, metabolic syndrome, and neurodegenerative diseases (Hohos & Skaznik-Wikiel, 2017).

**2.2.2 Historical Perspective on Dietary Fat Consumption**

The role of dietary fat in human nutrition has undergone significant shifts over time, influenced by cultural practices, agricultural developments, and scientific advancements (Bragazzi *et al*., 2024). In early human history, hunter-gatherer diets were highly variable but often included substantial amounts of animal fat from hunted game, nuts, and seeds (Pontzer & Wood, 2021). Anthropological studies suggest that prehistoric humans consumed diets rich in animal fats, particularly in colder regions where carbohydrate sources were scarce (Alt *et al*., 2022).

During the Agricultural Revolution (~10,000 years ago), the composition of human diets began to change with the domestication of plants and animals (Lieberman *et al*., 2023). Grains and plant-based foods became more prominent, leading to a relative decrease in fat intake compared to the hunter-gatherer era. However, in pastoral societies, dairy products provided a continued source of dietary fat (Hebelstrup *et al*., 2023).

In the 19th and early 20th centuries, industrialization brought about mass production of processed foods, including refined vegetable oils and hydrogenated fats (trans fats). The rise of the Western diet, characterized by high levels of saturated fats, processed foods, and refined sugars, led to increased concerns about obesity and cardiovascular diseases (Clemente-Suárez *et al*., 2023).

The mid-to-late 20th century saw a major dietary shift following the publication of studies linking saturated fat consumption to heart disease (Huebbe & Rimbach, 2020). The Seven Countries Study by Ancel Keys was influential in shaping dietary guidelines, promoting low-fat, high-carbohydrate diets to reduce cardiovascular risk (Bhupathiraju & Tucker, 2011). As a result, governments and health organizations encouraged reduced fat intake, leading to the popularity of low-fat food products. However, emerging research later questioned the oversimplified demonization of fats, highlighting the differential effects of healthy unsaturated fats versus processed and trans fats (Pipoyan *et al*., 2021).

In the 21st century, a more interesting understanding of dietary fat has emerged (Tufford *et al*., 2023). The ketogenic and Mediterranean diets, both of which involve high-fat intake but emphasize healthy fat sources, have gained prominence for their potential benefits in metabolic health and disease prevention (Dominguez *et al*., 2023). Current research continues to explore the role of dietary fats in obesity, cardiovascular health, brain function, and inflammation, reshaping nutritional recommendations and public perceptions of high-fat diets (Ahmad *et al*., 2024; Xiao *et al*., 2024).

**2.3 Classification of High-Fat Diets**

High-fat diets (HFDs) vary widely in their composition, fat sources, and health implications (Martinez-Lomeli *et al*., 2023). While some are associated with negative metabolic outcomes (e.g., obesity, cardiovascular disease), others have potential therapeutic benefits (e.g., ketogenic diet for epilepsy) (Zimmerman *et al*., 2021). The classification of high-fat diets is based on the type of fat consumed, macronutrient distribution, and overall dietary pattern (Nishi *et al*., 2024). The major types of HFDs include the Western Diet, Ketogenic Diet, Mediterranean High-Fat Diet, and other variations such as Atkins and Paleo Diets (An *et al*., 2022).

**2.3.1 Western Diet**

The Western diet (WD), also known as the Standard American Diet (SAD), is characterized by high consumption of saturated fats, refined carbohydrates, processed foods, and low intake of fiber and essential micronutrients (Clemente-Suárez *et al*., 2023). It is known by high intake of saturated and trans fats from processed meats, fried foods, and fast food; excessive consumption of refined sugars and carbohydrates (e.g., white bread, sugary beverages); low consumption of dietary fiber, fresh fruits, and vegetables; and associated with overconsumption of calories, leading to obesity and metabolic disorders (Więckowska-Gacek *et al*., 2021; Anwar *et al*., 2025).

The health implications of western diets are numerous. Studies have linked the Western diet to numerous chronic diseases, including: Obesity and metabolic syndrome (Ogden *et al*., 2020); Cardiovascular diseases (CVD) due to high levels of saturated fat and trans fats (J. H. Lee *et al*., 2021); Type 2 diabetes mellitus (T2DM) due to insulin resistance induced by high saturated fat and refined carbohydrate intake (Clemente-Suárez *et al*., 2022); Neurodegenerative disorders (e.g., Alzheimer’s disease) due to oxidative stress and inflammation caused by processed foods (López-Taboada *et al*., 2020). The Western diet is often cited as a major contributor to the global obesity epidemic and non-communicable diseases (NCDs) (A. Severino *et al*., 2024).

**2.3.2 Ketogenic Diet (Very Low-Carb, High-Fat Diet)**

The ketogenic diet (KD) is a very high-fat, low-carbohydrate, and moderate-protein diet that shifts the body’s primary fuel source from glucose to ketone bodies (Alhamzah *et al*., 2023). It was originally developed in the 1920s to treat epilepsy but has gained popularity for its role in weight loss and metabolic health (Sandoval Karamian & Wusthoff, 2019).

Key Characteristics:

* Fat intake: ~70-80% of daily calories.
* Protein intake: ~15-20% of daily calories.
* Carbohydrate intake: ~5-10% of daily calories (typically below 50g/day).
* Promotes ketosis, where the body produces ketone bodies from fatty acids as an alternative energy source (Ashtary-Larky *et al*., 2022; Zhu *et al*., 2022).

Health Implications:

The ketogenic diet has been studied extensively for its potential benefits, including:

* Weight loss: Enhances fat oxidation and appetite suppression (Dyńka *et al*., 2025).
* Type 2 diabetes management: Improves insulin sensitivity and glycemic control (Firman *et al*., 2024).
* Epilepsy treatment: Reduces seizure frequency in drug-resistant epilepsy patients (Çağıran & Yılmaz, 2024).
* Neuroprotective effects: May reduce the risk of Alzheimer’s and Parkinson’s disease by decreasing neuroinflammation (Gough *et al*., 2021).

However, the long-term effects of the ketogenic diet are debated, with concerns about nutrient deficiencies, potential cardiovascular risks, and liver/kidney strain due to excessive fat metabolism (Athinarayanan *et al*., 2024; Weimbs *et al*., 2024; Biesiekierska *et al*., 2025).

**2.3.3 Mediterranean High-Fat Diet (Healthy Fats from Olive Oil, Nuts, and Fish)**

The Mediterranean diet (MD) is moderately high in fat but primarily consists of healthy unsaturated fats from plant-based sources (Guasch‐Ferré & Willett, 2021). It is associated with longevity and reduced risk of chronic diseases (Almanza-Aguilera *et al*., 2023).

Key Characteristics:

* Fat intake: 35-45% of daily calories, predominantly unsaturated fats.
* Key fat sources: Olive oil, nuts, seeds, avocados, and fatty fish.
* Rich in: Vegetables, legumes, whole grains, and lean protein.
* Low in: Processed foods, red meat, and added sugars (Godos *et al*., 2024; Hashim *et al*., 2024).

Health Implications:

The Mediterranean diet is widely studied for its cardiovascular and metabolic benefits, including:

* Reduced cardiovascular disease risk: Decreases LDL cholesterol and improves HDL cholesterol levels (Perrone & D’Angelo, 2025).
* Anti-inflammatory effects: The presence of omega-3 fatty acids from fish reduces systemic inflammation (Sikalidis *et al*., 2021).
* Improved cognitive function: Associated with a lower risk of dementia and cognitive decline (Maggi *et al*., 2023).
* Better weight management: Compared to the Western diet, the Mediterranean diet prevents obesity while supporting metabolic health (Scaglione *et al*., 2025).

**2.3.4 Other High-Fat Diet Variations (Atkins, Paleo, etc.)**

Several other high-fat diets have gained popularity, each with distinct carbohydrate, protein, and fat compositions (Preston *et al*., 2023; Kripp *et al*., 2024):

**2.3.4.1 Atkins Diet**

Similar to the ketogenic diet but less restrictive on protein intake (Kossoff, 2023). Focuses on phases of carbohydrate restriction, gradually increasing carb intake (Vargas *et al*., 2021). Its health benefits are seen in weight loss and improved metabolic markers (Ehrlicher *et al*., 2022). On the other hand, it has its criticisms arising from higher intake of saturated fats which may pose cardiovascular risks (Modi & Priefer, 2020).

**2.3.4.2 Paleo Diet**

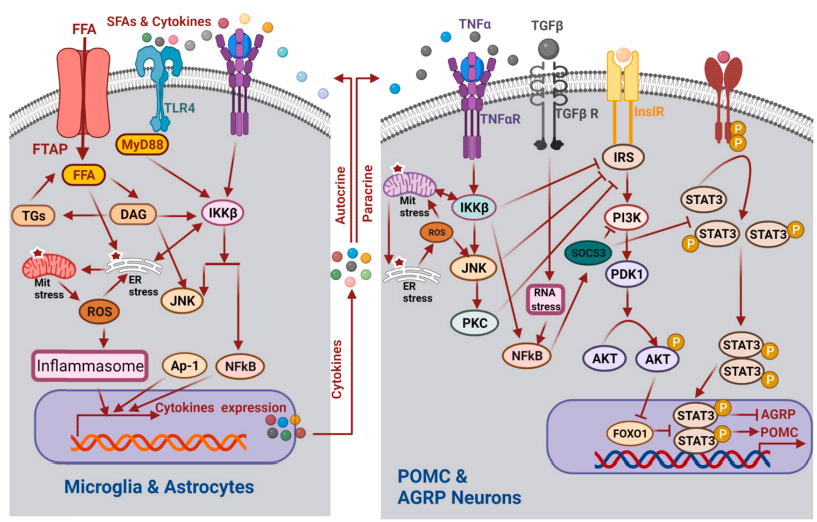
Based on hunter-gatherer diets, eliminating processed foods, grains, and dairy. High in animal fats, nuts, and plant-based fats (e.g., coconut oil) (Singh & Singh, 2023). Health benefits include improved glucose metabolism and reduced inflammation. However, its criticism arise from nutrient deficiencies due to exclusion of dairy and whole grains (Jamka *et al*., 2020).

**2.3.4.3 High-Fat, High-Protein Diets (Carnivore Diet)**

Primarily animal-based, with little to no carbohydrate intake (Goedeke *et al*., 2024). Some studies suggest short-term metabolic benefits, but long-term effects remain unknown (Sousa *et al*., 2018; Pruszyńska-Oszmałek *et al*., 2021; Iatan *et al*., 2024).

**2.4 Mechanisms of High-Fat Diets in Metabolism**

HFDs significantly impact metabolism through intricate biochemical pathways that regulate energy balance (Chadt & Al-Hasani, 2020), lipid metabolism, insulin sensitivity, and glucose homeostasis (Liu *et al*., 2025). The body’s ability to efficiently process and utilize dietary fats determines whether an HFD leads to metabolic benefits (such as improved endurance and weight loss in ketogenic diets) (Milstein & Ferris, 2021) or metabolic disorders (such as insulin resistance and dyslipidaemia in Western diets high in saturated and trans fats) (Elkanawati *et al*., 2024; M. Sun *et al*., 2024). The mechanism is divided into the following patterns as shown in the Figure 5 below;



**Figure 4: Mechanistic insight into high-fat diet-induced metabolic distortions (Ullah *et al*., 2021).**

**2.4.1 Fat Digestion and Absorption**

The digestion and absorption of dietary fats involve bile acids, pancreatic enzymes, and specialized transport mechanisms that facilitate the breakdown and assimilation of lipids (Omer & Chiodi, 2024). As dietary fats are hydrophobic, their digestion begins in the stomach and is completed in the small intestine with the aid of bile salts and enzymes (Cheng *et al*., 2020). The emulsification process, mediated by bile salts from the liver, breaks large fat droplets into micelles, increasing the surface area for enzymatic action. Pancreatic lipase, secreted from the pancreas into the duodenum, hydrolyzes triglycerides (TGs) into monoglycerides and free fatty acids (FFAs), which are then absorbed by intestinal cells (McQuilken, 2021). Phospholipids and cholesterol esters undergo similar hydrolysis by phospholipase A2 and cholesterol esterase, ensuring efficient uptake of all dietary lipids (Grabner *et al*., 2021).

Once inside intestinal enterocytes, monoglycerides and FFAs are re-esterified into triglycerides and packaged into chylomicrons, which enter the lymphatic system before being transported into circulation via the thoracic duct (Xiao *et al*., 2020). In the bloodstream, chylomicrons interact with lipoprotein lipase (LPL), an enzyme on capillary endothelial cells, which hydrolyzes their triglyceride content into glycerol and free fatty acids, allowing their uptake by adipose and muscle tissue for energy storage or utilization (Gugliucci, 2024a, 2024b). The efficiency of fat digestion and absorption plays a critical role in metabolic regulation, influencing postprandial lipid levels, energy storage, and inflammatory responses (Xiao *et al*., 2019).

**2.4.2 Role of Lipids in Energy Metabolism**

Lipids serve as the primary energy source in high-fat diets, providing more than twice the energy per gram (9 kcal/g) compared to carbohydrates (4 kcal/g) (Gugliucci, 2023). Once absorbed, free fatty acids are either stored as triglycerides in adipose tissue or used immediately for oxidative metabolism (Dilworth *et al*., 2021). The oxidation of fatty acids occurs primarily in the mitochondria via β-oxidation, where long-chain fatty acids are broken down into acetyl-CoA. This acetyl-CoA enters the tricarboxylic acid (TCA) cycle, generating ATP through oxidative phosphorylation in the electron transport chain (Dikalov *et al*., 2024).

In conditions of low carbohydrate availability, such as in ketogenic diets or prolonged fasting, excess acetyl-CoA is diverted into ketogenesis in the liver, producing ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone) (Kolb *et al*., 2021). These ketones serve as an alternative energy source, particularly for the brain and skeletal muscles (Nakamura, 2024). In contrast, high-fat diets rich in saturated fats can contribute to lipotoxicity, where excessive fatty acid accumulation in non-adipose tissues disrupts cellular function, leading to mitochondrial dysfunction, oxidative stress, and inflammation (Nakamura, 2024). The balance between fat oxidation and fat storage plays a key role in determining whether an HFD leads to metabolic health benefits or metabolic syndrome (Ceja-Galicia *et al*., 2025; Song *et al*., 2025).

**2.4.3 Impact on Insulin Sensitivity and Glucose Metabolism**

High-fat diets exert significant effects on insulin sensitivity and glucose regulation, depending on the composition of dietary fats (Sivri & Akdevelioğlu, 2024). Chronic consumption of an HFD rich in saturated fats has been associated with insulin resistance, a key factor in type 2 diabetes mellitus (T2DM). This occurs due to an increase in intramuscular and hepatic lipid accumulation, leading to the production of inflammatory cytokines (TNF-α, IL-6) and oxidative stress, which impair insulin signaling pathways. Specifically, fatty acid intermediates such as diacylglycerol (DAG) and ceramides activate protein kinase C (PKC) isoforms, inhibiting insulin receptor substrate (IRS) phosphorylation and reducing glucose uptake by muscle and adipose tissue (Chen *et al*., 2023; Gugliucci, 2023; Wali *et al*., 2023).

On the other hand, unsaturated fats, particularly monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs), have been shown to enhance insulin sensitivity by modulating lipid signaling pathways and reducing inflammation (Mallick *et al*., 2024; Mititelu *et al*., 2024). The Mediterranean diet, which emphasizes healthy fats from olive oil, nuts, and fish, has been linked to improved glucose metabolism and a reduced risk of metabolic syndrome (Miki *et al*., 2023). The type of fat consumed, rather than total fat intake alone, determines whether an HFD promotes insulin resistance or metabolic efficiency (Liu *et al*., 2023).

**2.4.4 Effects on Lipid Profile (Cholesterol, Triglycerides)**

The impact of high-fat diets on lipid profiles is highly dependent on the type of fats consumed (Saleh *et al*., 2024). Saturated fats and trans fats tend to raise low-density lipoprotein (LDL) cholesterol, which is associated with an increased risk of atherosclerosis and cardiovascular disease (CVD) (Stojko *et al*., 2024). In contrast, unsaturated fats, particularly omega-3 fatty acids from fish and plant-based sources, have been shown to lower triglycerides and LDL cholesterol (Velissaridou *et al*., 2024) while increasing high-density lipoprotein (HDL) cholesterol, which is protective against heart disease (McMullan *et al*., 2023; Sherratt *et al*., 2023).

HFDs can also alter hepatic lipid metabolism, leading to the development of non-alcoholic fatty liver disease (NAFLD) (Pei *et al*., 2020). Excess dietary fats promote hepatic triglyceride accumulation, impairing very-low-density lipoprotein (VLDL) secretion and increasing circulating free fatty acids (Radhakrishnan *et al*., 2020). Over time, this leads to liver inflammation, fibrosis, and an increased risk of metabolic syndrome (Gowda *et al*., 2023). The balance of lipid intake—favouring unsaturated fats over saturated and trans fats—plays a crucial role in determining the effects of HFDs on cardiovascular and metabolic health (Flessa *et al*., 2022).

**2.5 Neurological Effects of High-Fat Diets**

HFDs have been widely studied due to their significant effects on human health, particularly in relation to metabolic, cardiovascular, neurological, and reproductive health (Zimmerman *et al*., 2021). The impact of HFDs is largely dependent on the type, quantity, and source of fats consumed, as well as individual genetic predispositions and lifestyle factors (Martinez-Lomeli *et al*., 2023). While certain high-fat diets, such as the Mediterranean diet and ketogenic diet, have been associated with health benefits (Dominguez *et al*., 2023), excessive consumption of unhealthy fats, particularly saturated fats and trans fats, has been linked to various chronic diseases (Pipoyan *et al*., 2021).

The relationship between high-fat diets and brain function is complex. While omega-3 fatty acids have been linked to enhanced cognitive function and reduced risk of neurodegenerative diseases, excessive intake of saturated fats has been associated with impaired memory and cognitive decline (Song *et al*., 2025). Studies suggest that high-fat diets may promote neuroinflammation, increasing the risk of Alzheimer’s disease and Parkinson’s disease through mechanisms involving oxidative stress and β-amyloid accumulation (Batarseh & Al Thaher, 2023; Tchekalarova & Tzoneva, 2023).

Brain plasticity, or the ability of the brain to adapt and form new neural connections, is negatively affected by chronic HFD consumption (Marzola *et al*., 2023). Research shows that HFDs impair hippocampal function, reducing synaptic plasticity and memory performance in rodents. This is largely attributed to increased inflammation and insulin resistance in the brain, which disrupt neurogenesis (Pickersgill *et al*., 2022; Zeine *et al*., 2024).

In contrast, the ketogenic diet, a very low-carbohydrate, high-fat diet, has shown therapeutic benefits in epilepsy treatment (Nkole *et al*., 2020). KD induces ketosis, where ketone bodies (β-hydroxybutyrate) replace glucose as the brain’s primary fuel source, reducing seizure frequency in drug-resistant epilepsy patients. This diet has also been explored for its potential neuroprotective effects in neurodegenerative diseases (Tagliabue *et al*., 2024).

**2.6 Bisphenol-A**

**2.6.1 Overview**

Xenoestrogens or endocrine disruptors are natural or synthetic compounds harmful to the endocrine system because they stop endogenous hormone production and normal functioning (Ma *et al*., 2019). Due to rapid advancement in human lifestyle, endocrine-disrupting chemicals are being introduced competently into the environment extensively, and living beings are directly or indirectly exposed to harmful chemicals such as Bisphenol A (BPA) (Khan *et al*., 2021; Wang *et al*., 2021; Zhang *et al*., 2022).

Bisphenol A is among toxic chemicals, first highlighted by Aleksandr Dianin in 1891, then in 1905, they were made by Zincke using acetone condensation with two correspondents of phenol. In the mid-twentieth century (1940), a sudden rise in polymers (polycarbonates, polysulfone, polyacrylate, and epoxy resins) was observed with BPA. The polymers were also used as an antioxidant and endpoint for inhibiting polymerization in polyvinyl chloride plastics. Besides, flame retardant polymers, including tetrabromobisphenol-A were also prepared using the polymers (Wang *et al*., 2022). It makes different polymers, such as epoxy resins, polycarbonates, and other polymer materials (Wang *et al*., 2019). Epoxy resins and polycarbonates were in high demand in 2015, 64 and 34%, respectively. Demand increases are expected with each passing year (Tözüm *et al*., 2021).

Additionally, in recent years, their uses have expanded to produce optical and electronic materials. Polymers also produce plastic food containers, drinking glasses, bowls, cups, and microwave-safe utensils (Hamed & Li, 2022). Canned materials can be a significant source for food adulteration owing to direct contact since epoxy resins are utilized to protect the can from the inside (Neufeld *et al*., 2015). They are used in other industries like the ink and paint industry, manufacturing of thermal papers, compact discs, electronics etc (Brown *et al*., 2022).

Since then, BPA has been abundantly used in food packaging materials, take-away water bottles, and lacquer coatings for tin cans causing human exposure to BPA via food and drinks (Khan *et al*., 2021; Wang *et al*., 2021; Zhang *et al*., 2022). Furthermore, occupational workers get BPA exposure through direct contact with skin or inhalation, whereas the standard population is exposed to BPA by dust inhalation (Erren, 2022; Hahladakis *et al*., 2023). BPA has been linked to several serious health issues in animal model research. Numerous human-based epidemiological and observational studies on BPA exposure revealed similar results. BPA exposure is associated with the incidence of growth disruption, halting normal development, infertility, endocrine system disruption, immune system suppression, and carcinogenicity (Gerona *et al*., 2013).

**2.6.2 Physico-chemical properties**

The molecular weight of BPA [4, 4-isopropylidene diphenol; 2, 2-bis (4-hydroxyphenyl)-propane] is 228.29 g/cm3, with a white crystal-like appearance and highly reactive due to the presence of hydroxyl group in the structure. The melting and boiling points of the toxic chemical are 156 and 220◦C (at 5 hPa), respectively. The coefficient of BPA in water octanol is expressed in a logarithmic form value of 3.32 (log P = 3.32), indicating its high solubility in fats and less soluble in water (about 200 mg/dm3 at 25◦C). Moreover, it can also be transformed into ether, esters, and salts like other phenols. Additionally, the electrophilic substitution of BPA generally includes sulphonation, alkylation, and nitration (Vasiljevic & Harner, 2021; Desai & Jagtap, 2022).

**2.6.3 Applications of Bisphenol A**

Bisphenol A is a well-known synthetic chemical globally used to manufacture different polymers, including epoxy resins, polycarbonates, and other polymer materials. Polycarbonates and epoxy resins are prominent polymers in significant bisphenol applications. Some other uses of bisphenol A include the production of different resins (unsaturated polyester, polysulfone, polyetherimide, and polyacrylate) (Wang *et al*., 2019; Tözüm *et al*., 2021). In 2015, global demand for polycarbonates and epoxy resins was 64 and 34%, respectively. Moreover, the rise in demand for these two polymers will be observed with an average annual rate of 3 and 4% for the next 5 years. Furthermore, in recent years, their applications extended to manufacturing optical and electronic materials. Plastic cups, bottles, bowls, food containers, and utensils used for microwaves are also synthesized with polymers (Hamed & Li, 2022; Lambré *et al*., 2023).

Epoxy resins protect the can from the inside; therefore, they can be a considerable source for the adulteration of food items due to direct contact (Neufeld *et al*., 2015). The storage bottles are also layered with epoxy resins for a similar purpose (Cao *et al*., 2011). Nonetheless, epoxy resins are also successfully applied in the paint and ink industry. Beyond this, epoxy resins also have a well-established reputation in manufacturing thermal paper, compact discs (CD), and digital video discs (Neufeld *et al*., 2015; Brown *et al*., 2022). Whereas the derivate compounds from BPA are used in tickets and newspapers for antioxidants and stabilizers (Hahladakis *et al*., 2023) and, in the textiles industry, it is employed for infant sock preparation (Freire *et al*., 2019).

**2.6.4 Exposure to Bisphenol A**

Bisphenol A is present almost everywhere in our surroundings and significantly affects our life. It can be part of the food and environment directly or indirectly, affecting living organisms.

**2.5.4.1 Environment**

Bisphenol A is an ‘omnipresent’ contaminant due to its presence in all possible resources that might be the source of its human exposure through air, water, and soil (Huang *et al*., 2012). There are three main routes for human exposure environmental, occupational, and contaminated food consumption (Kang *et al*., 2006). Workers synthesizing BPA and their related derivative compounds (i.e., polycarbonate, epoxy resins, and polyvinyl chloride) are easy targets for occupational exposure. The main reason for the environmental exposure is the contamination of the atmosphere, soil, and aquatic systems owing to the BPA entering the environment due to its use in thermal paper recycling and relevant industries (Kang *et al*., 2006; Rene *et al*., 2015).

According to various studies, approximately 56 µg/L of BPA can be ingested from the aquatic environment, 1– 150 µg/kg from soil (Langdon *et al*., 2012; Corrales *et al*., 2015), while 2–208 ng/m3 of BPA can be inhaled from the surroundings and dust contributes 0.2–17.6 µg/g contamination (Rudel *et al*., 2001). In addition, contaminated seafood ingestion, metallic food cans, and plastic bottles can contribute 13.3–213 µg/kg, 2–82 ng/g, and 0.234 µg/L, respectively (Basheer *et al*., 2004), whereas landfill leachates (17.2 mg/L) (37), dermal route (7.1–71 µg/day) (Yamamoto *et al*., 2001), and dental material (0.013– 30 mg/day) also contaminate the environment (Biedermann *et al*., 2010).

**2.6.4.2 Food**

Food exposure is the most important because fulfilling daily dietary needs is essential for survival (Manzoor *et al*., 2022b). Contamination of BPA through food exposure occurs due to the use of BPA for manufacturing different types of plastic containers [polycarbonate (PC) and polyvinylchloride (PVC) plastics] used for food serving and exposing their direct interaction with food. Epoxy resins are also used to manufacture food cans for inner coatings. Therefore, canned food products also play a significant role in adulterating food items. Residual monomers of these compounds migrate from the can to the food product, and food consumption causes safety issues in individuals (Neufeld *et al*., 2015). Besides, food packaging materials are the primary cause of BPA accumulation in human beings. It is due to the penetration of BPA from packaging into foodstuff and beverages (Vandenberg *et al*., 2010; Usman & Ahmad, 2016). There are also secondary reasons which lead to exposure to BPA and hence the infected human population (Molina-Molina *et al*., 2019; Morgan *et al*., 2018).

**2.6.5 Metabolism of Bisphenol A**

Bisphenol A is highly metabolized and secreted into urine, primarily as a glucuronide conjugate with a half-life of 2 h (Völkel *et al*., 2002). BPA’s half-life also depends on the glucuronidase enzyme, which activates BPA through deconjugation in the bloodstream, and other organs (Ginsberg & Rice, 2009). Furthermore, the valid biomarker of BPA exposure is total BPA (including free or conjugated) urinary concentration (Calafat *et al*., 2008). The health aspect of free BPA (a weak estrogen) has been primarily observed in animal models. At the same time, limited neonatal human researches are available to check behavioral and executive functional effects, especially during critical child developmental stages and in the shortening of congenital space in male offspring (Chevrier *et al*., 2012). However, several experiments revealed that BPA initially affects hepatic injury (Tominaga *et al*., 2006). After ingestion, most BPA in the liver and gut is rapidly bound with glucuronic acid to release BPA glucuronide (BPA-G) by the glucuronidation process, facilitated by many enzymes (Shelby, 2008).

Moreover, being fat-soluble, BPA has high adipose tissue affinity and is then released steadily to other histological structures in humans and mice (Doerge *et al*., 2011). An investigation to estimate the BPA division in humans highlighted that BPA is demonstrable in almost all human histological structures. In adipose tissues, it ranged from 1.13 to 12.27 ng/g, 0.78 to 3.34 ng/g in the liver, and 1 to 2.35 ng/g in the brain. In breast milk, total BPA was observed as 1.09 ng/mL, out of which 0.41 ng/mL content was identified as unconjugated BPA (Wang *et al*., 2019).

Furthermore, the conjugated BPA does not combine with the estrogen receptor (ER); therefore, they are biologically inactive and inert. However, another investigation revealed that BPA-conjugated forms could disturb cellular responsive action throughout membrane ERα contacts, which is responsible for quick signaling feedback (Viñas *et al*., 2013). In contrast, in trace concentrations, unconjugated BPA (free BPA) can convert into other compounds such as BPA sulfate or BPA-S.

Bio-monitoring records reveal that BPA interaction with humans is prevalent (Teeguarden & Hanson-Drury, 2013). However, there is still massive controversy on the legality of the reported measure of unconjugated BPA in whole blood, plasma, or serum. The discussion point is that adult human blood samples have up to 0.5–2 ng/mL (2.2–8.8 nM) unconjugated BPA. It is very high than the predicted levels of 0.51 µg/kg of body weight per day calculated based on adults’ estimated daily intake. Presumably, few of the even most substantial daily consumption records in this range (and lower) depend on the whole day urinary output, with back calculations of 596 German women and men (Lorber *et al*., 2015).

**2.7 Effects of co-exposure of HFD and BPA on the cerebellum**

There are limited specific studies directly addressing this exact combination in the cerebellum. Nonetheless, few studies have looked at the parameters studied.

**2.7.1 High-Fat Diet and Cerebellar Neuroinflammation**

High-fat diets, characterized by elevated saturated fat content (typically ≥45% kcal from fat), are known to induce systemic and central nervous system (CNS) inflammation (Dias *et al*., 2020). Studies demonstrate that HFD consumption triggers neuroinflammation in brain regions such as the hypothalamus, hippocampus, and cerebral cortex, with emerging evidence suggesting cerebellar involvement (Gómez-Apo *et al*., 2021; Lama *et al*., 2022; Schmitt & Gaspar, 2023; Ubaldo-Reyes *et al*., 2024; Ullah *et al*., 2021). For instance, Cavaliere *et al*. (2019) found that male C57Bl/6 mice fed an HFD for 18 weeks exhibited increased levels of pro-inflammatory cytokines (TNF-α and IL-1β) and oxidative stress markers (malondialdehyde, MDA) in the cerebral cortex and synaptosomal fractions, alongside reduced antioxidant defenses (glutathione, GSH). While this study focused on the cortex, the cerebellum shares similar vulnerabilities due to its high density of microglia, which express AIF-1 (also known as Iba-1), a marker of microglial activation.

In the cerebellum, HFD-induced neuroinflammation is less studied but has been linked to microglial activation and cytokine upregulation (Song *et al*., 2025). A study by Netam (2024) reported that short-term (10 days) HFD feeding in male Wistar rats increased inflammatory markers (IL-6, NFKBIA) and reactive oxygen species (ROS) in the arcuate nucleus, suggesting rapid onset of neuroinflammation in metabolically sensitive brain regions. Although the cerebellum was not specifically examined, its susceptibility to HFD-induced inflammation is plausible due to its role in energy homeostasis and its exposure to circulating inflammatory mediators. AIF-1, a calcium-binding protein expressed by activated microglia, is a reliable indicator of neuroinflammation (De Leon-Oliva *et al*., 2023). Studies on obesity models show elevated AIF-1 expression in the hippocampus following HFD (Mazzei *et al*., 2021; Niu *et al*., 2022; Sanchez *et al*., 2024), correlating with increased IL-1β and TNF-α, suggesting a similar mechanism may occur in the cerebellum.

**2.7.2 Bisphenol A and Cerebellar Effects**

BPA, a ubiquitous EDC found in plastics and food packaging, crosses the blood-brain barrier and exerts neurotoxic effects (Costa & Cairrao, 2024). While most research on BPA’s CNS effects focuses on the hippocampus and prefrontal cortex (Hyun & Ka, 2024; C. Li *et al*., 2023; W. Zhang *et al*., 2024), limited studies address the cerebellum. Nagarajan *et al*. (2024) demonstrated that high-dose BPA exposure in rats impairs mitochondrial bioenergetics in the liver, leading to oxidative stress and inflammation, which could extend to the CNS, including the cerebellum. In a study by Khan *et al*. (2019), subchronic BPA exposure (40 and 400 μg/kg for 60 days) in male C57Bl/6J mice caused neuroinflammation in the cerebral cortex, with increased mRNA and protein expression of inflammatory cytokines and reduced expression of myelin-related proteins (e.g., myelin basic protein, MBP). This suggests BPA may induce cerebellar myelin degeneration, potentially detectable via routine staining techniques like H&E or Luxol Fast Blue (LFB), which visualize myelin and neuronal structure.

BPA’s neuroinflammatory effects are mediated by pathways such as toll-like receptor-4 (TLR4) and nuclear factor-κB (NF-κB), which upregulate pro-inflammatory cytokines (Charles & Prince, 2024; L. Wu *et al*., 2022). These pathways are relevant to cerebellar microglia (Cai & Lin, 2022), which express AIF-1. Although direct evidence of BPA’s effects on cerebellar AIF-1 expression is scarce, its role in microglial activation in other brain regions suggests a potential mechanism for cerebellar neuroinflammation.

**2.7.3 Co-Exposure to HFD and BPA: Synergistic Effects**

The combined exposure to HFD and BPA is hypothesised to exacerbate neuroinflammation and structural changes due to their convergent effects on oxidative stress and inflammatory pathways. Studies on peripheral organs, particularly the liver, provide insights into potential CNS effects. Pirozzi *et al*. (2020) showed that BPA (50 μg/kg/day) in HFD-fed male C57Bl/6J mice worsened hepatic steatosis, inflammation, and fibrosis, with increased TLR4, NF-κB, and NLRP3 inflammasome activation, alongside elevated hepatic triglycerides and oxidative stress. These effects were accompanied by histological changes (e.g., ballooning degeneration, inflammatory foci) detected via H&E and MTC staining, suggesting that similar techniques could reveal cerebellar structural changes.

In the CNS, co-exposure studies are limited, but Figueiredo *et al*. (2020) reported that perinatal BPA exposure combined with HFD in male rat offspring exacerbated nonalcoholic steatohepatitis-like phenotypes, with increased lipogenic gene expression and inflammation. While this study did not examine the cerebellum, the systemic inflammation and metabolic dysregulation observed could affect cerebellar microglia and neurons. Lin *et al*. (2019) investigated combined fructose and BPA exposure in developmental male Wistar rats, finding synergistic increases in hepatic TLR4 and NF-κB expression, lipogenesis, and lipid accumulation, with H&E staining revealing increased lipid droplets. These findings suggest that co-exposure may amplify cerebellar neuroinflammation (detectable via AIF-1) and structural damage (observable via H&E or MTC staining).

**2.7.4 Structural Changes in the Cerebellum**

Routine staining techniques, such as H&E and MTC, are widely used to assess structural changes in neural tissues. H&E staining reveals cellular morphology, inflammation, and necrosis, while MTC highlights fibrosis and collagen deposition. In the context of HFD and BPA, these techniques could detect cerebellar changes such as neuronal degeneration, microglial activation, or myelin loss. For example, Khan *et al*. (2019) used H&E to observe axonal and myelin degeneration in the cortex of BPA-exposed mice, alongside increased AIF-1 expression, indicating microglial activation and neuroinflammation. Similarly, HFD studies report neuronal damage and gliosis in the hippocampus and cortex (Ledreux *et al*., 2016; S. Tian *et al*., 2023; Ubaldo-Reyes *et al*., 2024), detectable via H&E, which may extend to the cerebellum.

In the cerebellum, structural changes may include Purkinje cell loss, white matter disruption, or glial proliferation, all of which connection between the cerebellum and cortex is another brain region vulnerable to inflammation. These changes could be visualized using LFB for myelin or Nissl staining for neuronal integrity, alongside H&E for broader histological assessment (X. Zhang *et al*., 2005).

**2.7.5 AIF-1 as a Neuroinflammation Marker**

AIF-1 is a key marker of microglial activation and neuroinflammation, widely used in immunohistochemical and molecular studies. In obesity and EDC exposure models, AIF-1 expression is elevated in brain regions like the hippocampus and hypothalamus, reflecting microglial-driven inflammation. For instance, Ledreux *et al*. (2016) found increased AIF-1 and IL-1β expression in the hippocampus of HFD-fed rats, correlating with cognitive deficits. While cerebellar-specific AIF-1 studies are limited, the protein’s role in microglial activation suggests it could be used to quantify neuroinflammation in HFD- and BPA-exposed cerebella. Immunohistochemical staining for AIF-1, combined with routine histological techniques, could provide a comprehensive assessment of microglial activation and structural changes in the cerebellum.

**CHAPTER THREE**

**MATERIALS AND METHODS**

**3.1 Materials**

The materials for this study were of various types. They were grouped into biological materials, chemical materials, instruments and software materials

**3.1.1 Biological materials**

The biological materials used for this experiment include Male Wister Rats, Eva distilled water, Cooking Devon margarine, Cooked egg yolk, Chikun Feed, king’s Oil.

**3.1.2 Chemical materials**

Bisphenol A, BUA Sugar, Ethanol, 10% Neutral buffer, Eva distilled water, were among the materials used for this research work.

**3.1.3 Instruments**

Cages, Weighing Balance, Dissecting Set/Kits, Dissecting Board, Recording Instruments, Reagent bottles (Universal Containers), sieving cloth, hand gloves, feeding containers, slides and coverslips, Serviette.

**3.1.4 Software materials**

Laptop (1terabyte hard disk for images and video storage), GNU Image Manipulation Program (GIMP) Version 3.0.4, Compound Microscope (Model: XSZ-107BN), Image view software (Version S64, 4.11.1812.20201123), Camera YW500.

**3.1.5 Materials’ Information**

These were some of the nutritional and configurations data on the materials used:

* **Devon cooking margarine:**

The manufacturer’s date was 27/10/23, Best Before was 27/07/24, Batch Number was 23300 20:22, and the size was 250g \* 40 pieces. The stocking configuration was as follows; Cases per layer=0, Layers per pallet =4, Cases per pallet = 40.

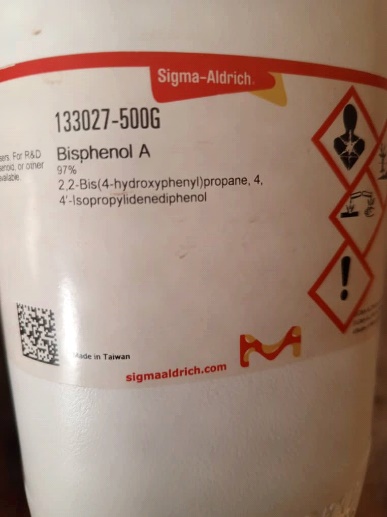
* **BUA Sugar**

The size of the sugar used was 50kg with NAFDAC Number 08-2037, the energy as carbohydrate was 20Kcal per teaspoon, 395Kcal per 100mg.

**3.2 Method**

**3.2.1 Procurement of Bisphenol A**

The bispehenol A contains 97% 2, 2 Bis (4-hydroxyphenyl) propane, 4,4-isopropylindenediphonel with molecular formula C15H16O2 , density of 1.2g/ and molecular weight of 228.29g/mol, with a case number 80-05.7, produced from Sigma-Aldrich.





**3.2.2 Composition of Original Rat Feed**

The normal chow was purchased from chikun feed and it is composed of the nutrients outlined in table 1 below

**Table 1: Showing Composition of original Rat Feed**

|  |  |
| --- | --- |
| Nutrients | Composition(%) in 25kg |
| Crude protein | 17 |
| Crude Fat | 4 |
| Crude fibre | 5 |
| Calcium | 0.85 |
| Available Phosphorus | 0.45 |
| Lysine | 0.90 |
| Methionine | 0.40 |

In this study, the High Fat Diet was constituted by the addition of margarine, sugar and cooked egg yolk as shown in table 2 below. The 50g of the cooked egg yolk has an equivalent of 13.23g of fat according to United States Department of Agriculture (USDA) (2020).

**Table 2: Indicating the Composition of High Fat Diet used for the study**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **HIGH FAT DIET Composition** | **Percentage** | **Composition** | **Fat contents in % based** | **Total nutritional** |
|  | **(%)** | **(g)** | **on the composition in g** | **contents (g)** |
| Chikun Feed | 60 | 300 | 14 | 85.71 |
| Margarine | 20 | 100 | 99.38 | 80.50 |
| Sugar | 10 | 50 |  | 50 |
| Cooked egg yolk | 10 | 50 | 5.2 | 13.23 |
| **Total** | **100** | **500** | **118.58** | **229.461** |

**3.2.3 Wister Rats Grouping and Designation:**

In this study, a total of sixteen (16) male albino Wistar rats, weighing between 50-70g, were purchased from the Faculty of Basic Medical Sciences’ Animal House at Ebonyi State University. These animals were assigned randomly into Galvanised aluminium cages, under a 12-hour light-dark cycle at a room temperature of 32℃, and were provided with standard commercial pelleted finisher feed (Chikun Feed, Nigeria Ltd) and tap water *ad* *libitum*. They were acclimatised for two weeks before the study commenced. Markings were made upon each rat to differentiate them into groups for easy distinctions.

Furthermore, the rats were culled to about 12-15 rats per day to prevent over-nutrition and under-nutrition of the rats due to survival and were randomly assigned to groups. The rats were divided into four (4) groups namely; A, B, C and D. Group A served as a control group and was fed with only the normal feed, kings oil and water; Group B were fed with Bisphenol A and water, Group C were fed with High Fat Diet and water, Group D were fed with High Fat Diet and Bisphenol A as shown in **Table 3** below.

**Table 3: Showing Animal Grouping and Feeding with Normal, High Fat Diet, Bisphenol A and water**

|  |  |  |  |
| --- | --- | --- | --- |
| **GROUPS** | **FEEDING** | **DURATION (WEEKS)** | **RATS** |
| A | Normal feed, kings oil and water | 12 | 4 |
| B | Bisphenol A | 12 | 4 |
| C | High Fat Diet | 12 | 4 |
| D | High Fat Diet and Bisphenol A | 12 | 4 |
|  |  | **Total number of rats =** | **16** |

**3.2.4 Tissue Collection**

On day 85 (24 hours after the study ended), cerebellar tissues were collected from all six groups. The procedure involved cervical dislocation, pinning the rat to a dissecting board, dissecting the brain, and isolating the cerebellum.

**3.2.5 Tissue processing**

Cerebellar tissues were fixed in 10% neutral buffer (specific to BPA and HFD studies). Tissue processing for routine H&E staining and AIF-1 immunohistochemistry followed these steps:

* Deparaffinization: Slides were flamed and placed in xylene.
* Hydration: Xylene was drained, and tissues were hydrated through decreasing alcohol concentrations and water.
* Nuclear Staining: Tissues were stained with haematoxylin for 3–5 minutes and washed in running water for 5 minutes.
* Differentiation: Tissues were dipped in 1% acid alcohol (1% HCl in 70% alcohol).
* Blueing: Tissues were rinsed in running water, dipped in ammonia water until blue, and washed in tap water.
* Counterstain: Tissues were stained with 1% eosin for 10 minutes and washed in tap water for 1–5 minutes.
* Dehydration: Tissues were dehydrated in increasing alcohol concentrations.
* Clearing: Slides were placed in two xylene baths and coverslipped.

**3.2.6 Photomicrograph of the Cerebellum**

This photomicrograph was done using the camera, light microscope and software. The details are as follows

Camera: the name of the camera used is YW500

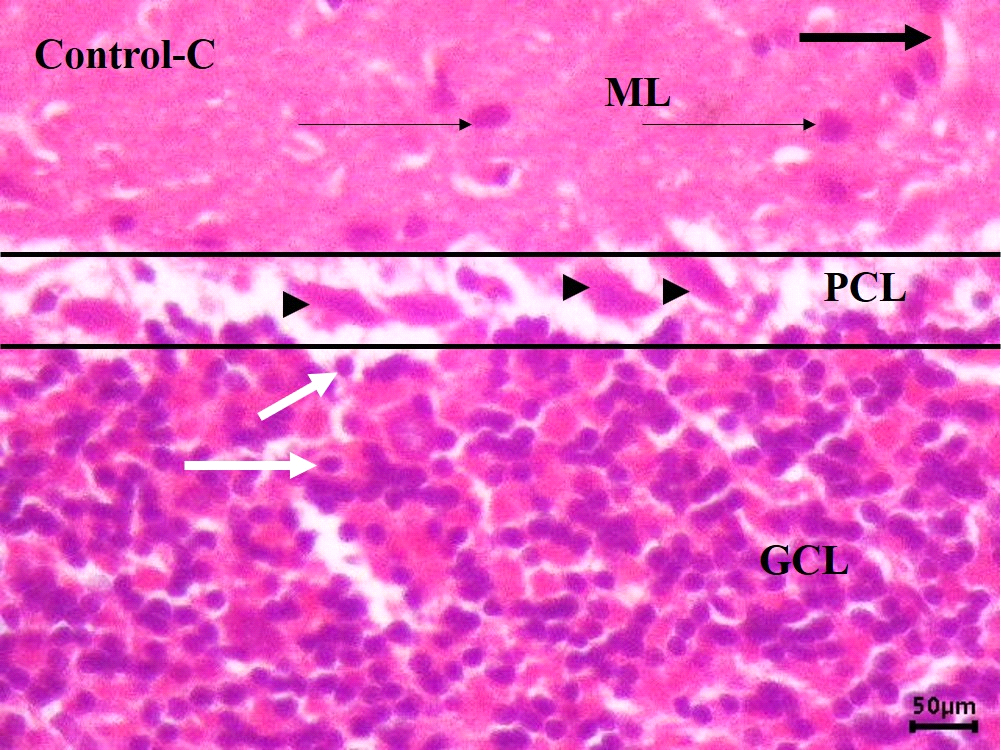
Software: the software used was image view of Version X64, 4.11.18012.20201123. It was built on November 24, 2020.

**CHAPTER FOUR**

**RESULTS**

**4.1 Histological Findings**

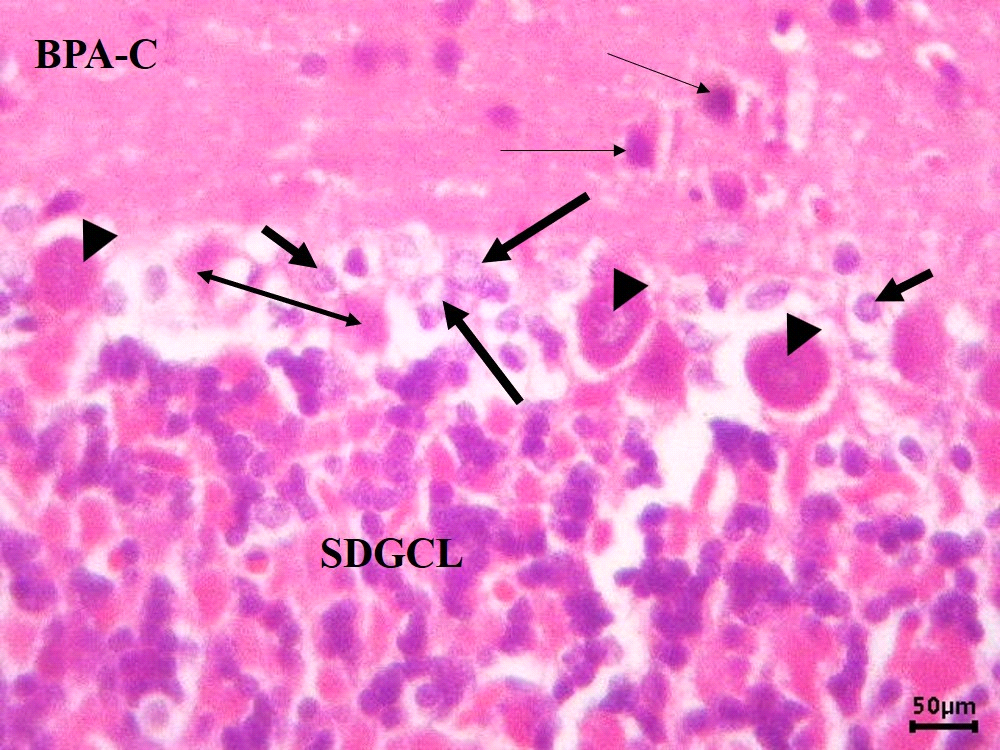
**4.1.1 Control of Cerebellar Cortex (Control-C)**



**Plate 1: Photomicrograph of cerebellar cortex of control group.**

This cerebellar section indicated the three layers of the cerebellar cortex, namely the molecular layer (ML), the Purkinje cell layer (PCL) and the granular cell layer (GCL). The ML contains glial cells (thin black arrow), blood vessels (long bold black arrow). The Purkinje cells (black arrowheads) are found in the PCL, while the GCL houses the granule cells (white arrows), as shown in the Plate 1.

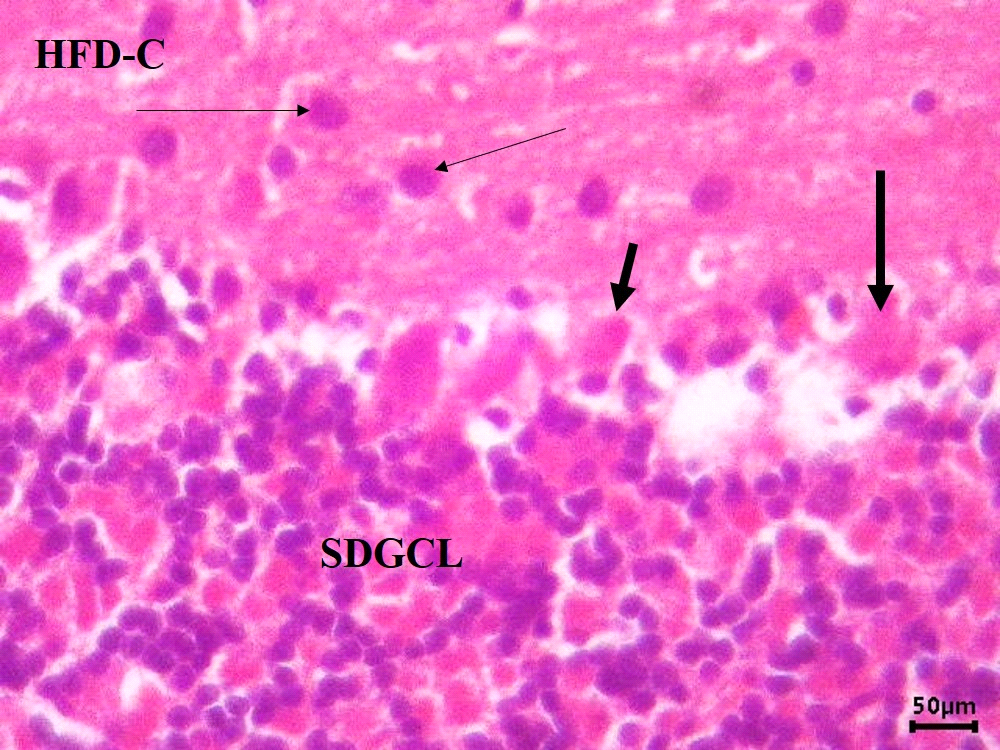
**4.1.2 Cerebellar cortex of Bisphenol-A Exposed rats (BPA-C)**



**Plate 2: Photomicrograph of cerebellar cortex of Bisphenol-A exposed group.**

The results from the photomicrograph of this section showed enlarged glial cells (thin black arrows), degenerating glial cells (shorter bold black arrows) and complete loss of cellular contents of the glial cells (longer bold black arrows) close to the degenerating Purkinje cells (bidirectional arrow). This section also revealed Purkinje cells with distorted appearance, condensed nucleus (black arrow head) as well as severe distortion of GCL as indicated in the Plate 2.

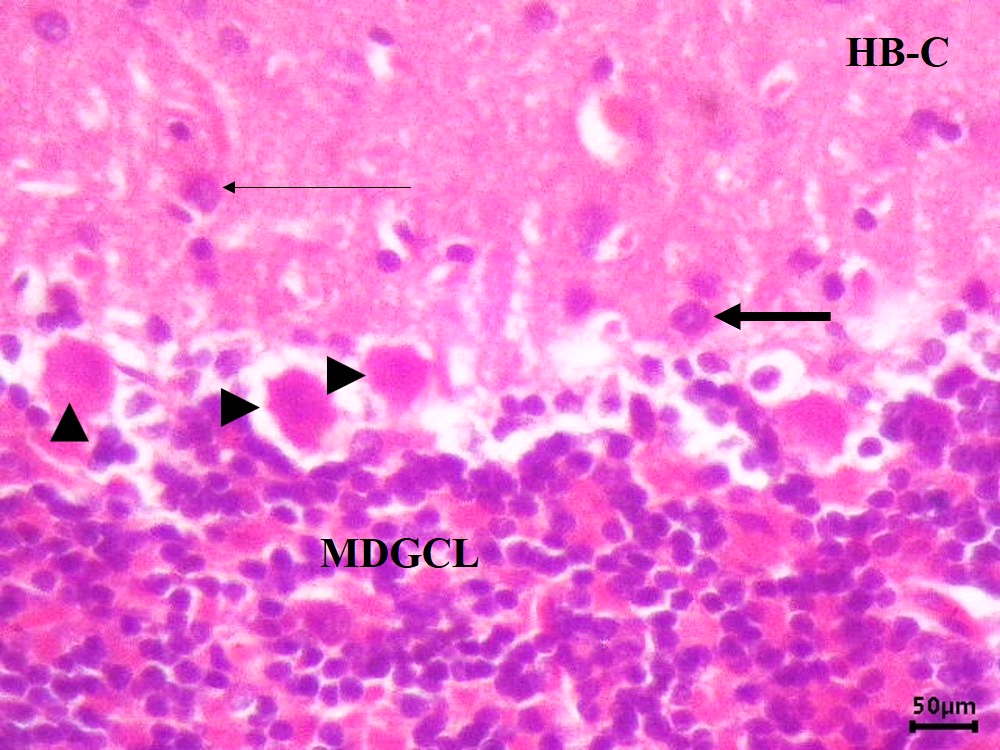
**4.1.3 Cerebellar cortex of high-fat diet Exposed rats (HFD-C)**



**Plate 3: Photomicrograph of cerebellar cortex of high-fat diet exposed rats.**

The examination of the photomicrograph of this section also showed enlarged glial cells (thin black arrows) and degenerating Purkinje cells (short and long bold black arrows). This section also showed severe distortion of the GCL as indicated in the Plate 3.

**4.1.4 Cerebellar cortex of high-fat diet and Bisphenol-A exposed rats (HB-C)**

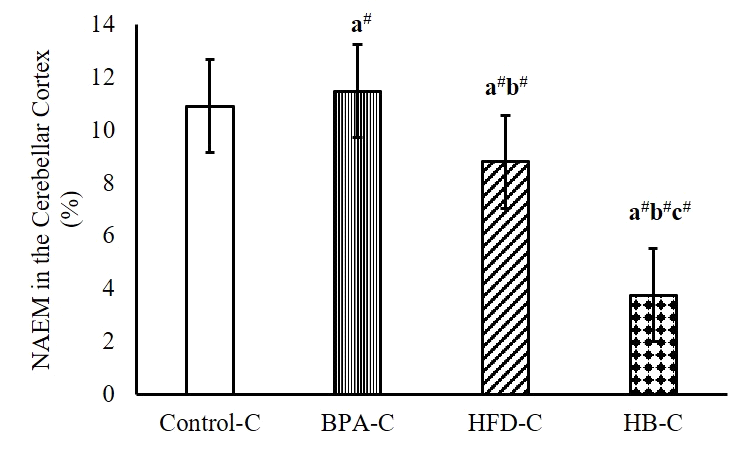


**Plate 4: Photomicrograph of cerebellar cortex of high-fat diet and BPA exposed rats.**

The section of cerebellar cortex from this group showed enlarged glial cells with condensed nuclei (thin and bold long arrows). This section further indicated distorted Purkinje cells (arrowheads) and mild distortion of the GCL, as indicated in the Plate 4.

**4.2 Mean Values of Nuclear Areas Expressing Microglia (NAEM) in the Cerebellar Cortex**

From the results in this study, the NAEM in the cerebellar cortex of the male Wistar rats of the control (Control-C), bisphenol-A (BPA) only, high fat diet (HFD) only and Combination of HFD and BPA (HB) groups had mean ± SEM of 10.91±2.90, 11.48±2.85, 8.81±1.23, 3.75±0.63, respectively. This study indicated no significant difference in NAEM when groups BPA-C, HFD-C and HB-C were compared to Control-C. The comparison of NAEM in groups HFD-C and HB-C to NAEM in group BPA-C and the comparison of NAEM in group HFD-C to NAEM in group HB-C were shown to have no significant difference, as indicated in Figure 5.



**Figure 5: Bar Chart of the Mean Values of NAEM in the cerebellar cortex of the Control-C, BPA-C only, HFD-C only and HB-C**

**a, b and c denote comparison of NAEM in the cerebellar cortex to Control-C, BPA-C only, HFD-C only and HB-C, respectively. # represent no significant difference at P < 0.05**

**CHAPTER FIVE**

**DISCUSSION, CONCLUSION AND RECOMMENDATIONS**

This study investigated the effects of co-exposure to HFD and BPA on the cerebellum of male Wistar rats, focusing on neuroinflammation and structural changes using routine histological staining and AIF-1 as a marker of microglial activation.

**5.1 Histological Changes in the Cerebellar Cortex**

The control group (Control-C) exhibited a normal cerebellar cortex structure with well-defined molecular layer (ML), Purkinje cell layer (PCL), and granular cell layer (GCL), consistent with the previous studies describing the cerebellum’s laminated organisation (Roostaei *et al*., 2014; Schmahmann, 2019). The presence of glial cells, blood vessels, Purkinje cells, and granule cells in their respective layers aligns with the established microanatomy of the cerebellum, as described by Voogd and Glickstein (1998) and Buffo and Rossi (2013). This baseline structure serves as a reference for evaluating pathological changes in the experimental groups.

In the BPA-exposed group (BPA-C), histological findings included enlarged and degenerating glial cells, complete loss of cellular contents in some glial cells, and distorted Purkinje cells with condensed nuclei, alongside severe distortion of the GCL. These observations are consistent with the neurotoxic effects of BPA reported in studies. Costa and Cairrao (2024) noted that BPA crosses the blood-brain barrier, inducing oxidative stress and inflammation in brain tissues, including the cerebellum. Khan *et al*. (2019) reported similar cortical damage, including axonal and myelin degeneration, in BPA-exposed mice, which supports the cerebellar degeneration observed in this study. The severe GCL distortion may reflect BPA’s disruption of granule cell integrity, potentially impairing cerebellar circuitry, as granule cells are critical for parallel fibre inputs to Purkinje cells (Mugnaini *et al*., 2011).

The HFD-exposed group (HFD-C) showed enlarged glial cells and degenerating Purkinje cells with severe GCL distortion, corroborating studies linking HFD to neuroinflammation and neuronal damage. Song *et al*. (2025) and Cavaliere *et al*. (2019) reported increased pro-inflammatory cytokines (e.g., TNF-α, IL-1β) and oxidative stress markers in HFD-fed rodents, particularly in metabolically sensitive brain regions. Although these studies focused on the cortex and hippocampus, the cerebellum’s high microglial density (Roostaei *et al*., 2014) makes it similarly vulnerable to HFD-induced inflammation. The observed Purkinje cell degeneration aligns with reports of neuronal loss in other brain regions due to HFD-induced lipotoxicity and oxidative stress (Ledreux *et al*., 2016; Ubaldo-Reyes *et al*., 2024).

The co-exposure group (HB-C) exhibited enlarged glial cells with condensed nuclei, distorted Purkinje cells, and mild GCL distortion. The milder GCL distortion compared to BPA-C and HFD-C suggests a complex interaction between HFD and BPA, potentially indicating a synergistic or modulatory effect. Pirozzi *et al*. (2020) demonstrated that HFD and BPA co-exposure exacerbate hepatic inflammation and structural damage via TLR4 and NF-κB pathways, which may extend to the CNS, as suggested by Lin *et al*. (2019).

**5.2 Expression of AIF-1 and Microglial Activation**

The study measured the mean values of nuclear areas expressing microglia (NAEM) as an indicator of AIF-1 expression and microglial activation. The results showed mean ± SEM values of 10.91±2.90 (Control-C), 11.48±2.85 (BPA-C), 8.81±1.23 (HFD-C), and 3.75±0.63 (HB-C), with no significant differences between groups (P < 0.05). These findings contrast with expectations based on previous studies, which associates both HFD and BPA with increased microglial activation and AIF-1 expression in other brain regions (Ledreux *et al*., 2016; Mazzei *et al*., 2021; Sanchez *et al*., 2024).

The lack of significant NAEM differences may be attributed to several factors. First, the cerebellum’s unique microanatomy, with its high density of granule cells and Purkinje cells, may modulate microglial responses differently compared to the hippocampus or cortex, where AIF-1 upregulation is well-documented (Niu *et al*., 2022). De Leon-Oliva *et al*. (2023) noted that AIF-1 expression varies by brain region, reflecting local microglial heterogeneity. The cerebellum’s lower baseline microglial activity, as described by Buffo and Rossi (2013), may limit the detectable range of AIF-1 changes in response to HFD and BPA.

Second, the duration of exposure (12 weeks for most groups, 16 weeks for Group F) may not have been sufficient to induce significant microglial proliferation or AIF-1 upregulation in the cerebellum. Cavaliere *et al*. (2019) observed significant cytokine increases after 18 weeks of HFD, suggesting that longer exposure periods may be required for robust cerebellar microglial activation. Similarly, Khan *et al*. (2019) reported BPA-induced inflammation after 60 days at higher doses (40–400 μg/kg), whereas this study used a standard dose, potentially below the threshold for significant AIF-1 changes.

The lower NAEM in the HB-C group (3.75±0.63) compared to other groups is intriguing and may suggest a suppression of microglial activation in co-exposure conditions. This could reflect a synergistic interaction where combined HFD and BPA exposure overwhelms microglial capacity, leading to reduced proliferation or AIF-1 expression, possibly due to chronic stress or microglial exhaustion. Pirozzi *et al*. (2020) reported synergistic hepatic inflammation in HFD-BPA co-exposure, but CNS-specific studies are limited, and this study’s findings suggest a need for further investigation into cerebellar microglial dynamics.

**5.3 Comparison of Cerebellar Structural Alterations**

The comparative analysis of cerebellar alterations across groups reveals distinct patterns of damage. The BPA-C group exhibited the most severe GCL distortion, suggesting that BPA’s neurotoxic effects, mediated by oxidative stress and estrogen receptor disruption (Costa & Cairrao, 2024), may preferentially target granule cells. The HFD-C group showed similar Purkinje cell degeneration but less severe GCL distortion, consistent with HFD’s role in inducing lipotoxicity and inflammation (Song *et al*., 2025). The HB-C group’s milder GCL distortion, despite combined exposure, suggests a potential modulatory effect, possibly due to altered inflammatory signalling or cellular adaptation.

These findings partially align with available literature. Khan *et al*. (2019) reported myelin and axonal degeneration in BPA-exposed cortex, detectable via H&E, which parallels the neuronal and glial changes observed in this study’s BPA-C group. Similarly, Ledreux *et al*. (2016) noted hippocampal gliosis and neuronal damage in HFD-fed rats, supporting the HFD-C group’s findings. However, the milder GCL distortion in HB-C contrasts with Pirozzi *et al*. (2020), who found exacerbated hepatic damage in co-exposure, highlighting tissue-specific responses.

**5.4 Extent of Microglial Activation and Inflammatory Response**

The histological evidence of enlarged and degenerating glial cells across BPA-C, HFD-C, and HB-C groups indicates microglial activation, consistent with the role of microglia in responding to neurotoxic insults (Jurga *et al*., 2020). However, the lack of significant NAEM differences suggests that AIF-1 expression, as measured in this study, may not fully capture the extent of microglial activation in the cerebellum. This discrepancy could be due to methodological limitations, such as the sensitivity of NAEM quantification or the specific immunohistochemical protocol used for AIF-1 detection.

Previous studies suggest that AIF-1 is a reliable marker of microglial activation in other brain regions (Ledreux *et al*., 2016; Mazzei *et al*., 2021). The absence of significant NAEM changes in this study may reflect the cerebellum’s lower baseline microglial density or a delayed inflammatory response compared to the hippocampus or cortex. Alternatively, other inflammatory markers, such as IL-1β or TNF-α, as used by Cavaliere *et al*. (2019), may be more sensitive for detecting cerebellar inflammation in this study.

**5.5 Relationship Between Cerebellar Neuroinflammation and Functional Impairment**

Although this study did not directly assess functional outcomes, the observed histological changes—particularly Purkinje cell degeneration and GCL distortion—suggest potential motor and cognitive impairments, as the cerebellum is critical for motor coordination and cognitive processing (Manto *et al*., 2012; Schmahmann, 2019). Studies supports this inference: HFD-induced hippocampal inflammation is linked to cognitive deficits (Ledreux *et al*., 2016), and BPA exposure impairs motor coordination in rodents (Hyun & Ka, 2024). The severe GCL distortion in BPA-C and HFD-C groups may disrupt granule cell-Purkinje cell circuitry, leading to ataxia or dysmetria, as described by Gupta (2017).

The milder GCL distortion in the HB-C group could indicate a complex interplay between HFD and BPA, potentially mitigating certain aspects of cerebellar damage while exacerbating others (e.g., glial cell enlargement). This aligns with Figueiredo *et al*. (2020), who noted exacerbated systemic inflammation in HFD-BPA co-exposure but did not explore cerebellar effects.

**5.2 Conclusion**

The combination of BPA and HFD distorted the histological architecture of the cerebellar cortex. This damaging observation may not depend on microglia activities.

**5.3 Recommendation**

Future studies should extend the exposure period beyond 12 weeks to better capture chronic neuroinflammatory changes in the cerebellum due to HFD and BPA. I recommend including additional inflammatory markers, such as IL-6 and NF-κB, alongside AIF-1, to provide a more robust evaluation of microglial activation.

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