A Review On

"Neuroinflammation and Its Contribution to Neurodegenerative Diseases"

In the partial fulfilment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

Submitted To

Department of Pharmacy

Faculty of Allied Health Sciences

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APPROVAL

This project paper, **"Review on Neuroinflammation & Its Contribution to Neurodegenerative Diseases''** submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

In accordance with the Bachelor of Pharmacy (B. Pharm) Degree Requirement, I thus declare that I'm conducting this thesis work under the guidance of Aklima Akter, Lecturer (Senior Scale), Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University. I, therefore, state that this project is entirely my original work. I further declare that neither this thesis nor any portion of it has been submitted for the bachelor's award or any other degree outside of the university.

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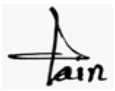

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Md. Tain Hossan

Author

DEDICATION

"Dedicated to my beloved parents, whose unwavering love, encouragement, and sacrifices have made all my achievements possible. Your guidance and support have been my anchor, and I am forever grateful for everything you have done for me.

To my teachers, who have taught & motivated with their unwavering support, and understanding. Your constant encouragement and positivity have kept me going, and I cannot thank you enough.

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This paper is dedicated to all of you, with deep gratitude and appreciation. Thank you for being a constant source of inspiration and motivation."

Abstract

Neuroinflammation is a complex process that occurs in the brain and nervous system in response to injury, infection, or disease. While acute inflammation is a necessary protective mechanism, chronic neuroinflammation has been implicated in the pathogenesis of several neurodegenerative diseases, including Alzheimer's disease, Multiple Sclerosis, Amyotrophic Lateral Syndrome and Parkinson's disease. In these conditions, the presence of abnormal proteins and other molecules triggers an immune response, which leads to chronic inflammation and damage to nerve cells. The resulting neuroinflammation disrupts normal neural function and contributes to the progressive loss of cognitive and motor function that characterizes these diseases. A better understanding of the mechanisms underlying neuroinflammation and its contribution to neurodegenerative disease may lead to the development of novel therapeutic approaches aimed at reducing inflammation in the brain and slowing or halting disease progression.

Keywords: Neuroinflammation, Microglia, Neurodegenerative Diseases, Signaling Pathway

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Chapter-1
INTRODUCTION

1. Introduction

"Neuroinflammation" is the term for inflammation that affects the brain and nervous system. In reaction to damage, infection, or illness, the immune system is stimulated, and pro-inflammatory chemicals are released. Invading microorganisms are killed by an efficient inflammatory response mechanism, which also starts angiogenesis and wound healing [1]. Inflammation may harm acute and chronic brain diseases [2]. To counteract the adverse effects of inflammation, neurons in the brain remove cellular waste and regulate the release of neurotrophic factors, cytokines, and proteases. While inflammation in the brain might impede damage healing, some responses seem required and advantageous. According to this view, local immune responses to a danger to the neuronal microenvironment include a complicated sequence of localized inflammation [2]. A neuroinflammatory response from peripheral inflammation involves the blood-brain barrier, glia, and neurons. The immunological reactions of the central nervous system, as opposed to the immune responses of the rest of the body, are referred to as "neuroinflammation."

The central cells involved experience inflammation in many ways, including through astrocytes and microglia. The blood-brain barrier, a highly specialized type of endothelium, was once thought to completely isolate the central nervous system from the peripheral immune system. Nevertheless, in addition to being permeable to pro-inflammatory mediators derived from peripheral inflammation, it may also be triggered to release and convey these mediators and allow leukocyte migration into the brain [3] [4].

The brain connects neurons and sends information to regulate how each body's other organ’s function. The human body's central nervous system (CNS) is the most intricate and poorly understood. Neuroinflammatory diseases interfere with the brain's neural pathways and functions [5]. A defense mechanism in the body, inflammation works to repair, regenerate, and eliminate damaged tissues, cells, infectious organisms, parasites, or toxins [6]. Among the immune and inflammatory cells that react to inflammation are T cells, neutrophils, macrophages, microglia, and mast cells. Similarly, neuroinflammation is a protective process that aids in the recovery of damaged glial and neuronal cells in the CNS. Neuroinflammation is mediated by the resident brain macrophage, the microglia, astrocytes, neurons, T-cells, neutrophils, mast cells, and inflammatory mediators produced by these cells [7]. Although excessive inflammatory responses are detrimental and prevent neuronal renewal, neuroinflammation arises in the brain as a defensive reaction [8]. The onset and progression of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis, are all associated with persistent neuroinflammation (MS) [9].

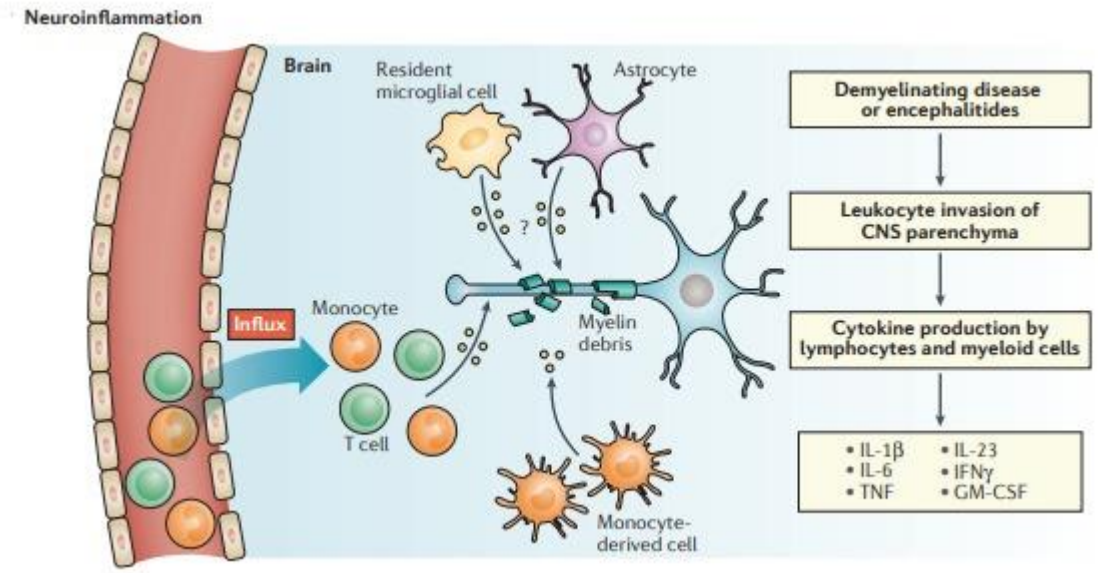

Figure-1: Neuroinflammation

Neurodegeneration occurs when the structure and functioning of neurons in the CNS are altered, resulting in decreased neuronal survival and increased neuronal death [10]. In neurodegenerative disease cases, neurons and glial cells in specific brain areas are affected and degenerate, causing these patients to experience particular disease symptoms [11]. Parkinson's disease motor symptoms include bradykinesia, stiffness of the muscles, and resting tremors. Olfactory dysfunctions, cognitive deficiencies, behavioral illnesses, and autonomic dysfunction are among the non-motor symptoms experienced by these patients. Patients with Parkinson's disease experience a histopathological decline in dopaminergic neurons in the substantia nigra [10]. Patients with Alzheimer's experience neurodegeneration first in their short-term memory-storing temporal lobes and later in their parietal lobes (storing long-term memory). Alzheimer's disease symptoms include cognitive and behavioral (depression) problems, and protein clumps (neurofibrillary tangles, or NFT) develop in affected individuals' neurons. Currently, no specific drugs can restore damaged neurons, cause neurodegeneration, or stop it from happening in AD, PD, or MS patients.

In order to protect the body and restore tissue damage, tissues must be cleared of invasive infectious microorganisms, toxins, and wounded or dead cells [12]. Growth factors, proteases, cytokines, chemokines, and innate immunity are required for healthy angiogenesis, tissue repair, innate immunity, and neuronal development [13]. Brain-derived neurotrophic factor (BDNF) production in astrocytes is stimulated by TNF-α, which also mediates neurotrophic and neuroprotective activities in the brain [14]. Nevertheless, persistent and amplified inflammatory responses with increased levels of inflammatory mediators and inflammatory cell accumulation and activation have the opposite effect by mediating the harmful onset and development of neurodegenerative diseases [15].

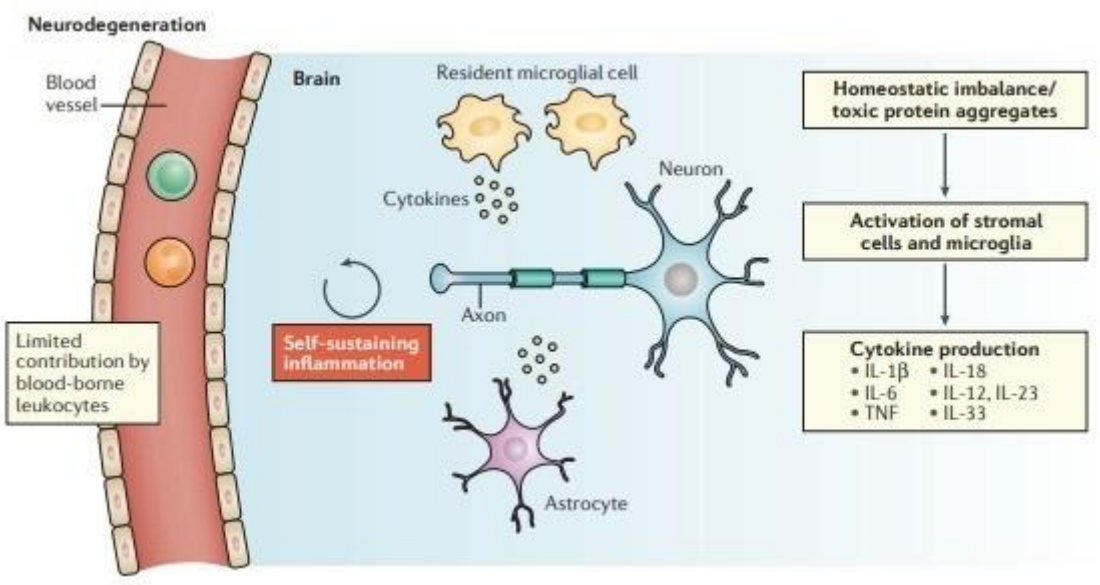

Figure-2: Neurodegeneration

Consequently, neuroinflammation causes neurodegeneration, while neurodegenerative processes exacerbate neuroinflammation. We evaluated how these inflammatory mechanisms contribute to neurodegenerative disorders in our review.

1.1 Epidemiology

Higher blood levels of systemic inflammatory markers, such as C-reactive protein, interleukin-6, and 1-antichymotrypsin, have been linked to dementia and cognitive decline in prospective population studies [16], [17] [18], [19]. Recent research has demonstrated that aging is associated with a low-grade elevation of specific innate immune inflammatory responses. Francheschi et al. [20] came up with the word "inflammaging" to describe this chronic, low-grade, and systemic inflammation that gets worse with age [21]. Most older people with age-related hyperactive innate immunity may remain subclinical, but others may develop one or more age-related disorders from a state of "normal" or subclinical inflammaging. It is thought that these people may have a "high responder inflammatory genotype" since there is evidence that the process of inflammaging is genetically controlled [22].

Around 50% of individuals with moderate cognitive impairment had amyloid accumulation and activated microglia in vivo, according to new PET research that used the Pittsburgh compound B to see fibrillar beta-amyloid and the PK-11195 ligand to activate it [23]. According to twin studies, flowing inflammatory mediators of innate immunity have a modest (20%) heritability. Contrary to circulating inflammatory mediators, endotoxin stimulation of cytokine production is tightly genetically regulated, with heritability estimates in populations free of illness ranging from 53 to 86% [24].

1.2 Pathology

A living tissue's reaction to injury is inflammation. Fundamentally, pathology distinguishes between acute and chronic inflammation. Acute inflammation is a quick and early reaction to a harmful substance. It is a form of protection that enables the healing of the injured area. The ongoing stimulus causes chronic inflammation. Neutrophils, polymorphonuclear cells, are present in leukocytic infiltrates in acute inflammation. Mononuclear cells (macrophages, lymphocytes, and plasma cells) are peripheral in chronic inflammation. Both acute and chronic neuroinflammation must be included in evaluating these broad pathogenic concepts in neuroinflammation, which are covered individually in the following sections.

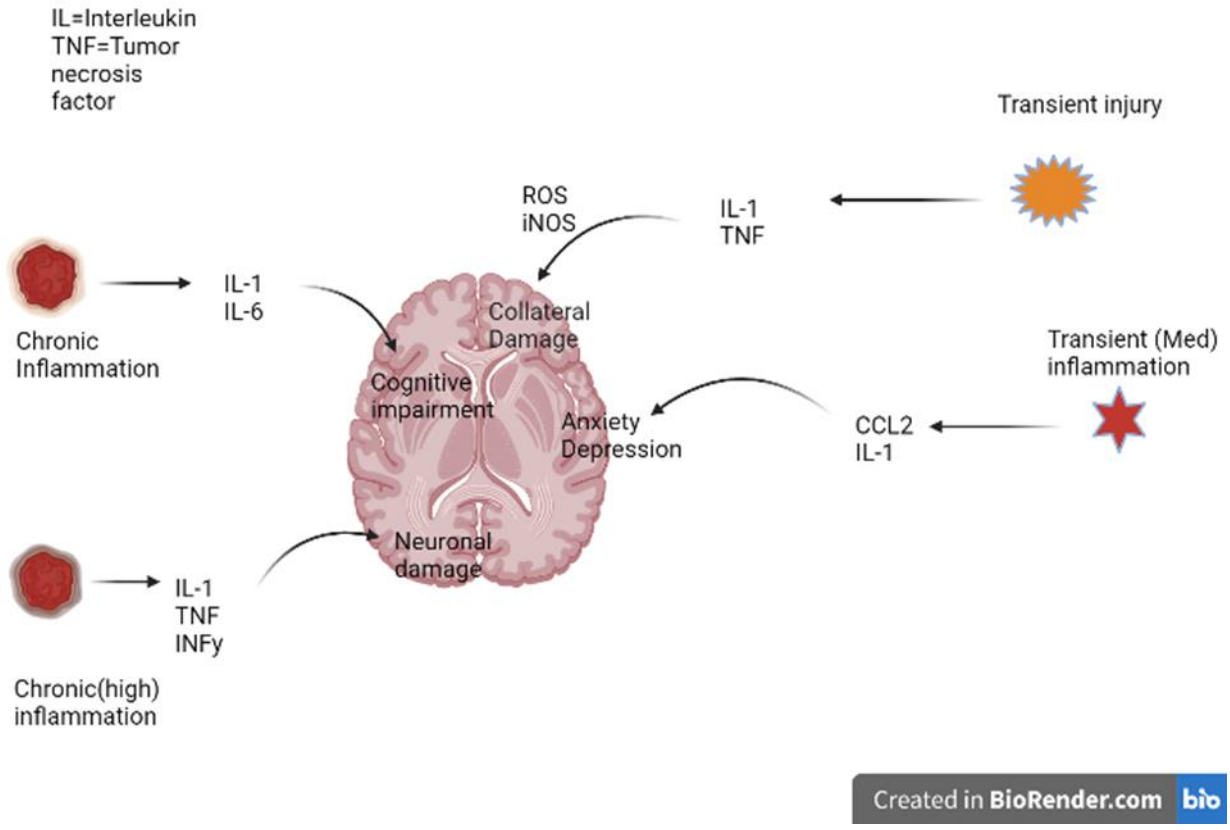

Figure-3: Pathology of Neuroinflammation

1.2.1 Acute Neuroinflammation

Neuroscientists formerly referred to the independent responses of injured brain tissues as "reactive gliosis" before the term "neuroinflammation" gained popularity. Reactive gliosis was characterized as the rapid appearance following brain injury of other large glial cells, mainly microglia and astrocytes. Glial activation suggests a more aggressive role in responding to activating stimuli than glial reactivity, which suggests a largely passive response to injury. Activated glial cells release substances that act on and trigger responses in target cells, like activated immune cells in the periphery. Leukocyte infiltration of organs arises from immune cell activation in the periphery; however, this is absent in the brain unless the blood-brain barrier has been damaged or disrupted [25].

In limited, acute responses to damage without blood-brain barrier rupture, the brain's immune system responds more subtly, primarily by rapid activation of glial cells. These responses reflect the other end of the injury spectrum for the central nervous system (CNS), where restricted neuronal lesions result in glial cell activation without a break of the blood-brain barrier or corresponding leukocytic infiltration. This "pure" glial response type develops when afferent or efferent loss causes neuronal damage—for instance, axotomy results in neuronal chromatolysis, a well-known illustration of possibly repairable neuronal injury [26]. To benefit the entire organism, microglial and astrocytic responses carry out the roles they have evolved to play in a reparative response.

1.2.2 Chronic Neuroinflammation

Although the term "neuroinflammation" may refer to these specific responses, as it is generally understood, the term refers to longer-lasting, more persistent cycles of injury and response in which the cumulative adverse effects of immunological microglial and astrocytic activation add to and expand the initial neuro-destructive effects, maintaining the disease and making it worse.

The idea of chronic inflammation (as opposed to acute inflammation) is particularly relevant in the context of understanding CNS illness since the term "disease" implies chronicity (as opposed to CNS injury). Of course, a well-known example of an inflammatory brain disease is chronic multiple sclerosis.

It is safe to assume that the persistently harmful stimulus causing the neuroinflammation in MS (multiple sclerosis) is a myelin-related protein that has eluded self-tolerance and has developed into an autoimmune disease, even though the fundamental cause(s) of MS (multiple sclerosis) has not yet been discovered. The chronic endurance of the autoimmunity is consistent with a permanent buildup of blood-derived mononuclear leukocytes in the brain parenchyma, comparable to that observed in other autoimmune diseases such as rheumatoid arthritis or polymyositis [27].

1.3 Components that affect Neuroinflammation

1.3.1 Cellular

Understanding how peripheral inflammation may result in persistent and harmful neuroinflammation requires understanding the blood-brain barrier (BBB), an endothelial layer. People once thought that cytokines and other proteins that cause inflammation were too big to get to the brain from the blood. However, various transport methods have been discovered during the last several decades. Through active transport mechanisms, cytokines like TNF and IL can enter the brain through the BBB [28]. The BBB's integrity is also negatively impacted by TNF-α, IL-6, IL-1β, and other cytokines, allowing leukocytes to enter the brain [4], [29]. BBB permeability is influenced by cytokine levels, which also change the resistance of tight junctions in endothelial cells in the brain vasculature [30]. Chemokines and other humoral substances also affect how leukocytes move across the BBB. For instance, CCL19 and CCL21 encourage T cell adherence to the BBB, but CXCL12 may be required to reduce T cell infiltration [31]. Microglial cells, or CNS resident macrophages, are essential in neuroinflammation. When cytokines and other signaling molecules are released during acute inflammation, they cause microglia to change from a branched, inactive state to an active, phagocytic state. These cells can remain active for a long time during chronic neuroinflammation, producing cytokines and other neurotoxic substances that gradually harm nerve cells [32]. Another kind of glial cell, an astrocyte, produces pro-inflammatory signaling molecules like TNF-α when activated in the cortex and midbrain [33]. While microglia produce far more inflammatory cytokines, the combined glial response may play a significant role in developing the neurodegeneration found in dementia [34]. The dynamic interactions between BBB endothelial cells, glia, and neurons are well established, and a neuroinflammatory response from one cell type would probably directly affect another [35].

1.3.2 Molecular

Cytokines are cell-signaling proteins that can increase or decrease neuroinflammation. Interleukin-1 (IL-1) and tumor necrosis factor (TNF), two pro-inflammatory cytokines, are essential for pathological inflammation, just like they are for their work. Some cytokines, such as IL-4, have anti-inflammatory characteristics in contrast [36]. As demonstrated by IL-6 activating T cells and promoting the creation of other inflammatory markers, including C-reactive protein (CRP) and fibrinogen, initial cytokine release can drive the manufacturing of secondary signaling molecules [37]. TNF signaling is also directly pro-apoptotic via the Fas-Associated Protein with Death Domain (FADD)-mediated production of the enzyme Caspase-8, which is significantly associated with apoptosis and neurodegeneration [38]. Chemokines are tiny chemotactic cytokines involved in neuroinflammation. Despite low normal levels in the brain, some chemokines, such as monocyte chemoattractant protein-1, significantly increase during chronic neuroinflammation [39]. These substances are associated with the activation and chemotaxis of astrocytes and microglia in response to inflammatory stimuli. They may also disrupt neuronal function and adversely influence neurogenesis.

1.4 Factors that Drive Neuroinflammation

1.4.1 Pharmacological Factors

1.4.1.1 TBI (Traumatic Brain Injury)

Traumatic brain injury is characterized by a complicated array of various head injuries that cause metabolic damage to the brain and other tissues. Primary and secondary components of traumatic brain injuries serve to describe their biphasic nature [40]. The damage results from mechanical disturbance of both large and small structures inside and around the brain, which causes tissue destruction. This may result from apparent tissue destruction from a piercing injury or diffuse axonal damage from accelerating and rotating stressors, depending on the kind of injury.

Damage that progresses past the scope of the primary injury is caused by tissue disease and cell malfunction, which are characteristics of secondary injury. Cell death, neurotransmitter excitotoxicity, electrolyte imbalances, mitochondrial dysfunction, and ischemic damage are secondary injuries associated with TBI [40]. Many research investigations demonstrate that focal (penetrating) and diffuse (non-penetrating) TBI result in various inflammatory processes in the brain, which are partially mediated by regional microglia and astrocytes [41], [42]. Following a TBI, microglia respond to injured cells, other activated glia, and peripherally generated stimuli once the blood-brain barrier is breached [43], [44]. After damage, active microglia quickly promote the production and release of cytokines and chemokines [45], [46]. Additional research reveals that intact p38a MAPK activation, a mechanism that encourages the production of pro-inflammatory cytokines, was necessary for the morphological changes in microglia following widespread TBI [47]. Other myeloid cells within the damaged brain, in addition to resident microglia, contribute to acute neuroinflammation. When there is penetrating brain damage, it can be hard to tell the difference between the effects of resident microglia and those of invading macrophages. It is due to the relative expression of their surface markers when monocytes differentiate into brain macrophages, which histologically resemble microglia. Still, TBI causes microglia to become active, which makes them make chemokines like CCL2 that bring monocytes and granulocytes to the site of damage [48]. Finding inflammatory proteins in blood or cerebrospinal fluid may be a valuable indicator of macrophage and microglia-induced inflammation in clinical practice.

1.4.1.2 Spinal Cord Injury

Damage to the spinal cord is a different kind of traumatic CNS injury (SCI). SCI is marked by a localized contusion that happens right away and widespread secondary damage caused by ischemia, excitotoxicity, and inflammation [49]. The early, acute stage of inflammation in the damaged region of the spinal cord is identified by an influx of neutrophils and monocytes [50].

In the second phase of inflammation, things keep getting worse over time. This is caused by cells called lymphocytes [51]. After SCI, IL1b, and TNFa are turned up quickly by microglia, astrocytes, neurons, and oligodendrocytes in the CNS. This happens within hours [52]. Microglia activation in the cord, even distant from the injury, is related to tissue reconfiguration and obstruction to functional recovery [53]. Furthermore, peripheral immune cells are crucial for the inflammatory response to SCI. For example, neutrophils move in quickly after damage but only stay for three days before leaving [54].

1.4.1.3 Systemic Inflammation

Animal studies show systemic inflammation can worsen acute brain function symptoms (sickness syndrome), speed up neurodegeneration, and make neuronal death worse [55], [56]. Unexpectedly, systemic inflammation in AD and PD mice increases the immune response, most likely due to the local innate immune system's priming impact [57]. Similar to how microglial cells in people can be impacted by peripheral inflammation, which could result in neurodegenerative processes. Pro-inflammatory mediators cannot cross the blood-brain barrier (BBB) but can enter the central nervous system (CNS) through the choroid plexus. Peripheral inflammation can trigger a neuroinflammatory response in glial cells and neurons, stimulating the release and transmission of inflammatory mediators and promoting leukocyte migration into the CNS [58].

The effects of peripheral inflammation and the inflammatory response in the brain have been studied using various experimental animal models. Most studies showed a connection between AD, oxidative stress, and peripheral inflammation. Some cytokines' ability to slow the progression of Alzheimer's disease has been the subject of some investigation [59]. The relationship between metabolic inflammation and cognition has been examined in several clinical investigations [60]. It is generally recognized that metabolic alterations like metabolic syndrome or obesity leads to a greater release of pro-inflammatory cytokines than conventional systemic inflammatory illnesses. It causes a persistent peripheral inflammatory condition [61]. Obesity and metabolic changes have been linked to the development of MCI and AD, according to research [62]. Also, other research has found a link between cognitive deficiency and peripheral chronic inflammatory diseases, such as periodontitis [63]. Metabolic disorders and chronic inflammatory conditions may contribute to neurodegeneration in Alzheimer's disease (AD) by causing oxidative stress in the central nervous system (CNS) or chronic neuroinflammation, which is caused by peripheral inflammation [64]. Microglial cell activity could be why peripheral inflammation has a different effect on central inflammation in the CNS during the progression of Alzheimer's disease. In neurodegenerative diseases, peripheral inflammatory/anti-inflammatory mediator switching in either activated phenotypes (M1 or M2) may impact CNS cells [65].

There is mounting evidence that shows peripheral inflammation, particularly in the digestive system, may contribute to the neurodegeneration seen in people with PD [66]. Increased expression of TNF-α, IFN-γ, IL-6, and IL-1β has been detected in this context (similar to that seen in inflammatory bowel disease) [67]. Devos et al. [68] showed that PD enteric inflammation is closely related to glial dysregulation. They accomplished this by demonstrating that the expression of glial markers is greater and coincides with the expression of pro-inflammatory cytokines in colonic biopsies from Parkinson’s Disease patients. Moreover, several epidemiological studies have discovered that NSAID users have a lower risk of developing PD [69].

1.4.2 Non-Pharmacological Factors

1.4.2.1 Aging

An organism ages due to its homeostatic mechanisms gradually degrading throughout its existence. For instance, the proinflammatory and anti-inflammatory cytokines in the adult brain are balanced, but as people age, this equilibrium shifts in favor of the pro-inflammatory. Increased neuroinflammation in the aging brain makes it more susceptible to disease, infection, and stress, which can be detrimental [70]. Immune cells of the central nervous system called microglia mediate the brain's reaction to injury, illness, and infection. Most of the time, microglia remain dormant, but an outside antigen can awaken them—a phenotypic shift results in modifications in the expression of cell surface markers [71], [72]. Age-related changes in how the brain reacts to and recovers from trauma may be explained by more microglia activation in the elderly brain, indicating increased neuroinflammation and heightened reactivity. In addition to resting microglia, a subpopulation is in an intermediate state that resembles activated microglia but does not produce cytokines. Shorter processes and the expression of cell surface markers characterize this subpopulation. Since it activates more quickly and generates more cytokines than usually activated non-primed microglia, this microglia subset is known as "primed" [73], [74]. Microglia are thought to be primed by aberrant proteins particular to each illness. More and more evidence suggest that normal, aging brains may have primed microglia, similar to the priming paradigm linked to neurodegenerative diseases. According to research by Streit et al., a 68-year-old's brain has ten times more microglial abnormalities than a 38-year-olds. Old's Also, it has been suggested that microglial senescence and the subsequent modifications to microglial function may cause neurodegenerative diseases like Alzheimer's and exacerbate the cognitive issues associated with aging [27] [75].

1.4.2.2 Stress

While neuroinflammation resulting from immune-brain communication is helpful, certain conditions might throw this balance off. The response to repeated or traumatic stimuli is an excellent example of whether short-term or long-term stressors cause the brain to have more microglia and macrophages from the bone marrow [76]. Many studies on rodents have shown that microglia are essential for releasing inflammatory signals and responding to chronic or traumatic stress [77]. For instance, when social failure occurs repeatedly, microglia are activated, increasing the number of cytokines and chemokines produced in the brain that promote inflammation [77]. Increased Iba1 immunoreactivity in microglia is associated with these inflammatory inductions, especially in stress-responsive brain regions (i.e., fear and threat appraisal centers) [78]. Foot shock and unexpected stress are other stressors that exhibit symptoms of local microglia activation [74]. The movement of inflammatory monocytes from the bone marrow to the brain in persistent social defeat is also connected to threat interpretation and microglial activation (RSD). It is crucial because it allows the immune system to send messages to the brain and affect behavior. In RSD, sympathetic activation results in the production of and release of Ly6Chi/CD45+ pro-inflammatory monocytes [79]. These monocytes are activated by long-term stress, which facilitates the development of long-term anxiety-like behavior. It is interesting to note that inhibiting either monocyte recruitment to the brain or release from the bone marrow prevents the development of anxiety. Many neuroimmune and behavioral responses to psychosocial stress are prevented by adrenergic

receptor antagonists, benzodiazepines, and antidepressants that influence neural adaptation. These responses include anxiety and social avoidance [77]. Consequently, stress-induced neuroinflammatory responses are crucial in developing mood disorders and immunological dysfunction.

It is essential because clinical research demonstrates that individuals who experience chronic stress have ongoing cognitive and emotional dysregulation, which negatively affects their quality of life and overall mental health [80]. Studies with caregivers and college-age students, for example, show that persistent stress is substantially linked to cognitive impairments and hastened cognitive decline [81]. Several studies have linked the activation of the neuroinflammatory system brought on by stress to psychological issues. In certain brain areas of depressed suicide victims, elevated pro-inflammatory cytokines, activated microglia, and enlarged brain macrophages were all discovered. Hence, stress-related neuropsychiatric diseases may have less neuroplasticity due to the increased neuroinflammatory signaling, recruitment of monocytes, and activation of microglia [82], [83].

1.5 Neuroinflammation & Microglia

The brain's resident microglia and macrophages are crucial to an organism's defense and tissue healing. They are crucial in developing neurodegenerative, inflammatory diseases and brain inflammation [84]. Neuroinflammation is always discussed in microglia. The CNS's primary immune surveillance and macrophage-like behaviors, such as the production of cytokines and chemokines, are regulated by these innate immune cells. Moreover, microglia are responsible for a significant portion of the CNS's innate immune potential. The white and gray matter of the brain and spinal cord may contain these resident CNS cells. 10% of the cells in the CNS are microglia. Microglia have a role in immunological watchfulness. For instance, great two-photon imaging experiments show that microglia actively scan their surroundings [85], [86]. The coordinated communication between the immune system and the brain depends on these responses. For instance, when an infection or disease occurs, microglia "activate" and function as inflammatory cellular mediators. Microglia swiftly alter their transcriptional profile when activated and discharge inflammatory cytokines and chemokines. When cytokines and chemokines are produced, depending on the circumstance, they may aid in bringing leukocytes to the brain [87]. Active microglia also change their cytoskeletons, changing how the cell surface receptors are expressed. Moreover, these changes allow microglia to move to areas of damage or infection [12]. Signaling molecules are produced in excess during neuroinflammation. Hence, microglia can be activated, and neuroinflammation can directly affect neuronal death [2].

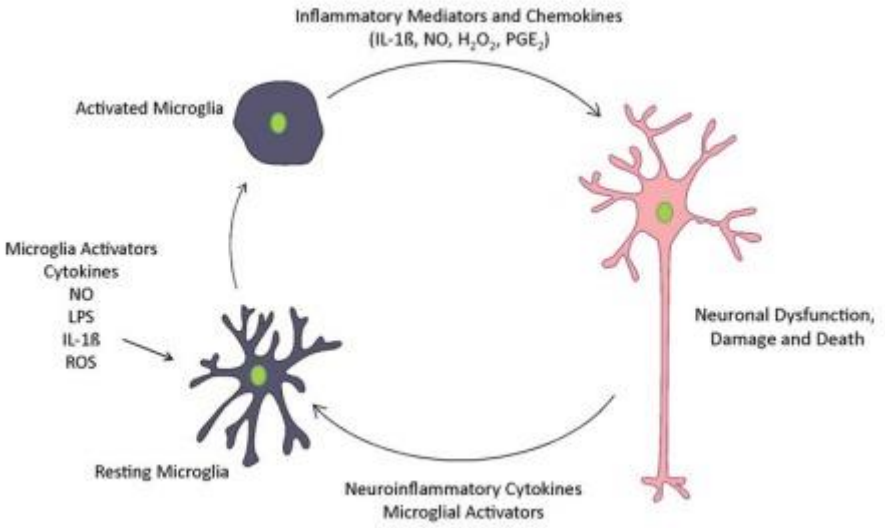

Figure-4: Relation between Microglial Activation & Neuroinflammation

1.5.1 Microglial Activation

Microglia's neuroprotective and neurotoxic effects on the brain demonstrate their complicated biological relevance. Dead cells, protein clusters, and infections can activate microglia in a typical, healthy brain. The activation is distinguished by a sharp change from a highly ramified morphology to an ameboid shape, [88] furthermore, an array of inflammatory mediators causes harmful substances, such as nitric oxide (NO), reactive oxygen species (ROS), and prostaglandins, to be produced due to cellular and molecular processes. [89]. Microglia carefully regulate immunological responses in order to preserve tissue homeostasis.

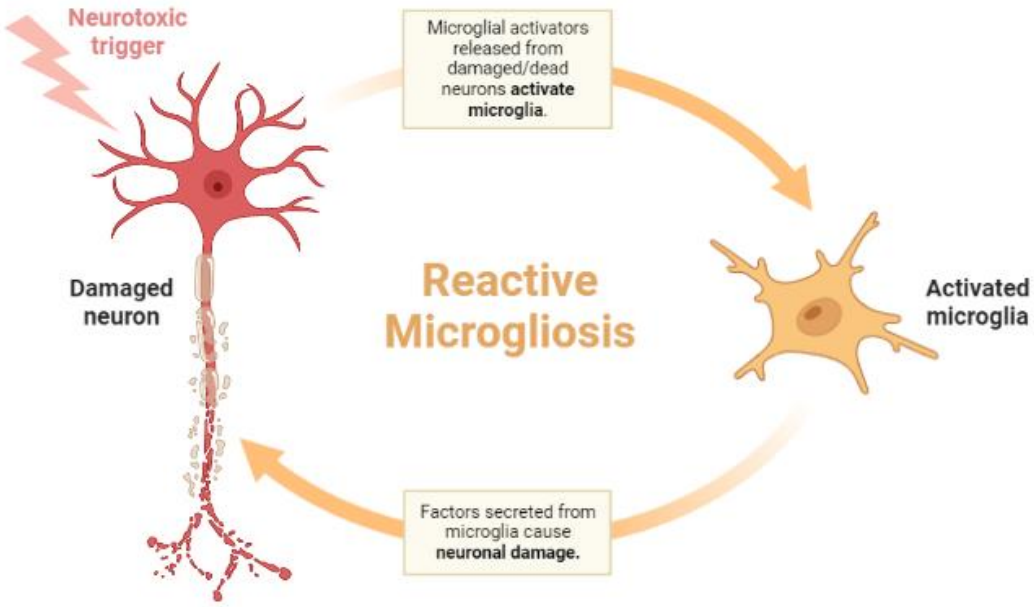

Figure-5: Microglial Activation

Microglia can develop into polarized phenotypes of either traditional activation, the proinflammatory M1 phenotype, or alternative activation, the immune-suppressing M2 phenotype, depending on the damage and stimulus. Nevertheless, this form of dichotomous categorization needs to simplify the mechanism of microglial activation [90].

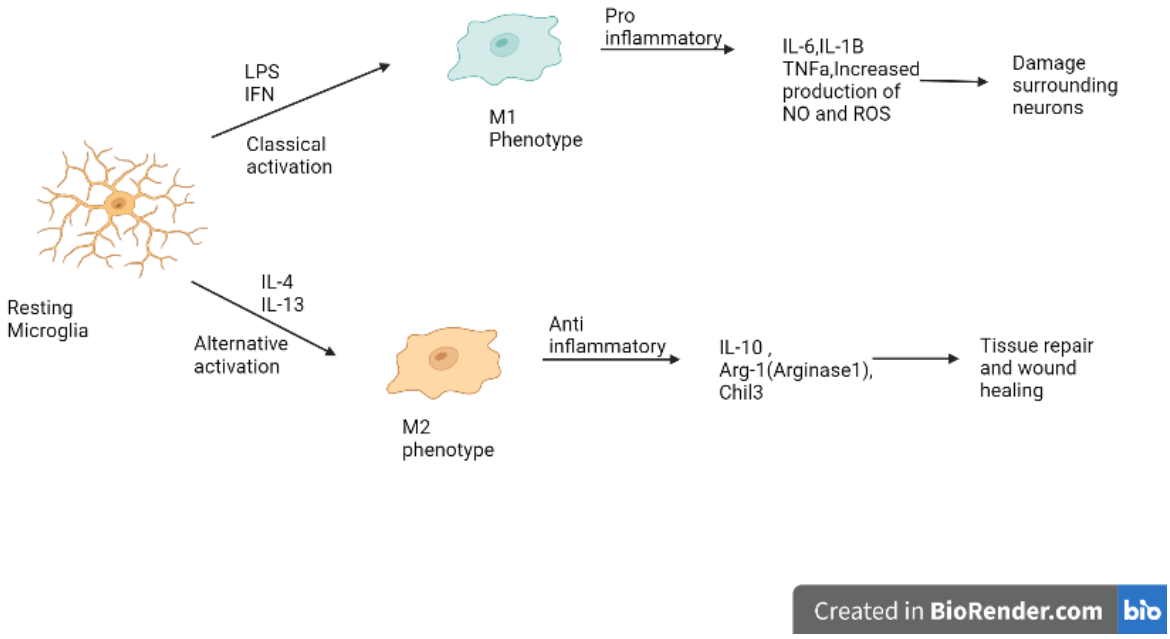

Figure-6: Classification of Microglial Activation; Depending on the type of stimuli, microglia can be activated and directed toward different phenotypes in a dichotomy paradigm. M2-phase microglia generate anti-inflammatory, neuroprotective, and wound-healing factors, but M1-phase cells frequently produce pro-inflammatory cytokines, chemokines, and neurotoxic substances.

1.5.1.1 Classical Microglial Activation

It has been demonstrated that several triggers, including lipopolysaccharide (LPS), interferon (IFN)-γ, β-amyloid (Aβ), and α-synuclein, cause microglia to activate in a typical manner both in vitro and in vivo [91]. Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and TNF-α are the proinflammatory substances that microglia release in response to the assault. They also produce more NO and ROS, harming neighboring neuronal cells [92]. The M1 phenotype of activated microglia was previously believed to exist [90]. As they may eliminate invasive infections by secreting proinflammatory/cytotoxic mediators, they serve as the first line of defense. Nevertheless, an overabundance of these chemicals brought on by persistent microglial activation results in neuronal damage [93]. This theory has been supported by the post-mortem examination of many brain disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [90], [92].

1.5.1.2 Alternative Microglial Activation

With the previously mentioned pro-inflammatory response, microglia can also activate along a pathway known as the M2 phenotype. Activated cells release anti-inflammatory cytokines like Interleukin-10 (IL-10), as well as helpful substances for tissue repair and extracellular matrix (ECM) rebuilding like arginase (Arg-1) and chitinase-3. It can be started by Interleukin-4 (IL-4) or Interleukin-13 (IL-13) (Chil3) [92]. These microglia are involved in the phagocytosis of cellular debris and wound healing. In order to effect tissue regeneration and wound healing, the anti-inflammatory phase must be activated sequentially when microglia acquire the M1 phenotype to promote the death of invading pathogens [90]. Without this, proinflammatory cytokines, NO, and ROS would be overproduced. Tissue damage and progressive cell death may result from this. Hence, to promote the removal of debris and the deposition of extracellular matrix for tissue repair, cells must switch from the proinflammatory to the M2 phenotype [92].

1.5.2 Microglia Priming

Microglia in the aging CNS of mice, rats, and primates exhibit heightened sensitivity to inflammatory stimuli, [94] similar to microglia in brains with continuing neurodegeneration. This is referred to as "priming." Priming could be caused by microglial senescence and linked to aging. At the transcriptome level, endogenous ligands are turned down as a person ages, while host defense and neuroprotection factors are turned up [95]. Whether age-related microglia priming originates from cell-autonomous cellular aging or extended exposure to the aged brain environment is unclear.

Senescence-accelerated and physically aged animals undergoing extensive microglia priming had higher levels of cytokines, reactive oxygen species, and phagocytic capacity. This model demonstrated that environmental effects like neuronal aging could induce microglial priming [96]. Microglia priming has been studied extensively from the perspective of systemic inflammation and neurodegenerative diseases. Microglia priming is induced by repeated exposure to systemic immunological challenges. [97].

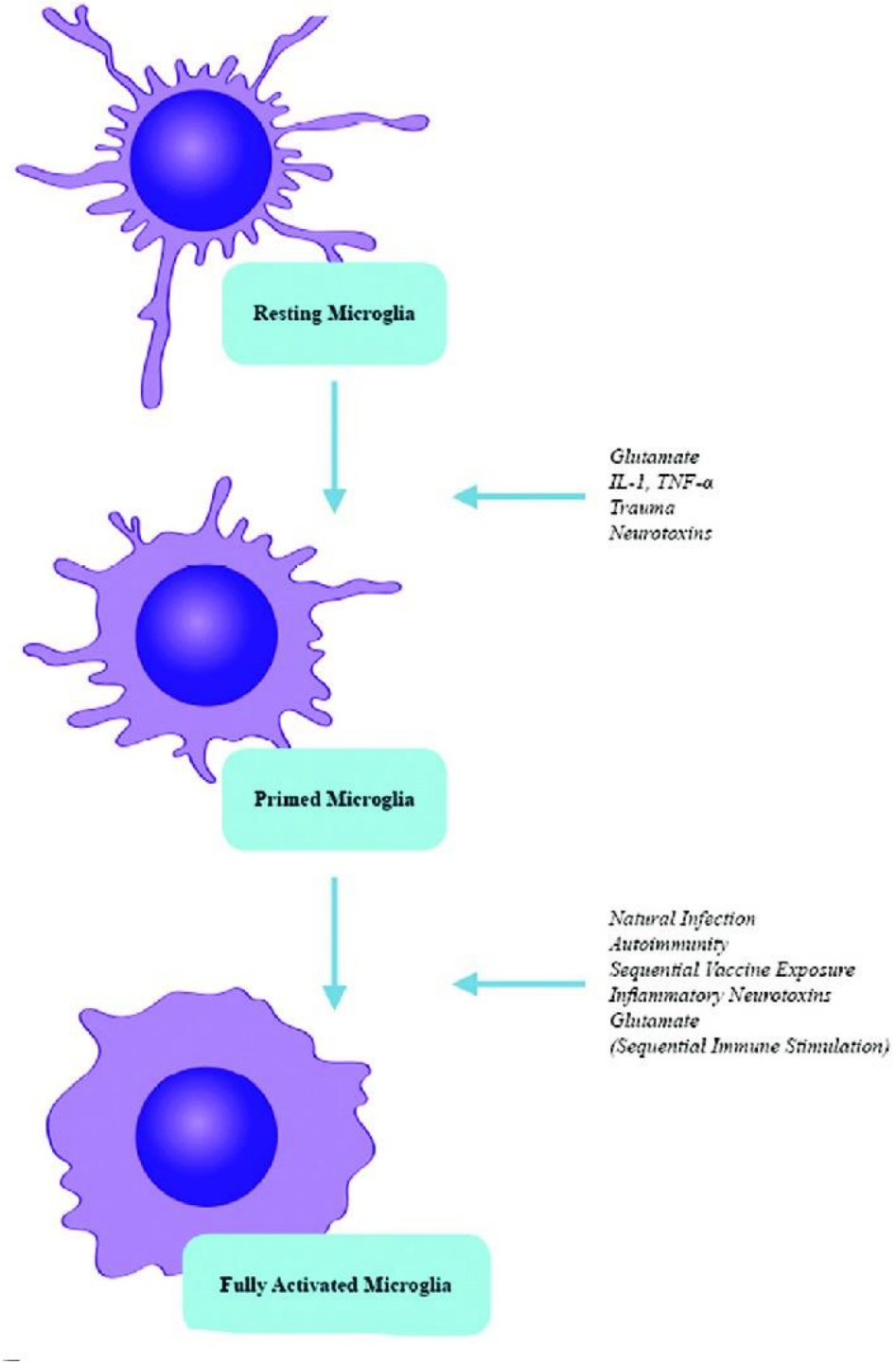

Figure-7: Microglial Priming

1.6 Mediators & Modulators of Neuroinflammation

1.6.1 Cytokine

Each stage of neuroinflammation, including pro- and anti-inflammatory processes, bystander neuronal injury, chemoattraction, and microglial responsiveness to A deposition, is influenced by cytokines [96]. Cytokines both characterize and influence microglia activation. Increases in Aβ concentrations are associated with higher levels of proinflammatory cytokines such as TNFα, interleukin-6, interleukin-1β, and GM-CSF [98]. Microglia actions related to an innate immune response are connected to TNF-α signaling and its modulation of inflammation and apoptosis. TNF-α messenger ribonucleic acid (mRNA) levels influence the amount of hippocampus neuron apoptosis, and a TNF-α concentration threshold may be necessary to start apoptotic pathways [99]. Prior to neuronal death, it has been discovered that TNF-α and IL-1β levels increase. Proinflammatory cytokines, including TNF-α, IL-1β, and adhesion molecules, are released, which serves as both a definition and a determinant of inflammation. TNF-α significantly influences the development of illness and pathological inflammation, as does IL-1β [100]. They may disrupt the blood-brain barrier (BBB), enhance the expression of adhesion molecules, and facilitate the movement of dangerous substances like nitric oxide (NO) [101]. IL-1β is crucial for the progression of acute neuroinflammatory conditions, including stroke, ischemia, and brain damage, as well as chronic neurodegenerative diseases like Alzheimer's and Parkinson's [102].

Table-1: The origin and consequences of popular inflammatory cytokines

Effects	Source				
	TNFα	IL-1β	IL-6	IFNγ	References
CNS origin	Glia, mast cells and other leucocytes	Microglia	Microglia	T-cells	[103]
Effect on Neurons	Neurogenesis↓ Apoptosis↑	Apoptosis↑	Neurogenesis↓	Apoptosis↑	[104]
Effects on glia	Microglial Priming Astrocyte Activation	Microglia Priming Astrocyte Activation	Glial activation	Microglial Activation	[105]
Other effects	BBB Integrity↓ Aβ synthesis↑	BBB Inflammation	Tau Phosphorylation	Aβ synthesis↑	[106]

1.6.2 Chemokines

Small heparin-binding proteins known as “Chemokines” can be activated during an immune response to draw immune cells to an infection site. Specific chemokines are pro-inflammatory. Others are homeostatic and regulate cell migration during average tissue growth or maintenance activities [107]. Chemokine receptors are classified as CXCR1–CXCR6, CCR1–CCR11, CX3CR1, and XCR according to the chemokine group to which they bind [108]. Most chemokines bind to multiple receptors, and most receptors conjugate to multiple chemokines [109].

Neuroinflammation is believed to reduce prolonged pain by enhancing signaling connections between neurons and glial cells [110]. As their receptors are produced differentially in neurons and glial cells, chemokines, in particular, are ideally positioned to mediate these interactions. Neuron-glial interactions mediated by chemokines are reciprocal. First, glial cells express chemokine receptors, whereas neurons first express chemokines. Second, whereas neurons produce chemokine receptors, glial cells do not [111]. The regulation of peripheral leukocyte migration and activation, cell adhesion, T-cell activation, and the creation of peripheral sensitization are all significantly influenced by chemokines [112].

Table-2: Pro-inflammatory Chemokines in rodent models of pain

Mediators	Pain Conditions	Sources	Targets	Roles in the Alleviation of Pain	Ref.
CX3CL1	Nerve injury, cancer, arthritis	Neurons	CX3CR1 in microglia	Increases neuropathic pain, cancer pain, and inflammatory pain by activating microglia.	[113] [114]
CXCL1	Nerve injury	Astrocytes	CXCR2 in neurons	Maintains neuropathic pain and central sensitization	[115]

Mediators	Pain Conditions	Sources	Targets	Roles in the Alleviation of Pain	Ref.
CCL2	Nerve injury	Neurons	CCR2 in microglia	Activates microglia and causes neuropathic pain	[116] [117]
		Astrocytes	CCR2 in neurons	Maintains neuropathic pain and central sensitization	[118] [111]
CCL21	Nerve injury, spinal cord injury	Neurons	CXCR3 in microglia	Activates microglia and causes neuropathic pain	[119]
CCL7	Nerve injury	Astrocytes	CCR2 in microglia	Maintains neuropathic pain and microglia activation	[120]

1.7 Signaling Pathways of Neuroinflammation

1.7.1 NF-κB Activation

TLRs are membrane proteins that transmit signals and are essential for the innate immune system and the inflammatory response. The first line of defense against infections is TLR (Toll-like receptor) activation, which causes pathogen death or disposal. The structural domains of TLRs are highly conserved and contain binding sites for their ligands and co-receptors. In order to encourage microglial phagocytosis, cytokine release, and the creation of co-stimulatory molecules required for adaptive immunity, they detect specific ligands and activate signaling molecules like NF-κB. Microglia-expressed TLRs activate these cells, resulting in a neuroinflammatory reaction [100].

NF-κB proteins are a link in a chain that travels from outside the cell to the nucleus. Pro-inflammatory cytokines and chemokines are created, move to different tissue locations, inflict tissue damage, and modify the tissue's structural and functional properties [121]. All eukaryotic cells can activate NF-κB in response to most external signals, such as infections, inflammatory cytokines, and stressful situations. Apoptosis, inflammation, immunity, cell survival, and cancer are all influenced by NF-κB, which controls the inducible expression of immune and inflammatory response genes [122]. NF-κB activation unexpectedly improves neuronal survival and plasticity. On the other hand, neurodegenerative and inflammatory processes need NF-κB activation in glial cells. [123].

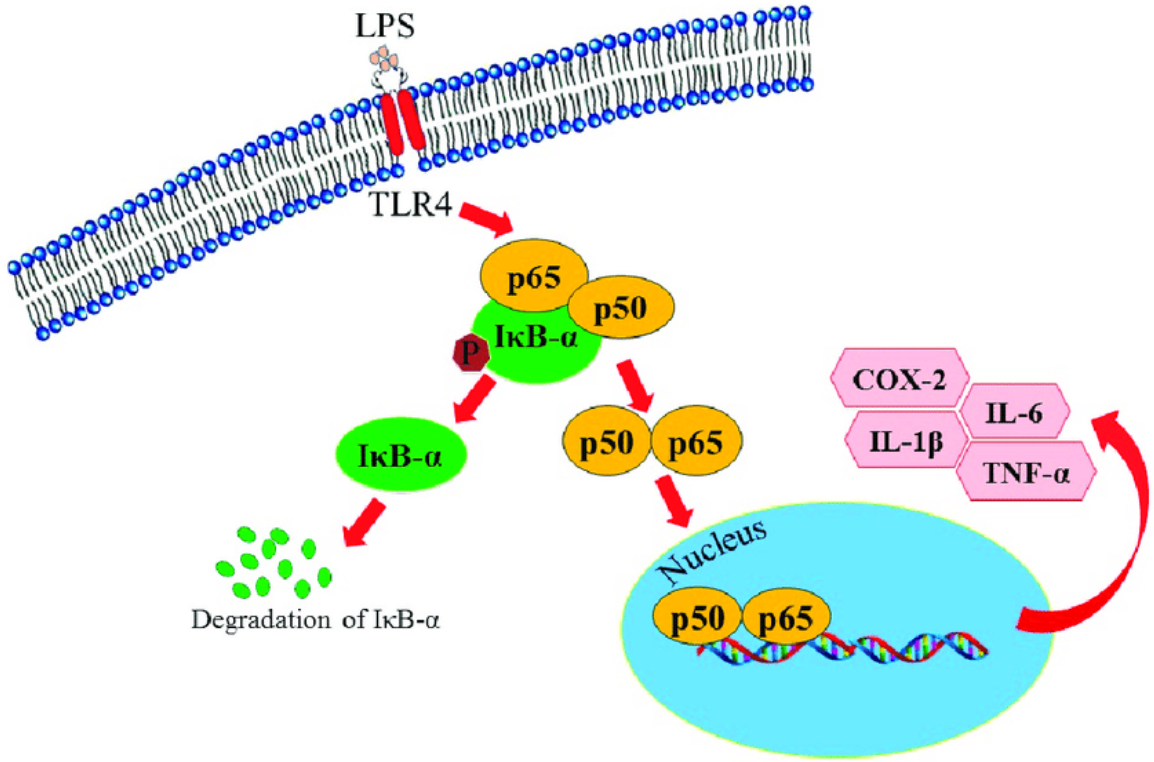

Figure-8: TLR4-mediated NF-κB signaling pathway.

An inhibitory molecule called IκB and nuclear translocation are necessary to control NF-κB. NF-κB dimers are inactive in the cytoplasm due to their association with the I-κB inhibitory

family. They must remove the inhibitory IκB protein and nuclear translocation of the liberated NF-κB dimer. The cascade is triggered when the cells are exposed to the right stimuli, such as the necrosis factors TNF-α and IL-1β. The inhibitor of B kinase gamma (IKK) or NF-κB essential modifier (NEMO) component of a ternary I-κB kinase (IKK) complex, which consists of two catalytic subunits, IKK and IKK, and a regulatory/structural subunit, causes the phosphorylation and subsequent ubiquitination of the I-B inhibitory protein. Because IκB and NF-κB are no longer linked, NF-κB is freed, allowing p65/RelA to go from the cytoplasm to the nucleus, where it binds to specific promoter areas to activate the expression of particular cellular genes [124].

1.7.2 Reactive Oxygen Species (ROS) Pathway

Oxidative stress and DNA damage brought on by inflammation lead macrophages and microglia to overproduce ROS. Oxidatively stressed cells generate more inflammatory mediators, which speed up microglial aging [125]. Free radicals and oxidative stress, which can cause or affect several disorders, are continually present in the brain. ROS are chemical atoms or molecules with unpaired electrons that can move around and do signal transduction when stimulated from the outside.

ROS can cause inflammation by turning on several genes that control the inflammatory signaling cascades and directly damaging biological macromolecules. Some of the main things that cause too much ROS production are acute and chronic inflammatory diseases and aging.

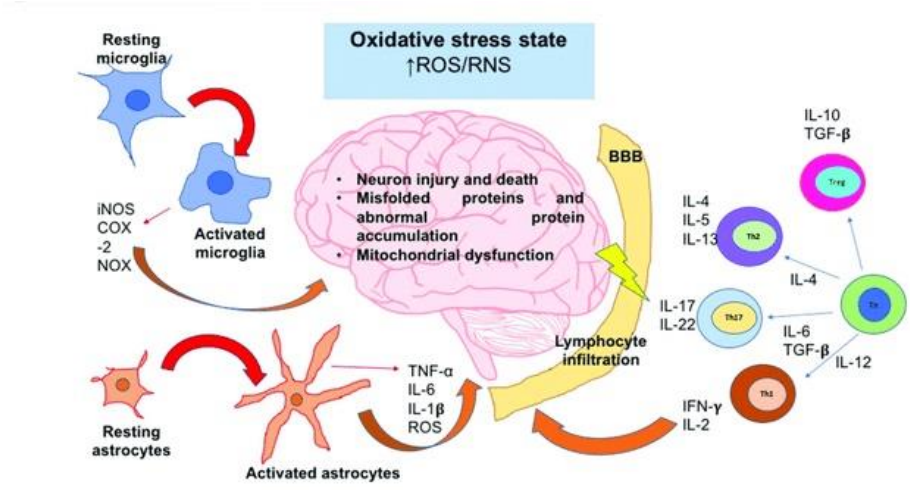

Figure-9: The oxidative stress state induces neuroinflammation and neurodegeneration.

Excitatory amino acids and neurotransmitters are two examples of oxidative stress sources specific to neural tissue. During the metabolism of certain amino acids and neurotransmitters, ROS are generated [126]. Mitochondrial failure can trigger the redox-sensitive factor NF-κB pathway via oxidative stress. Several neurodegenerative illnesses, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), alcohol-related dementia, and brain ischemia-reperfusion damage, are characterized by mitochondrial dysfunction. However, the causes of each of these neurological conditions are different. It restores mitochondrial

function to normal, which may help prevent or cure metabolic and neurological illnesses. Antioxidants that target mitochondria also reduce neuroinflammation and systemic inflammation [127].

1.7.3 Nitric Oxide (NO) Pathway

NO, a free gaseous signaling molecule, controls the neurological and immunological systems. NO synthesis is accounted for by three isoforms of nitric oxide synthase (NOS), namely neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS), and inducible nitric oxide synthase (iNOS). iNOS may become relevant in pathological situations, although it does not affect the brain under normal physiological conditions [128]. The neuritic plaques of Alzheimer's disease patients contain iNOS-expressing microglia. iNOS expression can be induced by LPS, interferon-gamma (IFN-γ), TNF-α, and IL-1β [129]. The inducible isoform of iNOS catalyzes the conversion of l-arginine to l-Citrulline and NO, another method by which neuroinflammation can directly impact neuronal death [100], [130]. High NO levels have been shown to trigger the nitration of several proteins in the neural tissues of individuals with neurodegenerative illnesses such as AD, PD, HD, and amyotrophic lateral sclerosis (ALS). Increased levels of superoxide anion and NO can be formed under pathological conditions and after exposure to neurotoxic substances, resulting in nitro-oxidative stress in the brain. The coexistence of NO and superoxide anion can produce additional cytotoxic chemicals, which have been linked to neuronal cell death [127]. In low concentrations, NO and ROS signaling molecules govern cell growth. They are, nevertheless, essential cytotoxic compounds in large quantities [7].

1.7.4 P13K Signaling Pathway Activation

One or more PI3K enzymes are typically activated by ligand binding to RTKs or GPCRs via a regulatory subunit such as p85. Under typical circumstances, the catalytic p110 subunit's N-terminus is bound by p85 via its iSH2 region, inhibiting its activity. In response to significant biological stimuli such as various cytokines and growth hormones, as well as insulin and LPS, the SH2 regions link to active receptors or adaptor proteins. This phosphoryl-tyrosine binding results in allosteric activation of the PI3K p110 catalytic subunits [131] [132]. PtdIns (4,5)P2 in the cellular membrane is converted to PIP3 by the activation of class I PI3Ks, whereas PtdIns (3,4)P2 can come from PIP3 via the SHIP family of phosphatases (SHIP-1 and SHIP-2) [133]. Furthermore, class II PI3Ks that use PI4P as a substrate can produce PI3,4P2 [134]. The outcome is the same, regardless of how distinct PI3K isoforms are activated during a particular biological process: numerous signaling proteins are repositioned and activated by binding to conserved regions like the PH (pleckstrin-homology) regions.

As a result, PIP3 or PI3,4P2 function as ligands to attract the proteins with the PH region to the inside of the plasma membrane. These proteins include PKB and Akt (protein serine/threonine kinase), which both include a PH region that is selective for PIP3 and/or PtdIns 3,4-P2 [135].

Three isoforms of Akt (Akt1, Akt2, and Akt3) have the same architecture: an N-terminal PH domain, a central serine/threonine catalytic region, and a brief C-terminal regulatory region. The PI3K/Akt signaling pathway requires the presence of the PH region [136].

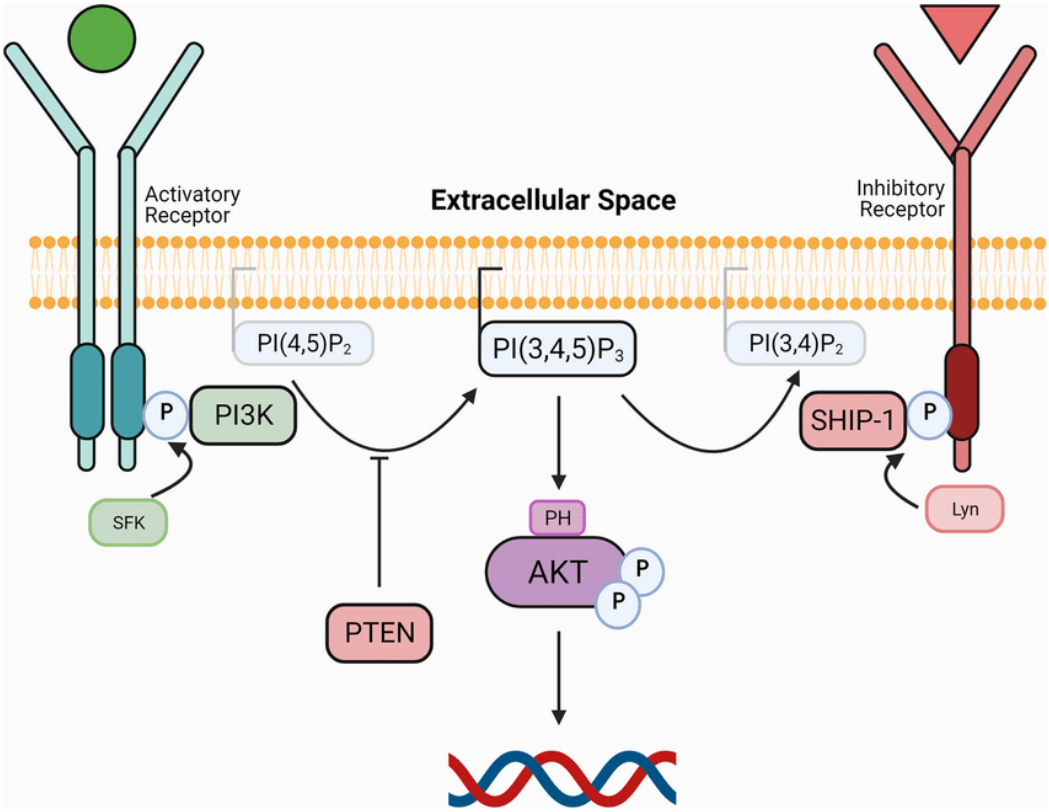

Figure-10: The signaling pathways of PI3K and Akt. The PI3K-Akt pathway controls several essential biological processes, including protein synthesis, cell proliferation, and survival.

Chapter-2
Purpose of the Study

2. Purpose of the Study

There are few main purposes of this study, which has been tried to discuss throughout the article. Mainly, the importance of the neovascularization and its therapeutic approach for different cardiovascular diseases has been focused. Nevertheless, the main objectives are;

- To know about the mechanism of Neuroinflammation
- To give an idea how Neuroinflammation contributes to neurodegenerative diseases
- To increase the awareness about Neuroinflammation.

Chapter-3

Methodology

3. Literature Search & Data collection

Fundamentally, I wanted to perform this literature review to satisfy the prerequisites for the Bachelor of Pharmacy degree (B. Pharm.). That is why I started writing this literature. A literature review is a piece of academic writing that shows understanding and awareness of the material accessible in a particular field of study. A literature review also includes a dispassionate evaluation of the references. Literature reviews, like other academic papers, must include at least three primary sections: an introduction or background information section; the review's body, which addresses the sources; and, finally, a conclusion and/or suggestions section to wrap up the research. The introduction, findings and discussion, and conclusion are the three components of this paper, as you can see.

There are over 80 published papers (from anytime) were described in which possible findings for, Integrated biological concept of Neuroinflammation, microglia, neuropathway activation, cytokines like TNF-α, IL-6, IL-β as well as chemokines, M1 and M2 phenotype, Neuro injury, Alzheimer's disease, Perkinson's disease etc. A succinct search method was initiated in order to find articles written with care in well-known publications.

Data sources such as Elsevier, Lancet, Scopus, Springer, PubMed, Cochrane, Crossref, Google Scholar, CAS, EBSCO, and Science Direct are used to collect information.

I evaluated the reference patterns of around 55 of the chosen literature using more accurate, appropriate, and accurate data.

Education, reading, knowing the purpose of the research, maintaining a laser-like focus on the topic, and knowing the boundaries of the material at the disposal in addition to talents are all important. In addition to that, I utilized a few more regular tools and programs. As- Microsoft Word, Sci-hub, Quillbot, Grammarly, Biorender, Mendeley, Turnitin.

a. **Microsoft Word:** It is used to create a better bibliography and serve as a basic text editor.

b. **Sci-hub:** In essence, Sci-Hub offers free access to more than 50 million publications, and researchers may easily do searches using a paper's headline or DOI to receive quick, free access, making it a convenient search engine for discovering academic papers.

c. **Quillbot:** Its main function is to paraphrase any text using artificial intelligence in a variety of distinct ways.

d. **Grammarly:** It makes sure that what we write complies to appropriate spelling, punctuation, and grammar in addition to being clear, compelling, and easy to read.

e. **Biorender:** Making schematics, graphical abstractions, and figures using it is appropriate.

f. **Mendeley:** It is a web-based desktop tool created to assist in compiling, organizing, and citing all of the references.

g. **Turnitin:** It is a tool that students and researchers used to spot possible plagiarism.

Chapter-4
Result & Discussion

4.1 Chronic pain and Neuroinflammation in Neurodegenerative Diseases

Chronic pain following peripheral injury differs significantly from neuroinflammation in the central nervous system (CNS) in neurodegenerative illnesses (such as Alzheimer's). Direct CNS damage causes neuroinflammation in neurodegenerative illnesses and spinal cord injuries, which then causes neuronal degeneration and cell death (secondary injury) [137]. In chronic pain, peripheral injury and primary sensory neurons' increased neuronal activity are common causes of neuroinflammation (neuropathic and inflammatory pain). Hence, peripheral injury only slightly increases CNS neuroinflammation, which has a negligible impact on the rate of neuronal death [138].

Pro-inflammatory cytokines have different functions in neurodegenerative illnesses than in inflammatory pain. TNF (formerly known as TNF-α) and IL-1β (interleukin 1β) induce neurodegeneration and impair memory and synaptic plasticity (such as long-term potentiation) in several brain areas that are linked to brain dysfunction in neurodegenerative diseases (for example, the hippocampus and dentate gyrus) [139]. On the other hand, after peripheral injury, TNF and IL-1β operate as neuromodulators in the spinal cord's dorsal horn, causing or increasing synaptic plasticity (such as long-term potentiation) as well as inflammatory and neuropathic pain [140]. Patients with rheumatoid arthritis have shown that TNF neutralization inhibits chronic pain much more quickly than it reduces inflammation symptoms (like joint swelling), most likely by preventing TNF-mediated nociceptive neurotransmission (synaptic plasticity) in the spinal cord dorsal horn before inflammation reduction [141].

4.2 Evidence of Neuroinflammation in Neurodegenerative Disorders in Preclinical and Pathological Conditions

4.2.1 Alzheimer's Disease (AD)

Alzheimer's is a neurodegenerative condition that affects older people and is characterized by the buildup of A plaques and neurofibrillary tangles. The orbitofrontal and transentorhinal cortices of the frontal neocortex, among others, start an aggregation that builds up across neurons and results in synaptotoxicity [142]. Many studies have discovered that tau pathology correlates better with cognitive loss given that Aβ plaques might build up more than a decade before cognitive symptoms in AD patients become apparent [143]. Like Aβ aggregation, tau tangles build up in the entorhinal cortex and become visible in brain regions responsible for higher-order cognitive processes, such as memory formation and decision-making [144]. Recent studies suggest that Aβ aggregates encourage the formation of tau tangles and that the disease caused by Aβ aggregates and tau aggregates results in cognitive impairment [145].

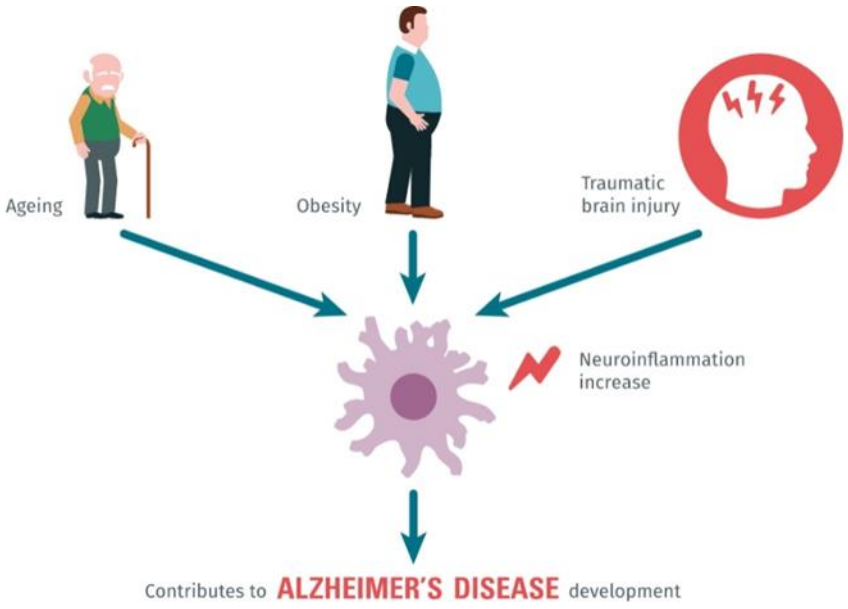

Figure-11: Contribution to Alzheimer's disease by Neuroinflammation [PerkinElmer]

A variety of genetic and environmental variables influence AD risk. Several of these elements support neuroinflammation and accelerate the beginning of the disease [146]. Brain shrinkage is accelerated by APOE-ε4, a genetic risk factor for Alzheimer's disease. The APOE- ε4 allele is linked to microglial hypersensitivity, as shown by the increased production of proinflammatory cytokines in APOE-ε4 allele-bearing mice in response to LPS stimulation. PIN1, a different gene implicated in preventing Alzheimer's disease, when deactivated, results in the accumulation of pTau and an increase in neuroinflammation [147]. Furthermore, prevalent throughout the progression of Alzheimer's disease, inflammation directly contributes to its pathogenesis. Increased prostaglandin production, which encourages inflammation at damaged locations, is one of the early neuronal alterations in AD pathogenesis. Microglial

activity is shown before astrocyte activation and brain deterioration [148]. In the middle to late phases of the disease, Aβ and pTau levels rise, which causes astrocyte activation. As a result, the generation of cytokines and neuroinflammation is still increasing [149]. Inflammatory processes can have a complex and wide-ranging influence on Alzheimer's, leading to ideas like the "damage signals theory." According to this theory, accumulating cell stress brought on by oxidative stress or neuronal damage culminates in persistent neuroinflammation and long-term activation of the innate immune system, eventually leading to neurodegeneration and AD. As a result, it offers a unified framework for considering the variety of risk factors that, over time, may place various people on similar paths leading to AD [150]. Recent research supporting the positive effects of exercise, IL-6 supplementation, and anti-inflammatory medications on TNF-α in AD models supports the hypothesis that lowering TNF-α may mitigate or prevent AD etiology [151].

4.2.2 Amyotrophic Lateral Sclerosis (ALS)

The loss of motor neurons in the motor cortex, brainstem, and spinal cord is a defining feature of amyotrophic lateral sclerosis and exhibits inflammation-related characteristics. Even though the disease's mechanisms are still unknown, mutations in ALS-associated genes like C9orf72 or SOD1 may activate microglia, increasing the risk of developing ALS [152]. In ALS brains, microglia, astrocytes, and T lymphocytes are activated in every area of motor neuron degeneration. ALS patients frequently have immunological responses to autoantigens, which indicate immune system failure [152]. Moreover, increased NF-κB activation and subsequent inflammation cause motor neuron degeneration in ALS disease models [153].

C9orf72 mutations are the most common genetic cause of ALS, accounting for around 40% of familial ALS cases and 5–10% of sporadic ALS cases, according to family studies of the disease [154].

The protein C9orf72, whose mutation established the first genetic connection to the development of ALS and frontotemporal dementia, is thought to control endosomal trafficking. Some ALS patients have shown a cognitive decline, which has been associated with TDP-43, a prominent source of ALS and FTD proteinopathy, and microglial activation in frontotemporal brain regions [155]. Rodent studies have demonstrated a relationship between higher microglial activation and inflammation in the spinal cord and the expression of TREM2, a protein produced mainly in microglia inside the CNS and connected to more substantial phagocytosis of cell debris and pathogens [156]. Elements in ALS patients' CSF-activated astroglial and microglial cultures from rats and motor neuron cocultures showed increased levels of neurodegenerative factors and inflammatory cytokines and decreased levels of neuroprotective factors [157].

4.2.3 Parkinson’s Disease (PD)

Parkinson's disease is a progressive motor phenotype marked by tremors, stiffness, and bradykinesia. It is an age-related neurodegenerative condition.

Lewy bodies, which are intracellular proteinaceous inclusions primarily made of insoluble synuclein clumps, are what neuropathologically identify Parkinson's disease. Due to increased production of inflammatory cytokines like TNF-α, these aggregates lead the striatal fibers and substantia nigra pars compacta (SN) to degenerate DA neurons [158] [159]. Post-mortem autopsies and molecular studies have revealed a connection between neuroinflammation and Parkinson's disease. Post-mortem, substantial numbers of activated microglia and high levels of inflammatory markers, including TNF-α, IL-1β, IL-6, and IFN-γ are consistently observed in the brains of PD patients. Moreover, DA neurons in the midbrain, which are most sensitive to cytokines and oxidative stress, appear to have the densest microglia population in the brain. In cocultures of neurons and astrocytes, beta-synuclein induces astrogliosis and sensitizes the inflammatory pathway, eventually resulting in the death of neurons [160].

As the condition worsens, neuroinflammation develops, and mounting evidence suggests that inflammation may contribute to the pathology of Parkinson's disease [161]. This study focuses on the relationships between genes associated with the immunological function (for example, LRRK-2, HLA-DR, Nurr1) [162] and high levels of phosphorylated-synuclein proteins and an increased risk and incidence of Parkinson's disease. According to some theories, inflammatory mechanisms that cause α-synuclein to accumulate in the gut lumen or olfactory bulb cause it to migrate to the striatum through the vagus nerve, spinal cord, or olfactory tract [163]. Also, there is proof that oxidative stress, which induces inflammation, results in increased α-synuclein aggregation. Parkinson's patients may be particularly susceptible to chronic inflammation in this regard since it encourages α-synuclein aggregation [161].

4.2.4 Multiple Sclerosis (MS)

Multiple sclerosis is a demyelinating neurological disorder that causes myelin, axonal, and neuronal degeneration when immune cells from the periphery invade the CNS boundaries and attack the myelin sheath surrounding axons [164]. The pathophysiological underpinnings of disease onset are currently being researched. It is unclear whether MS develops in the brain, where oligodendrocyte degeneration drives peripheral immune cells to activate and invade, or if autoimmune processes in the periphery cause MS to develop [165].

In the early stages of MS, microglial activation aids in its prevention and healing. Nevertheless, it also accelerates the development of the disease by secreting inflammatory cytokines that boost the recruitment of peripheral immune cells and cause demyelination [166]. Among the inflammatory cytokines implicated in MS development, TNF-α has been at the forefront of MS pathology, with autopsy studies demonstrating higher TNF- levels in regions of active lesion formation. TNF-α levels were significantly higher in the CSF of patients with chronic progressive MS than those with stable MS, proving a link between high TNF-α levels and MS progression. In experimental autoimmune encephalomyelitis (EAE), one of the most critical MS models in preclinical research, lowering proinflammatory cytokines, notably TNF-α, has been shown to lower demyelination and immune cell infiltration into the brain [167].

4.3 Therapeutic Strategies for Neurodegenerative Diseases

4.3.1 Gene Therapy

In theory, the process of gene therapy is straightforward. A disease is treated by delivering a transgene that either fixes or replaces a broken gene or benefits cells in the disease environment generally. It is much more complex in practice, and various variables must be tuned. The transgene must be chosen, the appropriate vector must be selected, and the appropriate delivery method must be optimized. The host immune system's interaction with the vector or transgene may make treatment more challenging. The characteristics of the target tissue make neurodegenerative diseases even more difficult to treat [168]. There have been several clinical studies for neurodegenerative illnesses using gene therapy. One of the earliest trials using AAV-mediated gene therapy was on the condition known as Canavan disease, which is caused by a mutation in the aspartoacylase (ASPA) gene. Patients received an injection of AAV2-ASPA into the brain and were monitored for up to 10 years following surgery.

Patient recruitment has just begun for the first trial using intrathecally administered AAV9 to deliver the gigaxonin gene (GAN) to treat giant axonal neuropathy (GAN). Sadly, several clinical investigations have yet to demonstrate effectiveness successfully [169].

Attempts to improve vectors, target delivery, and broaden the range of possible transgenes should lead to greater efficacy in gene therapy trials [168]

Table-3: Neurodegenerative disease gene therapy

Disease	Gene Therapy	Delivery Route	Current Status
ALS	ASOs to SOD1	Intrathecal	Phase I safety trial successful
Alzheimer's Disease	AAV2-NGF	Injection into the basal forebrain	Phase I successful, treatment well tolerated.
Parkinson's Disease	AAV2-GAD	Injection into the subthalamic nucleus	Successful phase 1 safety testing. Phase II safety trials did not demonstrate superiority to control groups.
	AAV2-AADC	Injection into the putamen	Phase I safety trial successful

4.3.2 Inhibition of P13K Signaling

Several prevalent diseases, such as cancer, diabetes, cardiovascular disease, and neurological problems, are linked to the PI3K pathway [133]. Its dysregulation, in particular, plays a role in various brain disorders, including epilepsy, aging-related neurodegeneration, brain cancer, and developmental brain abnormalities [170].

Class I PI3Ks are primarily implicated in the TLR transduction pathway in immune cells like macrophages and dendritic cells, whereas PI3K stimulates NF-B at the systemic level. It has been shown that Akt activation occurs before NF-κB-dependent transcription of pro-inflammatory genes in activated microglia. Hyperactive microglia may cause neuronal dysfunction and synapse loss [171]. Numerous lines of evidence suggest that inhibiting the LPS-activated microglial PI3K/Akt pathway reduces the number of proinflammatory factors [172].

Table-4: Substances involved in the inhibition of P13K pathways

Substances	Nature	Reference
Myricetin	Flavonoid	[173]
Apigenin	Flavonoid	[174]
Curcumin	Polyphenol	[175]
TGF-1α	Pleiotropic cytokine	[176]
6-MP	Thiopurine	[177]
ZSTK474	Class I PI3K inhibitor	[178]
LY294002	Inhibitor	[179]

4.3.3 Thalidomide & Its Analogue

Although thalidomide studies for neurological disorders have been ineffective, future trials for treating neurological diseases should concentrate on more powerful new-generation IMiDs. New analogs must improve over thalidomide before they can be used to treat neuroinflammation effectively. Future clinical investigations should include drug dose adjustments to reduce toxicity and increase efficacy through better drug-to-target attraction and bioavailability knowledge. In contrast to thalidomide, the diffusion of lenalidomide into the brain is unexpectedly minimal [180].

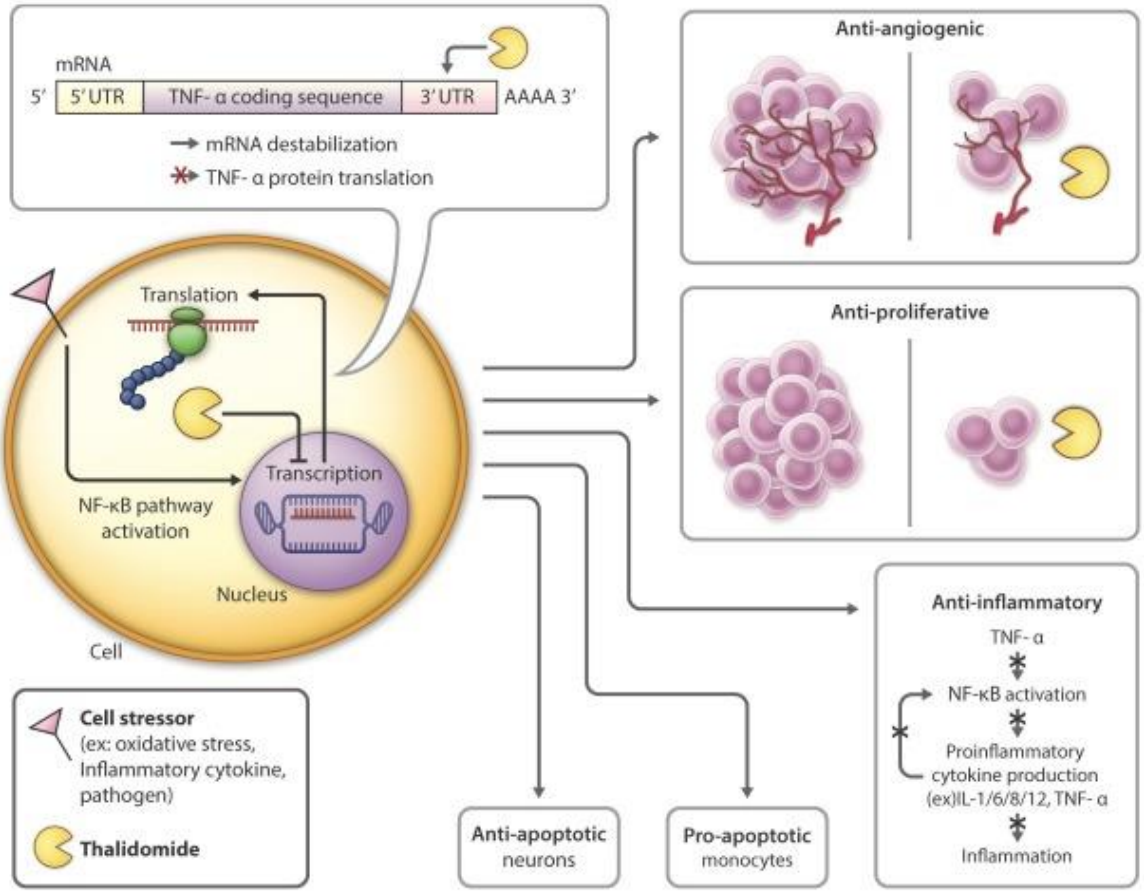

Figure-12: Thalidomide mode of action and pleiotropic effects: The NF-κB transcription factor is activated when pathogens or inflammatory cytokines are introduced into cells, which increases TNF-α translation. Thalidomide binds to the 30 -UTR of TNF-α mRNA, causing the mRNA to become unstable and decreasing the generation of TNF-α cytokines. [Jung, Yoo Jin, et al. (2019)]

4.3.4 Other Strategies

There are other strategies that can be used in terms of inhibit neuroinflammation. Following table shows the different compounds and their role in Neuroinflammation.

Table-5: Different strategies for the treatment of neurodegenerative diseases

Clinical Strategy	Role
Stem Cell therapy	In treatment of AD & PD
Antioxidant Nutrients	Activated microglia's ability to produce TNF-α, IL-6, and NO is reduced in a concentration-dependent way.
Vitamin E	It defends the brain by decreasing the synthesis of TNF-α, NO, and the ROS and IL-6 that LPS causes to rise in microglia.
Polyphenolic compounds	Prevent age-related neurodegenerative diseases
Flavonoid	Reduce protein oxidation, obstruct the JNK and p38 pathways, and prevent the generation of ROS to safeguard neuronal cells.
Nanomedicine	Access to drug molecules across the BBB is restricted.

Chapter-5
Conclusion

Conclusion

Research on the connection between neuroinflammation and neuronal degeneration has gotten much attention lately. The study found that neuroinflammation is a crucial factor in the onset, development, and progression of neurodegeneration and neuronal death in neurodegenerative diseases. Additionally, peripheral inflammation increases the permeability of the BBB and activates glial cells, and neurons, all of which support neuroinflammatory pathways. Moreover, a dysfunctional BBB allows peripheral immune and inflammatory cells to enter the brain. The proliferation of these migratory immune cells at the site of brain inflammation can increase neuroinflammation directly or indirectly through glial and neuronal cells. Suppression of neuroinflammation can lessen the amount of neurodegeneration and ameliorate the symptoms of neurodegenerative diseases. Consequently, newer therapeutic medications are needed to restore damaged neurons and regenerate new neurons at the site of neuronal injury in the brain.

Chapter-6

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Annexure

Abbreviations

CNS: Central nervous system

BBB: Blood–brain barrier

PIC: Proinflammatory cytokines

AD: Alzheimer's disease

PD: Parkinson's disease

TNF-α: Tumor necrosis factor-α

IL-1β: Interleukin-1β

TNFR1: TNF receptor-1

MS: Multiple sclerosis

APP: Amyloid precursor protein

Aβ: β-Amyloid

NF-κB: Nuclear factor-κB

TLR: Toll-like receptor

PI3K/Akt/mTOR: Phosphoinositide 3-kinase/Akt/mammalian target of rapamycin

ROS: Reactive oxygen species

IL-1R: IL-1 family receptor

TIR: Toll/IL-1 receptor

NO: Nitric oxide

LPS: Lipopolysaccharide

MAPK: Mitogen-activated protein kinase

tmTNF-α: Transmembrane TNF-α

IFN-γ: Interferon-γ

NK cells: Natural killer cells

IFN-γR: Interferon-γ receptor