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Review

Inflammation and Late-Life Depression: Unraveling the Complex Relationship and Potential Therapeutic Strategies

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Abstract

The origins of late-life depression are multifaceted and remain challenging to fully understand. While the traditional monoamine neurotransmitter hypothesis provides some insights, it falls short in explaining the disease's onset and progression, leaving treatments often less than optimal. There is an emergent need to uncover new underlying mechanisms. Among these, the "inflammation hypothesis" has been gaining traction in scientific discussions regarding late-life depression. There is compelling evidence linking inflammation processes to the emergence of this form of depression. This review delves into the nuanced relationship between inflammation and late-life depression, emphasizing the pivotal role and implications of inflammation in its pathogenesis. Changes in Ca^{2+} homeostasis, cytokine levels, brain-derived neurotrophic factor (BDNF), white cell ratios, and the involvement of the NOD-, LRR-, and Pyrin domain-containing protein 3 (NLRP3) inflammasome have all been suggested as potential biomarkers that tie inflammation to late-life depression. Furthermore, factors such as aging-induced DNA damage, oxidative stress, mitochondrial impairments, disruptions in the hypothalamic-pituitary-adrenal axis, activated microglia and associated neuroinflammation, as well as the gut-brain axis dynamics, could serve as bridges between inflammation and depression. Deepening our understanding of these connections could usher in innovative anti-inflammatory treatments and strategies for late- life depression.

Keywords: late life depression; inflammation; molecular mechanisms; pathway; personalized target and therapy

1. Introduction

Aging is a global trend, with the number and proportion of individuals aged 60 and over increasing [1], expected to rise from 10.0% in 2000 to 21.8% in 2050 [2]. Late-life depression (LLD) is a mental health disorder that primarily impacts older adults, typically those aged 60 years and older. This condition is characterized by ongoing feelings of sadness and hopelessness, coupled with a decreased interest in activities that were previously enjoyed [3]. It is a significant public health issue among the elderly and a leading cause of disability worldwide [4]. The prevalence of LLD varies significantly across the world [5]. A recent meta-analysis reported that the average estimated prevalence of LLD is 31.74%, with developing countries having a higher overall prevalence (40.78%) compared to developed countries (17.05%) [6]. The lifetime prevalence of severe depression in older adults in Western countries is 16.52% [7], while in European countries, it is 29% [8]. In China, the overall prevalence of depressive symptoms in the elderly population is 20.0% [9].

LLD has become a severe public health issue both in China and globally, with high prevalence, increased risk of suicide, and prolonged duration contributing to the growing disease burden [10]. The traditional "monoamine hypothesis" proposes that depression is linked to reduced levels of monoamine neurotransmitters in the brain, including norepinephrine (NE), 5-hydroxytryptamine (5-HT), and dopamine (DA) [11]. However, the etiology and pathogenesis of late-life depression (LLD) are complex, involving brain atrophy, vascular changes, white matter degradation, inflammatory responses, and genetic polymorphisms [12]. Compared to younger depressed patients, older patients with depression often have multiple comorbid physical illnesses and cognitive impairment [13]. The traditional monoamine neurotransmitter hypothesis alone cannot fully explain the pathogenesis and outcomes of LLD.

Currently, pharmacotherapy is the primary treatment for LLD. However, the effectiveness of antidepressants in managing LLD can be limited [14]. The response rate to antidepressants is typically lower in older versus younger depressed patients [15], and older individuals are more prone to relapse [16]. Therefore, exploring novel etiological theories and treatment approaches for LLD is critical.

Inflammatory aging is an inevitable phenomenon during the aging process. It begins with a low-grade "cold" inflammatory phase. Compared to healthy adults, older individuals exhibit only a slight elevation in plasma proinflammatory mediators, which helps maintain homeostasis [17]. However, with advancing age, the body's homeostatic balance progressively deteriorates, leading to amplified cytokine responses mediated by the chronically activated innate immune system, typically increasing by two- to four-fold [18]. Elevated proinflammatory cytokines significantly modulate neuroplasticity and neurogenesis [19], triggering neuroinflammation [20], and impacting mood and cognition. Studies indicate LLD is closely tied to inflammation, with increased inflammatory responses potentially contributing critically to LLD development [21,22]. By managing the inflammatory response, it is anticipated that LLD symptoms may be reduced, ultimately enhancing the quality of life for older adults [23]. In the future, further exploration of the relationship between inflammation and LLD is needed to enhance the effectiveness of prevention and treatment strategies for LLD.

2. Biological Basis of Inflammation and LLD

2.1 Inflammatory Pathways and Mediators

2.1.1 Cytokines

In the inflammatory mechanism of LLD, cytokines are among the important regulatory factors. Elevated peripheral cytokine levels are associated with depressive symptoms in the elderly, with the most consistent findings related to IL-6 [24], as well as IL-1β, IL-8, and tumor necrosis factor (TNF-α) [25,26]. Dhabhar *et al.* [27] found that pro-inflammatory cytokines are increased in patients with depression, while anti-inflammatory cytokines such as IL-4, IL-10, IL-13, transforming growth factor β, and adiponectin are decreased. Elderly patients are often in a chronic pro-inflammatory state, which increases the activation and initiation of microglial cells, leading to continuous production of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α and a reduction in anti-inflammatory molecules [28]. This results in a rise in pro-inflammatory cytokines and activation of microglial cells, which contribute to brain pathology by increasing blood-brain barrier (BBB) permeability and cytokine production, ultimately leading to the onset of depression [29]. Some studies have found [30] that older individuals with clinical depression do not exhibit elevated levels of inflammation unless they also have other inflammatory conditions such as arthritis. However, Kim *et al.* [31] conducted a study on LLD and cytokines, providing support for cytokine-mediated inflammatory pathways. The variability in major depressive disorder (MDD) research findings might be attributed to certain studies incorporating depressed patients without systemic inflammation, while others focus on patients with inflammatory depression. Moreover, age disparities among study participants could be a factor, as older populations frequently experience chronic pro-inflammatory states, making them more fitting subjects for examining the inflammatory underpinnings of depression.

2.1.2 Acute Phase Proteins (APPs)

Acute phase proteins (APPs) are a class of proteins synthesized and released during acute inflammation and injury in the body, with important biological functions. They include C-reactive protein (CRP), pre-albumin (PA), and albumin (Alb) [32]. IL-6 is the main regulatory factor for APP synthesis and release, and studies have shown that IL-6 levels are positively correlated with APP levels. IL-6 can also regulate APP synthesis and release through the activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway [33]. Among these, CRP has been the most extensively studied in LLD. In a case-control study, Mishra *et al.* [34] found that CRP levels in patients with late-onset depression were 40% higher than in age-matched non-depressed individuals. Additionally, numerous studies have shown [35–38] a strong positive correlation between CRP levels and the severity of depression. In a Mendelian randomization study [39], genome-wide association study (GWAS) data revealed shared genetic associations between CRP levels and individual depressive symptoms. Furthermore, several studies have determined that inflammatory markers like CRP, albumin (Alb), and pro-albumin (PA) are positively correlated with the severity of LLD [40,41]. This association might be attributed to several factors. Firstly, elderly individuals with depression exhibit inflammation-related factors in their systems, which are often paired with the activation of inflammatory responses. Inflammatory factors can directly cause protein breakdown by activating the calpain-calpastin proteolytic system within cells [42]. In addition, inflammatory factors can increase the breakdown of insulin-like growth factor-1 [43], thereby inhibiting protein synthesis in the liver, which is clinically manifested as a decrease in negative APP levels. Second, LLD is often accompanied by physiological metabolic abnormalities, reduced appetite, and impaired digestive function, leading to a decrease in protein and energy intake, lowered serum Alb and PA levels, and eventually resulting in hypoalbuminemia [44]. Further research is necessary to investigate the role of APPs in LLD, as well as the complex relationships between APPs and other relevant factors, such as lifestyle factors in the elderly. Additionally, more consideration should be given to the potential value of APPs as therapeutic targets for the treatment and prevention of LLD, and further exploration of the feasibility of their application is warranted.

2.1.3 White Cell Ratios

The Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), and Monocyte to Lymphocyte Ratio (MLR) have been extensively studied in patients with mental disorders. These ratios are considered prac-

tical, low-cost, and easily accessible novel inflammatory markers [45,46]. Numerous studies have demonstrated that NLR, PLR, and MLR are elevated in patients with depression [47–50]. Some research has suggested that MLR may be a risk factor for the development of depression [51], and PLR parameters might be more predictive than NLR in assessing the prognosis of major depression [52]. However, there is a relative scarcity of research focusing on the white blood cell ratio in the elderly depression population.

In 1964, Walford [53] proposed "The Immunologic Theory of Aging", further developing and deriving the concept of immune aging. Immunosenescence of neutrophils occurs in a low-grade inflammatory environment, characterized by specific abnormalities in metabolism and function, along with increased apoptosis [54]. Hematopoietic stem cell senescence forms the basis of immunosenescence. Aging hematopoietic stem cells (HSCs) tend to differentiate into myeloid cells, while their ability to support lymphoid cell maturation decreases. This leads to a reduction in the number of T and B cell precursors with age [55]. It has been observed that an age-related B cell population accumulates in the peripheral blood as the body ages [56]. Additionally, the aging of the immune system has a complex relationship with inflammation. This relationship induces neuroinflammation and systemic inflammation through its interaction with the nervous system [57,58] which in turn affects mood and may trigger depression. As the body ages, most immune cells exhibit characteristics of aging, impacting the number of neutrophils and lymphocytes in the peripheral blood. Future research needs to further explore the underlying mechanisms between blood cell ratios and LLD to evaluate the clinical potential of these biomarkers in the treatment and prevention of LLD.

2.1.4 NLRP3 Inflammasome

The NOD-, LRR-, and Pyrin domain-containing protein 3 (NLRP3) inflammasome is composed of NLRP3, apoptosis-associated speck-like protein containing CARD (ASC), and caspase-1 [59–61]. This complex plays a vital role in the aging process of various organs, including the thymus [62], kidney [63], and brain [64].

The activation signals for the NLRP3 inflammasome include two primary pathways: first, NF-κB activators [65] and IL-1β [66]; second, multiple risk signals or damage-associated molecular patterns (DAMPs) that have been identified as activators of the NLRP3 inflammasome. These include reactive oxygen species (ROS) [67], cholesterol crystals [68], urate crystals [69] and lipotoxic ceramides [70], all of which are endogenous metabolites that increase with age. Activation of the NLRP3 inflammasome is a response to the accumulation of various DAMPs and can induce systemic chronic inflammation during aging [71]. The mechanism underlying this process is that the NLRP3 inflammasome provides a platform for caspase-1 activation. Activated caspase-1 cleaves gasdermin D (GSDMD) to form pores in the cell membrane, leading to IL-1β and IL-18 leakage and pyroptosis. This causes an inflammatory storm, damages cells, and expands inflammation [72]. It can further lead to blood-brain barrier damage in the elderly [73], induce and aggravate neuroinflammation, and eventually result in depression [74].

Other studies have demonstrated that the activation of NLRP3 inflammasomes present in neurons, astrocytes, and microglia [75,76] can cause the release of neurotoxic astrocytes and trigger a neurotoxic response. This has significant implications for the onset and progression of depression [77]. In light of the potential role of the NLRP3 inflammasome in geriatric depression, molecules regulating the NLRP3/ASC/caspase-1/GSDMD/IL-1β/IL-18 axis may hold clinical value in the development of antidepressant drugs [78]. Previous research has indicated that the dysregulation of the acetylation switch of the NLRP3 inflammasome is the origin of aging-related chronic inflammation, and NLRP3 deacetylation can prevent and target to reverse this inflammation [79]. In the future, comprehensive clinical studies on the correlation between the NLRP3 inflammasome and LLD in a larger population are needed. Such an approach may lead to a more profound understanding of the pathology of LLD, better stratification of patients, and enhanced improvement of treatment outcomes.

2.1.5 Brain-Derived Neurotrophic Factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is a vital neurotrophic factor that plays a crucial role in brain function and the development of the nervous system [80]. Studies have shown that circulating levels of BDNF decrease with age in humans [81], and in the hippocampus and hypothalamus of male rats, BDNF expression has also been found to diminish with age [82].

Upon binding to high-affinity tropomyosin-associated kinase family (Trk) receptors, mature BDNF is internalized with its receptors and transported through axons to somatic cells. This initiates multiple effects in the nucleus [83], including increasing cell survival and differentiation, complicating dendritic spines [84], regulating synaptic plasticity [85], and rebuilding neural networks [86]. In the central nervous system (CNS), BDNF and downstream pro-survival pathways have been demonstrated to protect neurons from injury and enhance neuronal network reorganization following injury [87]. The dysfunction of synaptic transmission and plasticity is associated with damage to the BDNF/TrkB/CREB pathway, which can affect emotion, behavior, learning, and memory [88]. The decrease of BDNF during aging impacts BDNF-mediated antioxidant capacity, metabolic stress resistance, neurogenesis, and synaptic plasticity of nerve cells [89]. These changes can further influence mood, and a reduction in neurotransmission at hippocampal synapses and BDNF levels has been linked to an increased susceptibility to depression [90,91]. Research has indicated that decreased BDNF-TrkB signaling during

aging promotes microglial activation. Conversely, the up-regulation of BDNF signaling inhibits microglial activation through the TrkB-Erk-CREB pathway, thereby reducing the production of inflammation [92]. This finding unveils the potential of BDNF in treating depression in the elderly.

By inhibiting microglial activation and associated inflammatory responses, BDNF may serve as a protective agent, helping to preserve and restore the function of the aging brain. This insight opens new avenues for understanding the complex interplay between neurotrophic factors, aging, and mental health, and may guide future therapeutic strategies for depression and other age-related neurological conditions. Hence, BDNF holds significant importance in the development and treatment of LLD [93,94] and may act as a potential therapeutic target and biomarker [95]. Continued investigation into BDNF could pave the way for more effective treatment approaches.

2.1.6 Calcium (Ca^{2+}) Homeostasis Imbalance

Intracellular Ca^{2+} serves as a crucial second messenger that orchestrates a myriad of vital cellular processes, notably influencing aging [96] and neurodegenerative diseases [97]. As neurons age, they experience calcium overload, characterized by heightened Ca^{2+}concentrations [98], augmented Ca^{2+} storage, and an elevated transfer of Ca^{2+} from the endoplasmic reticulum (ER) to the mitochondria [99]. Aging or neurodegenerative conditions directly impact proteins responsible for maintaining Ca^{2+} balance. Notably, mass spectrometry has unveiled an age-correlated decline in the functional cysteine residues of sarco/endoplasmic reticulum ATPase (SERCA) [100], subsequently influencing the regulation of diverse physiological and pathological neuronal activities. Ca^{2+} conveys its effects through binding to calmodulin (CaM). This binding induces allosteric modifications in CaM, reshaping its interactions with target proteins such as kinases and phosphatases, and subsequently influencing neurotransmitter release, transcription factor regulation, axonal extension, and growth [101]. Research has highlighted that disruptions in ER calcium balance activate cellular stress mechanisms and are intrinsically tied to neurodegeneration and neuronal demise [102]. Aging-induced aberrations in Ca^{2+} signaling precipitate anomalies in synaptic plasticity and neuronal functionality, further advancing the onset of depression [103]. Further research has found that extracellular Ca^{2+} or other NLRP3 inflammasome activators can trigger intracellular Ca^{2+} signaling cascades through the interaction between the calcium-sensing receptor (CASR) and phospholipase C (PLC), thereby affecting NLRP3 [104], ultimately contributing to inflammation and the development of LLD. Investigations aiming to better understand the connection between Ca^{2+} homeostasis imbalance, inflammation, and LLD could also contribute to identifying potential preventive and therapeutic strategies for LLD through the regulation of Ca^{2+} homeostasis.

2.1.7 Other Proteins

In addition to the factors mentioned earlier, several protein molecules, such as S100 proteins and neutrophil gelatinase associated lipocalin (NGAL), are believed to play crucial roles in the pathogenesis of LLD. The levels of S100 proteins are closely related to the severity of depressive symptoms, and they can predict the response to antidepressant treatment [105,106]. Plasma NGAL levels are elevated in elderly individuals with depression and are not influenced by the use of antidepressant medications or the age of onset, making it a potential new inflammatory biomarker for LLD [107–109]. Heat shock proteins, which regulate the immune system through their anti-inflammatory effects, may contribute to the treatment of LLD [110,111]. while receptors such as Toll-like receptors (TLRs) and advanced glycation end products (AGEs), might also be involved in the condition's development. The TLR signaling pathway is a potential common inflammatory pathway and could serve as a potential biomarker for identifying inflammatory subtypes of depression. Based on this, some antidepressant medications may exert anti-inflammatory effects by modulating TLR-dependent and independent inflammatory responses [112,113]. In addition, changes in the receptor for AGEs (RAGE) signaling pathway may be related to the onset and exacerbation of late-life depressive symptoms [114,115]. Furthermore, plasminogen activator inhibitor-1 (PAI-1), the primary inhibitor of plasminogen activation, has been shown to be involved in the pathogenesis of LLD through its regulation [116–118].

Factors like heat shock proteins, S100 proteins, TLRs, RAGE, NGAL, and PAI-1 are crucial in the development of LLD. Adjusting these factors could aid in devising more effective treatment strategies and offer novel perspectives and methods for the diagnosis and treatment of LLD (Table 1).

2.2 Abnormalities in Neurotransmitter Systems

Neuroinflammation refers to an inflammatory reaction that takes place within the central nervous system (including the brain and spinal cord) or the peripheral nervous system. The connection between aging, heightened inflammation, and chronic disease has become well established in recent scientific literature. In the elderly, serum levels of inflammatory molecules such as IL-6, TNF-α, and IL-18 are found to be increased [119,120]. These inflammatory agents can penetrate the central nervous system either through the circulatory system or by crossing the blood-brain barrier, thereby initiating a neuroinflammatory response [121]. This understanding of the mechanisms underlying neuroinflammation provides valuable insights into the complex interactions between aging and inflammation, potentially guiding future research and therapeutic interventions for age-related neurological conditions.

Neuroinflammation may result in disturbances in neuronal function and neurotransmitter regulation. Previous consensus primarily emphasized the impact on serotonin-

Table 1. Potential inflammatory pathways and mediators linked to late-life depression.

Category	Mediators/Pathways
Cytokines	Pro-inflammatory: IL-1β, IL-6, TNF-α, IL-8 Anti-inflammatory: IL-4, IL-10, IL-13, transforming growth factor β, adiponectin
Acute phase proteins (Apps)	C-reactive protein (CRP), Albumin (Alb), pre-albumin (PA) Janus kinase (JAK) Signal transducer and activator of transcription (STAT)
White cell ratios	neutrophil-to-lymphocyte ratio (NLR) platelet-to-lymphocyte ratio (PLR) monocyte-to-lymphocyte ratio (MLR) hematopoietic stem cells (HSCs)
NLRP3 inflammasome	apoptosis-associated speck-like protein containing(ASC) NF-κB, damage-associated molecular patterns (DAMPs) reactive oxygen species (ROS), gasdermin D (GSDMD) NLRP3/ASC/caspase-1/GSDMD/IL-1β/IL-18 axis
Brain-derived neurotrophic factor (BDNF)	kinase family (Trk), central nervous system (CNS) BDNF/TrkB/CREB pathway, BDNF-TrkB signaling TrkB-Erk-CREB pathway
Calcium (Ca^{2+}) homeostasis imbalance	endoplasmic reticulum (ER) sarco/endoplasmic reticulum ATPase (SERCA), calmodulin (CaM) calcium-sensing receptor (CASR), phospholipase C (PLC)
Other proteins	S100 proteins, neutrophil gelatinase associated lipocalin (NGAL) Toll-like receptors (TLRs), advanced glycation end products (AGEs) plasminogen activator inhibitor-1 (PAI-1)

ergic and adrenergic systems. However, some studies propose that neuroinflammation is closely linked to dopamine [122], purinergic [123], and glutamatergic systems [124]. Dopamine is an important neurotransmitter that regulates mood and reward systems. Normal aging, along with age-related proinflammatory processes, is linked to a reduction in the function of dopaminergic molecules and a subsequent impairment of dopamine signaling [125,126]. Inflammatory cytokines may negatively impact the dopaminergic system by restricting the availability of tetrahydrobiopterin (BH4), thereby reducing dopamine synthesis [127]. Additionally, these cytokines may hinder dopamine release and reuptake mechanisms [128,129]. The decline in dopamine levels further contributes to the emergence of depressive symptoms. Research has shown that depression-like behaviors can be ameliorated by enhancing dopamine signaling [130]. This understanding of the intricate relationship between inflammation, dopamine, and depression may offer valuable insights for the development of targeted therapeutic strategies to address age-related mood disorders.

The purinergic system consists of various neurotransmitters and receptors, such as adenosine, ATP, P2X, and P2Y receptors. Inflammatory responses and cellular injuries can lead to the release of purine nucleotides, which subsequently activate purine receptors. Purinergic substances are known to stimulate the release of inflammatory mediators and regulate the activity of inflammation-related signaling pathways [131]. Specifically, A2A and P2X7Rs in astrocytes mediate the release of cytokines such as IL-1β and TNF-α, resulting in neuroinflammation [132] and contributing to the onset of depression.Several studies have highlighted that functional changes in the purinergic system, including abnormal adenosine levels, irregular expression of purine receptors, reduced adenosine triphosphate (ATP) release from astrocytes, and activation of P2X7 receptors in the medial prefrontal cortex and hippocampus, are significant factors in the development of depression [133,134]. Given the role of purinergic signaling in inflammation and depression, research has indicated that purinergic P2X7 receptor antagonists may be vital in treating depression [135]. Targeting purinergic receptors could emerge as a potential strategy for treating depression in the elderly.

Glutamate, the primary excitatory neurotransmitter in the brain [136], plays a complex role in aging and depression. Aging-induced neuroinflammation activates microglial cells, which express metabotropic glutamate receptor 2 (mGluR2) on their surface. The binding of glutamate to microglial cells can trigger the release of inflammatory cytokines and nitric oxide, exerting toxic effects on neural circuits involved in emotion and cognition [137], and ultimately leading to depression. It has been proposed that a reduction in the glutamate to gamma-aminobutyric acid (GABA) ratio may be associated with a decrease in depressive symptoms [138]. The N-methyl-d-aspartate (NMDA) receptor, a member of the glutamate receptor family, plays

a role in the transmission of neurotransmitter glutamate and the regulation of synaptic plasticity [139]. Ketamine, a glutamate NMDA receptor antagonist, has demonstrated rapid antidepressant effects [140], and its impact on synaptic plasticity has proven effective in treatment-resistant depression [140–142]. However, research focusing on the treatment of depression in the elderly remains scarce, and long-term safety data for elderly patients with depression are limited. More empirical research is needed to establish individualized safety dosages and treatment plans, ensuring that these promising avenues for treatment are explored with the necessary caution and rigor. The interplay between purinergic signaling, glutamate pathways, and depression presents a rich field for further investigation, with the potential to yield innovative therapeutic approaches for age-related mental health disorders.

3. Potential Mechanisms Linking Inflammation and LLD

3.1 Aging-DNA Damage

DNA damage is an unavoidable consequence of aging, and inflammation is a response triggered by such damage. DNA damage induces inflammatory responses by activating DNA damage response (DDR) pathways [143,144]. Factors like age-related DNA damage accumulation, transposon activation [145,146], cellular senescence [147], and persistent R loop accumulation [148] serve as catalysts. Through the activation of the cGAS-STING axis [149] and ATM [150] mediated NF-κB activation [151], signaling cascades such as NF-κB and IRF3 work together to activate type I interferons [152] and other inflammatory factors. This, in turn, triggers neuroinflammatory responses and contributes to the development of LLD.

A study on rats also suggests that the accumulation of DNA damage during aging may activate DDR [153], triggering neuroinflammatory responses and leading to LLD. Another study found a negative correlation between DNA methylation levels in the brain tissue of older adults and LLD, suggesting that DNA damage and inflammatory responses are related to the onset and development of LLD [154]. Investigating the interaction between DDR and inflammatory responses may help understand the pathogenesis of LLD and provide new treatment ideas.

3.2 Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress and mitochondrial dysfunction may be closely related to the onset and progression of LLD. Evidence supporting this hypothesis includes studies showing abnormal manifestations of oxidative stress and mitochondrial dysfunction in patients with LLD [155–157]. The relationship between oxidative stress, mitochondrial dysfunction, and LLD may involve the activation of sterile inflammation and damage-associated molecular patterns (DAMPs) pathways [158]. The combined effect of oxidative stress and mitochondrial dysfunction leads to cellular damage, releasing DAMPs [159]. The release of DAMPs further stimulates immune responses, In addition to eliciting a type I interferon response, mitochondrial DNA activates Toll-like receptor 9 and NLRP3 inflammasome, ultimately leading to inflammation [160]. Furthermore, reactive oxygen species (ROS) may be harmful to neurons and synaptic transmission when the body is under high levels of oxidative stress and low antioxidants [161]. Increased oxidative stress may cause further mitochondrial damage, increased apoptosis, and ultimately inflammatory signaling [162–164], leading to depression-like behavior.

3.3 Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction

The HPA axis is an essential neuroendocrine regulation system that modulates stress responses, helping the body maintain stability. When the HPA axis becomes dysregulated, stress responses become uncontrolled, affecting mental health and promoting the onset and worsening of depression. Recent studies have suggested that individuals with LLD may exhibit hyperactivity and sustained activation of the HPA axis [165,166]. Excessive activation of the HPA axis leads to an overproduction of cortisol, which negatively impacts neurons and exacerbates LLD symptoms [167]. LLD may be related to the dysregulation of the HPA axis induced by inflammatory pathways. Many researchers have found elevated pro-inflammatory cytokines in patients with LLD, and studies have shown that increased IL-1, IL-6, and TNF-α can activate the HPA axis [168], leading to persistent activation of glucocorticoid receptors (GR), GR dysfunction, and loss of HPA axis negative feedback regulation, ultimately inducing or exacerbating the development of depression. Additionally, cytokines may stimulate indoleamine 2,3-dioxygenase (IDO) to participate in cortisol-mediated negative feedback inhibition of the HPA axis [169]. Recent research also indicates that gut microbiota can activate the HPA axis through microbial antigens, cytokines, and prostaglandins that cross the blood-brain barrier [170,171], and evidence suggests that various microbial species can affect the production of corticosterone in the ileum, thus influencing HPA axis activity [172]. Consequently, HPA axis dysregulation mediated by inflammatory pathways might be a critical mechanism in LLD. Overactivation of the HPA axis worsens LLD symptoms and interacts with inflammation and gut microbiota, further affecting HPA axis function and creating a detrimental cycle. In-depth investigation of these mechanisms may help develop more effective treatment strategies.

3.4 Microglial Activation and Neuroinflammation

Block ML *et al.* [173] have shown that individuals with LLD exhibit significantly increased levels of microglial activation and neuroinflammation. Older adults often have vascular diseases and vascular risk factors that can cause chronic ischemic hypoxia in brain tissue, damag-

ing oligodendrocytes, and persistently activating microglia and astrocytes. This results in the release of inflammatory factors such as IL-2, IL-6, IL-1β, TNF-α, and IFN-γ, inducing neuroinflammation [174–176]. Cytokines and other molecules released during inflammation, such as nitric oxide and free radicals, may produce direct cytotoxic effects, leading to neuronal damage [177]. Moreover, central inflammation may indirectly participate in the pathophysiology of depression through the kynurenine pathway. Inflammatory mediators can activate IDO, shifting tryptophan metabolism from serotonin production to kynurenine production, resulting in a decrease in 5-HT [178,179], leading to depression. In addition, the imbalance of tryptophan metabolism in the kynurenine pathway may cause neurotransmitter imbalances, affecting neural plasticity and function [180].

On the other hand, neuroinflammation can cause changes in emotion-related monoamine neurotransmitters, HPA axis dysfunction, neuronal apoptosis, and downregulation of BDNF, ultimately leading to the onset of depression [181–183]. Furthermore, neuroinflammation may lead to blood-brain barrier disruptionand infiltration of inflammatory cells into the central nervous system [184], which may collectively contribute to the development and progression of LLD. A complex interplay exists between microglial activation, neuroinflammation, and LLD. Depression may trigger microglial activation and neuroinflammation, which in turn intensify depressive symptoms and impact neural plasticity and function. The presence of neuroinflammation could further aggravate depressive symptoms, forming a detrimental cycle. Additional research may enhance our understanding of the relationship between microglial activation, neuroinflammation, and LLD.

3.5 Gut-Brain Axis

Age-related changes in the gut microbiota can weaken the function of the intestinal barrier, leading to gut microbial dysbiosis [185,186], which in turn triggers the release of bacterial products and promotes inflammation, damaging the body's immune function [187]. The resulting inflammatory factors can increase the permeability of the blood-brain barrier [188], leading to neuroinflammation and subsequent depression. Furthermore, gut microbiota dysbiosis can result in changes in metabolic products such as short-chain fatty acids (SCFAs) and neurotransmitters (GABA, DA, NA, 5-HT) [189,190], which may contribute to depression. SCFAs can also promote the repair of the intestinal mucosal barrier [191] and the blood-brain barrier [192]. Both SCFAs deficiency and intestinal inflammation can increase the permeability of the intestinal mucosal and blood-brain barriers, leading to neuroinflammation. Recent genomic research, coupled with Mendelian randomization studies, suggests that gut microbiota may play a role in regulating mood and anxiety, potentially via shared genetic pathways. A heightened genetic predisposition to depression has also been linked to this phenomenon [193,194]. The gut-brain axis and gut microbiota, along with their role in inflammatory responses, could be one of the potential mechanisms underlying LLD. The gut microbiota can impact brain function and mood through several pathways, thus influencing the onset and advancement of LLD (Fig. 1).

4. Therapeutic Implications and Future Directions

4.1 Anti-Inflammatory Treatments and Their Impact on Depressive Symptoms

Treatment-resistant LLD (TRLLD) is a common problem, affecting up to one-third of patients. The inflammatory hypothesis of LLD provides a new direction for treatment [195]. Studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) [196–199], omega-3 fatty acids [200–202], statins [203,204], cytokine inhibitors [205], corticosteroids [206,207], and minocycline [208–210] have significant antidepressant effects when used as adjunctive therapies. Infliximab monotherapy also demonstrates some antidepressant effects [211]. Ketamine may alleviate depressive symptoms through various mechanisms, such as regulating inflammation-mediated cytokine dysregulation and neurotrophic factors [212–214]. Exercise and meditation therapies can indirectly reduce inflammation by lowering CRP levels in depressed patients, with good results [215]. Anti-inflammatory diets may potentially serve as an intervention for depression; pro-inflammatory diets are closely related to increased risk of depression diagnosis or symptoms, while anti-inflammatory diets mainly consist of fish, olive oil, and fresh vegetables and fruits [216–218]. Moreover, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may exert antidepressant, anti-inflammatory, and neuroprotective effects. Borsini's [219] study provided evidence for LOX and CYP450-derived EPA/DHA bioactive lipid metabolites as molecular targets for human hippocampal neurogenesis and depression, emphasizing the importance of soluble epoxide hydrolase (sEH) inhibitors as potential therapeutic strategies for depression. However, some researchers found no statistically significant differences between vitamin D3 [220] and omega-3 fatty acid [221] treatments for depression compared to control groups. The contradictory results may be due to the heterogeneity of the depression subtypes included in the studies. Anti-inflammatory treatment has been recognized as beneficial in alleviating depressive symptoms, and the evidence supporting the antidepressant effect of such treatment opens the door to more personalized therapeutic plans for patients with depression. However, this approach is not without its challenges and limitations. The use of anti-inflammatory treatment, particularly in conjunction with antidepressants, has been a subject of controversy and debate [222,223]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk of adverse cardiovascular events [224],

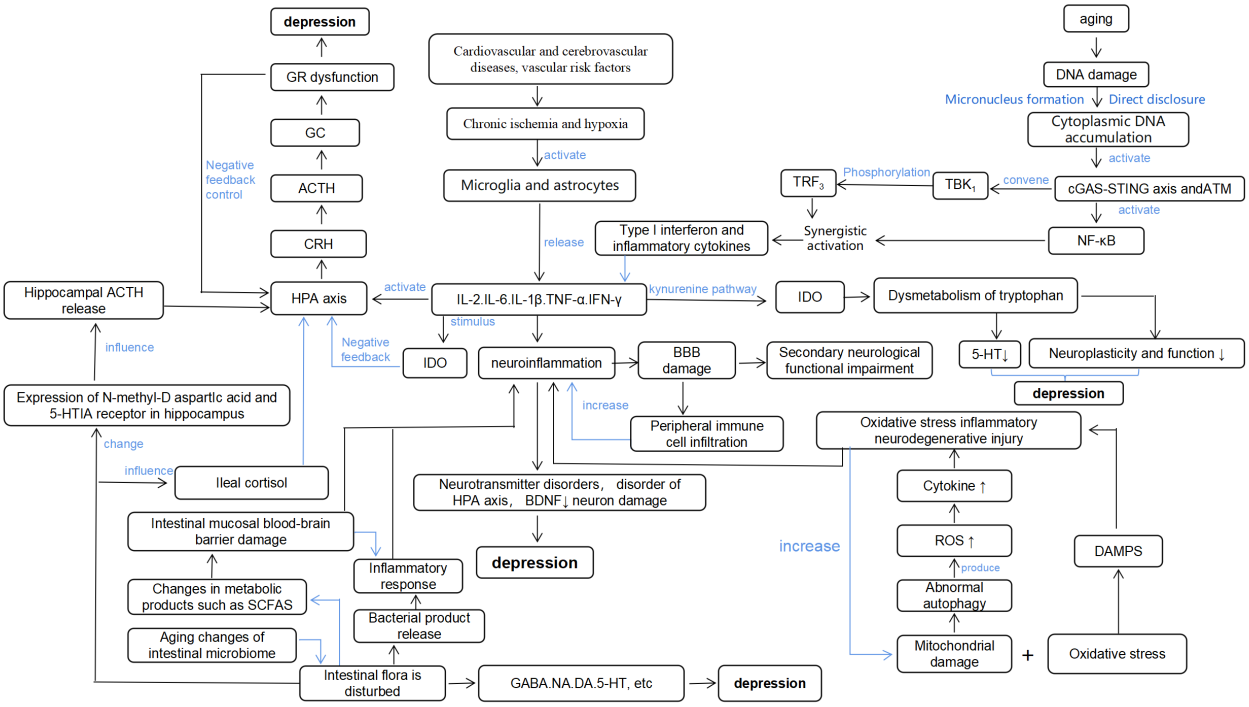

Fig. 1. Metabolic pathways potentially associated with late-life depression. For clarity and ease of reference, the full expansions of all acronyms presented in this figure are listed in alphabetical order as follows. 5-HT: 5-hydroxytryptamine (serotonin); ACTH: adrenocorticotropic hormone; ATM: ataxia telangiectasia mutated; BDNF: brain-derived neurotrophic factor; BBB: blood-brain barrier; cGAS-STING: cyclic gmp-amp synthase and stimulator of interferon genes; CRH: corticotropin-releasing hormone; DA: dopamine; DAMPS: damage-associated molecular patterns; GABA: gamma-aminobutyric acid; GC: glucocorticoid; GR: glucocorticoid receptors; HPA: hypothalamic-pituitary-adrenal; IDO: indoleamine 2,3-dioxygenase; IFN-γ: interferon-gamma; IL-1β: interleukin 1 beta; IL-2: interleukin 2; IL-6: interleukin 6; NA: noradrenaline; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; ROS: reactive oxygen species; SCFAS: short-chain fatty acids; TBK1: tank-binding kinase 1; TNF-α: tumor necrosis factor alpha; TRF3: Interferon regulatory factor 3.

and cytokine inhibitors have been linked to a heightened risk of infection [225]. These concerns underscore the complexity of implementing anti-inflammatory strategies in a clinical setting. Currently, there is a notable absence of large-sample, randomized, double-blind clinical studies focusing on anti-inflammatory treatment for geriatric depression. The need for extensive, high-quality research is paramount to assess the efficacy and safety of these therapies. The lack of such studies hampers our understanding of the precise impact of anti-inflammatory treatment on late-life depression and the best methods for administering this treatment.

Inflammation is a multifaceted biological process, involving numerous mediators and pathways. Developing drugs with high selectivity for specific inflammatory pathways or molecular targets presents a formidable challenge. Additionally, elderly patients with depression often suffer from comorbid physical ailments and may be on multiple medications, leading to potential interactions with anti-inflammatory drugs and subsequent safety risks. Therefore, a comprehensive evaluation of the benefits and risks of anti-inflammatory treatment is essential. More large-scale, randomized, double-blind clinical trials are needed to confirm the effectiveness of anti-inflammatory treatment in late-life depression. Such studies would not only contribute to our understanding of which patients are most likely to benefit from this approach but also help to refine treatment regimens, enhancing the likelihood of treatment success. In conclusion, while anti-inflammatory treatment offers promising avenues for depression therapy, especially in the elderly, careful consideration of its complexities and potential risks is vital. Continued research and clinical trials will be instrumental in unlocking its full potential and integrating it safely and effectively into the broader landscape of depression treatment.

4.2 Identifying Patient Subgroups That May Benefit from Anti-Inflammatory Treatment

With the deepening of the understanding of the role of anti-inflammatory treatment in depression, exploring the subgroups of late-life depression patients who may benefit from anti-inflammatory treatment can improve the treat-

ment effect and reduce the risk of treatment. Related studies have confirmed that depressive patients with high inflammatory activity have poor response to antidepressant treatment, while the adjunctive treatment with anti-inflammatory drugs can significantly improve the clinical response rate of treatment-resistant depressive patients. Depressive patients with high baseline hs-CRP levels and treatment resistance have better antidepressant efficacy when combined with anti-inflammatory therapy [226]. Not all inflammatory factors have a direct correlation with antidepressant treatment responses. Some researchers have undertaken a systematic review and identified that inflammatory markers such as IL-6, CRP, and hsCRP show promise as indicators for predicting the effectiveness of treatments for resistant depression. In contrast, markers like IL-1β, IL-10, INF-γ, and TNF-α seem to lack predictive capabilities [227]. Many researchers have delved into ketamine, an antidepressant known for its anti-inflammatory properties, as a potential gauge for treatment outcomes. Some investigations suggest that elevated levels of IL-1β, IL-6, and IL-8 post-ketamine infusion [228,229] correlate with improved treatment outcomes, though other studies present conflicting findings. Specific findings indicate that existing baseline measurements of IL-1β, IL-6, and IL-8 [230,231] don't necessarily predict a response to ketamine treatments. Moreover, patients with chronic inflammatory conditions like rheumatoid arthritis [232], cardiovascular ailments [233], chronic obstructive pulmonary disease (COPD) [234], inflammatory bowel disease [235], and liver cirrhosis [236] that are linked with depression may witness an improvement in depressive symptoms when treated with anti-inflammatory medications. Additionally, fluctuations in blood glucose and cholesterol could be intrinsically linked to responses to treatments like infliximab [237]. Presently, some study outcomes are inconclusive, possibly due to variances in sample sizes, methodologies, or the intricate nature of inflammatory responses in depression. Existing data is insufficient for establishing a consistent threshold for inflammation parameters that can steer these treatments. Yet, overall, inflammatory markers hold the potential not just to anticipate responses to antidepressant treatments, but also to forecast the success of supplementary anti-inflammatory therapies for depression. Future research endeavors should aim at elucidating the patient groups that stand to gain the most from specific anti-inflammatory interventions. The provided review paves the way for deeper inquiries into discerning subsets of elderly individuals with depression who might benefit from treatments targeting inflammation. Such insights could revolutionize precision treatments for late-life depression, bearing significant clinical value in enhancing treatment outcomes and minimizing associated risks.

5. Conclusions

LLD is a common mental illness with complex pathogenesis. Inflammatory responses are one of the potential mechanisms of LLD. Numerous studies have shown that inflammatory responses are significantly increased in patients with LLD, including Ca^{2+} homeostasis disturbances, cytokines, BDNF, NLR, PLR, MLR, and NLRP3 inflammasomes. These biomarkers are associated with late-life depressivesymptoms. Inflammatory responses affect brain function and emotions through various pathways, such as triggering neuroinflammation that influences neuronal plasticity, regulating neurotransmitter and hormone synthesis and release, ultimately impacting the onset and progression of LLD. Furthermore, oxidative stress and mitochondrial damage, dysbiosis of the gut microbiota, and aging-induced DNA damage-related changes can lead to increased inflammatory responses, further influencing the onset and progression of LLD.

This review delves into the intricate relationship between inflammation and late-life depression, with the goal of shedding light on potential applications in clinical practice:

(1) Identifying New Therapeutic Targets: By unraveling the mechanisms of inflammation in late-life depression, we can forge new therapeutic strategies that go beyond traditional antidepressants. This exploration opens avenues for the creation of more effective and personalized treatment plans. (2) Clinical Assessment of Inflammatory Markers: The detection of inflammatory markers may prove valuable in the clinical assessment and diagnosis of depression in later life. By analyzing these markers in the blood, healthcare providers can obtain objective indicators to gauge the level of inflammation, thereby aiding in informed treatment decisions. (3) Advancement of Personalized Medicine and Precision Psychiatry: The identification of patient subgroups that may benefit from anti-inflammatory treatment allows for more precise targeting of therapies to individual patient needs. This specificity enhances both the targeting and effectiveness of treatment, aligning with the principles of personalized medicine. (4) Holistic Health Management: The link between inflammation and late-life depression underscores the importance of a comprehensive approach to patient care. Beyond the focus on anti-inflammatory treatment, a holistic strategy should encompass maintaining a healthy lifestyle, providing psychological support, and implementing rehabilitation programs. These elements, when integrated, can enhance the overall treatment outcome and improve the quality of life for patients. In conclusion, the complex interplay between inflammation and late-life depression presents both challenges and opportunities. By embracing a multifaceted approach that includes novel therapeutic targets, precise diagnostics, personalized treatment, and holistic care, we can make strides in improving the management and outcomes of depression in the elderly. This review serves as a foun-

dation for future research and clinical innovation, aiming to transform our understanding and treatment of this prevalent and impactful condition.

6. Limitations and Prospects

Although numerous studies have confirmed that inflammation plays a crucial role in the pathogenesis of LLD, the causal relationship between inflammation and LLD remains unclear. Furthermore, existing research faces many challenges and limitations. Firstly, there are inconsistent results and contradictory research findings, possibly due to factors such as sample size, research design, and methodology. Most relevant studies have used small-scale samples and primarily focused on specific populations, such as the elderly and patients with inflammatory diseases. In these cases, both the population size and the generalizability of research results are limited. Moreover, many related studies use cross-sectional designs, which cannot determine the causal relationship between inflammation and LLD. Heterogeneity in research findings may also lead to a lack of universal conclusions. Secondly, although inflammation appears to be related to LLD, the exact biological mechanism remains unclear. Many biomarkers lack sufficient specificity, and there is a shortage of effective biomarkers to assess the extent of the inflammatory response and treatment outcomes, which may also contribute to biases in research results. Lastly, there is currently a lack of personalized treatment plans for patients with LLD. Although some anti-inflammatory drugs have been developed for treating depression, their efficacy is uncertain, and adverse reactions may occur. Most research on inflammation and late-life depression is observational, and more interventional studies are needed to demonstrate the effectiveness and safety of inflammation-modulating treatments for LLD.

Therefore, future research areas need to include larger sample clinical trials, long-term follow-up studies, molecular biology, genomics, proteomics, and Mendelian randomization studies using interdisciplinary research methods. Further exploration of the relationship between inflammation and LLD and the establishment of more accurate prediction models and biomarkers are necessary to better understand the pathophysiological mechanisms of LLD. Various approaches and perspectives should be used to identify patient subgroups that may benefit from anti-inflammatory treatments, as well as to explore more effective treatment strategies and intervention measures.

Abbreviations

LLD, Late-life depression; NE, norepinephrine; 5-HT, 5-hydroxytryptamine; DA, dopamine; TNF-α, tumor necrosis factor; BBB, blood-brain barrier; MDD, major depressive disorder; APPs, Acute phase proteins; CRP, C-reactive protein; JAK, Janus kinase; STAT, Signal transducer and activator of transcription; GWAS, genome-wide association study; Alb, albumin; PA, pre-albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; HSCs, hematopoietic stem cells; NLRP3, NOD-, LRR-, and Pyrin domain-containing protein 3; ASC, apoptosis-associated speck-like protein containing; GSDMD, gasdermin D; BDNF, Brain-derived neurotrophic factor; Trk, kinase family; CNS, central nervous system; ER, endoplasmic reticulum; SERCA, sarco/endoplasmic reticulum ATPase; CaM, calmodulin; CASR, calcium-sensing receptor; PLC, phospholipase C; NGAL, neutrophil gelatinase associated lipocalin; TLRs, Toll-like receptors; AGEs, advanced glycation end products; PAI-1, plasminogen activator inhibitor-1; ATP, Adenosine triphosphate; BH4, tetrahydrobiopterin; mGluR2, metabotropic glutamate receptor 2; NMDA, N-methyl-d-aspartate; GABA, gamma-aminobutyric acid; DDR, DNA damage response; DAMPs, damage-associated molecular patterns; ROS, reactive oxygen species; HPA, Hypothalamic-Pituitary-Adrenal; GR, glucocorticoid receptors; IDO, indoleamine 2,3-dioxygenase; SCFAs, short-chain fatty acids; TR-LLD, Treatment-resistant LLD; NSAIDs, nonsteroidal anti-inflammatory drugs; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; sEH, soluble epoxide hydrolase; NF-κB, Nuclear Factor-kappa B; IRF3, Interferon regulatory factor 3; COPD, chronic obstructive pulmonary disease.

Author Contributions

JX, MC, HS, and SW were instrumental in the conceptualization, drafting of the manuscript, supervision, and validation. JX, JY, MZ, WL, SZ, and HC were responsible for literature management and review. SW and HS undertook the tasks of reviewing, editing, and proofreading the manuscript. All authors contributed to editorial changes in the manuscript. All authors have reviewed and approved the final manuscript, ensuring significant participation and agreeing to be accountable for all facets of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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