REVIEW

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Understanding the neurobiological mechanisms of LPS-induced memory impairment

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In recent years, growing evidence suggests that lipopolysaccharide (LPS), a bacterial endotoxin found in the outer membrane of gram-negative bacteria, can influence cognitive functions, particularly memory formation and retrieval. However, the underlying mechanisms through which LPS exerts its effects on memory remain incompletely understood. This review used various electronic databases, including PubMed, Scopus, and Web of Science, to identify relevant studies published between 2000 and 2024. Articles were selected based on their focus on LPS-induced memory impairments, including experimental models, molecular pathways, and neurochemical alterations. LPS administration has been consistently shown to disrupt memory processes in both animals and humans, although the magnitude and duration of memory impairments might vary depending on factors such as dose, timing, and context of LPS exposure. Several potential mechanisms have been proposed to explain LPS-induced memory deficits, including neuroinflammation, alterations in synaptic plasticity, disruption of neurotransmitter systems, and dysfunction of the blood-brain barrier. Moreover, LPS has been found to activate immune signaling pathways, such as toll-like receptors, interleukins, and microglia, which can further contribute to cognitive impairments. Such insights may pave the way for the development of targeted therapeutic interventions aimed at ameliorating memory deficits associated with conditions involving LPS exposure, including bacterial infections, sepsis, and neuroinflammatory disorders.

Key words: lipopolysaccharide, memory impairment, neuroinflammation

INTRODUCTION

Memory impairment refers to a significant decline or loss in the ability to acquire, encode, store, or retrieve information in the brain (Da Ré et al., 2020). This can affect various types of memory, including short-term (working) memory, long-term memory, spatial memory, and episodic memory (Belarbi et al., 2012). Memory impairment can stem from various causes including aging (Jiménez-Balado & Eich, 2021), neurodegenerative diseases (Wang et al., 2021), brain injuries (Calvillo & Irimia, 2020), mental health disorders (Aprilia & Aminatun, 2022), medications, substance abuse (Polles et al., 2020), and inflammation (Melo et al., 2020). Lipopolysaccharide (LPS) is a component found on the surface of certain bacteria, such as gram-negative bacteria (Jerala, 2007). LPS-induced inflammation is known as a common model to induce general inflammation in animal models to investigate the harmful effects of LPS-induced inflammation (Hedayati-Moghadam et al., 2024; Jalilvand et al., 2024).

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Furthermore, according to the results of previous studies LPS-induced inflammation can result in various memory and cognitive dysfunction (Lykhmus et al., 2016; Zakaria et al., 2017; Beheshti et al., 2023). Previous studies have also revealed that LPS-induced inflammation can compromise the integrity of the blood-brain barrier, which normally regulates the passage of substances between the bloodstream and the brain (Asahina et al., 2024). Moreover, inflammatory molecules or immune cells can finally cross the disrupted blood-brain barrier more easily and enter the central nervous system (CNS). As LPS crosses the blood-brain barrier it can trigger an immune response in the brain, which causes the release of pro-inflammatory cytokines and activation of immune cells such as microglial cells (Seoane et al., 2024). This neuroinflammation can disrupt normal neuronal function, and impair memory formation and retrieval processes (Zhang et al., 2024). Moreover, in this regard, many studies have demonstrated that LPS-induced neuroinflammation leads to enhancing oxidative stress in brain tissues such as the hippocampus (Liang et al., 2024). Excessive reactive oxygen species (ROS) can damage neurons and impair synaptic function, leading to memory deficits (Patki et al., 2013). LPS has been found to interfere with synaptic plasticity, which is the ability of synapses to strengthen or weaken in response to activity (Liu et al., 2018). Synaptic plasticity is essential for learning and memory, and disruption of this process by LPS can lead to memory deficits (Basir et al., 2024). LPS-induced inflammation can also lead to an increase in the release of excitatory neurotransmitters, such as glutamate (Wu et al., 2016). Excessive glutamate release can trigger excitotoxicity, which refers to the overactivation of excitatory receptors and subsequent neuronal damage (Vaglio-Garro et al., 2024). It is well known that that overactivation of glutamate receptors can result in neuronal damage which finally induces memory impairments (Meng et al., 2024). Previous studies have also reported that chronic administration of LPS resulted in a decrease in neurogenesis or the process of generating new neurons in the brain (Wu et al., 2007; Domínguez-Rivas et al., 2021). Reduced neurogenesis by LPS-induced inflammation particularly in the hippocampus, can cause impaired memory formation and cognitive function (Winocur et al., 2012). The hippocampus, a brain region crucial for memory formation, is particularly vulnerable to LPS-induced inflammation. Inflammation can lead to structural and functional changes in the hippocampus, including neuronal loss, synaptic disruption, and impairments in neurogenesis, which these events finally lead to memory impairment (Keymoradzadeh et al., 2020). Experimental studies have also demonstrated that LPS administration can impair spatial and contextual memory tasks. Animal models, particularly rodents, have been extensively used to study the effects of LPS on memory. For instance, a study by Cui et al. (2008) found that LPS administration in rats impaired spatial memory performance in a maze task. Another study conducted on Wistar rats showed that LPS-induced inflammation disrupted episodic-like memory (Wang et al., 2010). Experimental studies have also investigated the inflammatory markers associated with LPS-induced memory impairment. For example, Cazareth et al. (2014) found that LPS administration increased levels of pro-inflammatory cytokines in the brain, such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). These elevated cytokine levels were associated with memory deficits. Other studies have also examined the role of specific inflammatory pathways, such as the nuclear factor kappa B (NF-κB) pathway, in mediating LPS-induced memory impairment (Mahmoud et al., 2024). Moreover, chronic exposure to LPS has been associated with cognitive decline in various neurodegenerative diseases, including Alzheimer's disease (Abareshi et al., 2016). It's worth noting that LPS-induced memory impairment is a complex process, and researchers are still unraveling its underlying mechanisms. Understanding the impact of LPS on memory can aid in the development of therapeutic approaches for neuroinflammatory conditions and associated cognitive deficits. It has been well documented that LPS-induced inflammation leads to disruptions in brain-derived neurotrophic factor (BDNF) signaling, and increased apoptosis, which all together is an important cause cognitive deficit. Reduced BDNF levels or signaling have been associated with memory impairment, as it affects the growth and survival of neurons. Excessive apoptosis, particularly in brain regions critical for memory processing, can lead to the loss of neurons and further impair cognitive function. Understanding the relationships among BDNF, long-term potentiation (LTP), apoptosis, and memory impairment is complex and the subject of ongoing research. However, disruptions in these processes can contribute to memory deficits and related cognitive impairments.

LPS-induced memory impairment in animal models

LPS has been widely used as a model of inflammation in preclinical studies. A growing body of evidence suggests that LPS exposure can induce memory

impairment in animal models, providing valuable insights into the mechanisms underlying LPS-induced cognitive decline. Acute administration of LPS has been shown to induce memory impairment in various animal models, including mice and rats. A study has demonstrated that LPS administration can impair spatial memory, as measured by the Morris water maze task, and working memory, as measured by the Y-maze task (Keymoradzadeh et al., 2020). Furthermore, LPS administration has been shown to disrupt LTP, a form of synaptic plasticity thought to be involved in learning and memory (Murtishaw et al., 2016). Chronic administration of LPS has also been shown to induce memory impairment in animal models. Studies have demonstrated that chronic LPS administration can lead to cognitive decline, as measured by the radial arm maze task, and impair spatial memory, as measured by the Morris water maze task (Hosseini et al., 2021; 2024). Furthermore, chronic LPS administration has been shown to induce neuroinflammation, oxidative stress, and neuronal death, which may contribute to memory impairment (Na et al., 2021). The mechanisms underlying LPS-induced memory impairment in animal models are thought to involve the activation of inflammatory pathways, including the production of pro-inflammatory cytokines and the activation of microglia (Xin et al., 2019). Additionally, LPS has been shown to disrupt the gut-brain axis, leading to changes in the gut microbiome and the production of neurotoxins that can contribute to cognitive decline and memory impairment (Cowan et al., 2020). LPS has also been shown to induce oxidative stress, which can lead to neuronal damage and death, and disrupt synaptic plasticity, which is critical for learning and memory (Nowory-ta-Sokołowska et al., 2013). Overall, preclinical evidence suggests that LPS exposure can induce memory impairment in animal models, providing valuable insights into the mechanisms underlying LPS-induced cognitive decline. Further research is needed to fully elucidate the mechanisms underlying LPS-induced memory impairment and to develop effective therapeutic strategies for the prevention and treatment of LPS-induced cognitive decline.

LPS and memory impairment in human studies

LPS has been implicated in the pathogenesis of various neurological disorders, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis (Taylor et al., 2013). While animal studies have consistently demonstrated the ability of LPS to induce memory impairment, the clinical correlates of LPS-induced memory impairment in humans are less well understood. However, a growing body of evidence suggests that LPS exposure is associated with cognitive decline and memory impairment in humans. Studies have shown that individuals with sepsis, a condition characterized by a systemic inflammatory response to infection, often experience cognitive impairment and memory dysfunction (Barichello et al., 2019). Furthermore, LPS has been detected in the cerebrospinal fluid of individuals with sepsis, suggesting that LPS may play a role in the development of cognitive impairment in these individuals (Nakajima et al., 2015). In addition to sepsis, LPS has also been implicated in the pathogenesis of Alzheimer's disease. Studies have shown that LPS levels are elevated in the brains of individuals with Alzheimer's disease, and that LPS exposure can induce the production of amyloid-β, a hallmark of Alzheimer's disease (Lee et al., 2008). Furthermore, LPS has been shown to disrupt the blood-brain barrier, allowing for the passage of toxins and inflammatory mediators into the brain, which can contribute to cognitive decline and memory impairment (Huang et al., 2021). The mechanisms underlying LPS-induced memory impairment in humans are not fully understood, but are thought to involve the activation of inflammatory pathways, including the production of pro-inflammatory cytokines and the activation of microglia (Heneka, 2017). In conclusion, while the clinical correlates of LPS-induced memory impairment in humans are not yet fully understood, a growing body of evidence suggests that LPS exposure is associated with cognitive decline and memory impairment in humans.

Underlying mechanisms of LPS-induced memory impairment

This review aims to comprehensively examine the current state of researches on LPS and memory impairment. A summary of the results of the studies is included in Tables 1-4.

LPS-activated neuroinflammatory response

Inflammation is a natural process that occurs in the body as a response to harmful stimuli, such as infection, injury, or irritation. It is a vital part of the immune system's defense mechanism, aiming to protect the body from further damage and promote healing. When the body detects tissue damage or the presence of pathogens, immune cells release signaling molecules called cytokines. These cytokines trigger a se-

ries of biochemical reactions that lead to the expansion and activation of immune cells in the affected area (Ahmed, 2011). LPS and inflammation have an interconnected relationship in the immune response. LPS is classified that can trigger the release of pro-inflammatory compounds such as cytokines (Jerala, 2007; Diz-Chaves et al., 2013). Moreover, it has been reported that memory impairment can occur due to general inflammation in the body. Inflammatory processes can affect the brain's functioning and lead to various cognitive impairments, including memory disorders (Chen et al., 2018). There are several possible mechanisms through which inflammation can affect memory. One of these involves disruption of normal communication between brain cells, affecting the formation and retrieval of memories (Gyoneva & Ransohoff, 2015). Inflammatory molecules can interfere with the proper functioning of neurotransmitters and impair synaptic plasticity, which is important for forming and maintaining memories (Hosseini et al., 2024). Inflammation can also cause damage to brain cells directly, leading to neurodegeneration and cognitive decline, which has been associated with conditions such as Alzheimer's disease and other neurodegenerative disorders, which eventually can cause memory impairments (Chitnis & Weiner, 2017). Macrophages, a type of immune cell, play a key role in this process. When LPS binds to macrophages, it activates a signaling pathway called the toll-like receptor 4 (TLR4) pathway. This activation leads to the production and release of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8 (Ciesielska et al., 2021). Moreover, cyclooxygenase-2 (COX-2) is an enzyme involved in the synthesis of prostaglandins, which are lipid compounds that play a role in inflammation. COX-2 is induced in response to pro-inflammatory signals, such as cytokines and growth factors, and it catalyzes the conversion of arachidonic acid into prostaglandins, this increase in COX-2 gene expression will ultimately intensify the inflammatory response of the target tissue (Murakami & Ohigashi, 2007). The other important pathway which is activated by LPS is Ras/mitogen activated protein kinase (MAPK) that initiates a signaling cascade leading to activation of inflammatory responses. Activation of extracellular signal-regulated kinase (ERK), a very important MAPK, has various advantages for the host such as activating genes in order to produce TNF-α, IL-1β and contributes to synthesis of nitric oxide (NO) and prostaglandins (Zhang et al., 2024). The other two important MAPK are Jun N-terminal kinase (JNK) and P38, which modulate apoptosis and regulate immune cells function. Any excess in activation of these MAPK could cause various inflammatory disorders and conditions. Understanding the interplay between LPS and the MAPK pathway provides insight into molecular mechanism of immune responses, which could be the goal of developing therapeutic strategies to modulate inflammatory responses due to LPS (Rai et al., 2023). Moreover, the administration of LPS has been shown to induce memory impairment (Xin et al., 2019), which is often studied in the context of neuroinflammation. When LPS enters the system, it activates the immune response, leading to the production of pro-inflammatory cytokines such as IL-1β and TNF-α (Ciesielska et al., 2021). These cytokines can profoundly impact neuronal function and cognitive processes, particularly memory (Stenfors et al., 2017). One of the critical pathways involved in memory impairment following LPS administration is the MAPK pathway (Chen et al., 2014; Hashimoto et al., 2017). The activation of this pathway, particularly the ERK, is crucial for the regulation of various cellular processes, including neuronal survival, plasticity, and synaptic function (Iroegbu et al., 2021). However, LPS-induced inflammation alters the normal signaling cascade by promoting an overactive inflammatory response. This can lead to dysregulation of the MAPK pathway, affecting neuronal health and impairing synaptic plasticity, which is essential for learning and memory. As synaptic connections weaken and neuronal communication is disrupted, cognitive abilities, including memory, are adversely impacted (Singh et al., 2022). Additionally, the involvement of cholecystokinin (CCK) in this context further complicates the relationship between neuroinflammation and memory impairment. CCK is a neuropeptide that plays various roles in the brain, including the modulation of anxiety, satiety, and cognitive processes. Under normal physiological conditions, CCK can facilitate learning and memory through its action on the CCK1 receptor, which can influence synaptic plasticity and neurotransmitter release (Asim et al., 2024). However, following LPS administration and the subsequent inflammatory response, CCK levels may become dysregulated (Rezaei et al., 2024). Moreover, the interplay between the MAPK pathway and CCK signaling suggests a complex network where inflammation not only impacts individual pathways but can also create a cascade of impairments by altering neuropeptide functions (Juanola et al., 1998; Ramalingam et al., 2020; Behl et al., 2022). As LPS continues to exert its effects, the neuroinflammation can culminate in chronic cognitive deficits, highlighting the importance of understanding these mechanisms in the broader context of neurodegenerative diseases and cognitive decline (Lee et al., 2008; Zhao et al., 2019). This multifaceted interaction implies that interven-

Table 1. Effects of LPS on the some inflammatory factors in different parts of the brain.

Tissue	Doses and administration LPS	TNF-α	NF-kB	COX2	IL-6	IL-1	iNOS	TLR4	Species	References
Brain	0.25 mg/kg, i.p.	↑	–	–	↑	–	–	–	Swiss albino mice	(Thingore et al., 2021)
	1 mg/kg/day, i.p.	↑	↑	–	↑	↑	–	–	Adult Wistar rats	(Alshehri & Imam, 2021)
	5 mg/kg/day, i.p.	↑	–	↑	↑	↑	–	–	male C57BL/6 mice	(Sorrenti et al., 2018)
	1 mg/kg, i.p.	↑	–	–	↑	–	–	–	Wistar rats	(Marefati et al., 2021)
	10 mg/kg, i.p.	↑	–	–	↑	↑	–	–	Male and female Kunming mice	(Xin et al., 2019)
Cortex	250 μg/kg	↑	↑	–	↑	↑	–	–	Male imprinting control region (ICR) mice	(Wang et al., 2020)
	25 μg ICV	↑	↑	↑	–	–	–	↑	Wistar rats	(Goel et al., 2018)
	0.25 mg/kg, i.p.	–	↑	↑	–	–	↑	–	Male ICR mice	(Choi et al., 2012)
	0.5 mg/kg i.p. twice a week	–	↑	–	↑	↑	–	↑	Sprague-Dawley rats	(Hu et al., 2020)
	50 μg into the right lateral ventricle	↑	↑	–	↑	↑	–	–	Male Sprague-Dawley rats	(Li et al., 2011)
	250 μg/kg/day	↑	↑	–	–	↑	–	↑	C57BL/6 N mice	(Muhammad et al., 2019)
Peripheral blood	1 mg/kg/day	↑	–	–	↑	↑	–	–	Male Wistar rats	(Vasconcelos et al., 2014)
	0.5 mg/kg, i.p. twice a week	–	↑	–	↑	↑	–	↑	Sprague-Dawley rats	(Hu et al., 2020)
Hippo-campus	830 μg/kg, i.p.	↑	–	–	↑	↑	–	–	C57BL/6J male mice	(Alboni et al., 2021)
	250 μg/kg/day for 1 week	↑	–	↑	–	↑	–	↑	C57BL/6N mice	(Ahmad et al., 2019)
	1 mg/kg, i.p	↑	–	–	–	↑	–	–	Wistar rats	(Keymoradzadeh et al., 2020)
	250 mg/kg daily 7 times	↑	↑	↑	–	↑	↑	–	Male ICR mice	(Kim et al., 2017)
	50 μg into the right lateral ventricle	↑	↑	–	↑	↑	–	–	Male Sprague-Dawley rats	(Li et al., 2011)
	1 mg/kg; i.p.	↑	–	–	↑	–	–	–	Male Wistar rats	(Norouzi et al., 2019)
	250 μg/kg/day	↑	↑	–	–	↑	–	↑	C57BL/6 N mice	(Muhammad et al., 2019)
	50 μg into the lateral ventricle	↑	–	↑	–	↑	–	–	Male Sprague-Dawley rats	(Lee et al., 2013)
	2 μg ICV	↑	–	–	–	↑	–	–	Adult C57BL/6 mice	(Zhang et al., 2015)
	0.5 mg/kg, i.p.	↑	–	–	↑	–	–	–	Male C57BL/6J mice	(Zhao et al., 2019)
	50 μg into the lateral ventricle	↑	↑	–	–	↑	–	–	Sprague–Dawley rats	(Song et al., 2016)
	1 μg/ml	↑	↑	↑	–	↑	↑	↑	microglial cells	(Badshah et al., 2016)
	0.25 mg/kg; i.p.	↑	–	–	↑	–	–	–	mice	(Daroi et al., 2022)
	1 mg/kg; i.p.	↑	–	–	↑	–	–	–	Male Wistar rats	(Abareshi et al., 2016)
	30 mg/kg; i.p.	↑	–	–	↑	↑	–	–	Male Wistar rats	(Anaeigoudari et al., 2015)
	0.25 mg/kg, i.p.	–	↑	↑	–	–	↑	–	Male ICR mice	(Choi et al., 2012)
	25 μg ICV	↑	↑	↑	–	–	–	↑	Wistar rats	(Goel et al., 2018)
	250 μg/kg	↑	↑	–	↑	↑	–	–	male ICR mice	(Wang et al., 2020)
	1 mg/kg/day	↑	–	–	–	↑	↑	↑	Male Wistar rats	(Vasconcelos et al., 2014)
	10 μL ICV	–	↑	–	↑	↑	↑	↑	Sprague–Dawley rats	(Lee et al., 2018)

TNF-α: Tumor necrosis factor-alpha, NF-kB: Nuclear factor k B, COX2: Cyclooxygenase 2, IL-6: Interleukin-6, IL-1: Interleukin-1, iNOS: Inducible nitric oxide synthase, TLR4: Toll-like receptor 4, ↓: Decrease; ↑: Increase.

tions targeting either the inflammatory response or the restoration of normal CCK function may serve as therapeutic strategies to mitigate memory impairment, ultimately pointing toward a potential to preserve cognitive health in inflammatory conditions (Zhang et al., 2024).

On the other hand, NF-κB is a transcription factor that plays a crucial role in regulating genes involved in immune responses (Hayden & Ghosh, 2011). In the context of LPS stimulation, the binding of LPS to TLR4 initiates a signaling pathway that activates NF-κB. Then, the activated NF-κB translocates to the nucleus and promotes the expression of pro-inflammatory genes, leading to the production of various cytokines, chemokines, and other mediators of inflammation (Afroz et al., 2022). Another inflammatory compound that plays a key role in inflammatory responses is induced-nitric oxide synthase (iNOS) (inducible nitric oxide synthase). It is an enzyme that catalyzes the production of NO from the amino acid L-arginine. Unlike the constitutive forms of nitric oxide synthase (NOS), iNOS is not expressed under normal physiological conditions, but it can be induced in response to inflammatory situations, such as cytokines, pathogens, and other immune signals. iNOS is primarily expressed in immune cells, such as macrophages and

Table 2. Effects of LPS on the antioxidant enzymes and the oxidative status in different parts of the brain.

Tissue	Doses and administration LPS	Thiol	SOD	GPx	CAT	GSH	Lpx	Species	References
Cortex	1 mg/kg; i.p.	↓	↓	–	↓	–	↑	Male Wistar rats	(Norouzi et al., 2019)
	250 µg/kg; i.p.	↓	–	–	–	–	↑	Female Wistar rats	(Pourganji et al., 2014)
	1 mg/kg; i.p.	↓	↓	–	↓	–	↑	Male Wistar rats	(Bargi et al., 2017)
Hippocampus	167 µg/kg for 7 days	–	↓	–	↓	↓	↑	Male albino Wistar rats	(Khajevand-Khazaei et al., 2018)
	250 µg/kg/day for 1 week	–	–	–	–	↓	↑	C57BL/6N mice	(Ahmad et al., 2019)
	1 mg/kg; i.p.	↓	↓	–	↓	–	↑	Wistar rats	(Marefati et al., 2021)
	1 mg/kg; i.p.	↓	↓	–	↓	–	↑	Male Wistar rats	(Norouzi et al., 2019)
	0.5 mg/kg; i.p.	–	↓	–	–	–	↑	Male C57BL/6J mice	(Zhao et al., 2019)
	1 mg/kg; i.p.	↓	↓	–	↓	–	↑	Male Wistar rats	(Bargi et al., 2017)
	250 µg/kg; i.p.	↓	–	–	–	–	↑	Female Wistar rats	(Pourganji et al., 2014)
	1 mg/kg; i.p.	↓	↓	–	↓	–	↑	Male Wistar rats	(Hosseini et al., 2018)
	1.14 g/kg; i.p.	–	↓	–	–	↓	↑	Male Wistar albino rats	(Kheir-Eldin et al., 2001)
Brain	0.25 mg/kg; i.p.	–	↓	–	–	↓	↑	Mice	(Daroi et al., 2022)
	8 mg/kg; b.w.	–	↓	–	↓	–	↑	Male Wistar rats	(Sebai et al., 2009)
	200 µg/kg	–	↑	–	↓	–	–	pregnant Wistar rats	(Stigger et al., 2013)
	250 mg/kg daily 7 times	–	–	–	–	↓	↑	Male ICR mice	(Kim et al., 2017)
	0.25 mg/kg	–	↓	↓	↓	↓	↑	Male ICR mice	(Musa et al., 2017)
	50 µg into the lateral ventricle	–	–	↓	–	–	–	Sprague-Dawley rats	(Song et al., 2016)
	200 µg/kg	–	–	↓	–	↓	↑	Swiss male albino mice	(Abdel-Salam et al., 2014)
	2 µg ICV	–	↓	–	–	–	↑	Adult C57BL/6 mice	(Zhang et al., 2015)
	200 µg/kg	–	–	–	–	↓	↑	Swiss male albino mice	(Abdel-Salam et al., 2011)

SOD: Superoxide dismutase, GPx: Glutathione peroxidase. Lpx: Lipid peroxidation. CAT: Catalase, GSH: Reduced glutathione, ↓: Decrease; ↑: Increase.

neutrophils, as well as in other cell types including endothelial cells and certain neurons (Ghasemi-Dehnoo et al., 2023). In the LPS challenge stimulation, LPS can induce the expression and activity of iNOS in immune cells. The produced NO can act as a signaling molecule and mediate various effects. NO synthesized by iNOS can have both beneficial and harmful effects depending on the context and the balance of its production (Wu et al., 2022). It is well-documented that LPS injection led to increased levels of NF-κB, TNF-α, COX2, and glial fibrillary acidic protein (GFAP) in the hippocampus and cerebral cortex. Furthermore, chronic injection of LPS significantly upregulates TLR4 expression (Zanikov et al., 2023). Recent studies have shown that chronic and acute administration of LPS, in addition to increasing the level of NF-κB, leads to the overproduction of COX2, iNOS, and TNF-α in the hippocampal tissue (Miwa et al., 2011). Based on the results of the previous study, LPS injection increased the mRNA of LPS receptor, TLR4, and iNOS. In addition, the level of IL-1β, and TNF-α in the hippocampus increased. LPS challenge increased serum levels of TNF-α, IL-1β, and IL-6 (Wang et al., 2022). A growing body of evidence shows that the administration of LPS in animal models results in an intense inflammatory response in the hippocampus and cortex. Moreover, it has been reported that the administration of LPS leads to remarkable enhancement in the expression of iNOS, COX2, GFAP, and NF-κB DNA binding (Patel & Singh, 2022). It is important to pay attention that the hippocampus is very vulnerable to inflammation due to the presence of many receptors of cytokines in the hippocampus (Anaeigoudari et al., 2015). The results of a study conducted by Yanfei Li et al. (2011) stated that LPS-induced overproduction of pro-inflammatory cytokines, which this overrate of cytokines can cause nerve dysfunction and inflammation and induce signaling in neurons.

LPS increased oxidative stress

LPS causes cell damage in different organs through the induction of inflammation and various mecha-

Table 3. Effects of LPS on apoptosis and BDNF in different parts of the brain.

Tissue	Doses and administration LPS	Bcl-2	Bax	Caspase 3	TrkB	BDNF	Species	References
Hypothalamus	1 mg/kg	–	–	–	–	↓	Sprague- Dawley	(Nowacka et al., 2015)
Pituitary	1 mg/kg	–	–	–	–	↓	Sprague- Dawley	(Nowacka et al., 2015)
Hippocampus	1 mg/kg	–	–	–	–	↓	Wistar rats	(Vasconcelos et al., 2014)
	250 µg/kg	–	–	–	↓	↓	Swiss albino	(Frühauf-Perez et al., 2018)
	0.5 mg/kg, i.p.	–	–	–	–	↓	C57BL/6	(Zhao et al., 2019)
	1 mg/kg	–	–	–	–	↓	Wistar rats	(Vasconcelos et al., 2014)
Cortex and Hippocampus	25 µg	↓	↑	↑	–	↓	SHR s	(Goel et al., 2018)
Cerebral Cortex	250 µg/kg	–	–	–	↓	↓	Swiss albino	(Frühauf-Perez et al., 2018)
PC12	200 µg/kg	–	↑	↑	–	–	Rat	(Sharifi et al., 2010)
Brain	1 µg/µl	↓	↑	↑	–	–	Wistar rats	(Burguillos et al., 2011)
		–	↑	↑	–	–	EOC-20 mouse	(Guadagno et al., 2013)
	200 mg/kg	–	–	↑	–	–	Male Sprague-Dawley	(Wang et al., 2017)
	for 7 days (0.250 mg/kg; i.p.)	–	–	↑	–	–	Swiss albino	(Thingore et al., 2021)
	2 µl / 1 min (total 5 min)	–	–	–	–	↓	Sprague-Dawley	(Lee et al., 2018)

Bcl-2: B-cell lymphoma-2, Bax: bcl-2-like protein 4, Trk: Tropomyosin receptor kinase B, BDNF: brain-derived neurotrophic factor. ↓: Decrease; ↑: Increase.

nisms, such as oxidative stress (Skibska et al., 2022). Oxidative stress refers to an imbalance between the production of ROS and antioxidants that neutralize them (Storz & Imlayt, 1999). According to the previous statements, human cells need to maintain ROS at a non-toxic level based on a protective system of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), paraoxonase-1 enzyme (PON-1) (which is one of the important antioxidant enzymes), total thiol content, and peroxidase (G-POX), so that they can prevent ROS damage despite using its signaling reactions (Krishnamurthy & Wadhwani, 2012). Glutathione (GSH) contains a thiol group that is easily oxidized and is also known as a main endogenous non-protein antioxidant. GSH reduces oxidative damage by performing two activities. First, it quenches ROS with the cooperation of G-POX. Second, it makes proteins resistant to oxidation. SOD perform their antioxidant activity by catalyzing the conversion of superoxide to molecular oxygen. In addition, SOD, like catalase enzyme, provide cell defense conditions against oxidative damage by converting H_2O_2 into water and non-toxic oxygen (Liu et al., 2022). By attacking lipids and taking their electrons, oxidants cause lipid peroxidation and increase the possibility of cell membrane rupture and ultimately cell death. Nowadays, malondialdehyde (MDA), main marker for evaluating oxidative stress in tissues, or TBARS are measured to reveal the level of lipid peroxidation (Moore & Roberts, 1998). Also, based on the results of studies, oxidative stress acts as a major character in causing various diseases neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, rheumatoid arthritis, diabetes, cancer, cardiovascular diseases, and aging (Phaniendra et al., 2015). The brain is more vulnerable to oxidative stress due to its high demand for oxygen (approximately 2% of body weight and 20% of oxygen consumption) and the abundance of substrates capable of peroxidation among all body tissues (Gandhi & Abramov, 2012). Many shreds of evidence have been presented that the administration of LPS results in an enhancement of oxidative damage in brain tissues, which was reflected in increase in the level of MDA or lipid peroxidation (Musa et al., 2017). Today, the term ROS is used for various types of reactive species, which include superoxide (O2•–), hydroxyl radical (OH•), and non-radicals. In the circumstances of overproduction of these radicals or weakness of the body's antioxidant system, these ROS can easily cause damage to cellular elements such as proteins, DNA, or nerve cell death (Gandhi & Abramov, 2012). Furthermore, evidence have confirmed that free radicals in the body act as a double-edged sword, in fact, in normal condi-

Table 4. Effects of LPS on some neurotransmitters in different parts of the brain.

Tissue	Dose and administration LPS	5-HT	Glutamate	Dopamine	Tryptophan	Species	References
Hippocampus	3 mg/kg, i.p	↑	↑	↑	–	Sprague-Dawley	(Guo et al., 2016)
	2-week (500 µg/kg every day) i.p	↓	↑	↓	–	Sprague-Dawley	(Guo et al., 2016)
	(0.5 mg/kg, i.p.)	↓	–	–	–	C57BL/6	(Zhao et al., 2019)
Substantia nigra	(5 µg LPS/5 µl PBS) i.p	–	–	↓	–	Sprague Dawley	(Sharma & Nehru, 2015)
	2.0 µl was injected into the left SN	↓	–	↓	–	Wistar	(Castano et al., 1998)
	10,000 endotoxin units (EU)/kg	–	–	↓	–	timed-gravid, Sprague-Dawley	(Ling et al., 2006)
	10–80 µg/ml	–	–	↓	–	Sprague-Dawley rats	(Gayle et al., 2002)
Brain	100 µg/kg; s.c	↓	–	–	–	C57BL/6	(Hsueh et al., 2017)
	0.83 mg/kg	–	↓	–	–	CD-1 mice	(Chan et al., 2020)
	1µg; i.p.	↑	–	↑	↑	Rats	(Dunn et al., 1999)
	10 mg/kg	–	↑	–	–	C57BL/6	(Müller et al., 2019)
Striatum	2.0 was µl injected into the left SN	↓		↓	–	Wistar	(Castano et al., 1998)

5-HT: 5-hydroxy tryptamine. ↓: Decrease; ↑: Increase.

tions when the concentration of free radicals is within the normal range, the ROS can act as specific second messengers in the signaling cascades. But in the conditions of overgeneration of ROS, these radicals *via* damage to cell membranes, proteins, and DNA can cause cell death or tissue dysfunction (Juan et al., 2021; Mittler, 2017). Moreover, it has been suggested that enhanced ROS results in the activation of the JNK pathway through phosphorylation JNK, which finally the activated this pathway can cause an elevation in apoptosis *via* upregulation of pro-apoptotic genes (Chen et al., 2012). The results of previous studies have shown that mitochondrial dysfunction can be one of the possible mechanisms in which neuroinflammation through it causes overaccumulation of ROS in the brain. Then, this over-accumulated ROS can cause nerve cell damage and develop a progressive cycle of neurodegeneration. In fact, growing evidence has shown that TNF-α through activation of TNF alpha receptor 1 (TNFR1) leads to increased gene expression of enzymes and molecules iNOS, NOX2, COX2, ICAM, VCAM that play an important role in increasing ROS production. Furthermore, according to previous studies, the oxidative stress induced through inflammation results in induced apoptosis or neurodegeneration in brain tissue especially the hippocampus which finally can cause various neurological disorders such as memory impairment (Fischer & Maier, 2015). In a recent study, chronic administration of LPS led to increased generation and buildup of ROS, resulting in oxidative stress. Analysis of LPO and GSH levels in the hippocampus indicated a notable rise in LPO levels compared to the control group. Additionally, the LPS-injected rats exhibited lower GSH levels in the brain when compared to the saline-injected group. In addition, immunofluorescence reactivity of 8-OxOG, which is one of the dominant parameters of oxidative stress, increased strongly in parts of the hippocampus such as CA1, CA3, DG under the influence of LPS (Ahmad et al., 2019). In another study conducted by Khajevand-Khazaei et al. (2018), a significant increase in MDA activity and a decrease in SOD and CAT enzymes were observed in the LPS group, whereas GSH levels in the hippocampus showed lower values compared to the control group. To brighten up the induction of oxidative damage caused by repeated injection of different doses of LPS in the brain of animal models, here, we review some of the studies conducted in this field. In research conducted by Kim et al. (2017) various factors of oxidative damage were evaluated. They demonstrated that the levels of MDA and ROS in the brain of rats receiving LPS were significantly increased compared to the control group that was only subjected to the stress of saline injection. On the contrary, their result also showed that GSH/GSSG ratio was decreased (Kim et al., 2017). The comparison between the brain tissue of the LPS-injected group and the control group, concluded that repeated injection of LPS reduces the levels of CAT (44%), SOD (25%), GSH (58%), Gpx (61%) but the levels of MDA increased significantly compared to the control group (Musa et al., 2017). Additionally, the results of some previous studies have revealed that in LPS-treated rats the level of MDA in brain tissue was significantly enhanced, while the activity of SOD enzyme was significantly decreased in comparison to none-LPS-treated rats (Zhang et al., 2015). In another study, after separating and preparing the brain in LPS-treated mice, the levels of MDA, GSH, and Gpx were evaluated in the LPS-treated and non-LPS-treated rats. Analysis of the results indicated that the level of MDA was significantly increased in the LPS-treated group, while the levels of glutathione and Gpx were significantly decreased. Furthermore, it should be noted that the administration of LPS in mice results in decreased activity of the PON-1 enzyme in the brain in the LPS-treated rats (Abdel-Salam et al., 2014). Moreover, according to previous studies analysis of the hippocampus and cerebral cortex of adult mice after chronic systemic injection of LPS indicated that the level of MDA was considerably increased in the LPS-treated rats, while the activity of CAT or SOD enzymes, and total thiol content were remarkably decreased in both tissues (Bargi et al., 2017). The activation of microglia cells in the brain is also one of the critical pathways that LPS can cause oxidative damage (Kaneko et al., 2012; Tsukahara et al., 2021). As highlighted by previous studies, activated microglia cells result in the release of pro-inflammatory cytokines such as IL-1β and TNF-α that leading to the activation of NADPH oxidase and xanthine oxidase enzymes (Soares et al., 2022; Yeh et al., 2024). Consequently, the NADPH oxidase and xanthine oxidase produce reactive oxygen species (ROS), such as superoxide anion (O2-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH), which are highly reactive and can damage cellular components (Qin et al., 2004; Widmer et al., 2007). Excessive ROS production overwhelms the endogenous antioxidant defense mechanisms, leading to oxidative stress in the brain. This imbalance between ROS production and antioxidant capacity can damage lipids, proteins, and DNA in neuronal cells. ROS can also target mitochondria, disrupting electron transport chain function, and leading to further ROS generation and mitochondrial dysfunction. This creates a vicious cycle of oxidative damage in neurons (Czapski et al., 2004; Qin et al., 2013). Prolonged exposure to LPS-induced oxidative

stress can activate apoptotic pathways in neurons, leading to cell death and contributing to neurodegenerative conditions (Xiao et al., 2022).

LPS impaired level and function of neurotrophic factors

Neurotrophic factors play a significant role in various cell functions across different stages of the nervous system during development, maturity, and after injury. Recent research has shed light on the receptors responsible for these effects and the subsequent intracellular mechanisms triggered upon ligand binding. While it was previously understood that growth factors originated from non-neuronal cells located in the targets and pathways of neuronal projections, it is now evident that neurons can also independently produce these essential signaling molecules (Barbacid, 1995; Skaper, 2018; Ning et al., 2024). According to the effect of LPS on BDNF in this topic, it can aggravate the process of neurodegenerative diseases, which can eventually cause cognitive and memory disorders by impairing the brain's ability to withstand stressors and maintain proper neuronal function. Nerve growth factor (NGF) was discovered due to its ability to promote growth, survival, and differentiate promoting effects on neurons (Levi-Montalcini & Angeletti, 1968). A member of this family is BDNF, a protein that is widely distributed throughout the central nervous system and peripheral blood which has crucial effects on the development, function, maintenance of neurons, helps regulate synaptic activity, plays an essential role in neuroplasticity, learning, and memory (Binder & Scharfman, 2004). Evidence have shown that BDNF levels in the blood reflect BDNF levels in the brain (Karege et al., 2002; Katoh-Semba et al., 2007). BDNF protein is synthesized in the endoplasmic reticulum as a pro-BDNF then moves to the Golgi apparatus which is then secreted by neurons in the synaptic space. The terminal domain of pro-BDNF is cleaved by a convertase enzyme and forms mature BDNF that binds to specific TrkB receptors on the axons and dendrites of cortical neurons. Once bound, BDNF promotes the growth and maintenance of these neurons by enhancing their survival, growth, and differentiation (Guldager et al., 2024). Evidence also have shown that BDNF plays an important role in memory and neuroprotection (Pandya et al., 2013). Studies have shown that inflammation and oxidative stress induced by LPS can lead to decreased BDNF level in the brain tissues, which finally can induce apoptosis in neurons cells. For instance, an experimental study conducted on rats found that administration of LPS led to a decrease in BDNF expression in certain regions of the brain, including the hypothalamus and pituitary gland (Nowacka et al., 2015), which are involved in the controlling many functions (Puelles et al., 2012) and maintaining homeostasis (a physiologic balance) within the body (Cheung & Camper, 2018). In addition, Vasconcelos et al. (2014) demonstrated that a single dose injection of LPS decreases BDNF levels in the hippocampus of the rat's brain, which is play critical role in memory and cognitive processes. The reduced BDNF levels due to the administration of LPS cause to inflammatory response, and the production of pro-inflammatory cytokines such as IL-1β, TNF-α, and interferon-gamma (IFN-γ). Subsequently, these cytokines can interact with neurons in the brain, leading to an inflammatory response and impairment of critical brain functions such as learning and memory (Frühauf-Perez et al., 2018). As discussed before BDNF has an important role in neurodevelopment or neurogenesis. Therefore, any changes in BDNF levels may contribute to the progression of neurodegenerative diseases. As an example, prenatal exposure to LPS elevates BDNF levels similarly to autistic patients, suggesting a correlation between autism and BDNF levels (Kirsten et al., 2015). In fact, the increased level of BDNF may reflect a compensatory mechanism as an intrinsic component of the disease process (Tsai, 2005). Additionally, it is also reported that the expression level of BDNF is reduced in Parkinson's disease (Fumagalli et al., 2006). Moreover, stress itself has been implicated in the reduction of BDNF levels. It has been revealed that chronic stress conditions lead to decreased BDNF expression in the hippocampus, an area crucial for learning and memory. This reduction is associated with impairments in synaptic plasticity and cognitive function (Asim et al., 2022). In addition to the effects of stress, the role of antidepressant treatments in reversing BDNF deficits is noteworthy. Antidepressants have been shown to increase BDNF levels in the brain, thereby promoting neurogenesis and enhancing synaptic plasticity. Various antidepressant such as ketamine treatments can restore BDNF levels in animal models subjected to stress (Asim et al., 2021). This restoration may contribute to the therapeutic effects of antidepressants, facilitating recovery in cognitive functions that are impaired due to stress-induced BDNF depletion. The interplay between LPS-induced oxidative stress, stress-related reductions in BDNF, and the potential for antidepressant treatments to reverse these effects presents a compelling case for further investigation. Understanding these relationships is crucial for developing therapeutic strategies aimed at improving memory function and mitigating cognitive impair-

ments associated with inflammatory conditions. In general, the decrease in BDNF levels resulting from LPS administration and oxidative stress has significant implications for memory function (Siuda et al., 2017). The evidence supporting the role of stress in reducing BDNF, as well as the ability of antidepressant treatments to restore these levels, emphasizes the need for a multifaceted approach to understanding and addressing the cognitive deficits associated with LPS exposure. Future research should aim to explore the potential of pharmacological interventions that target neurotrophic factors to improve cognitive outcomes in conditions characterized by elevated inflammatory responses.

LPS alters level and function of neurotransmitters

Numerous studies have demonstrated that chronic LPS injection leads to alterations in neurotransmitter levels in various brain regions disrupting memory and cognitive function (Guo et al., 2016). The studies also shed light on the involvement of oxidative stress in LPS-induced neurotransmitter dysregulation. Chronic LPS exposure triggered the modulation of antioxidant enzyme activities, leading to an imbalance between ROS formation and elimination, which contributed to the observed alterations in neurotransmitter dynamics (Sharma & Nehru, 2015; Barua et al., 2018). This elevated neuroinflammation correlated with decreased levels of important neurotransmitters such as serotonin, norepinephrine, and dopamine in specific brain regions (Rawani et al., 2024). Inflammation-induced changes in neurotransmitter systems have been reported in the hippocampus, prefrontal cortex, amygdala, striatum, and other brain areas implicated in cognitive, emotional, and motor functions. Chronic LPS administration results in reduced levels of serotonin and dopamine in the hippocampus, leading to disturbances in mood regulation, learning, and memory processes. These changes have been linked to the development of depressive-like symptoms and impaired spatial learning (Miller et al., 2013; Fasick et al., 2015). The prefrontal cortex, responsible for executive functions and decision-making, experiences alterations in GABA and glutamate neurotransmission following chronic LPS injection. These changes are associated with cognitive impairments, including attention deficits and cognitive inflexibility (Crowley et al., 2016). Chronic LPS-induced neuroinflammation in the amygdala disrupts serotonin and GABAergic neurotransmission, contributing to anxiety-like behaviors and emotional dysregulation (Zheng et al., 2021). Dysregulation of the GABAergic system contributes to anxiety-like behaviors and emotional dysregulation observed in animal models following LPS exposure (Rezaei et al., 2024). Research has demonstrated that GABA dysfunction is closely linked to the pathophysiology of depression (Della Vecchia et al., 2022; Prévot & Sibille, 2021). For instance, the study by Asim et al. (2024) highlights that alterations in GABAergic signaling can lead to decreased inhibitory control over excitatory pathways, resulting in heightened neural excitability and increased susceptibility to mood disorders. This is especially relevant in the context of LPS administration, where inflammatory cytokines can modulate GABA receptor expression and function, further exacerbating emotional dysregulation. Furthermore, other studies underscore the role of GABA in regulating mood and anxiety (Felice et al., 2020; Ochoa-de la Paz et al., 2021). The authors found that GABAergic dysfunction is prevalent in various models of depression and anxiety, suggesting that restoring GABAergic transmission may have therapeutic potential. In LPS models, the disruption of GABA signaling not only contributes to anxiety-like behaviors but may also impair cognitive functions, as GABA is essential for maintaining the balance of synaptic plasticity necessary for memory processing (Asim et al., 2024). However, the relationship between LPS-induced neuroinflammation and GABA dysfunction is significant in understanding the broader implications for both mood and cognitive disturbances. By highlighting the interplay between GABAergic neurotransmission and depressive-like behaviors, we underscore the need for further research into targeted therapeutic strategies that could ameliorate these effects, potentially improving outcomes for individuals affected by conditions characterized by elevated inflammatory responses. The striatum, a key brain region involved in motor control and reward processing, demonstrates compromised dopamine signaling following chronic LPS injection. This disruption can lead to motor deficits, altered reward processing, and contribute to the development of Parkinson's disease-related symptoms (Abg Abd Wahab et al., 2019). Moreover, studies have shown that LPS can have adverse effects on glutamate, and acetylcholine, which are both vital neurotransmitter in the central nervous system (Zhou et al., 2006; Tyagi et al., 2010). It is important to note that exposed to LPS also can lead to dysregulation of glutamate homeostasis. This dysregulation may result in excessive release of glutamate, leading to excitotoxicity, which can damage neurons and contribute to various neurological disorders (Zhou et al., 2006). When LPS interacts with acetylcholine, it can lead to disruption of the cholinergic signaling pathways. This interference can

result in decreased acetylcholine release, impaired transmission at cholinergic synapses, and ultimately lead to cognitive dysfunction, memory impairment, and other neurological problems (Tyagi et al., 2008; Xia et al., 2022). Additionally, the inflammatory response triggered by LPS can further exacerbate the negative impact on acetylcholine, and glutamate contributing to conditions such as neuroinflammation and neurodegeneration (Lee, 2013). The long-term impact of chronic LPS-induced neuroinflammation on neurotransmitter levels appears to be persistent. Even after the inflammatory response subsides, neurotransmitter disturbances can persist, contributing to prolonged behavioral abnormalities and increasing susceptibility to neurodegenerative diseases (Brothers et al., 2013).

LPS-induced apoptosis

Apoptosis, also known as programmed cell death, is a highly regulated and essential physiological process that plays a crucial role in various biological events, whereas its fundamental mechanism involved in the development, homeostasis, and elimination of unwanted or damaged cells in multicellular organisms (Ekundayo et al., 2024). Apoptosis is characterized by a series of morphological and biochemical changes that result in removal of cells without causing inflammation or damage to neighboring cells. This process is tightly controlled by a complex network of signaling pathways and involves the activation of specific cellular machinery (Wyllie, 1997; Fadok & Henson, 1998). Two main pathways can initiate apoptosis (Zimmermann & Green, 2001). The extrinsic pathway is activated by external signals, typically through the binding of specific ligands to cell surface death receptors. Ligand binding triggers the formation of a death-inducing signaling complex (DISC), leading to the activation of caspases, a family of proteases that orchestrate apoptosis (Nair et al., 2014). The intrinsic pathway, also known as the mitochondrial pathway, is triggered by a variety of intracellular stresses, such as DNA damage, oxidative stress, or growth factor deprivation (Inoue et al., 2009). These stress signals cause the release of mitochondrial proteins, including cytochrome c, into the cytoplasm. Cytochrome c, together with other proteins, forms a complex called the apoptosome, which activates caspases and initiates cell death (Silvestro et al., 2024). Once apoptosis is triggered, a series of events occur, including cytoplasmic and nuclear condensation, DNA fragmentation, membrane blebbing, and the formation of apoptotic bodies that are subsequently recognized and eliminated by neighboring cells or phagocytes in a process called phagocytosis (Fadok & Henson, 1998). Apoptosis serves several critical functions in maintaining the overall health and functioning of an organism such as development and tissue remodeling (Lorda-Diez et al., 2015), immune system regulation (Opferman, 2008), removal of damaged cells (Ekundayo et al., 2024), prevention of autoimmunity (Vaux & Flavell, 2000; Hughes et al., 2008). Imbalance in apoptotic regulation can lead to various pathological conditions, such as neurodegenerative diseases, cancer, autoimmune disorders, and developmental defects (Ekundayo et al., 2024). The main goal of this essential and fundamental function regardless of the downstream pathway is, cell removal without damaging the tissue (Fadok & Henson, 1998). Therefore, studying the mechanisms underlying apoptosis is crucial for understanding normal physiological processes and developing therapeutic interventions for associated diseases. LPS-induced apoptosis has been studied in many cell lineages but primarily in immune cells, such as macrophages and lymphocytes. According to previous studies LPS, a pattern recognition receptor (PAMP), activates TLR4, a member of the pattern recognition receptors (PRR) family, which triggers a signaling cascade leading to the activation of pro-inflammatory pathways (Thingore et al., 2021). Furthermore, previous studies also have revealed that low-dose exposure to LPS can play a neuroprotective role by activating TLR4 receptors against cellular apoptosis. However, further studies are required with respect to the mechanism involved (Sangaran et al., 2021). Among the downstream signaling pathways, NF-κB and MAPKs are known to be involved in LPS-induced apoptosis (Sangaran et al., 2021). Many evidence confirm that activation of NF-κB by LPS can promote cell survival by upregulating anti-apoptotic genes (Bannerman & Goldblum, 2003). However, under certain conditions, LPS-induced NF-κB activation can also lead to apoptosis (Lv et al., 2020). This apoptotic response can be mediated by the induction of pro-apoptotic mediators or the inhibition of anti-apoptotic factors (Bannerman & Goldblum, 2003; Lv et al., 2020). Additionally, the results of the previous study have revealed that MAPK signaling pathways, including ERKs, JNKs, and p38 MAPK, have also been implicated in LPS-induced apoptosis, activation of these pathways by LPS can result in the induction of pro-apoptotic factors or the inhibition of anti-apoptotic signaling pathways, ultimately leading to apoptosis (Mizumura et al., 2010). In addition, growing evidence has shown that LPS-induced apoptosis can occur in various cell types, including immune cells, endothelial cells, cardiac cells, hepatic cells, and neu-

ronal cells (Watson et al., 1996; Meresman et al., 2000; George et al., 2019; Song et al., 2020; Ji et al., 2021; Xu et al., 2022). LPS triggers apoptosis in immune cells. For instance, an experimental study found that LPS treatment induced apoptosis in mouse macrophages through the activation of caspase-3, a key executioner of caspase involved in apoptosis (George et al., 2019). Another study showed that LPS-induced apoptosis in human neutrophils involved the upregulation of pro-apoptotic Bcl-2 family members and the activation of caspase-3 (Vier et al., 2016). LPS also induces apoptosis in various non-immune cell types. In neuronal cells, LPS-induced apoptosis has been associated with the release of pro-inflammatory cytokines, oxidative stress, and disruption of mitochondrial function (Noworyta-Sokołowska et al., 2013). *In vitro* studies using neuronal cell cultures have demonstrated that exposure to LPS leads to increased caspase activation, DNA fragmentation, and morphological changes characteristic of apoptosis (Nimmervoll et al., 2013). Animal models, such as mice or rats, have also been utilized to investigate the impact of LPS on neuronal apoptosis *in vivo* (Kubera et al., 2011). These studies have shown that LPS administration induces neuronal cell death in specific brain regions, further supporting the role of LPS in apoptosis induction. Several studies have implicated LPS-induced neuronal apoptosis in neurodegenerative diseases (Tanaka et al., 2006). In certain neurological disorders or conditions, increased apoptosis in neural cells can lead to memory impairment. As an example, enhancing of apoptosis in the hippocampus and other memory-related brain regions contributes to the cognitive decline and memory impairment seen in Alzheimer's disease (Maiti et al., 2008). Various neurodegenerative disorders, such as Parkinson's disease and Huntington's disease, also involve excessive apoptosis in specific brain areas which often have associated memory deficits and cognitive decline (Stefanis et al., 1997). Furthermore, previous studies have reported that LPS binding to TLR4 on microglia initiates a signaling cascade, leading to the release of pro-inflammatory cytokines like IL-1β and TNF-α (Muhammad et al., 2019). The pro-inflammatory cytokines stimulate astrocytes to release excessive amounts of glutamate, the major excitatory neurotransmitter in the brain (Persson et al., 2005; Huang et al., 2008). This glutamate release contributes to excitotoxicity, damaging neuronal cells (Bal-Price & Brown, 2001; Zhou et al., 2006; Qu et al., 2022). The increased glutamate in the extracellular space can overstimulate glutamate receptors, particularly N-methyl-D-aspartate receptors (NMDARs), leading to an influx of calcium ions into neurons (Chang et al., 2001; Zhang et al., 2017). The excessive calcium influx disrupts cellular homeostasis, triggering mitochondrial dysfunction, oxidative stress, and activation of pro-apoptotic pathways (Bakaeva et al., 2021). Prolonged exposure to LPS-induced glutamate excitotoxicity can lead to neuronal cell death, contributing to neurodegenerative conditions and cognitive impairments (Zhou et al., 2006).

LPS impaired LTP

LPS and LTP are two important processes that play different roles in the brain. LTP is a process that occurs in the brain when neurons become more sensitive to the synaptic transmission of signals (Sandkühler, 2007). This process is involved in learning and memory, and it is believed to be the cellular mechanism that underlies long-term memory formation (Asim et al., 2024). There is evidence to suggest that administration of LPS can impair LTP in brains tissues. In this regards, to give an illustration, Zhao et al. (2019) have indicated that LPS impairs LTP in several regions of the brain such as the hippocampus and prefrontal cortex. This impairment is attributed to the activation of specific receptors, notably TLR4 and CD14, leading to inflammatory responses. This activation triggers the production of inflammatory cytokines like IL-1β, TNF-α, and IL-6. These cytokines are generated by microglia and astrocytes, with astrocytes likely producing more IL-6 and less TNF-α in this context (Cowley et al., 2012; Hosseini et al., 2021). Moreover, activation of microglial cells by LPS could also lead to excessive production of ROS which could alter LTP in numerous ways. As an example, high levels of ROS can lead to oxidative damage of proteins, lipids, and DNA, which can disrupt normal cellular function and impair synaptic plasticity mechanisms. Oxidative stress-induced damage can result in synaptic dysfunction, neuronal injury, and ultimately contribute to LTP impairment and cognitive deficits (Knapp & Klann, 2002). Many papers have reported that interleukin IL-1β has a concentration-dependent inhibitory effect on LTP (Lynch, 2015). As Lynch (2015) discussed, LPS enhances the adaptation of microglia to the M1 state, which may cause a deficit in LTP. However, the factors that switch microglia from the M1 to the M2 phenotype are associated with restoration of LTP. As an example, inhibition of IL-1β resulted in macrophages adopting the M2 state (Mirza et al., 2013) and this opposes the inhibition of LTP (Kelly et al., 2003). A correlation between LPS-induced inflammation and impaired LTP has been identified in several models. Many studies have been reported that administration of LPS in animal models results in impaired in LTP (Nolan et al., 2004; Abareshi et al., 2016; Hosseini et al.,

2021) and spatial learning (Zarifkar et al., 2010; Valero et al., 2014). It has been observed that intraperitoneal administration of LPS leads to an increase in apoptosis through elevating caspase-1 activity and IL-1β concentration in the hippocampus which, finally can decrease number of neurons in Schaffer projections to hippocampal CA1 cells that can cause LTP impairment (Vereker et al., 2000). In addition, for further confirmation, studies have been illustrated that administration of inflammatory cytokines receptor blockers such as an interlukin-1 receptor (IL-1R) blocking antibody results in an improvement of synaptic plasticity (Kitazawa et al., 2011). Additionally, apart from IL-1β, Curran and O'Connor (2001) have demonstrated that administration of inflammatory cytokine such as IL-18 results in LTP impairment in the dentate gyrus of animal models. Furthermore, it has been well documented that BDNF plays a crucial role in the process of LTP, which is a key mechanism underlying learning and memory in the brain. BDNF enhances the strength of synaptic connections by promoting the survival and growth of neurons, as well as by modulating synaptic plasticity (Thomas & Davies, 2005). As discussed previously LPS alters BDNF levels which could then impair LTP as the result. According to previous studies, it was also found that induction of chronic neuroinflammation results in significant impairment in LTP within the dentate gyrus (a well-characterized model of cellular synaptic plasticity) of the hippocampus (Hauss-Wegrzyniak et al., 2002).

Relationship between memory impairment and depressive-like behavior in LPS models

The relationship between memory impairment and depressive-like behavior in the context of LPS administration has also gained increasing attention in neurobiological research. As described, LPS is widely used in experimental models to investigate the effects of inflammation on cognitive and emotional functions. This relationship is complex and multifaceted, involving various molecular and cellular mechanisms that intertwine the pathways responsible for cognitive decline and affective disorders. LPS administration induces a robust neuroinflammatory response, characterized by the activation of microglia and the release of pro-inflammatory cytokines (Murtaj et al., 2019; Niaz et al., 2021). This inflammatory cascade not only impacts neuronal circuits involved in memory but also significantly affects circuits associated with mood regulation (Chistyakov et al., 2018). The hippocampus is particularly vulnerable to the effects of neuroinflammation (Vasic & Schmidt, 2017). Studies have shown that LPS can disrupt synaptic plasticity and LTP, both essential for memory processes (Hauss-Wegrzyniak et al., 2002; Lynch, 2015). The detrimental effects of LPS on memory performance often coincide with the emergence of depressive-like behaviors as (Hosseini et al., 2024) discussed, suggesting a shared underlying pathology.

One of the main mechanisms linking memory impairment to depressive-like behavior is the dysregulation of neurotrophic factors, specifically BDNF (Zborowski et al., 2021). Under normal conditions, BDNF plays a crucial role in promoting neuronal survival, synaptic plasticity, and cognitive functions (Thomas & Davies, 2005). However, LPS administration has been shown to decrease BDNF levels in the hippocampus, which correlates with observed deficits in both memory and mood (Hritcu & Gorgan, 2014; Nowacka et al., 2015). This reduction in BDNF not only disrupts the signaling pathways necessary for LTP but also impairs the brain's ability to adapt to stress, thereby increasing susceptibility to depressive symptoms (Duncan et al., 2009; Hing et al., 2018). The interplay between BDNF signaling and neuroinflammation indicates that interventions aimed at modulating BDNF levels could potentially alleviate both memory deficits and depressive-like behaviors. Another key aspect of the relationship between memory impairment and depressive-like behavior in LPS models is the role of neurotransmitter systems, particularly serotonin and norepinephrine. Chronic neuroinflammation has been associated with altered neurotransmitter dynamics, leading to imbalances that can contribute to mood disturbances and cognitive decline (Leite et al., 2017). LPS exposure has been shown to decrease serotonin availability, which is critical for mood regulation and cognitive functions such as attention and memory (Korte-Bouws et al., 2018). This serotonergic dysfunction is often accompanied by alterations in norepinephrine signaling, which together can exacerbate feelings of helplessness and despair, characteristic of depressive-like states (Anand & Charney, 2000; Goddard et al., 2010). Moreover, the interaction between neuroinflammation and oxidative stress further complicates this relationship. LPS-induced neuroinflammation is associated with the generation of reactive ROS, which can lead to oxidative damage in neuronal cells (Mizuno, 2015; Kempuraj et al., 2016). Oxidative stress has been implicated in both memory impairment and the development of depressive-like behavior (Patki et al., 2013). The hippocampus, being highly susceptible to oxidative damage, may exhibit cellular changes that impair neurogenesis and synaptic function, thereby contributing to cognitive deficits (Head, 2009). This

oxidative pathway may also influence the expression of genes involved in mood regulation, compounding the effects on depressive-like behaviors (Wigner et al., 2020). The hypothalamic-pituitary-adrenal (HPA) axis also plays a significant role in the relationship between memory impairment and depressive-like behavior in the context of LPS administration. Chronic inflammation can lead to dysregulation of the HPA axis, resulting in altered cortisol levels (Straub & Cutolo, 2016). Elevated cortisol, often seen in states of chronic stress and depression (Bertollo et al., 2020), can impair hippocampal function and contribute to memory deficits (Liu et al., 2023). Furthermore, the feedback loop between stress hormones and neuroinflammation suggests that elevated inflammatory markers can further exacerbate HPA axis dysregulation, creating a vicious cycle that perpetuates both cognitive and emotional dysfunction (Lawrence & Scofield, 2024). In addition to these molecular mechanisms, behavioral studies utilizing LPS models have provided valuable insights into the connection between memory and mood (Morimoto et al., 2023; Yin et al., 2023). Animals subjected to LPS administration often display a range of behavioral changes indicative of both memory deficits and depressive-like symptoms, such as anhedonia, social withdrawal, and increased immobility in forced swim tests (Bassi et al., 2012; Couch et al., 2016). These behavioral changes correlate with neurobiological alterations, reinforcing the notion that cognitive and affective processes are interconnected. The impact of environmental factors on this relationship cannot be overlooked. Chronic stressors and adverse experiences can exacerbate the effects of neuroinflammation induced by LPS (Ritchie, 2004; Aprilia & Aminatun, 2022). For instance, a history of early-life stress or chronic social stress can prime the brain's inflammatory response, making individuals more susceptible to both memory impairments and depressive behaviors following LPS exposure (Patki et al., 2013). This highlights the importance of considering individual differences and environmental contexts when assessing the interplay between inflammation, cognition, and mood.

Therapeutically, targeting the underlying mechanisms shared by memory impairment and depressive-like behavior in LPS models offers promising avenues for intervention. Potential strategies include the use of anti-inflammatory agents (Brod, 2022), antioxidants (Ataie et al., 2010), and modulators of neurotrophic factors (Sharma et al., 2023). For example, compounds that enhance BDNF signaling or reduce oxidative stress could provide dual benefits, improving cognitive functions while alleviating depressive symptoms (Shimada et al., 2014). Additionally, lifestyle interventions such as exercise, which has been shown to increase BDNF levels and reduce inflammation (Walsh & Tschakovsky, 2018), may offer a holistic approach to mitigate the cognitive and emotional consequences of LPS exposure. Overall, the relationship between memory impairment and depressive-like behavior in LPS models is complex and multifaceted, involving intricate molecular mechanisms that highlight the interplay between neuroinflammation, neurotrophic factors, neurotransmitter systems, oxidative stress, and HPA axis regulation. Understanding these interconnected pathways is crucial for developing targeted interventions that address both cognitive and emotional dysfunctions associated with inflammatory processes. As research continues to unravel the nuances of this relationship, it will pave the way for innovative therapeutic strategies aimed at improving outcomes for individuals affected by conditions characterized by elevated inflammatory responses, such as infections, sepsis, and neuroinflammatory disorders.

CONCLUSION

In conclusion, this review has collected articles with subject of the impact of LPS on memory impairment and the underlying mechanisms involved. The findings of this review indicate that LPS significantly impairs memory processes. The mechanisms through which LPS exerts its effects on memory impairment have been introduced. The review sheds light on the role of neuroinflammation, oxidative stress, apoptosis induction, neurotrophic factors, neurotransmitters and synaptic dysfunction as key contributors to the observed memory impairments. Neuroinflammation, characterized by the activation of microglia and the release of pro-inflammatory cytokines, has been identified as a key contributor to the observed memory impairments. Additionally, oxidative stress and synaptic dysfunction have been implicated as important mechanisms underlying LPS-induced memory impairment. Understanding these mechanisms is crucial for the development of potential therapeutic interventions for memory-related disorders. By targeting neuroinflammation, oxidative stress, apoptosis, neurotrophic factors, and synaptic dysfunction, it may be possible to mitigate the memory impairments caused by LPS. This review article provides a comprehensive overview of the complex relationship between LPS and memory impairment. The majority of the studies included were conducted on animal models, and further research is needed to validate these findings in human populations.

REFERENCES

Abareshi, A., Anaeigoudari, A., Norouzi, F., Shafei, M. N., Boskabady, M. H., Khazaei, M., & Hosseini, M. (2016). Lipopolysaccharide-induced spatial memory and synaptic plasticity impairment is preventable by captopril. *Advances in medicine*, *2016,* 7676512. https://doi.org/10.1155/2016/7676512

Abareshi, A., Hosseini, M., Beheshti, F., Norouzi, F., Khazaei, M., Sadeghnia, H. R., Boskabady, M. H., Shafei, M. N., & Anaeigoudari, A. (2016). The effects of captopril on lipopolysaccharide induced learning and memory impairments and the brain cytokine levels and oxidative damage in rats. *Life Sci*, *167*, 46–56. https://doi.org/10.1016/j.lfs.2016.10.026

Abdel-Salam, O. M. E., Morsy, S. M. Y., & Sleem, A. A. (2011). The effect of different antidepressant drugs on oxidative stress after lipopolysaccharide administration in mice. *EXCLI J*, *10*, 290–302.

Abdel-Salam, O. M., Youness, E. R., Mohammed, N. A., Morsy, S. M., Omara, E. A., & Sleem, A. A. (2014). Citric acid effects on brain and liver oxidative stress in lipopolysaccharide-treated mice. *Journal of medicinal food, 17*(5), 588–598. https://doi.org/10.1089/jmf.2013.0065

Abg Abd Wahab, D. Y., Gau, C. H., Zakaria, R., Muthu Karuppan, M. K., Abdullah, Z., Alrafiah, A., Abdullah, J. M., & Muthuraju, S. (2019). Review on cross talk between neurotransmitters and neuroinflammation in striatum and cerebellum in the mediation of motor behaviour. *BioMed Research International 2019(1), 1767203.* https://doi.org/10.1155/2019/1767203

Afroz, R., Tanvir, E., Tania, M., Fu, J., Kamal, M. A., & Khan, M. A. (2022). LPS/TLR4 pathways in breast cancer: insights into cell signalling. *Current Medicinal Chemistry*, *29*(13), 2274–2289. https://doi.org/10.2174/0929867328666210811145043

Ahmad, A., Ali, T., Rehman, S. U., & Kim, M. O. (2019). Phytomedicine-Based Potent Antioxidant, Fisetin Protects CNS-Insult LPS-Induced Oxidative Stress-Mediated Neurodegeneration and Memory Impairment. *J Clin Med*, *8*(6), 850. https://doi.org/10.3390/jcm8060850

Ahmed, A. U. (2011). An overview of inflammation: mechanism and consequences. *Frontiers in Biology*, *6*(4), 274–281. https://doi.org/10.1007/s11515-011-1123-9

Alboni, S., Benatti, C., Colliva, C., Radighieri, G., Blom, J., Brunello, N., & Tascedda, F. (2021). Vortioxetine prevents lipopolysaccharide-induced memory impairment without inhibiting the initial inflammatory cascade. *Frontiers in Pharmacology*, *11*, 603979. https://doi.org/10.3389/fphar.2020.603979

Alshehri, S., & Imam, S. S. (2021). Rosinidin Attenuates Lipopolysaccharide-Induced Memory Impairment in Rats: Possible Mechanisms of Action Include Antioxidant and Anti-Inflammatory Effects. *Biomolecules*, *11*(12), 1747. https://doi.org/10.3390/biom11121747

Anaeigoudari, A., Shafei, M. N., Soukhtanloo, M., Sadeghnia, H. R., Reisi, P., Beheshti, F., Mohebbati, R., Mousavi, S. M., & Hosseini, M. (2015). Lipopolysaccharide-induced memory impairment in rats is preventable using 7-nitroindazole. *Arquivos de Neuro-psiquiatria*, *73*, 784–790. https://doi.org/10.1590/0004-282X20150121

Anand, A., & Charney, D. S. (2000). Norepinephrine dysfunction in depression. *J Clin Psychiatry*, *61(10)*, 16–24.

Aprilia, A., & Aminatun, D. (2022). Investigating memory loss: How depression affects students'memory endurance. *Journal of English Language Teaching and Learning*, *3*(1), 1–11. https://doi.org/10.33365/jeltl.v3i1.1719

Asahina, R., Takahashi, M., Takano, H., Yao, R., Abe, M., Goshima, Y., & Ohshima, T. (2024). The role of CRMP4 in LPS-induced neuroinflammation. *Brain Res*, *1841*, 149094. https://doi.org/10.1016/j.brainres.2024.149094

Asim, M., Hao, B., Waris, A., Liang, Y. M., & Wang, X. G. (2022). Ketamine attenuates the PTSD-like effect via regulation of glutamatergic signaling in the nucleus accumbens of mice. *Mol Cell Neurosci*, *120*, 103723. https://doi.org/10.1016/j.mcn.2022.103723

Asim, M., Wang, B., Hao, B., & Wang, X. (2021). Ketamine for post-traumatic stress disorders and it's possible therapeutic mechanism. *Neurochem Int*, *146*, 105044. https://doi.org/10.1016/j.neuint.2021.105044

Asim, M., Wang, H., & Chen, X. (2024). Shedding light on cholecystokinin's role in hippocampal neuroplasticity and memory formation. *Neurosci Biobehav Rev*, *159*, 105615. https://doi.org/10.1016/j.neubiorev.2024.105615

Asim, M., Wang, H., Chen, X., & He, J. (2024). Potentiated GABAergic neuronal activities in the basolateral amygdala alleviate stress-induced depressive behaviors. *CNS Neurosci Ther*, *30*(3), e14422. https://doi.org/10.1111/cns.14422

Asim, M., Wang, H., Waris, A., & He, J. (2024). Basolateral amygdala parvalbumin and cholecystokinin-expressing GABAergic neurons modulate depressive and anxiety-like behaviors. *Transl Psychiatry*, *14*(1), 418. https://doi.org/10.1038/s41398-024-03135-z

Ataie, A., Sabetkasaei, M., Haghparast, A., Moghaddam, A. H., & Kazeminejad, B. (2010). Neuroprotective effects of the polyphenolic antioxidant agent, Curcumin, against homocysteine-induced cognitive impairment and oxidative stress in the rat. *Pharmacol Biochem Behav*, *96*(4), 378–385. https://doi.org/10.1016/j.pbb.2010.06.009

Badshah, H., Ali, T., & Kim, M. O. (2016). Osmotin attenuates LPS-induced neuroinflammation and memory impairments via the TLR4/NFkappaB signaling pathway. *Sci Rep*, *6*(1), 24493. https://doi.org/10.1038/srep24493

Bakaeva, Z., Lizunova, N., Tarzhanov, I., Boyarkin, D., Petrichuk, S., Pinelis, V., Fisenko, A., Tuzikov, A., Sharipov, R., & Surin, A. (2021). Lipopolysaccharide From E. coli Increases Glutamate-Induced Disturbances of Calcium Homeostasis, the Functional State of Mitochondria, and the Death of Cultured Cortical Neurons. *Front Mol Neurosci*, *14*, 811171. https://doi.org/10.3389/fnmol.2021.811171

Bal-Price, A., & Brown, G. C. (2001). Inflammatory neurodegeneration mediated by nitric oxide from activated glia-inhibiting neuronal respiration, causing glutamate release and excitotoxicity. *J Neurosci*, *21*(17), 6480–6491. https://doi.org/10.1523/jneurosci.21-17-06480.2001

Bannerman, D. D., & Goldblum, S. E. (2003). Mechanisms of bacterial lipopolysaccharide-induced endothelial apoptosis. *Am J Physiol Lung Cell Mol Physiol*, *284*(6), L899–914. https://doi.org/10.1152/ajplung.00338.2002

Barbacid, M. (1995). Neurotrophic factors and their receptors. *Current opinion in cell biology*, *7*(2), 148–155. https://doi.org/10.1016/0955-0674(95)80022-0

Bargi, R., Asgharzadeh, F., Beheshti, F., Hosseini, M., Sadeghnia, H. R., & Khazaei, M. (2017). The effects of thymoquinone on hippocampal cytokine level, brain oxidative stress status and memory deficits induced by lipopolysaccharide in rats. *Cytokine*, *96*, 173–184. https://doi.org/10.1016/j.cyto.2017.04.015

Barichello, T., Sayana, P., Giridharan, V. V., Arumanayagam, A. S., Narendran, B., Della Giustina, A., Petronilho, F., Quevedo, J., & Dal-Pizzol, F. (2019). Long-Term Cognitive Outcomes After Sepsis: a Translational Systematic Review. *Mol Neurobiol*, *56*(1), 186–251. https://doi.org/10.1007/s12035-018-1048-2

Barua, C. C., Haloi, P., Saikia, B., Sulakhiya, K., Pathak, D. C., Tamuli, S., Rizavi, H., & Ren, X. (2018). Zanthoxylum alatum abrogates lipopolysaccharide-induced depression-like behaviours in mice by modulating neuroinflammation and monoamine neurotransmitters in the hippocampus. *Pharm Biol*, *56*(1), 245–252. https://doi.org/10.1080/13880209.2017.1391298

Basir, H. S., Mirazi, N., Komaki, A., & Hosseini, A. (2024). Cacao consumption improves passive avoidance memory impairment in a rat model of Alzheimer's disease: the role of hippocampal synaptic plasticity and oxidative stress. *Front Pharmacol*, *15*, 1379264. https://doi.org/10.3389/fphar.2024.1379264

Bassi, G. S., Kanashiro, A., Santin, F. M., de Souza, G. E., Nobre, M. J., & Coimbra, N. C. (2012). Lipopolysaccharide-induced sickness behaviour evaluated in different models of anxiety and innate fear in rats. *Ba-*

sic Clin Pharmacol Toxicol, *110*(4), 359–369. https://doi.org/10.1111/j.1742-7843.2011.00824.x

Beheshti, F., Hosseini, M., Bakhtiari-Dovvombaygi, H., Salmani, H., Ahmadabady, S., Marefati, N., & Baghcheghi, Y. (2023). Rosiglitazone attenuates amyloid beta and glial fibrillary acidic protein in the hippocampus and neuroinflammation associated learning and memory impairments in rats. *Behav Brain Res*, *452*, 114549. https://doi.org/10.1016/j.bbr.2023.114549

Behl, T., Rana, T., Alotaibi, G. H., Shamsuzzaman, M., Naqvi, M., Sehgal, A., Singh, S., Sharma, N., Almoshari, Y., Abdellatif, A. A. H., Iqbal, M. S., Bhatia, S., Al-Harrasi, A., & Bungau, S. (2022). Polyphenols inhibiting MAPK signalling pathway mediated oxidative stress and inflammation in depression. *Biomed Pharmacother*, *146*, 112545. https://doi.org/10.1016/j.biopha.2021.112545

Belarbi, K., Jopson, T., Tweedie, D., Arellano, C., Luo, W., Greig, N. H., & Rosi, S. (2012). TNF-alpha protein synthesis inhibitor restores neuronal function and reverses cognitive deficits induced by chronic neuroinflammation. *J Neuroinflammation*, *9*(1), 23. https://doi.org/10.1186/1742-2094-9-23

Bertollo, A. G., Grolli, R. E., Plissari, M. E., Gasparin, V. A., Quevedo, J., Reus, G. Z., Bagatini, M. D., & Ignacio, Z. M. (2020). Stress and serum cortisol levels in major depressive disorder: a cross-sectional study. *AIMS Neurosci*, *7*(4), 459–469. https://doi.org/10.3934/Neuroscience.2020028

Binder, D. K., & Scharfman, H. E. (2004). Brain-derived neurotrophic factor. *Growth Factors*, *22*(3), 123–131. https://doi.org/10.1080/08977190410001723308

Brod, S. A. (2022). Anti-Inflammatory Agents: An Approach to Prevent Cognitive Decline in Alzheimer's Disease. *J Alzheimers Dis*, *85*(2), 457–472. https://doi.org/10.3233/JAD-215125

Brothers, H. M., Bardou, I., Hopp, S. C., Marchalant, Y., Kaercher, R. M., Turner, S. M., Mitchem, M. R., Kigerl, K., & Wenk, G. L. (2013). Time-Dependent Compensatory Responses to Chronic Neuroinflammation in Hippocampus and Brainstem: The Potential Role of Glutamate Neurotransmission. *J Alzheimers Dis Parkinsonism*, *3*, 110. https://doi.org/10.4172/2161-0460.1000110

Burguillos, M. A., Hajji, N., Englund, E., Persson, A., Cenci, A. M., Machado, A., Cano, J., Joseph, B., & Venero, J. L. (2011). Apoptosis-inducing factor mediates dopaminergic cell death in response to LPS-induced inflammatory stimulus: evidence in Parkinson's disease patients. *Neurobiol Dis*, *41*(1), 177–188. https://doi.org/10.1016/j.nbd.2010.09.005

Calvillo, M., & Irimia, A. (2020). Neuroimaging and Psychometric Assessment of Mild Cognitive Impairment After Traumatic Brain Injury. *Front Psychol*, *11*, 1423. https://doi.org/10.3389/fpsyg.2020.01423

Castano, A., Herrera, A. J., Cano, J., & Machado, A. (1998). Lipopolysaccharide intranigral injection induces inflammatory reaction and damage in nigrostriatal dopaminergic system. *J Neurochem*, *70*(4), 1584–1592. https://doi.org/10.1046/j.1471-4159.1998.70041584.x

Cazareth, J., Guyon, A., Heurteaux, C., Chabry, J., & Petit-Paitel, A. (2014). Molecular and cellular neuroinflammatory status of mouse brain after systemic lipopolysaccharide challenge: importance of CCR2/CCL2 signaling. *J Neuroinflammation*, *11*(1), 132. https://doi.org/10.1186/1742-2094-11-132

Chan, S. Y., Probert, F., Radford-Smith, D. E., Hebert, J. C., Claridge, T. D. W., Anthony, D. C., & Burnet, P. W. J. (2020). Post-inflammatory behavioural despair in male mice is associated with reduced cortical glutamate-glutamine ratios, and circulating lipid and energy metabolites. *Sci Rep*, *10*(1), 16857. https://doi.org/10.1038/s41598-020-74008-w

Chang, R. C., Chen, W., Hudson, P., Wilson, B., Han, D. S., & Hong, J. S. (2001). Neurons reduce glial responses to lipopolysaccharide (LPS) and prevent injury of microglial cells from over-activation by LPS. *J Neurochem*, *76*(4), 1042–1049. https://doi.org/10.1046/j.1471-4159.2001.00111.x

Chen, H., Sohn, J., Zhang, L., Tian, J., Chen, S., & Bjeldanes, L. F. (2014). Anti-inflammatory effects of chicanine on murine macrophage by down-regulating LPS-induced inflammatory cytokines in IkappaBalpha/MAPK/ERK signaling pathways. *Eur J Pharmacol*, *724*, 168–174. https://doi.org/10.1016/j.ejphar.2013.12.016

Chen, T., Tian, P., Huang, Z., Zhao, X., Wang, H., Xia, C., Wang, L., & Wei, H. (2018). Engineered commensal bacteria prevent systemic inflammation-induced memory impairment and amyloidogenesis via producing GLP-1. *Appl Microbiol Biotechnol*, *102*(17), 7565–7575. https://doi.org/10.1007/s00253-018-9155-6

Chen, X., Guo, C., & Kong, J. (2012). Oxidative stress in neurodegenerative diseases. *Neural Regen Res*, *7*(5), 376–385. https://doi.org/10.3969/j.issn.1673-5374.2012.05.009

Cheung, L. Y. M., & Camper, S. A. (2018). Hypophysis Development and Disease in Humans. In *Reference Module in Biomedical Sciences*. Elsevier. https://doi.org/10.1016/b978-0-12-801238-3.65809-9

Chistyakov, D. V., Astakhova, A. A., & Sergeeva, M. G. (2018). Resolution of inflammation and mood disorders. *Exp Mol Pathol*, *105*(2), 190–201. https://doi.org/10.1016/j.yexmp.2018.08.002

Chitnis, T., & Weiner, H. L. (2017). CNS inflammation and neurodegeneration. *J Clin Invest*, *127*(10), 3577–3587. https://doi.org/10.1172/JCI90609

Choi, D. Y., Lee, J. W., Lin, G., Lee, Y. K., Lee, Y. H., Choi, I. S., Han, S. B., Jung, J. K., Kim, Y. H., Kim, K. H., Oh, K. W., Hong, J. T., & Lee, M. S. (2012). Obovatol attenuates LPS-induced memory impairments in mice via inhibition of NF-kappaB signaling pathway. *Neurochem Int*, *60*(1), 68–77. https://doi.org/10.1016/j.neuint.2011.11.005

Ciesielska, A., Matyjek, M., & Kwiatkowska, K. (2021). TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling. *Cell Mol Life Sci*, *78*(4), 1233–1261. https://doi.org/10.1007/s00018-020-03656-y

Couch, Y., Trofimov, A., Markova, N., Nikolenko, V., Steinbusch, H. W., Chekhonin, V., Schroeter, C., Lesch, K. P., Anthony, D. C., & Strekalova, T. (2016). Low-dose lipopolysaccharide (LPS) inhibits aggressive and augments depressive behaviours in a chronic mild stress model in mice. *J Neuroinflammation*, *13*(1), 108. https://doi.org/10.1186/s12974-016-0572-0

Cowan, C. S. M., Dinan, T. G., & Cryan, J. F. (2020). Annual Research Review: Critical windows - the microbiota-gut-brain axis in neurocognitive development. *J Child Psychol Psychiatry*, *61*(3), 353–371. https://doi.org/10.1111/jcpp.13156

Cowley, T. R., O'Sullivan, J., Blau, C., Deighan, B. F., Jones, R., Kerskens, C., Richardson, J. C., Virley, D., Upton, N., & Lynch, M. A. (2012). Rosiglitazone attenuates the age-related changes in astrocytosis and the deficit in LTP. *Neurobiol Aging*, *33*(1), 162–175. https://doi.org/10.1016/j.neurobiolaging.2010.02.002

Crowley, T., Cryan, J. F., Downer, E. J., & O'Leary, O. F. (2016). Inhibiting neuroinflammation: The role and therapeutic potential of GABA in neuro-immune interactions. *Brain Behav Immun*, *54*, 260–277. https://doi.org/10.1016/j.bbi.2016.02.001

Cui, C. A., Jin, D. Q., Hwang, Y. K., Lee, I. S., Hwang, J. K., Ha, I., & Han, J. S. (2008). Macelignan attenuates LPS-induced inflammation and reduces LPS-induced spatial learning impairments in rats. *Neurosci Lett*, *448*(1), 110–114. https://doi.org/10.1016/j.neulet.2008.10.035

Curran, B., & O'Connor, J. J. (2001). The pro-inflammatory cytokine interleukin-18 impairs long-term potentiation and NMDA receptor-mediated transmission in the rat hippocampus in vitro. *Neuroscience*, *108*(1), 83–90. https://doi.org/10.1016/s0306-4522(01)00405-5

Czapski, G. A., Cakala, M., Kopczuk, D., Kaminska, M., & Strosznajder, J. B. (2004). Inhibition of nitric oxide synthase prevents energy failure and oxidative damage evoked in the brain by lipopolysaccharide. *Pol J Pharmacol*, *56*(5), 643–646.

Da Re, C., Souza, J. M., Froes, F., Taday, J., Dos Santos, J. P., Rodrigues, L., Sesterheim, P., Goncalves, C. A., & Leite, M. C. (2020). Neuroinflammation induced by lipopolysaccharide leads to memory impairment and alterations in hippocampal leptin signaling. *Behav Brain Res*, *379*, 112360. https://doi.org/10.1016/j.bbr.2019.112360

Daroi, P. A., Dhage, S. N., & Juvekar, A. R. (2022). p-Coumaric acid mitigates lipopolysaccharide induced brain damage via alleviating oxidative stress, inflammation and apoptosis. *J Pharm Pharmacol*, *74*(4), 556–564. https://doi.org/10.1093/jpp/rgab077

Della Vecchia, A., Arone, A., Piccinni, A., Mucci, F., & Marazziti, D. (2022). GABA System in Depression: Impact on Pathophysiology and Psychopharmacology. *Curr Med Chem*, *29*(36), 5710–5730. https://doi.org/10.2174/0929867328666211115124149

Diz-Chaves, Y., Astiz, M., Bellini, M. J., & Garcia-Segura, L. M. (2013). Prenatal stress increases the expression of proinflammatory cytokines and exacerbates the inflammatory response to LPS in the hippocampal formation of adult male mice. *Brain Behav Immun*, *28*, 196–206. https://doi.org/10.1016/j.bbi.2012.11.013

Domínguez-Rivas, E., Avila-Munoz, E., Schwarzacher, S. W., & Zepeda, A. (2021). Adult hippocampal neurogenesis in the context of lipopolysaccharide-induced neuroinflammation: A molecular, cellular and behavioral review. *Brain, Behavior, and Immunity*, *97*, 286–302. https://doi.org/10.1016/j.bbi.2021.06.014

Duncan, L. E., Hutchison, K. E., Carey, G., & Craighead, W. E. (2009). Variation in brain-derived neurotrophic factor (BDNF) gene is associated with symptoms of depression. *Journal of affective disorders*, *115*(1–2), 215–219. https://doi.org/10.1016/j.jad.2008.08.016

Dunn, A. J., Wang, J., & Ando, T. (1999). Effects of Cytokines on Cerebral Neurotransmission. In R. Dantzer, E. E. Wollman, & R. Yirmiya (Eds.), *Cytokines, Stress, and Depression* (117–127). Springer US. https://doi.org/10.1007/978–0-585–37970–8_8

Ekundayo, B. E., Obafemi, T. O., Adewale, O. B., Obafemi, B. A., Oyinloye, B. E., & Ekundayo, S. K. (2024). Oxidative Stress, Endoplasmic Reticulum Stress and Apoptosis in the Pathology of Alzheimer's Disease. *Cell Biochem Biophys*, *82*(2), 457–477. https://doi.org/10.1007/s12013-024-01248-2

Fadok, V. A., & Henson, P. M. (1998). Apoptosis: getting rid of the bodies. *Curr Biol*, *8*(19), R693–695. https://doi.org/10.1016/s0960-9822(98)70438-5

Fasick, V., Spengler, R. N., Samankan, S., Nader, N. D., & Ignatowski, T. A. (2015). The hippocampus and TNF: Common links between chronic pain and depression. *Neuroscience & Biobehavioral Reviews*, *53*, 139–159. https://doi.org/10.1016/j.neubiorev.2015.03.014

Felice, D., Cryan, J. F., & O'Leary, O. F. (2020). GABAB receptors: Anxiety and mood disorders. In *Behavioral Neurobiology of GABAB Receptor Function,* 241–265 https://doi.org/10.1007/7854_2020_171

Fischer, R., & Maier, O. (2015). Interrelation of oxidative stress and inflammation in neurodegenerative disease: role of TNF. *Oxid Med Cell Longev*, *2015*, 610813. https://doi.org/10.1155/2015/610813

Fruhauf-Perez, P. K., Temp, F. R., Pillat, M. M., Signor, C., Wendel, A. L., Ulrich, H., Mello, C. F., & Rubin, M. A. (2018). Spermine protects from LPS-induced memory deficit via BDNF and TrkB activation. *Neurobiol Learn Mem*, *149*, 135–143. https://doi.org/10.1016/j.nlm.2018.02.012

Fumagalli, F., Racagni, G., & Riva, M. (2006). Shedding light into the role of BDNF in the pharmacotherapy of Parkinson's disease. *The pharmacogenomics journal*, *6*(2), 95–104. https://doi.org/10.1038/sj.tpj.6500360

Gandhi, S., & Abramov, A. Y. (2012). Mechanism of oxidative stress in neurodegeneration. *Oxid Med Cell Longev*, *2012*, 428010. https://doi.org/10.1155/2012/428010

Gayle, D. A., Ling, Z., Tong, C., Landers, T., Lipton, J. W., & Carvey, P. M. (2002). Lipopolysaccharide (LPS)-induced dopamine cell loss in culture: roles of tumor necrosis factor-alpha, interleukin-1beta, and nitric oxide. *Brain Res Dev Brain Res*, *133*(1), 27–35. https://doi.org/10.1016/s0165-3806(01)00315-7

George, L., Ramasamy, T., Sirajudeen, K., & Manickam, V. (2019). LPS-induced apoptosis is partially mediated by hydrogen sulphide in RAW 264.7 murine macrophages. *Immunological investigations*, *48*(5), 451–465. https://doi.org/10.1080/08820139.2019.1566355

Ghasemi-Dehnoo, M., Amini-Khoei, H., Lorigooini, Z., AnjomShoa, M., & Rafieian-Kopaei, M. (2023). Ferulic acid ameliorates ulcerative colitis in a rat model via the inhibition of two LPS-TLR4-NF-κB and NF-κB-INOS-NO signaling pathways and thus alleviating the inflammatory, oxidative and apoptotic conditions in the colon tissue. *Inflammopharmacology*, *31*(5), 2587–2597. https://doi.org/10.1007/s10787-023-01277-y

Goddard, A. W., Ball, S. G., Martinez, J., Robinson, M. J., Yang, C. R., Russell, J. M., & Shekhar, A. (2010). Current perspectives of the roles of the central norepinephrine system in anxiety and depression. *Depress Anxiety*, *27*(4), 339–350. https://doi.org/10.1002/da.20642

Goel, R., Bhat, S. A., Hanif, K., Nath, C., & Shukla, R. (2018). Angiotensin II Receptor Blockers Attenuate Lipopolysaccharide-Induced Memory Impairment by Modulation of NF-kappaB-Mediated BDNF/CREB Expression and Apoptosis in Spontaneously Hypertensive Rats. *Mol Neurobiol*, *55*(2), 1725–1739. https://doi.org/10.1007/s12035-017-0450-5

Guadagno, J., Xu, X., Karajgikar, M., Brown, A., & Cregan, S. P. (2013). Microglia-derived TNFalpha induces apoptosis in neural precursor cells via transcriptional activation of the Bcl-2 family member Puma. *Cell Death Dis*, *4*(3), e538. https://doi.org/10.1038/cddis.2013.59

Guldager, M. B., Biojone, C., Silva, N. R., Godoy, L. D., & Joca, S. (2024). New insights into the involvement of serotonin and BDNF-TrkB signalling in cannabidiol's antidepressant effect. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 111029. https://doi.org/10.1016/j.pnpbp.2024.111029

Guo, Y., Cai, H., Chen, L., Liang, D., Yang, R., Dang, R., & Jiang, P. (2016). Quantitative profiling of neurotransmitter abnormalities in the hippocampus of rats treated with lipopolysaccharide: Focusing on kynurenine pathway and implications for depression. *J Neuroimmunol*, *295–296*, 41–46. https://doi.org/10.1016/j.jneuroim.2016.04.006

Gyoneva, S., & Ransohoff, R. M. (2015). Inflammatory reaction after traumatic brain injury: therapeutic potential of targeting cell-cell communication by chemokines. *Trends Pharmacol Sci*, *36*(7), 471–480. https://doi.org/10.1016/j.tips.2015.04.003

Hashimoto, R., Kakigi, R., Nakamura, K., Itoh, S., Daida, H., Okada, T., & Katoh, Y. (2017). LPS enhances expression of CD204 through the MAPK/ERK pathway in murine bone marrow macrophages. *Atherosclerosis*, *266*, 167–175. https://doi.org/10.1016/j.atherosclerosis.2017.10.005

Hauss-Wegrzyniak, B., Lynch, M. A., Vraniak, P. D., & Wenk, G. L. (2002). Chronic brain inflammation results in cell loss in the entorhinal cortex and impaired LTP in perforant path-granule cell synapses. *Exp Neurol*, *176*(2), 336–341. https://doi.org/10.1006/exnr.2002.7966

Hayden, M. S., & Ghosh, S. (2011). NF-kappaB in immunobiology. *Cell Res*, *21*(2), 223–244. https://doi.org/10.1038/cr.2011.13

Head, E. (2009). Oxidative damage and cognitive dysfunction: antioxidant treatments to promote healthy brain aging. *Neurochem Res*, *34*(4), 670–678. https://doi.org/10.1007/s11064-008-9808-4

Hedayati-Moghadam, M., Seyedi, F., Hosseini, M., Mansouri, M., Sotoudeh, M. M., Beheshti, F., Askarpour, H., Kheirkhah, A., & Baghcheghi, Y. (2024). Selenium prevented renal tissue damage in lipopolysaccharide-treated rats. *J Complement Integr Med*, *21*(1), 53–60. https://doi.org/10.1515/jcim-2023-0154

Heneka, M. T. (2017). Inflammasome activation and innate immunity in A lzheimer's disease. *Brain pathology*, *27*(2), 220–222. https://doi.org/10.1111/bpa.12483

Hing, B., Sathyaputri, L., & Potash, J. B. (2018). A comprehensive review of genetic and epigenetic mechanisms that regulate BDNF expression and function with relevance to major depressive disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *177*(2), 143–167. https://doi.org/10.1002/ajmg.b.32616

Hosseini, M., Anaeigoudari, A., Beheshti, F., Soukhtanloo, M., & Nosratabadi, R. (2018). Protective effect against brain tissues oxidative damage as a possible mechanism for beneficial effects of L-arginine on lipopolysaccharide induced memory impairment in rats. *Drug and*

chemical toxicology, *41*(2), 175–181. https://doi.org/10.1080/01480545.2017.1336173

Hosseini, M., Bardaghi, Z., Askarpour, H., Jafari, M. M., Golkar, A., Shirzad, S., Rajabian, A., & Salmani, H. (2024). Minocycline mitigated enduring neurological consequences in the mice model of sepsis. *Behav Brain Res*, *461*, 114856. https://doi.org/10.1016/j.bbr.2024.114856

Hosseini, M., Salmani, H., & Baghcheghi, Y. (2021). Losartan improved hippocampal long-term potentiation impairment induced by repeated LPS injection in rats. *Physiol Rep*, *9*(10), e14874. https://doi.org/10.14814/phy2.14874

Hosseini, Z., Beheshti, F., Hosseini Kakhki, F. S., Hosseini, M., & Anaeigoudari, A. (2024). Sodium nitroprusside restored lipopolysaccharide-induced learning and memory impairment in male rats via attenuating inflammation and oxidative stress. *Physiol Rep*, *12*(11), e16053. https://doi.org/10.14814/phy2.16053

Hritcu, L., & Gorgan, L. D. (2014). Intranigral lipopolysaccharide induced anxiety and depression by altered BDNF mRNA expression in rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry*, *51*, 126–132. https://doi.org/10.1016/j.pnpbp.2014.01.016

Hsueh, P. T., Wang, H. H., Liu, C. L., Ni, W. F., Chen, Y. L., & Liu, J. K. (2017). Expression of cerebral serotonin related to anxiety-like behaviors in C57BL/6 offspring induced by repeated subcutaneous prenatal exposure to low-dose lipopolysaccharide. *PLoS One*, *12*(6), e0179970. https://doi.org/10.1371/journal.pone.0179970

Hu, Y., Li, H., Zhang, J., Zhang, X., Xia, X., Qiu, C., Liao, Y., Chen, H., Song, Z., & Zhou, W. (2020). Periodontitis induced by P. gingivalis-LPS is associated with neuroinflammation and learning and memory impairment in Sprague-Dawley rats. *Frontiers in neuroscience*, *14*, 658. https://doi.org/10.3389/fnins.2020.00658

Huang, W. T., Niu, K. C., Chang, C. K., Lin, M. T., & Chang, C. P. (2008). Curcumin inhibits the increase of glutamate, hydroxyl radicals and PGE2 in the hypothalamus and reduces fever during LPS-induced systemic inflammation in rabbits. *Eur J Pharmacol*, *593*(1–3), 105–111. https://doi.org/10.1016/j.ejphar.2008.07.017

Huang, X., Hussain, B., & Chang, J. (2021). Peripheral inflammation and blood-brain barrier disruption: effects and mechanisms. *CNS Neurosci Ther*, *27*(1), 36–47. https://doi.org/10.1111/cns.13569

Hughes, P. D., Belz, G. T., Fortner, K. A., Budd, R. C., Strasser, A., & Bouillet, P. (2008). Apoptosis regulators Fas and Bim cooperate in shutdown of chronic immune responses and prevention of autoimmunity. *Immunity*, *28*(2), 197–205. https://doi.org/10.1016/j.immuni.2007.12.017

Inoue, S., Browne, G., Melino, G., & Cohen, G. M. (2009). Ordering of caspases in cells undergoing apoptosis by the intrinsic pathway. *Cell Death Differ*, *16*(7), 1053–1061. https://doi.org/10.1038/cdd.2009.29

Iroegbu, J. D., Ijomone, O. K., Femi-Akinlosotu, O. M., & Ijomone, O. M. (2021). ERK/MAPK signalling in the developing brain: Perturbations and consequences. *Neurosci Biobehav Rev*, *131*, 792–805. https://doi.org/10.1016/j.neubiorev.2021.10.009

Jalilvand, N., Baghcheghi, Y., Fani, M., Beheshti, F., Ebrahimzadeh-Bideskan, A., Marefati, N., Moghimian, M., & Hosseini, M. (2024). The effects of olibanum on male reproductive system damage in a lipopolysaccharide induced systemic inflammation model in rat. *Heliyon*, *10*(16), e36033. https://doi.org/10.1016/j.heliyon.2024.e36033

Jerala, R. (2007). Structural biology of the LPS recognition. *Int J Med Microbiol*, *297*(5), 353–363. https://doi.org/10.1016/j.ijmm.2007.04.001

Ji, Q., Sun, Z., Yang, Z., Zhang, W., Ren, Y., Chen, W., Yao, M., & Nie, S. (2021). Protective effect of ginsenoside Rg1 on LPS-induced apoptosis of lung epithelial cells. *Mol Immunol*, *136*, 168–174. https://doi.org/10.1016/j.molimm.2018.11.003

Jiménez-Balado, J., & Eich, T. S. (2021). GABAergic dysfunction, neural network hyperactivity and memory impairments in human aging and Alzheimer's disease. Seminars in Cell & Developmental Biology, 116, 146–159. https://doi.org/10.1016/j.semcdb.2021.01.005

Juan, C. A., Pérez de la Lastra, J. M., Plou, F. J., & Pérez-Lebeña, E. (2021). The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. *International Journal of Molecular Sciences*, *22*(9), 4642. https://doi.org/10.3390/ijms22094642

Juanola, C., Giralt, M., Jimenez, M., Mourelle, M., & Vergara, P. (1998). Mucosal mast cells are involved in CCK disruption of MMC in the rat intestine. *Am J Physiol*, *275*(1), G63–67. https://doi.org/10.1152/ajpgi.1998.275.1.G63

Kaneko, Y. S., Ota, A., Nakashima, A., Mori, K., Nagatsu, I., & Nagatsu, T. (2012). Regulation of oxidative stress in long-lived lipopolysaccharide-activated microglia. *Clin Exp Pharmacol Physiol*, *39*(7), 599–607. https://doi.org/10.1111/j.1440-1681.2012.05716.x

Karege, F., Schwald, M., & Cisse, M. (2002). Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. *Neurosci Lett*, *328*(3), 261–264. https://doi.org/10.1016/s0304-3940(02)00529-3

Katoh-Semba, R., Wakako, R., Komori, T., Shigemi, H., Miyazaki, N., Ito, H., Kumagai, T., Tsuzuki, M., Shigemi, K., & Yoshida, F. (2007). Age-related changes in BDNF protein levels in human serum: differences between autism cases and normal controls. *International Journal of Developmental Neuroscience*, *25*(6), 367–372. https://doi.org/10.1016/j.ijdevneu.2007.07.002

Kelly, A., Vereker, E., Nolan, Y., Brady, M., Barry, C., Loscher, C. E., Mills, K. H., & Lynch, M. A. (2003). Activation of p38 plays a pivotal role in the inhibitory effect of lipopolysaccharide and interleukin-1β on long term potentiation in rat dentate gyrus. *Journal of Biological Chemistry*, *278*(21), 19453–19462. https://doi.org/10.1074/jbc.M301938200

Kempuraj, D., Thangavel, R., Natteru, P. A., Selvakumar, G. P., Saeed, D., Zahoor, H., Zaheer, S., Iyer, S. S., & Zaheer, A. (2016). Neuroinflammation Induces Neurodegeneration. *J Neurol Neurosurg Spine*, *1*(1), 1003.

Keymoradzadeh, A., Hedayati Ch, M., Abedinzade, M., Gazor, R., Rostampour, M., & Taleghani, B. K. (2020). Enriched environment effect on lipopolysaccharide-induced spatial learning, memory impairment and hippocampal inflammatory cytokine levels in male rats. *Behav Brain Res*, *394*, 112814. https://doi.org/10.1016/j.bbr.2020.112814

Khajevand-Khazaei, M. R., Ziaee, P., Motevalizadeh, S. A., Rohani, M., Afshin-Majd, S., Baluchnejadmojarad, T., & Roghani, M. (2018). Naringenin ameliorates learning and memory impairment following systemic lipopolysaccharide challenge in the rat. *Eur J Pharmacol*, *826*, 114–122. https://doi.org/10.1016/j.ejphar.2018.03.001

Kheir-Eldin, A. A., Motawi, T. K., Gad, M. Z., & Abd-ElGawad, H. M. (2001). Protective effect of vitamin E, beta-carotene and N-acetylcysteine from the brain oxidative stress induced in rats by lipopolysaccharide. *Int J Biochem Cell Biol*, *33*(5), 475–482. https://doi.org/10.1016/s1357-2725(01)00032–2

Kim, Y. E., Hwang, C. J., Lee, H. P., Kim, C. S., Son, D. J., Ham, Y. W., Hellstrom, M., Han, S. B., Kim, H. S., Park, E. K., & Hong, J. T. (2017). Inhibitory effect of punicalagin on lipopolysaccharide-induced neuroinflammation, oxidative stress and memory impairment via inhibition of nuclear factor-kappaB. *Neuropharmacology*, *117*, 21–32. https://doi.org/10.1016/j.neuropharm.2017.01.025

Kirsten, T. B., Queiroz-Hazarbassanov, N., Bernardi, M. M., & Felicio, L. F. (2015). Prenatal zinc prevents communication impairments and BDNF disturbance in a rat model of autism induced by prenatal lipopolysaccharide exposure. *Life Sci*, *130*, 12–17. https://doi.org/10.1016/j.lfs.2015.02.027

Kitazawa, M., Cheng, D., Tsukamoto, M. R., Koike, M. A., Wes, P. D., Vasilevko, V., Cribbs, D. H., & LaFerla, F. M. (2011). Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal beta-catenin pathway function in an Alzheimer's disease model. *J Immunol*, *187*(12), 6539–6549. https://doi.org/10.4049/jimmunol.1100620

Knapp, L. T., & Klann, E. (2002). Role of reactive oxygen species in hippocampal long-term potentiation: contributory or inhibitory? *J Neurosci Res*, *70*(1), 1–7. https://doi.org/10.1002/jnr.10371

Korte-Bouws, G. A., Van Heesch, F., Westphal, K. G., Ankersmit, L. M., Van Oosten, E. M., Güntürkün, O., & Korte, S. M. (2018). Bacterial lipopolysaccharide increases serotonin metabolism in both medial prefrontal cortex and nucleus accumbens in male wild type rats, but not in serotonin transporter knockout rats. *Pharmaceuticals*, *11*(3), 66. https://doi.org/10.3390/ph11030066

Krishnamurthy, P., & Wadhwani, A. (2012). Antioxidant enzymes and human health. *Antioxidant enzyme*, *1*, 3–18.

Kubera, M., Obuchowicz, E., Goehler, L., Brzeszcz, J., & Maes, M. (2011). In animal models, psychosocial stress-induced (neuro)inflammation, apoptosis and reduced neurogenesis are associated to the onset of depression. *Prog Neuropsychopharmacol Biol Psychiatry*, *35*(3), 744–759. https://doi.org/10.1016/j.pnpbp.2010.08.026

Lawrence, S., & Scofield, R. H. (2024). Post traumatic stress disorder associated hypothalamic-pituitary-adrenal axis dysregulation and physical illness. *Brain Behav Immun Health*, *41*, 100849. https://doi.org/10.1016/j.bbih.2024.100849

Lee, B., Shim, I., & Lee, H. (2018). Gypenosides Attenuate Lipopolysaccharide-Induced Neuroinflammation and Memory Impairment in Rats. *Evid Based Complement Alternat Med*, *2018*, 4183670. https://doi.org/10.1155/2018/4183670

Lee, B., Sur, B., Park, J., Kim, S. H., Kwon, S., Yeom, M., Shim, I., Lee, H., & Hahm, D. H. (2013). Ginsenoside rg3 alleviates lipopolysaccharide-induced learning and memory impairments by anti-inflammatory activity in rats. *Biomol Ther (Seoul)*, *21*(5), 381–390. https://doi.org/10.4062/biomolther.2013.053

Lee, J. W., Lee, Y. K., Yuk, D. Y., Choi, D. Y., Ban, S. B., Oh, K. W., & Hong, J. T. (2008). Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. *Journal of neuroinflammation*, *5*, 1–14. https://doi.org/10.1186/1742-2094-5-37

Lee, M. (2013). Neurotransmitters and microglial-mediated neuroinflammation. *Curr Protein Pept Sci*, *14*(1), 21–32. https://doi.org/10.2174/1389203711314010005

Leite, J. A., Orellana, A. M. M., Kinoshita, P. F., de Mello, N. P., Scavone, C., & Kawamoto, E. M. (2017). Neuroinflammation and neurotransmission mechanisms involved in neuropsychiatric disorders. In *Mechanisms of Neuroinflammation*. IntechOpen. http://dx.doi.org/10.5772/intechopen.69343

Levi-Montalcini, R., & Angeletti, P. U. (1968). Nerve growth factor. *Physiological Reviews*, *48*(3), 534–569. https://doi.org/10.1152/physrev.1968.48.3.534

Li, Y., Li, F., Gong, Q., Wu, Q., & Shi, J. (2011). Inhibitory effects of Dendrobium alkaloids on memory impairment induced by lipopolysaccharide in rats. *Planta Med*, *77*(2), 117–121. https://doi.org/10.1055/s-0030-1250235

Liang, L., Liu, P., Deng, Y., Li, J., & Zhao, S. (2024). L-lactate inhibits lipopolysaccharide-induced inflammation of microglia in the hippocampus. *Int J Neurosci*, *134*(1), 45–52. https://doi.org/10.1080/00207454.2022.2084089

Ling, Z., Zhu, Y., Tong, C., Snyder, J. A., Lipton, J. W., & Carvey, P. M. (2006). Progressive dopamine neuron loss following supra-nigral lipopolysaccharide (LPS) infusion into rats exposed to LPS prenatally. *Exp Neurol*, *199*(2), 499–512. https://doi.org/10.1016/j.expneurol.2006.01.010

Liu, M. S., Tian, Z. Y., Zhang, Z., Yang, F., Lou, Y., Wang, Y. J., Zeng, Y. J., Zhang, Z. W., Zhu, D. L., & Li, P. (2023). Impaired Cognitive Function in Patients With Autonomous Cortisol Secretion in Adrenal Incidentalomas. *J Clin Endocrinol Metab*, *108*(3), 633–641. https://doi.org/10.1210/clinem/dgac603

Liu, T., Sun, L., Zhang, Y., Wang, Y., & Zheng, J. (2022). Imbalanced GSH/ROS and sequential cell death. *J Biochem Mol Toxicol*, *36*(1), e22942. https://doi.org/10.1002/jbt.22942

Liu, Y., Zhang, Y., Zheng, X., Fang, T., Yang, X., Luo, X., Guo, A., Newell, K. A., Huang, X. F., & Yu, Y. (2018). Galantamine improves cognition, hippocampal inflammation, and synaptic plasticity impairments induced by lipopolysaccharide in mice. *J Neuroinflammation*, *15*(1), 112. https://doi.org/10.1186/s12974–018–1141–5

Lorda-Diez, C. I., Garcia-Riart, B., Montero, J. A., Rodriguez-León, J., Garcia-Porrero, J. A., & Hurle, J. M. (2015). Apoptosis during embryonic tissue remodeling is accompanied by cell senescence. *Aging (Albany NY)*, *7*(11), 974. PMCID: PMC4694067 PMID: 26568417

Lv, H., Liu, Y., Zhang, B., Zheng, Y., Ji, H., & Li, S. (2020). The improvement effect of gastrodin on LPS/GalN-induced fulminant hepatitis via inhibiting inflammation and apoptosis and restoring autophagy. *Int Immunopharmacol*, *85*, 106627. https://doi.org/10.1016/j.intimp.2020.106627

Lykhmus, O., Mishra, N., Koval, L., Kalashnyk, O., Gergalova, G., Uspenska, K., Komisarenko, S., Soreq, H., & Skok, M. (2016). Molecular Mechanisms Regulating LPS-Induced Inflammation in the Brain. *Front Mol Neurosci*, *9*, 19. https://doi.org/10.3389/fnmol.2016.00019

Lynch, M. A. (2015). Neuroinflammatory changes negatively impact on LTP: A focus on IL-1beta. *Brain Res*, *1621*, 197–204. https://doi.org/10.1016/j.brainres.2014.08.040

Mahmoud, N. S., Elbaset, M. A., Mohawed, O. A., & Ahmed, H. H. (2024). Trimetazidine attenuates neuroinflammation via TLR4/NF-KB pathway inhibition in lipopolysaccharides-induced dementia in rats. *Journal of Applied Pharmaceutical Science*, *14*(4), 125–142. https://doi.org/10.7324/JAPS.2024.166458

Maiti, P., Singh, S. B., Mallick, B., Muthuraju, S., & Ilavazhagan, G. (2008). High altitude memory impairment is due to neuronal apoptosis in hippocampus, cortex and striatum. *Journal of chemical neuroanatomy*, *36*(3–4), 227–238. https://doi.org/10.1016/j.jchemneu.2008.07.003

Marefati, N., Beheshti, F., Vafaee, F., Barabadi, M., & Hosseini, M. (2021). The Effects of Incensole Acetate on Neuro-inflammation, Brain-Derived Neurotrophic Factor and Memory Impairment Induced by Lipopolysaccharide in Rats. *Neurochem Res*, *46*(9), 2473–2484. https://doi.org/10.1007/s11064–021–03381–3

Melo, H. M., da Silva, G. d. S. S., Sant'Ana, M. R., Teixeira, C. V. L., Clarke, J. R., Coreixas, V. S. M., de Melo, B. C., Fortuna, J. T., Forny-Germano, L., & Ledo, J. H. (2020). Palmitate is increased in the cerebrospinal fluid of humans with obesity and induces memory impairment in mice via pro-inflammatory TNF-α. *Cell Reports*, *30*(7), 2180–2194. e2188. https://doi.org/10.1016/j.celrep.2020.01.072

Meng, L., Zheng, X., Xie, K., Li, Y., Liu, D., Xu, Y., Zhang, J., Wu, F., & Guo, G. (2024). Hyperexcitation of the glutamatergic neurons in lateral hypothalamus induced by chronic pain contributes to depression-like behavior and learning and memory impairment in male mice. *Neurobiol Stress*, *31*, 100654. https://doi.org/10.1016/j.ynstr.2024.100654

Meresman, G. F., Vighi, S., Buquet, R. A., Contreras-Ortiz, O., Tesone, M., & Rumi, L. S. (2000). Apoptosis and expression of Bcl-2 and Bax in eutopic endometrium from women with endometriosis. *Fertil Steril*, *74*(4), 760–766. https://doi.org/10.1016/s0015-0282(00)01522-3

Miller, A. H., Haroon, E., Raison, C. L., & Felger, J. C. (2013). Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. *Depress Anxiety*, *30*(4), 297–306. https://doi.org/10.1002/da.22084

Mirza, R. E., Fang, M. M., Ennis, W. J., & Koh, T. J. (2013). Blocking interleukin-1beta induces a healing-associated wound macrophage phenotype and improves healing in type 2 diabetes. *Diabetes*, *62*(7), 2579–2587. https://doi.org/10.2337/db12–1450

Mittler, R. (2017). ROS Are Good. *Trends Plant Sci*, *22*(1), 11–19. https://doi.org/10.1016/j.tplants.2016.08.002

Miwa, M., Tsuboi, M., Noguchi, Y., Enokishima, A., Nabeshima, T., & Hiramatsu, M. (2011). Effects of betaine on lipopolysaccharide-induced memory impairment in mice and the involvement of GABA transporter 2. *J Neuroinflammation*, *8*(1), 153. https://doi.org/10.1186/1742-2094-8-153

Mizumura, K., Gon, Y., Kumasawa, F., Onose, A., Maruoka, S., Matsumoto, K., Hayashi, S., Kobayashi, T., & Hashimoto, S. (2010). Apoptosis signal-regulating kinase 1-mediated signaling pathway regulates lipopolysaccharide-induced tissue factor expression in pulmonary microvascula-

ture. *Int Immunopharmacol*, *10*(9), 1062–1067. https://doi.org/10.1016/j.intimp.2010.06.006

Mizuno, T. (2015). Neuron–microglia interactions in neuroinflammation. *Clinical and Experimental Neuroimmunology*, *6*(3), 225–231. https://doi.org/10.1111/cen3.12228

Moore, K., & Roberts, L. J., 2nd. (1998). Measurement of lipid peroxidation. *Free Radic Res*, *28*(6), 659–671. https://doi.org/10.3109/10715769809065821

Morimoto, K., Watanuki, S., Eguchi, R., Kitano, T., & Otsuguro, K. I. (2023). Short-term memory impairment following recovery from systemic inflammation induced by lipopolysaccharide in mice. *Front Neurosci*, *17*, 1273039. https://doi.org/10.3389/fnins.2023.1273039

Muhammad, T., Ikram, M., Ullah, R., Rehman, S. U., & Kim, M. O. (2019). Hesperetin, a Citrus Flavonoid, Attenuates LPS-Induced Neuroinflammation, Apoptosis and Memory Impairments by Modulating TLR4/NF-kappaB Signaling. *Nutrients*, *11*(3), 648. https://doi.org/10.3390/nu11030648

Muller Herde, A., Schibli, R., Weber, M., & Ametamey, S. M. (2019). Metabotropic glutamate receptor subtype 5 is altered in LPS-induced murine neuroinflammation model and in the brains of AD and ALS patients. *Eur J Nucl Med Mol Imaging*, *46*(2), 407–420. https://doi.org/10.1007/s00259-018-4179-9

Murakami, A., & Ohigashi, H. (2007). Targeting NOX, INOS and COX-2 in inflammatory cells: chemoprevention using food phytochemicals. *Int J Cancer*, *121*(11), 2357–2363. https://doi.org/10.1002/ijc.23161

Murtaj, V., Belloli, S., Di Grigoli, G., Pannese, M., Ballarini, E., Rodriguez-Menendez, V., Marmiroli, P., Cappelli, A., Masiello, V., Monterisi, C., Bellelli, G., Panina-Bordignon, P., & Moresco, R. M. (2019). Age and Sex Influence the Neuro-inflammatory Response to a Peripheral Acute LPS Challenge. *Front Aging Neurosci*, *11*, 299. https://doi.org/10.3389/fnagi.2019.00299

Murtishaw, A. S., Heaney, C. F., Bolton, M. M., Sabbagh, J. J., Langhardt, M. A., & Kinney, J. W. (2016). Effect of acute lipopolysaccharide-induced inflammation in intracerebroventricular-streptozotocin injected rats. *Neuropharmacology*, *101*, 110–122. https://doi.org/10.1016/j.neuropharm.2015.08.044

Musa, N. H., Mani, V., Lim, S. M., Vidyadaran, S., Abdul Majeed, A. B., & Ramasamy, K. (2017). Lactobacilli-fermented cow's milk attenuated lipopolysaccharide-induced neuroinflammation and memory impairment in vitro and in vivo. *J Dairy Res*, *84*(4), 488–495. https://doi.org/10.1017/S0022029917000620

Na, S., Duan, X., Wang, R., Fan, Y., Xue, K., Tian, S., Yang, Z., Li, K., & Yue, J. (2021). Chronic neuroinflammation induced by lipopolysaccharide injection into the third ventricle induces behavioral changes. *Journal of Molecular Neuroscience*, *71*, 1306–1319. https://doi.org/10.1007/s12031-020-01758-7

Nair, P., Lu, M., Petersen, S., & Ashkenazi, A. (2014). Apoptosis initiation through the cell-extrinsic pathway. In *Methods in enzymology* (Vol. 544, pp. 99–128). Elsevier. https://doi.org/10.1016/B978-0-12-417158-9.00005-4

Nakajima, M., Miyajima, M., Ogino, I., Akiba, C., Sugano, H., Hara, T., Fusegi, K., Karagiozov, K., & Arai, H. (2015). Cerebrospinal fluid biomarkers for prognosis of long-term cognitive treatment outcomes in patients with idiopathic normal pressure hydrocephalus. *J Neurol Sci*, *357*(1–2), 88–95. https://doi.org/10.1016/j.jns.2015.07.001

Niaz, A., Karunia, J., Mandwie, M., Keay, K. A., Musumeci, G., Al-Badri, G., & Castorina, A. (2021). Robust Dopaminergic Differentiation and Enhanced LPS-Induced Neuroinflammatory Response in Serum-Deprived Human SH-SY5Y Cells: Implication for Parkinson's Disease. *J Mol Neurosci*, *71*(3), 565–582. https://doi.org/10.1007/s12031-020-01678-6

Nimmervoll, B., White, R., Yang, J. W., An, S., Henn, C., Sun, J. J., & Luhmann, H. J. (2013). LPS-induced microglial secretion of TNFalpha increases activity-dependent neuronal apoptosis in the neonatal cerebral cortex. *Cereb Cortex*, *23*(7), 1742–1755. https://doi.org/10.1093/cercor/bhs156

Ning, B., Ge, T., Wu, Y., Wang, Y., & Zhao, M. (2024). Role of Brain-Derived Neurotrophic Factor in Anxiety or Depression After Percutaneous Coronary Intervention. *Mol Neurobiol*, *61*(5), 2921–2937. https://doi.org/10.1007/s12035-023-03758-1

Nolan, Y., Martin, D., Campbell, V. A., & Lynch, M. A. (2004). Evidence of a protective effect of phosphatidylserine-containing liposomes on lipopolysaccharide-induced impairment of long-term potentiation in the rat hippocampus. *J Neuroimmunol*, *151*(1–2), 12–23. https://doi.org/10.1016/j.jneuroim.2004.02.001

Norouzi, F., Hosseini, M., Abareshi, A., Beheshti, F., Khazaei, M., Shafei, M. N., Soukhtanloo, M., Gholamnezhad, Z., & Anaeigoudari, A. (2019). Memory enhancing effect of Nigella Sativa hydro-alcoholic extract on lipopolysaccharide-induced memory impairment in rats. *Drug Chem Toxicol*, *42*(3), 270–279. https://doi.org/10.1080/01480545.2018.1447578

Nowacka, M. M., Paul-Samojedny, M., Bielecka, A. M., Plewka, D., Czekaj, P., & Obuchowicz, E. (2015). LPS reduces BDNF and VEGF expression in the structures of the HPA axis of chronic social stressed female rats. *Neuropeptides*, *54*, 17–27. https://doi.org/10.1016/j.npep.2015.09.003

Noworyta-Sokolowska, K., Gorska, A., & Golembiowska, K. (2013). LPS-induced oxidative stress and inflammatory reaction in the rat striatum. *Pharmacol Rep*, *65*(4), 863–869. https://doi.org/10.1016/s1734-1140(13)71067-3

Ochoa-de la Paz, L. D., Gulias-Cañizo, R., Ruíz-Leyja, E. D., Sánchez--Castillo, H., & Parodí, J. (2021). The role of GABA neurotransmitter in the human central nervous system, physiology, and pathophysiology. *Revista mexicana de neurociencia*, *22*(2), 67–76. https://doi.org/10.24875/rmn.20000050

Opferman, J. T. (2008). Apoptosis in the development of the immune system. *Cell Death Differ*, *15*(2), 234–242. https://doi.org/10.1038/sj.cdd.4402182

Pandya, C. D., Kutiyanawalla, A., & Pillai, A. (2013). BDNF-TrkB signaling and neuroprotection in schizophrenia. *Asian J Psychiatr*, *6*(1), 22–28. https://doi.org/10.1016/j.ajp.2012.08.010

Patel, M., & Singh, S. (2022). Apigenin Attenuates Functional and Structural Alterations via Targeting NF-kB/Nrf2 Signaling Pathway in LPS-Induced Parkinsonism in Experimental Rats : Apigenin Attenuates LPS-Induced Parkinsonism in Experimental Rats. *Neurotox Res*, *40*(4), 941–960. https://doi.org/10.1007/s12640-022-00521-7

Patki, G., Solanki, N., Atrooz, F., Allam, F., & Salim, S. (2013). Depression, anxiety-like behavior and memory impairment are associated with increased oxidative stress and inflammation in a rat model of social stress. *Brain Res*, *1539*, 73–86. https://doi.org/10.1016/j.brainres.2013.09.033

Persson, M., Brantefjord, M., Hansson, E., & Ronnback, L. (2005). Lipopolysaccharide increases microglial GLT-1 expression and glutamate uptake capacity in vitro by a mechanism dependent on TNF-alpha. *Glia*, *51*(2), 111–120. https://doi.org/10.1002/glia.20191

Phaniendra, A., Jestadi, D. B., & Periyasamy, L. (2015). Free radicals: properties, sources, targets, and their implication in various diseases. *Indian journal of clinical biochemistry*, *30*, 11–26. https://doi.org/10.1007/s12291-014-0446-0

Polles, A. G., Williams, M. K., Phalin, B. R., Teitelbaum, S., & Merlo, L. J. (2020). Neuropsychological impairment associated with substance use by physicians. *J Neurol Sci*, *411*, 116714. https://doi.org/10.1016/j.jns.2020.116714

Pourganji, M., Hosseini, M., Soukhtanloo, M., Zabihi, H., & Hadjzadeh, M. A. (2014). Protective role of endogenous ovarian hormones against learning and memory impairments and brain tissues oxidative damage induced by lipopolysaccharide. *Iran Red Crescent Med J*, *16*(3), e13954. https://doi.org/10.5812/ircmj.13954

Prevot, T., & Sibille, E. (2021). Altered GABA-mediated information processing and cognitive dysfunctions in depression and other brain disorders. *Mol Psychiatry*, *26*(1), 151–167. https://doi.org/10.1038/s41380-020-0727-3

Puelles, L., Martinez-De-La-Torre, M., Bardet, S., & Rubenstein, J. (2012). Hypothalamus. In *The mouse nervous system* (pp. 221–312). Elsevier. https://doi.org/10.1016/B978-0-12-369497-3.10008-1

Qin, L., Liu, Y., Hong, J. S., & Crews, F. T. (2013). NADPH oxidase and aging drive microglial activation, oxidative stress, and dopaminergic neurodegeneration following systemic LPS administration. *Glia*, *61*(6), 855–868. https://doi.org/10.1002/glia.22479

Qin, L., Liu, Y., Wang, T., Wei, S. J., Block, M. L., Wilson, B., Liu, B., & Hong, J. S. (2004). NADPH oxidase mediates lipopolysaccharide-induced neurotoxicity and proinflammatory gene expression in activated microglia. *J Biol Chem*, *279*(2), 1415–1421. https://doi.org/10.1074/jbc.M307657200

Qu, D., Ye, Z., Zhang, W., Dai, B., Chen, G., Wang, L., Shao, X., Xiang, A., Lu, Z., & Shi, J. (2022). Cyanidin Chloride Improves LPS-Induced Depression-Like Behavior in Mice by Ameliorating Hippocampal Inflammation and Excitotoxicity. *ACS Chem Neurosci*, *13*(21), 3023–3033. https://doi.org/10.1021/acschemneuro.2c00087

Rai, B., Naylor, P. E., Siqueiros-Sanchez, M., Wintermark, M., Raman, M. M., Jo, B., Reiss, A. L., & Green, T. (2023). Novel effects of Ras-MAPK pathogenic variants on the developing human brain and their link to gene expression and inhibition abilities. *Translational psychiatry*, *13*(1), 245. https://doi.org/10.1038/s41398-023-02504-4

Ramalingam, P., Poulos, M. G., Lazzari, E., Gutkin, M. C., Lopez, D., Kloss, C. C., Crowley, M. J., Katsnelson, L., Freire, A. G., Greenblatt, M. B., Park, C. Y., & Butler, J. M. (2020). Chronic activation of endothelial MAPK disrupts hematopoiesis via NFKB dependent inflammatory stress reversible by SCGF. *Nat Commun*, *11*(1), 666. https://doi.org/10.1038/s41467-020-14478-8

Rawani, N. S., Chan, A. W., Dursun, S. M., & Baker, G. B. (2024). The Underlying Neurobiological Mechanisms of Psychosis: Focus on Neurotransmission Dysregulation, Neuroinflammation, Oxidative Stress, and Mitochondrial Dysfunction. *Antioxidants (Basel)*, *13*(6), 709. https://doi.org/10.3390/antiox13060709

Rezaei, S., Prevot, T. D., Vieira, E., & Sibille, E. (2024). LPS-induced inflammation reduces GABAergic interneuron markers and brain-derived neurotrophic factor in mouse prefrontal cortex and hippocampus. *Brain Behav Immun Health*, *38*, 100761. https://doi.org/10.1016/j.bbih.2024.100761

Ritchie, K. (2004). Mild cognitive impairment: an epidemiological perspective. *Dialogues Clin Neurosci*, *6*(4), 401–408. https://doi.org/10.31887/DCNS.2004.6.4/kritchie

Sandkuhler, J. (2007). Understanding LTP in pain pathways. *Mol Pain*, *3*, 9. https://doi.org/10.1186/1744-8069-3-9

Sangaran, P. G., Ibrahim, Z. A., Chik, Z., Mohamed, Z., & Ahmadiani, A. (2021). LPS Preconditioning Attenuates Apoptosis Mechanism by Inhibiting NF-kappaB and Caspase-3 Activity: TLR4 Pre-activation in the Signaling Pathway of LPS-Induced Neuroprotection. *Mol Neurobiol*, *58*(5), 2407–2422. https://doi.org/10.1007/s12035-020-02227-3

Sebai, H., Gadacha, W., Sani, M., Aouani, E., Ghanem-Boughanmi, N., & Ben-Attia, M. (2009). Protective effect of resveratrol against lipopolysaccharide-induced oxidative stress in rat brain. *Brain Inj*, *23*(13–14), 1089–1094. https://doi.org/10.3109/02699050903379370

Seoane, N., Picos, A., Morana-Fernandez, S., Schmidt, M., Dolga, A., Campos-Toimil, M., & Vina, D. (2024). Effects of Sodium Nitroprusside on Lipopolysaccharide-Induced Inflammation and Disruption of Blood-Brain Barrier. *Cells*, *13*(10), 843. https://doi.org/10.3390/cells13100843

Sharifi, A. M., Hoda, F. E., & Noor, A. M. (2010). Studying the effect of LPS on cytotoxicity and apoptosis in PC12 neuronal cells: role of Bax, Bcl-2, and Caspase-3 protein expression. *Toxicol Mech Methods*, *20*(6), 316–320. https://doi.org/10.3109/15376516.2010.486420

Sharma, N., & Nehru, B. (2015). Characterization of the lipopolysaccharide induced model of Parkinson's disease: Role of oxidative stress and neuroinflammation. *Neurochem Int*, *87*, 92–105. https://doi.org/10.1016/j.neuint.2015.06.004

Sharma, V., Singh, T. G., Kaur, A., Mannan, A., & Dhiman, S. (2023). Brain-Derived Neurotrophic Factor: A Novel Dynamically Regulated Therapeutic Modulator in Neurological Disorders. *Neurochem Res*, *48*(2), 317–339. https://doi.org/10.1007/s11064-022-03755-1

Shimada, H., Park, H., Makizako, H., Doi, T., Lee, S., & Suzuki, T. (2014). Depressive symptoms and cognitive performance in older adults. *J Psychiatr Res*, *57*, 149–156. https://doi.org/10.1016/j.jpsychires.2014.06.004

Silvestro, S., Raffaele, I., Quartarone, A., & Mazzon, E. (2024). Innovative insights into traumatic brain injuries: biomarkers and new pharmacological targets. *International Journal of Molecular Sciences*, *25*(4), 2372. https://doi.org/10.3390/ijms25042372

Singh, S., Sahu, K., Singh, C., & Singh, A. (2022). Lipopolysaccharide induced altered signaling pathways in various neurological disorders. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *395*(3), 285–294. https://doi.org/10.1007/s00210-021-02198-9

Siuda, J., Patalong-Ogiewa, M., Żmuda, W., Targosz-Gajniak, M., Niewiadomska, E., Matuszek, I., Jędrzejowska-Szypułka, H., & Rudzińska-Bar, M. (2017). Cognitive impairment and BDNF serum levels. *Neurologia i neurochirurgia polska*, *51*(1), 24–32. https://doi.org/10.1016/j.pjnns.2016.10.001

Skaper, S. D. (2018). Neurotrophic Factors: An Overview. *Methods Mol Biol*, *1727*, 1–17. https://doi.org/10.1007/978-1-4939-7571-6_1

Skibska, B., Goraca, A., Skibska, A., & Stanczak, A. (2022). Effect of Alpha-Lipoic Acid on Rat Ventricles and Atria under LPS-Induced Oxidative Stress. *Antioxidants (Basel)*, *11*(4), 734. https://doi.org/10.3390/antiox11040734

Soares, N. L., Paiva, I., Bravo, J., Queiroga, C. S. F., Melo, B. F., Conde, S. V., Romao, C. C., Summavielle, T., & Vieira, H. L. A. (2022). Carbon Monoxide Modulation of Microglia-Neuron Communication: Anti-Neuroinflammatory and Neurotrophic Role. *Mol Neurobiol*, *59*(2), 872–889. https://doi.org/10.1007/s12035–021–02643-z

Song, X., Zhou, B., Zhang, P., Lei, D., Wang, Y., Yao, G., Hayashi, T., Xia, M., Tashiro, S., Onodera, S., & Ikejima, T. (2016). Protective Effect of Silibinin on Learning and Memory Impairment in LPS-Treated Rats via ROS-BDNF-TrkB Pathway. *Neurochem Res*, *41*(7), 1662–1672. https://doi.org/10.1007/s11064-016-1881-5

Song, Y. X., Ou, Y. M., & Zhou, J. Y. (2020). Gracillin inhibits apoptosis and inflammation induced by lipopolysaccharide (LPS) to alleviate cardiac injury in mice via improving miR-29a. *Biochem Biophys Res Commun*, *523*(3), 580–587. https://doi.org/10.1016/j.bbrc.2019.11.129

Sorrenti, V., Contarini, G., Sut, S., Dall'Acqua, S., Confortin, F., Pagetta, A., Giusti, P., & Zusso, M. (2018). Curcumin Prevents Acute Neuroinflammation and Long-Term Memory Impairment Induced by Systemic Lipopolysaccharide in Mice. *Front Pharmacol*, *9*, 183. https://doi.org/10.3389/fphar.2018.00183

Stefanis, L., Burke, R. E., & Greene, L. A. (1997). Apoptosis in neurodegenerative disorders. *Curr Opin Neurol*, *10*(4), 299–305. https://doi.org/10.1097/00019052–199708000–00004

Stenfors, C. U., Jonsdottir, I., Hanson, L. M., & Theorell, T. (2017). Associations between systemic pro-inflammatory markers, cognitive function and cognitive complaints in a population-based sample of working adults. *Journal of psychosomatic research*, *96*, 49–59. https://doi.org/10.1016/j.jpsychores.2017.03.010

Stigger, F., Lovatel, G., Marques, M., Bertoldi, K., Moyses, F., Elsner, V., Siqueira, I. R., Achaval, M., & Marcuzzo, S. (2013). Inflammatory response and oxidative stress in developing rat brain and its consequences on motor behavior following maternal administration of LPS and perinatal anoxia. *Int J Dev Neurosci*, *31*(8), 820–827. https://doi.org/10.1016/j.ijdevneu.2013.10.003

Storz, G., & Imlay, J. A. (1999). Oxidative stress. *Curr Opin Microbiol*, *2*(2), 188–194. https://doi.org/10.1016/s1369-5274(99)80033-2

Straub, R. H., & Cutolo, M. (2016). Glucocorticoids and chronic inflammation. *Rheumatology (Oxford)*, *55*(suppl 2), ii6–ii14. https://doi.org/10.1093/rheumatology/kew348

Tanaka, S., Ide, M., Shibutani, T., Ohtaki, H., Numazawa, S., Shioda, S., & Yoshida, T. (2006). Lipopolysaccharide-induced microglial activation induces learning and memory deficits without neuronal cell deathin rats. *Journal of neuroscience research*, *83*(4), 557–566. https://doi.org/10.1002/jnr.20752

Taylor, J. M., Main, B. S., & Crack, P. J. (2013). Neuroinflammation and oxidative stress: co-conspirators in the pathology of Parkinson's disease. *Neurochem Int*, *62*(5), 803–819. https://doi.org/10.1016/j.neuint.2012.12.016

Thingore, C., Kshirsagar, V., & Juvekar, A. (2021). Amelioration of oxidative stress and neuroinflammation in lipopolysaccharide-induced memory impairment using Rosmarinic acid in mice. *Metab Brain Dis*, *36*(2), 299–313. https://doi.org/10.1007/s11011-020-00629-9

Thomas, K., & Davies, A. (2005). Neurotrophins: a ticket to ride for BDNF. *Curr Biol*, *15*(7), R262–264. https://doi.org/10.1016/j.cub.2005.03.023

Tsai, S.-J. (2005). Is autism caused by early hyperactivity of brain-derived neurotrophic factor? *Medical hypotheses*, *65*(1), 79–82. https://doi.org/10.1016/j.mehy.2005.01.034

Tsukahara, T., Hara, H., Haniu, H., & Matsuda, Y. (2021). The Combined Effects of Lysophospholipids against Lipopolysaccharide-induced Inflammation and Oxidative Stress in Microglial Cells. *J Oleo Sci*, *70*(7), 947–954. https://doi.org/10.5650/jos.ess21069

Tyagi, E., Agrawal, R., Nath, C., & Shukla, R. (2008). Influence of LPS-induced neuroinflammation on acetylcholinesterase activity in rat brain. *J Neuroimmunol*, *205*(1–2), 51–56. https://doi.org/10.1016/j.jneuroim.2008.08.015

Tyagi, E., Agrawal, R., Nath, C., & Shukla, R. (2010). Cholinergic protection via alpha7 nicotinic acetylcholine receptors and PI3K-Akt pathway in LPS-induced neuroinflammation. *Neurochem Int*, *56*(1), 135–142. https://doi.org/10.1016/j.neuint.2009.09.011

Vaglio-Garro, A., Kozlov, A. V., Smirnova, Y. D., & Weidinger, A. (2024). Pathological Interplay between Inflammation and Mitochondria Aggravates Glutamate Toxicity. *International Journal of Molecular Sciences*, *25*(4), 2276. https://doi.org/10.3390/ijms25042276

Valero, J., Mastrella, G., Neiva, I., Sanchez, S., & Malva, J. O. (2014). Long-term effects of an acute and systemic administration of LPS on adult neurogenesis and spatial memory. *Front Neurosci*, *8*, 83. https://doi.org/10.3389/fnins.2014.00083

Vasconcelos, A. R., Yshii, L. M., Viel, T. A., Buck, H. S., Mattson, M. P., Scavone, C., & Kawamoto, E. M. (2014). Intermittent fasting attenuates lipopolysaccharide-induced neuroinflammation and memory impairment. *J Neuroinflammation*, *11*, 85. https://doi.org/10.1186/1742-2094-11-85

Vasic, V., & Schmidt, M. H. H. (2017). Resilience and Vulnerability to Pain and Inflammation in the Hippocampus. *Int J Mol Sci*, *18*(4), 739. https://doi.org/10.3390/ijms18040739

Vaux, D. L., & Flavell, R. A. (2000). Apoptosis genes and autoimmunity. *Curr Opin Immunol*, *12*(6), 719–724. https://doi.org/10.1016/s0952-7915(00)00168-0

Vereker, E., Campbell, V., Roche, E., McEntee, E., & Lynch, M. A. (2000). Lipopolysaccharide inhibits long term potentiation in the rat dentate gyrus by activating caspase-1. *J Biol Chem*, *275*(34), 26252–26258. https://doi.org/10.1074/jbc.M002226200

Vier, J., Groth, M., Sochalska, M., & Kirschnek, S. (2016). The anti-apoptotic Bcl-2 family protein A1/Bfl-1 regulates neutrophil survival and homeostasis and is controlled via PI3K and JAK/STAT signaling. *Cell death & disease*, *7*(2), e2103-e2103. https://doi.org/10.1038/cddis.2016.23

Walsh, J. J., & Tschakovsky, M. E. (2018). Exercise and circulating BDNF: Mechanisms of release and implications for the design of exercise interventions. *Appl Physiol Nutr Metab*, *43*(11), 1095–1104. https://doi.org/10.1139/apnm-2018–0192

Wang, A.-L., Liou, Y.-M., Pawlak, C. R., & Ho, Y.-J. (2010). Involvement of NMDA receptors in both MPTP-induced neuroinflammation and deficits in episodic-like memory in Wistar rats. *Behavioural Brain Research*, *208*(1), 38–46. https://doi.org/10.1016/j.bbr.2009.11.006

Wang, H., Meng, G. L., Zhang, C. T., Wang, H., Hu, M., Long, Y., Hong, H., & Tang, S. S. (2020). Mogrol attenuates lipopolysaccharide (LPS)-induced memory impairment and neuroinflammatory responses in mice. *J Asian Nat Prod Res*, *22*(9), 864–878. https://doi.org/10.1080/10286020.2019.1642878

Wang, S., Sun-Waterhouse, D., Waterhouse, G. I. N., Zheng, L., Su, G., & Zhao, M. (2021). Effects of food-derived bioactive peptides on cognitive deficits and memory decline in neurodegenerative diseases: A review. *Trends in Food Science & Technology*, *116*, 712–732. https://doi.org/10.1016/j.tifs.2021.04.056

Wang, T.-H., Xiong, L.-L., Yang, S.-F., You, C., Xia, Q.-J., Xu, Y., Zhang, P., Wang, S.-F., & Liu, J. (2017). LPS pretreatment provides neuroprotective roles in rats with subarachnoid hemorrhage by downregulating MMP9 and Caspase3 associated with TLR4 signaling activation. *Molecular neurobiology*, *54*, 7746–7760. https://doi.org/10.1007/s12035-016-0259-7

Wang, X., Wang, W.-M., Han, H., Zhang, Y., Liu, J.-L., Yu, J.-Y., Liu, H.-M., Liu, X.-T., Shan, H., & Wu, S.-C. (2022). Tanshinone IIA protected against lipopolysaccharide-induced brain injury through the protective effect of the blood–brain barrier and the suppression of oxidant stress and inflammatory response. *Food & Function*, *13*(15), 8304–8312. https://doi.org/10.1039/D2FO00710J

Watson, R. W., Redmond, H. P., Wang, J. H., & Bouchier-Hayes, D. (1996). Bacterial ingestion, tumor necrosis factor-alpha, and heat induce programmed cell death in activated neutrophils. *Shock*, *5*(1), 47–51. https://doi.org/10.1097/00024382-199601000-00010

Widmer, R., Engels, M., Voss, P., & Grune, T. (2007). Postanoxic damage of microglial cells is mediated by xanthine oxidase and cyclooxygenase. *Free radical research*, *41*(2), 145–152. https://doi.org/10.1080/10715760600978807

Wigner, P., Synowiec, E., Jozwiak, P., Czarny, P., Bijak, M., Barszczewska, G., Bialek, K., Szemraj, J., Gruca, P., Papp, M., & Sliwinski, T. (2020). The Changes of Expression and Methylation of Genes Involved in Oxidative Stress in Course of Chronic Mild Stress and Antidepressant Therapy with Agomelatine. *Genes (Basel)*, *11*(6), 644. https://doi.org/10.3390/genes11060644

Winocur, G., Becker, S., Luu, P., Rosenzweig, S., & Wojtowicz, J. M. (2012). Adult hippocampal neurogenesis and memory interference. *Behav Brain Res*, *227*(2), 464–469. https://doi.org/10.1016/j.bbr.2011.05.032

Wu, C. W., Chen, Y. C., Yu, L., Chen, H. I., Jen, C. J., Huang, A. M., Tsai, H. J., Chang, Y. T., & Kuo, Y. M. (2007). Treadmill exercise counteracts the suppressive effects of peripheral lipopolysaccharide on hippocampal neurogenesis and learning and memory. *J Neurochem*, *103*(6), 2471–2481. https://doi.org/10.1111/j.1471-4159.2007.04987.x

Wu, Y., Fu, Y., Rao, C., Li, W., Liang, Z., Zhou, C., Shen, P., Cheng, P., Zeng, L., Zhu, D., Zhao, L., & Xie, P. (2016). Metabolomic analysis reveals metabolic disturbances in the prefrontal cortex of the lipopolysaccharide-induced mouse model of depression. *Behav Brain Res*, *308*, 115–127. https://doi.org/10.1016/j.bbr.2016.04.032

Wu, Z., Huang, Y., Hu, W., Ren, L., Jiang, P., Margolskee, R. F., Wang, H., & Feng, S. (2022). Lipopolysaccharide-induced inflammation increases nitric oxide production in taste buds. *Brain Behav Immun*, *103*, 145–153. https://doi.org/10.1016/j.bbi.2022.04.016

Wyllie, A. H. (1997). Apoptosis: an overview. *Br Med Bull*, *53*(3), 451–465. https://doi.org/10.1093/oxfordjournals.bmb.a011623

Xia, Y., Wu, Q., Mak, S., Liu, E. Y. L., Zheng, B. Z. Y., Dong, T. T. X., Pi, R., & Tsim, K. W. K. (2022). Regulation of acetylcholinesterase during the lipopolysaccharide-induced inflammatory responses in microglial cells. *FASEB J*, *36*(3), e22189. https://doi.org/10.1096/fj.202101302RR

Xiao, X., Li, W., Xu, Z., Sun, Z., Ye, H., Wu, Y., Zhang, Y., Xie, L., Jiang, D., Jia, R., & Wang, X. (2022). Extracellular vesicles from human umbilical cord mesenchymal stem cells reduce lipopolysaccharide-induced spinal cord injury neuronal apoptosis by mediating miR-29b-3p/PTEN. *Connect Tissue Res*, *63*(6), 634–649. https://doi.org/10.1080/03008207.2022.2060826

Xin, Y. R., Jiang, J. X., Hu, Y., Pan, J. P., Mi, X. N., Gao, Q., Xiao, F., Zhang, W., & Luo, H. M. (2019). The Immune System Drives Synapse Loss During Lipopolysaccharide-Induced Learning and Memory Impairment in Mice. *Front Aging Neurosci*, *11*, 279. https://doi.org/10.3389/fnagi.2019.00279

Xu, X., Li, Z., Ai, X., Tang, Y., Yang, D., & Dou, L. (2022). Human three-dimensional dental pulp organoid model for toxicity screening of dental materials on dental pulp cells and tissue. *Int Endod J*, *55*(1), 79–88. https://doi.org/10.1111/iej.13641

Yeh, T. Y., Chu, W. J., & Huang, Y. S. (2024). GM1 ganglioside protects against LPS-induced neuroinflammatory and oxidative responses by inhibiting the activation of Akt, TAK1 and NADPH oxidase in MG6 microglial cells. *Glycobiology*, *34*(1), cwad087. https://doi.org/10.1093/glycob/cwad087

Yin, R., Zhang, K., Li, Y., Tang, Z., Zheng, R., Ma, Y., Chen, Z., Lei, N., Xiong, L., Guo, P., Li, G., & Xie, Y. (2023). Lipopolysaccharide-induced depression-like model in mice: meta-analysis and systematic evaluation. *Front Immunol*, *14*, 1181973. https://doi.org/10.3389/fimmu.2023.1181973

Zakaria, R., Wan Yaacob, W. M., Othman, Z., Long, I., Ahmad, A. H., & Al-Rahbi, B. (2017). Lipopolysaccharide-induced memory impairment in rats: a model of Alzheimer's disease. *Physiol Res*, *66*(4), 553–565. https://doi.org/10.33549/physiolres.933480

Zanikov, T., Gerasymchuk, M., Ghasemi Gojani, E., Robinson, G. I., Asghari, S., Groves, A., Haselhorst, L., Nandakumar, S., Stahl, C., Cameron, M., Li, D., Rodriguez-Juarez, R., Snelling, A., Hudson, D., Fiselier, A., Kovalchuk, O., & Kovalchuk, I. (2023). The Effect of Combined Treatment of Psilocybin and Eugenol on Lipopolysaccharide-Induced Brain Inflammation in Mice. *Molecules*, *28*(6), 2624. https://doi.org/10.3390/molecules28062624

Zarifkar, A., Choopani, S., Ghasemi, R., Naghdi, N., Maghsoudi, A. H., Maghsoudi, N., Rastegar, K., & Moosavi, M. (2010). Agmatine prevents LPS-induced spatial memory impairment and hippocampal apoptosis. *Eur J Pharmacol*, *634*(1–3), 84–88. https://doi.org/10.1016/j.ejphar.2010.02.029

Zborowski, V. A., Heck, S. O., Marques, L. S., Bastos, N. K., & Nogueira, C. W. (2021). Memory impairment and depressive-like phenotype are accompanied by downregulation of hippocampal insulin and BDNF signaling pathways in prediabetic mice. *Physiol Behav*, *237*, 113346. https://doi.org/10.1016/j.physbeh.2021.113346

Zhang, N., Sui, Y., Jendrichovsky, P., Feng, H., Shi, H., Zhang, X., Xu, S., Sun, W., Zhang, H., Chen, X., Tortorella, M. D., & He, J. (2024). Cholecystokinin B receptor agonists alleviates anterograde amnesia in cholecystokinin-deficient and aged Alzheimer's disease mice. *Alzheimers Res Ther*, *16*(1), 109. https://doi.org/10.1186/s13195-024-01472-1

Zhang, S., Wang, X., Ai, S., Ouyang, W., Le, Y., & Tong, J. (2017). Sepsis-induced selective loss of NMDA receptors modulates hippocampal neuropathology in surviving septic mice. *PLoS One*, *12*(11), e0188273. https://doi.org/10.1371/journal.pone.0188273

Zhang, X. Y., Cao, J. B., Zhang, L. M., Li, Y. F., & Mi, W. D. (2015). Deferoxamine attenuates lipopolysaccharide-induced neuroinflammation and memory impairment in mice. *J Neuroinflammation*, *12*(1), 20. https://doi.org/10.1186/s12974-015-0238-3

Zhang, Y. M., Wei, R. M., Feng, Y. Z., Zhang, K. X., Ge, Y. J., Kong, X. Y., Li, X. Y., & Chen, G. H. (2024). Sleep deprivation aggravates lipopolysaccharide-induced anxiety, depression and cognitive impairment: The role of pro-inflammatory cytokines and synaptic plasticity-associated proteins. *J Neuroimmunol*, *386*, 578252. https://doi.org/10.1016/j.jneuroim.2023.578252

Zhang, Z., Liu, D., Lv, R., Zhao, H., Li, T., Huang, Y., Tian, Z., Gao, X., Luo, P., & Li, X. (2024). FBL Promotes LPS-Induced Neuroinflammation by Activating the NF-kappaB Signaling Pathway. *J Inflamm Res*, *17*, 2217–2231. https://doi.org/10.2147/JIR.S451049

Zhao, J., Bi, W., Xiao, S., Lan, X., Cheng, X., Zhang, J., Lu, D., Wei, W., Wang, Y., Li, H., Fu, Y., & Zhu, L. (2019). Neuroinflammation induced by lipopolysaccharide causes cognitive impairment in mice. *Sci Rep*, *9*(1), 5790. https://doi.org/10.1038/s41598-019-42286-8

Zhao, W., Xu, Z., Cao, J., Fu, Q., Wu, Y., Zhang, X., Long, Y., Zhang, X., Yang, Y., Li, Y., & Mi, W. (2019). Elamipretide (SS-31) improves mitochondrial dysfunction, synaptic and memory impairment induced by lipopolysaccharide in mice. *J Neuroinflammation*, *16*(1), 230. https://doi.org/10.1186/s12974-019-1627-9

Zhao, X., Cao, F., Liu, Q., Li, X., Xu, G., Liu, G., Zhang, Y., Yang, X., Yi, S., Xu, F., Fan, K., & Ma, J. (2019). Behavioral, inflammatory and neurochemical disturbances in LPS and UCMS-induced mouse models of depression. *Behav Brain Res*, *364*, 494–502. https://doi.org/10.1016/j.bbr.2017.05.064

Zheng, Z. H., Tu, J. L., Li, X. H., Hua, Q., Liu, W. Z., Liu, Y., Pan, B. X., Hu, P., & Zhang, W. H. (2021). Neuroinflammation induces anxiety- and depressive-like behavior by modulating neuronal plasticity in the basolateral amygdala. *Brain Behav Immun*, *91*, 505–518. https://doi.org/10.1016/j.bbi.2020.11.007

Zhou, F., Yao, H. H., Wu, J. Y., Yang, Y. J., Ding, J. H., Zhang, J., & Hu, G. (2006). Activation of Group II/III metabotropic glutamate receptors attenuates LPS-induced astroglial neurotoxicity via promoting glutamate uptake. *J Neurosci Res*, *84*(2), 268–277. https://doi.org/10.1002/jnr.20897

Zimmermann, K. C., & Green, D. R. (2001). How cells die: apoptosis pathways. *Journal of Allergy and Clinical Immunology*, *108*(4), S99-S103. https://doi.org/10.1067/mai.2001.117819