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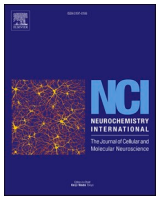

An overview of the relationship between inflammation and cognitive function in humans, molecular pathways and the impact of nutraceuticals

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ABSTRACT

Inflammation has been associated with cognitive decline, whether in the peripheral or central nervous systems. The primary mechanism involves the response of microglia, an immune cell in the brain, which generates pro-inflammatory mediators such as cytokines, chemokines, and adhesion molecules. The excessive production of pro-inflammatory mediators may accelerate the damage to neurons, contributing to the development of neurodegenerative diseases such as Alzheimer's disease, mild cognitive impairment, and vascular dementia, as well as a general decline in cognitive function. Various studies have supported the correlation between elevated pro-inflammatory mediators and a decline in cognitive function, particularly in aging and age-related neurodegenerative diseases. Moreover, this association has also been observed in other inflammatory-related conditions, including post-operative cognitive impairment, diabetes, stroke, obesity, and cancer. However, the interaction between inflammatory processes and cognitive function in humans remains unclear and varies according to different health conditions. Therefore, this review aims to consolidate and evaluate the available evidence from original studies as well as meta-analyses in order to provide a greater understanding of the inflammatory process in connection with cognitive function in humans. Furthermore, relevant biological cellular processes, putative inflammatory biomarkers, and the role of nutraceuticals on the interaction between cognitive performance and inflammatory status are outlined.

1. Introduction

The global aging population has been growing exponentially, and the number of people aged 65 and older is predicted to increase by 16%, or one in every six individuals by 2050, according to the report of World Population Prospects: the 2019 Revision, Unite Nation. One of the key consequences of population aging is an increased risk of cognitive impairment and age-related neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), mild cognitive impairment (MCI), vascular dementia, and stroke (Hou et al., 2019). The decline of cognitive function could be accelerated by various risk factors such as age, genetic susceptibility, brain injury, hyperglycemia, hypertension, hyperlipidemia, depression, stress, poor education, diet, smoking, alcohol, and sleep disturbances (Baumgart et al., 2015). It is still unclear which biological processes underlie the changes to cognitive function in the aging process and neurodegenerative diseases. One of the mechanisms which has gained increasing interest in the role of cognitive decline associated with age and neurodegenerative diseases is chronic inflammation (Sartori et al., 2012). Inflammation is a defense mechanism to protect the body against foreign stimuli. It is also a response to natural cellular metabolism and molecular processes. However, when the inflammatory process is prolonged or uncontrolled, the status becomes chronic, in which pro-inflammatory mediators are excessively produced, resulting in the pathogenesis of chronic inflammation and associated diseases (Medzhitov, 2008; Krishnamoorthy and Honn, 2006; Furman et al., 2019).

Chronic inflammatory processes can occur either in the periphery or central nervous system (CNS). The possible mechanistic underpinnings by which inflammation may accelerate cognitive impairment and neurodegenerative diseases include sustained microglia activation, excessive pro-inflammatory cytokines expression, and upregulated neuronal inflammatory signaling pathways. These mechanisms can deteriorate the neurons, resulting in the acceleration of cognitive dysfunction and neurodegeneration (Kaur et al., 2020; Kinney et al.,

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2018). Previous studies have demonstrated that the presence of sustained inflammatory responses in either the periphery or cerebrospinal fluid (CSF) may exacerbate cognitive dysfunction and the progression of neurodegenerative diseases, particularly in an older population (Janelidze et al., 2018; Yaffe et al., 2003; Alley et al., 2008). Data from prospective cohorts shows that higher levels of interleukin-6 (IL-6) and C-reactive protein (CRP) inflammatory markers were negatively correlated with worse cognitive performance in non-demented older age individuals (Yaffe et al., 2003; Alley et al., 2008). In addition, the expression of IL-6 and IL-1β genes in the hippocampus and prefrontal cortex has been detected in the postpartum brain of patients with AD pathology (Huell et al., 1995; Cacabelos et al., 1994). However, inflammation might not be only a direct factor contributing to the development of neurodegenerative diseases and cognitive impairment but also accompanied by other mechanistic-related pathologies such as oxidative stress, mitochondrial dysfunction, impairment of protein clearance, vascular impairment, reduction of synaptic plasticity, and cerebral blood flow (Jellinger, 2010; Sweeney et al., 2018). The aim of this review is to provide an overview of the current understanding of the acute and chronic inflammatory response with respect to its relationship with cognitive function in humans. We highlight the findings from original studies as well as the evidence from systematic reviews and meta-analyses that assessed the association between elevated inflammatory biomarkers and cognitive function. In addition, we outline the possible cellular mechanisms and potential inflammatory biomarkers which may support the relationship between cognitive decline and the inflammatory process as well as the role of nutraceuticals.

2. Inflammation: linking between central and peripheral

The link between peripheral and central inflammation is key to explaining why systemic inflammation can impact brain function and cognitive ability. A possible mechanism explaining the association between inflammation in the periphery and the central nervous system is disruption of the blood-brain barrier (BBB) (Takata et al., 2021; Huang et al., 2021). Generally, the BBB describes the unique properties of the endothelium cells in the brain, which tightly regulate the movement of molecules and cells crossing into the brain. This can protect the brain from invading pathogens or toxic molecules crossing through the CNS (Daneman and Prat, 2015). BBB dysfunction is described by the leaking of undesirable molecules penetrating through tight junctions, the gap between brain microvascular endothelium cells, and into the brain. Elevated inflammatory cytokines in the bloodstream as well as peripheral immune cells can disrupt BBB permeability both directly and indirectly. Then, the penetrated molecules and immune cells will stimulate the microglia as well as astrocytes to produce inflammatory mediators in the brain resulting in neuroinflammation and neurodegeneration. The blood pro-inflammatory cytokines, including IL-1β, IL-6, and tumor necrosis factor-α (TNF-α), are considered as important signaling molecules regulating the function of the BBB. These cytokines can transiently induce an increase in BBB permeability and a decrease in trans endothelial electrical resistance (TEER) by suppressing tight junction proteins, including occluding, claudin-5, and zonula occludens-1 (ZO-1), via the activation of upstream signaling including PI3K, protein kinase C (PKC), nuclear factor kappa B (NF-kB), P38 mitogen-activated protein kinases, and extracellular regulated kinase 1/2 (ERK1/2), resulting in the leakage of inflammatory mediators and immune cells into the brain (Takata et al., 2021; Yang et al., 2019).

Previous studies report a correlation between central and peripheral inflammatory mediators as well as dysfunction of the BBB. For instance, Bowman et al. (2018) showed that BBB impairment (the cerebrospinal fluid albumin index $\geq$9) was higher in MCI patients compared to cognitively intact controls. In addition, higher levels of inflammatory mediators such as serum amyloid A, soluble intercellular adhesion molecule-1 (sICAMP-1), vascular endothelium growth factor (VEGF), and IL-8 in CSF were associated with BBB dysfunction and the impairment of cognitive function in MCI patients (Bowman et al., 2018). A recent study by Vasunilashorn et al. (2021) assessed the correlation between plasma and CSF inflammatory biomarkers in patients aged 65 and over who underwent hip or knee arthroplasty. Significant correlations between plasma and CSF inflammatory markers were found in CRP, IL-6, and chitinase 3-like protein 1 (YKL-40) at baseline until 1 month after surgery (Vasunilashorn et al., 2021). In addition, the findings from Bettcher et al. (2018) demonstrated that levels of macrophage inflammatory protein-1β (MIP-1β) showed a strong association between plasma and CSF. While IL-8, IL-6, monocyte chemoattractant protein 1 (MCP-1) and interferon-γ inducible protein (IP)-10 had modest associations in AD patients (Bettcher et al., 2018). These findings indicated that peripheral inflammation could be possibly linked to neuroinflammation via the destruction of the BBB mechanism. However, the relationship between peripheral and central inflammatory mediators remains inconclusive, which might be attributed to differences in the research population, illness stages, and other confounding variables. A clinical trial by Danielson et al. (2018) demonstrated that using high-dose methylprednisolone, a corticosteroid, in cardiac surgery patients can attenuated the systemic inflammatory response (IL-6, IL-8, and TNF-α), but did not attenuate BBB permeability and the inflammatory mediators in the central nervous system (Danielson et al., 2018). Further research is still needed to better comprehend the actual interactions and mechanisms of central and peripheral inflammation in humans.

3. Possible mechanisms of neuroinflammation and cognitive decline

A possible mechanism associating cognitive decline with inflammation could be explained by the excessive synthesis of pro-inflammatory mediators by brain immune cells via upstream neuroinflammatory signaling pathways. The outcome of neuroinflammatory mechanisms such as neuronal apoptosis, activation of tau hyperphosphorylation and Aβ peptides accumulation, synaptic dysfunction, and inhibition of neurogenesis may result in accelerated cognitive dysfunction (Lyman et al., 2014). The activated microglia are a primary driver of neuroinflammation, either for prevention or exacerbating the pathology in the brain (Bachiller et al., 2018). In a normal state, microglia represent functions to control the CNS environment and communicate with surrounding cells in the brain, such as neurons, astrocytes, and oligodendrocytes (Kwon and Koh, 2020). When microglia respond to stimuli, they change their morphology, migrate to the affected site, and enhance phagocytosis's ability to eliminate pathogens and initiate neuronal tissue remodeling. In addition, activated microglia can interact with other cells in the brain such as astrocytes and neurons, to generate other biologically active substances related to the neuroinflammatory response (Bachiller et al., 2018). However, if the preventive inflammatory response is uncontrolled, the sustained microglia repeatedly generate the inflammatory mediators, resulting in damage to neurons and potentially brain lesions and neurodegenerative diseases (Lyman et al., 2014; Bachiller et al., 2018). In animal studies, the expression of pro-inflammatory cytokines in the blood and brain parenchyma showed an association with cognitive impairment. For instance, a study by d'Avila et al., 2018 demonstrated that LPS-induced young and aged Swiss mice showed increased systemic inflammation, which affected memory and learning ability. The activated microglia and the IL-1β and IL-6 cytokines were found to be higher in the hippocampus and entorhinal cortex in old-aged mice compared to young-aged mice (d'Avila et al., 2018). According to Sun et al. (2015), they showed that LPS induced the expression of TNF-α, IL-6, IL-17 A, iNOS, and COX-2 in the hippocampus in male Sprague-Dawley rats. Using IL-17 A-neutralizing antibody treatment can suppress microglia activation, reduce the neuroinflammatory response, and improve memory function (Sun et al., 2015). In neurodegenerative models, sustained microglia activation in the brain can induce the accumulation of β-amyloid plaques (Aβ) and

neuronal apoptosis in humans and rodents with AD pathology (Kinney et al., 2018; Hansen et al., 2018). A recent study by Zhang et al. (2021) showed that a rotenone-induced mouse Parkinson's model was associated with neuronal damage, synaptic loss, Ser129-phosphorylation of α-synuclein, and microglial activation in the hippocampal and cortical regions. The PLX3397 inhibitor and minocycline can decrease the number of microglia as well as their activities, resulting in improved learning and memory abilities (Zhang et al., 2021).

The expression of pro-inflammatory genes such as IFN-γ, IL-6, IL-1β, and TNF-α during the neuroinflammatory process is regulated through the activation of NF-κB signaling pathway (Tohidpour et al., 2017). NF-κB is a transcription factor playing a key role in the neuroinflammation process. When microglia are exposed to a pathogen, it binds to the Toll-like receptor 4 (TLR-4) on the cell membrane. TLR4 associates with accessory proteins, namely MD2 and Myd88, which activate PI3K by phosphorylating protein kinase B (Akt), subsequently activating the inhibitor kappa B (IkB) kinase (IKK). The IκB-α will be phosphorylated by activated IKK and subsequently degraded by the ubiquitinate-proteasomal system. Free NF-kB is translocated into the nucleus and binds to the corresponding promoter or enhancer region of various target genes, including pro-inflammatory cytokines, chemokines, and inflammatory enzymes, leading to the expression of the corresponding target genes such as TNF-α, IL-6, IL-1, IL-8, IFN-γ, and iNOS. Up-regulation of the expression of the pro-inflammatory cytokines through NF-κB activation contributes to the pathogenesis of degenerative diseases by the degeneration of neurons (Momtazmanesh et al., 2020; Shastri et al., 2013). The utilizing of NF-κB inhibitors can prevent neural loss as well as improve cognitive abilities by attenuating pro-inflammatory cytokine expression in neurodegenerative models (Srinivasan and Lahiri, 2015). Besides activation of NF-κB pathway, activated microglia via TLR4 also activates mitogen-activated protein kinases (MAPKs) cascades, a family of Ser/Thr kinases, to regulate important cellular processes including cell growth, proliferation, inflammation, apoptosis, and differentiation (Daneman and Prat, 2015). The MAPK signaling pathway is a three-tiered cascade, including the extracellular signal-regulated protein kinases (ERKs), the c-Jun N-terminal kinases/stress-activated protein kinases (JNKs/SAPKs), and the p38 family of kinases that are stimulated by specific MAP kinase kinase (MAPKK) and MAPKKK. These kinases are involved in the regulation of inflammation gene synthesis at transcription and translation through activation of NF-kB and AP-1 transcription factors (Chang and Karin, 2001). Among these MAPKs, the phosphorylation of p38 and JNK is triggered by stress and inflammation; sometimes they are referred to as stress-activated protein kinases (Kaminska, 2005). The phosphorylation of p38 MAP kinase has been activated by cytokines, which are associated with gene expression in neuroinflammatory processes. Increasing p38 phosphorylation is associated with several inflammatory gene expressions, such as TNF-α, IL-6, IL-1β, iNOS, and COX-2, via several transcription factors, including NF-kB, AP-1, and STAT-1 (Asih et al., 2020). The JNK signaling pathway, a major target for AP-1 transcription factor, consists of JNK1/2/3 that is activated by LPS through upstream MMK4 and MMK7. JNK is implicated in multiple biological processes, including cell death, cell proliferation, and pro-inflammatory cytokine and enzyme production (Yarza et al., 2015). The activation of MAPK signaling pathways has been associated with the pathogenesis of neurodegenerative diseases and inflammatory-related diseases such as AD, PD, cancer, and rheumatoid arthritis (Kim and Choi, 2010). Furthermore, the PI3K/Akt pathway has been involved in some important cellular processes, including protein synthesis, cell proliferation, neuronal plasticity, and neuroinflammation. The activation of PI3K/Akt intracellular pathways has been recently found to be associated with neuroinflammatory responses and microglia activation. The phosphorylation of the PI3K/Akt signaling cascade is stimulated by several substances, including LPS via TLR4, which facilitates Atk phosphorylation and stimulates the downstream expression of pro-inflammatory genes such as IL-6, IL-1β, TNF-α, and iNOS (Rai et al., 2019). The studies in rodent models support a mechanism of cognitive decline through these upstream signaling pathways. For instance, Denver et al. (2018) showed that the expression of inflammatory signaling molecules in plasma and brain tissue, including ERK2, IKKβ, mTOR, PKC, NF-κB, and TLR4, contributes toward impaired recognition or spatial memory in high-fat C57BL/6 mice (Denver et al., 2018). Similarly, Kothari et al. (2016) showed that a high-fat diet stimulated brain inflammation and insulin sensitivity via the activation of inflammatory pathways including NF-κB and JNK in the brain parenchyma, resulting in cognitive dysfunction in C57BL/6NHsd mice (Kothari et al., 2016). The interplay between activated microglia, the production of inflammatory molecules, and the activation of NF-κB, MAPK, and PI3K signaling pathways may play a pivotal role in neuroinflammation and cognitive impairment. The understanding of molecular mechanism of inflammation related to cognitive dysfunction is important for developing targeted therapeutic approaches for prevention or treatment of neurodegenerative diseases as well as cognitive impairment.

4. The relationship between inflammatory status and cognitive function in humans

4.1. Inflammatory mediators related to cognitive impairment

Cognitive function refers to mental processes involved in the receiving of knowledge, the manipulation of information, and the ability to understand and think reasonably, which can be measured in various domains such as attention, learning and memory, perception, decision-making, speed and language, social cognition, and executive control (Sachdev et al., 2014). In general, cognitive function, especially memory, gradually declines during aging because of a loss in brain volume and neuron cells, a decrease in synaptic plasticity, a reduction in vascular function and cerebral blood flow, as well as an increase in systematic inflammation (Murman, 2015). These factors might affect brain function, particularly cognitive performance, personality, and behavior. In the context of cause-and-effect, longitudinal cohort studies demonstrate that elevated inflammatory markers may accelerate cognitive impairments in the older population (Yaffe et al., 2003; Alley et al., 2008; Teunissen et al., 2003). For instance, Teunissen et al. (2003) showed that increased CRP concentrations in individuals over 50 years at baseline were negatively associated with learning and memory at 6-year follow-up (Teunissen et al., 2003). Another study by Yaffe et al. (2003) found that elevated plasma CRP and IL-6, but not TNF-α, in older adults was correlated with worse cognitive performance at baseline and 2-year follow-up (Yaffe et al., 2003). In addition, after 8-year follow-up, the participants who had lower CRP and IL-6 concentrations were likely to maintain their baseline cognitive abilities (Yaffe et al., 2009). In the elderly, elevated serum CRP and IL-6 may be prominent markers associated with the decline of cognitive abilities. CRP is a broad-spectrum inflammatory marker produced by the liver during acute and chronic inflammatory processes (Ansar and Ghosh, 2016). In healthy adults, the average serum CRP concentration is 0.2–3.0 mg/L. Elevated serum CRP of more than 3 mg/L might be considered low-grade inflammation (Osimo et al., 2019). In healthy elderly people aged 65 and over, the range of serum CRP was reported at 1–2.97 mg/L (Matsushima et al., 2015; Boots et al., 2020). Watanabe et al. (2016) showed that serum CRP greater than 1.09 mg/L may be associated with cognitive decline, but only in elderly women (Watanabe et al., 2016). IL-6, an important cytokine, acts as both a pro-inflammatory and anti-inflammatory substance depending on conditions. IL-6 is often used as a marker for acute-phase responses after tissue damage or infection. In healthy population, serum IL-6 concentration was approximately 0.11–0.82 pg/ml (Wyczalkowska-Tomasik et al., 2016). In elderly populations, the serum IL-6 concentrations varied from 1.87 pg/ml to 3.94 mg/ml in different studies (Matsushima et al., 2015; Boots et al., 2020; Akbaraly et al., 2013). A serum IL-6 concentration greater than 3.0 pg/ml may relate to global cognitive decline in the non-dementia older population (Yaffe

et al., 2003; Jordanova et al., 2007; Rafnsson et al., 2007; Weaver et al., 2002). However, elevated CRP and IL-6 might not be a single indicator associated with impairment of cognition in humans. They likely interact with other factors during the aging process or the pathology of diseases.

Observational studies have reported that elevated inflammatory molecules in the postmortem brain tissue, plasma, or CSF have been associated with poor cognitive outcomes in AD (Janelidze et al., 2018; Huell et al., 1995; Cacabelos et al., 1994; Taipa et al., 2019; Galimberti et al., 2006; Hesse et al., 2016; Schmitz et al., 2015). For example, elevated levels of YKl-40, ICAM-1, VCAM-1, and IL-15 in the CSF were positively associated with disease progression, cortical thinning, and subsequent cognitive deterioration in patients with AB^{+} pathologies (Janelidze et al., 2018). Galimberti et al. (2006) showed that elevated levels of IP-10 and MCP-1 concentrations in the CSF were 1.5-fold and 1.2-fold higher in AD patients compared to controls (Galimberti et al., 2006). Hesse et al. (2016) found that severe AD patients with poor cognitive performance had 1.9-fold higher levels of IL-1β, and a lower IL-8 concentration in CSF than controls (Hesse et al., 2016). In addition, Schmitz et al. (2015) reported that higher levels of IL-8 in the CSF and MIP-1β in serum and CSF were significantly correlated with the severity of cognitive decline in vascular dementia patients (Schmitz et al., 2015). Furthermore, not only have these associations been found in people with age and neurodegenerative diseases, but they have also been established in other inflammatory-related conditions, including obesity, schizophrenia, diabetes, HIV, cancer and post-operative cognitive dysfunction (Kálmán et al., 2006; Moreno-Navarrete et al., 2017; Williams et al., 2019; Miller et al., 2021; North et al., 2021; Schroyen et al., 2021; Dyer et al., 2020). For instance, Moreno-Navarrete et al. (2017), demonstrated that the plasma levels of LBP and hs-CRP were significantly higher in obese than non-obese groups, and that LBP concentrations were associated with a reduction of The Decision Support Tool (DST) scores in obese subjects (Moreno-Navarrete et al., 2017). In addition, the elevated serum TNF-α was inversely related to impairment of working memory in type 2 diabetes patients (Dyer et al., 2020). Although, there are some studies reporting adversely that elevated inflammatory status do not attenuate cognitive performance (Milà-Alomà et al., 2020; Lemstra et al., 2008; Nemeth et al., 2017), the majority of studies strongly suggested that high levels of inflammatory markers in either blood or CSF are associated with cognitive impairment.

Due to a large number of inflammatory markers and a difference in cognitive assessments, the inconsistent pattern of inflammatory markers and cognitive outcomes across various studies is perhaps not surprising, especially given further differences in research methodologies and population characteristics. Thus, it is difficult to identify a cut-off value at which potential inflammatory markers in both serum and CSF are associated with cognitive impairment in humans. Previous studies have attempted to develop biomarkers and their cutoffs to diagnose neurodegenerative diseases. Dayana et al. (2014) tried to establish cutoffs for blood IL-13 cytokine and IP-10 chemokines as potential markers for AD in Malaysian populations. IP-10 was found to be 4-fold higher (113.0 ± 5.8 vs. 28.2 ± 2.2 pg/ml), while IL-13, an anti-inflammatory cytokine, was found to be 18-fold lower in AD patients (1.6 ± 0.2 vs. 29.5 ± 1.2 pg/ml) compared to healthy controls. When compared with AD patients in European countries, the proportion of serum IP-10 and IL-13 was slightly lower at 2-fold and 9-fold, respectively (Dayana et al., 2014). In addition, using the data from the prospective and longitudinal Swedish BioFINDER study, Janelidze et al. (2018) assessed the CSF inflammatory biomarkers and their relation to AD pathologies. The result revealed elevated YKL-40, ICAM-1, and Flt-1 biomarkers in AD patients, and that these elevated markers, especially YKL-40, were associated with increased levels of total tau, cortical thinning, and disease progression in patients with dementia and AD (Janelidze et al., 2018). It is evident across these studies that there is variation in the inflammatory markers and their concentrations associated with cognitive decline. The variation might be due to the factors affecting the association between inflammation and cognitive function such as the medical conditions, severity of diseases, subject characteristics (age, race, sex, behavior), measurement techniques (an enzyme-linked immunosorbent assay (ELISA) or bead-based assay), and the sources of sample (plasma, serum, whole blood, and CSF). In future research, identifying the potential inflammatory markers as well as their cutoff's concentration related to the impairment of cognition, or the pathology of neurodegenerative diseases might be an important tool for early detection and prevention of cognitive impairment.

4.2. Stimulated acute inflammation alters cognitive function

Acute inflammation has also been associated with cognitive impairment, most notably following infection (Rock et al., 2004). The systematic search was conducted using PubMed and Web of Sciences until December 5, 2023 for evaluating the effect of acute inflammation on cognitive performance in human randomized controlled trials. The outcome was carried out using the search terms: (neuroinflammation OR inflammat* OR inflammatory marker* OR inflammatory mediator* OR cytokine* OR chemokine* OR "C reactive protein" OR CRP) AND (cognit* OR "cognitive function" OR "cognitive impairment" OR "cognitive decline" OR memory OR "executive function"). The summarized nine studies evaluated the effect of stimulated acute inflammation on cognitive function in human trials are shown in Table 1. To clarify the role of acute inflammation on cognitive function, an inflammatory response was typically stimulated by using endotoxins, and cognitive performance was measured at baseline and after stimulation. All studies showed that the endotoxins successfully induced an elevation of acute pro-inflammatory markers, including IL-6, TNF-α, and IL-1RA, compared to controls. Five trials suggested that the higher levels of serum inflammatory markers after receiving endotoxin stimulation led to poorer cognitive performance. According to Grigoleit et al. (2011), the findings showed that participants induced with high doses of E. coli reduced working memory compared to placebo (Grigoleit et al., 2011). According to Harrison et al. (2014), the result demonstrated impairment of spatial memory among individuals who received the S. typhi vaccination (Harrison et al., 2014). Another study by Reichenberg et al. (2001) demonstrated a decline in both verbal and non-verbal memory after using S. abortus equi-activated IL-6, TNF-α, and IL-1RA cytokines (Reichenberg et al., 2001). Similarly, Moieni et al. (2015) found that endotoxin-induced IL-6 and TNF-α cytokines were associated with the impairment of social cognitive processing (Moieni et al., 2015). In addition, Brydon et al. (2008) showed that S. typhi vaccination evoked an increase in IL-6, which was associated with slower reaction time responses (Brydon et al., 2008). On the contrary, four studies showed an inconsistent pattern in which cognitive performance was not altered after acute inflammation. Grigoleit et al. (2010) found that attention and memory were not altered after endotoxin-activated acute inflammation (Grigoleit et al., 2010). Similarly, Krabbe et al. (2005) demonstrated that participants who were higher in plasma IL-6, TNF-α, IL-1RA, and sTNF-R levels after being stimulated by E. coli did not show any deficits in memory (Krabbe et al., 2005). Similarly, Kullmann et al. (2013) showed that social and emotional processing was not changed after endotoxin-stimulated acute inflammation (Kullmann et al., 2013). A recent study by Balter et al. (2018) found consistently that S. typhi vaccination-induced IL-6 levels did not impact cognitive performance (Balter et al., 2018). Overall, studies demonstrated that elevated pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1RA may exacerbate cognitive dysfunction, particularly memory. However, some studies show no effects of acute inflammation on cognitive performance. This inconsistency might be due to the heterogeneity of methodologies which may alter the actual effect of cognitive function after an acute inflammatory response, such as the types and doses of stimuli, the domains and timing of cognitive assessments, and the magnitude of the acute inflammatory response.

Table 1
The relationship between stimulated acute inflammation and cognitive function: evidence from human randomized controlled trials.

Authors	Design	Population			Stimulant		Inflammatory markers measurement	Cognitive test	Main findings	Outcomes	
		subject	mean age	no.	type	intensity				inflammation	cognition
Grigoleit et al. (2011)	A cross-over, double-blind, experimental approach	Healthy men	24.2	34	E. coli	High dose 0.8 ng/kg and low dose 0.4 ng/kg	IL-6, TNF-α, IL-10, IL-1RA	2 back task, 24 h memory task	High dose E. coli can increase IL-1RA, TNF-α, and IL-10, while low dose can increase IL-6, TNF-α, and IL-10. High dose E. coli can reduce reaction time of 2 back task.	↑ IL-1RA, TNF-α, IL-10	↓ Reaction time of 2 back task
Harrison et al. (2014)	A double-blind, randomized crossover study	Healthy men	24.7	20	S. typhi vaccination	0.025 mg	IL-6, TNF-α, IL-1RA	Spatial Memory Task, Procedural Memory Task	S. typhi vaccination can induce IL-6, TNF-α, IL-1RA cytokines, and reduce spatial memory, but not procedural memory.	↑ IL-6, TNF-α, IL-1RA	↓ Spatial memory
Reichenberg et al. (2001)	A double-blind, crossover study	Healthy men	23.7	20	S.abortus equi	0.8 ng/kg	IL-6, TNF-α, IL-1RA	Story Recall, Figure Recall, Word List Learning, the Ruff 2 and 7 cancellation test, the Digit Span Forward, the Digit Symbol, computerized Simple Reaction Time test, the Continuous Performance Test, the colored TMT A and B and the Word Fluency test	S.abortus can activate IL-6, TNF-α, IL-1RA cytokines expression and decrease verbal and non-verbal memory.	↑ IL-6, TNF-α, IL-1RA	↓ Verbal and non-verbal memory
Moieni et al. (2015)	A randomized double-blinded placebo-controlled trial	Healthy participants	24.2	115	E. coli	0.8 ng/kg	IL-6, TNF-α	Reading the mind in the eye, social disconnection	E.coli can increase TNF-α and IL-6, and impaired social cognitive processing.	↑ TNF-α, IL-6	↓ Social cognitive processing
Brydon et al. (2008)	A double-blind, randomized, crossover-controlled design	Healthy men	24.9	16	S. typhi vaccination	0.025 mg	IL-6, TNF-α, IL-1RA	Color-Word Stroop Task	S. typhi vaccination evoked an increasing only IL-6, and decreased in reaction time responses.	↑ IL-6	↓ Reaction time responses
Grigoleit et al. (2010)	A randomized double-blinded placebo-controlled trial	Healthy men	24.9	24	E. coli	0.4 ng/kg	IL-6, TNF-α, IL-10	Wechsler memory scale-R attention score, stoop-color word naming test	E. coli can increase IL-6, TNF-α, IL-10, but did not affect cognitive function.	↑ IL-6, TNF-α, IL-10	↔
Krabbe et al. (2005)	A randomized double-blinded placebo-controlled trial	Healthy men	26	12	E. coli	0.2 ng/kg	TNF-α, IL-6, IL-1RA, sTNF-R	Digit symbol test, word list learning, letter number sequence test	E. coli can increase IL-6, TNF-α, IL-1RA, and sTNF-R, but did not affect cognitive function.	↑ IL-6, TNF-α, IL-1RA, sTNF-R	↔
Kullmann et al. (2013)	A randomized double-blinded placebo-controlled trial	Healthy men	26.4	18	E. coli	0.4 ng/kg	IL-6, TNF-α, IL-10, IL-1RA	Reading the mind in the eye	E. coli can increase IL-6, TNF-α, IL-10, IL-1RA, but not alter social/emotional processing.	↑ IL-6, TNF-α, IL-10, IL-1RA	↔
Balter et al. (2018)	A double-blind placebo-controlled cross-over trial	Healthy men	24.5	20	S. typhi vaccination	0.025 mg	IL-6	Attention Network Test, Behavioral and electrophysiological data acquisition	S. typhi induced IL-6 levels, while no behavioral task performance differences.	↑ IL-6	↔

↓: significantly reduce, ↑ significantly increase, ↔ non-significantly change.

4.3. Low-grade/systemic inflammation related to cognitive dysfunctions or cognitive related diseases

Due to a wide variety of individual studies regarding the role of inflammation on cognitive function in humans, the available evidence from meta-analyses investigating the relationship between inflammatory markers and cognitive decline or cognitive-related conditions in humans was systemically searched. The databases and search terms were identical to the above (acute inflammation and cognitive function). The search was restricted to only systematic reviews and meta-analyses, and we excluded studies related to diseases and/or conditions which strongly impact cognitive function, including psychotic disorders, immunodeficiency diseases, and alcoholic disorders. The summarized meta-analyses from nineteen studies which demonstrated the association between inflammation and cognitive decline or cognitively related diseases or conditions in humans are shown in Table 2. The potential inflammatory indicators associated with cognitive decline or cognitively related diseases differed slightly according to the research methodology and study population.

In older population, the meta-analysis by Yang et al. (2015) evaluated the association between peripheral levels of CRP and the risk of cognitive decline in longitudinal studies among non-dementia populations. The pooled results showed that higher serum CRP concentrations were weakly related to the decline in global cognitive function over 2–5 years of follow-up (OR 1.27, 95% CI [1.02, 1.58], $I^2 = 25.5\%$) (Yang et al., 2015). Another meta-analysis by Bradburn et al. (2017) assessed the association between plasma IL-6 levels and global cognitive decline in non-dementia elderly populations. The pooled results demonstrated that elevated serum IL-6 was significantly associated with global cognitive decline over 2–7-year follow-up (OR 1.42, 95% CI [1.18, 1.70], $I^2 = 14.\%$) (Bradburn et al., 2017). Recent meta-analysis by Feng et al. (2023) reported that high levels of blood CRP, IL-6 and TNF-α may have more chance to develop cognitive decline in non-dementia elderly (OR = 1.14, 95% CI [1.03, 1.27]). In addition, individuals with high IL-6 concentrations had a greater prevalence of cognitive impairment (Feng et al., 2023). A meta-analysis by Long et al. (2023) assessed the levels of CRP and their relation to the progression of cognitive impairment. The pooled data showed that high CRP levels were not related to future cognitive decline (OR = 1.115, 95 % CI [0.83, 1.49]) but were associated with an increased risk of conversion to dementia (Long et al., 2023). As a result, higher levels of CRP, IL6, and TNF- in the blood are obviously associated with an increased risk of cognitive decline in the elderly population.

Neurodegenerative conditions including AD, MCI and delirium commonly involve the impairment of memory, speed and language, perception, and executive function (Corey-Bloom, 2002). The powerful evidence from four meta-analyses demonstrated consistently that AD patients show an elevation of peripheral and central inflammatory markers compared to healthy controls. Su et al. (2019) indicated that peripheral inflammatory markers, including CRP, IL-1β, IL-2, IL-6, IL-12, IL-18, MCP-1, MCP-3, IL-8, and IP-10, increased significantly in AD patients (Su et al., 2019). Consistent with Shen et al. (2019), the results showed that levels of blood hs-CRP, IL-1β, IL-6, soluble tumor necrosis factor receptor 1–2 (sTNFR1, sTNFR2) concentrations, as well as YKL-40 in CSF, were significantly increased in AD patients (Shen et al., 2019). In a similar meta-analysis by Lai et al. (2017), inflammatory markers including IL-1β, IL-2, IL-6, IL-18, IFN-γ, homocysteine, hs-CRP, CXCL10, VCAM-1, TNF-α, and sTNFR1-2 increased significantly in AD patients (Lai et al., 2017). Another study by Liu et al. (2018) determined the role of CSF and plasma sTREM2 levels in preclinical AD (pre-AD), MCI, and AD dementia. The results showed that sTREM2 levels increased in the earlier stage of AD compared to controls (Liu et al., 2018). When comparing MCI patients and controls, two meta-analyses reported similarly that MCP-1 concentrations were higher in MCI patients (Su et al., 2019; Shen et al., 2019). In addition, levels of serum sTNFR2 and IL-6 concentrations, as well as CSF YKL-40, were higher in MCI patients than controls (Shen et al., 2019). According to a recent meta-analysis by Leonardo and Fregni (2023), higher blood CRP, IL-6, IL-1, TNF-α, and sTNFR1 levels were detected in AD and MCI patients. Furthermore, IL-6 levels significantly elevated the risk of cognitive deterioration throughout a 2- to 7-year follow-up period (Leonardo and Fregni, 2023). Lastly, Lozano-Vicario et al., 2023 revealed an increase in serum IL-6, CRP, and TNF-α in delirium patients compared to non-delirium controls (Lozano-Vicario et al., 2023). However, Saleem et al. (2015) conversely demonstrated no significant differences in the levels of inflammatory markers between MCI and controls (Saleem et al., 2015). The different types of inflammatory markers elevated in AD and MCI across the studies may be due to the heterogeneity of methodologies, such as the criteria of the included studies, the stage and severity of diseases, and statistical analysis. However, the overall findings strongly indicate that elevated inflammatory mediators, particularly IL-1β, IL-6, CRP, TNF-α, sTREM 1-2, and MCP-1, are found in cognitively related neurodegenerative patients compared to controls. The expression of these inflammatory markers might be associated with the severity of brain pathologies and the impairment of cognitive function.

Stroke is a serious neurological condition leading to cognitive impairment in many domains, including memory, attention, orientation, speed and language (Al-Qazzaz et al., 2014). After stroke, approximately 30% of patients can develop the onset of dementia or post-stroke cognitive impairment (PSCI) due to the damage to brain and vascular function (Cullen et al., 2007). A recent systematic review and meta-analysis by Kim et al. (2022) evaluated some blood-derived proteins for stroke related to brain damage and cognitive impairments in post-stroke cognitive impairment (PSCI) patients. The results showed that blood CRP levels (SMD = 0.374, 95% CI [0.121, 0.628]) were significantly higher in patients with PSCI than in the non-PSCI group (Kim et al., 2022). Consistently, a recent meta-analysis by Wang et al. (2023) found that higher CRP levels are related to an increased risk of cognitive impairment following an acute ischemic stroke compared to patients with lower CRP concentrations (SMD = 0.35, 95% CI [0.06, 0.64]) (Wang et al., 2023). Tack et al. (2023) found that increased systemic inflammatory response was related to lower cognitive scores (SDM = − 0.25, (95% CI [−0.34, −0.16], $I^2 = 75\%$). However, individual inflammatory markers such as CRP, IL-1β, IL-6, IL-10, and TNF-α did not differ substantially between PSCI and non-PSCI individuals (Tack et al., 2023). According to these meta-analyses, higher inflammation, particularly CRP, may relate with lower cognitive performance in PSCI patients.

Post-operative cognitive dysfunction (POCD) is an obvious condition, representing an opportunity to explore the relationship between systemic inflammation and cognitive impairment. During surgical processes, the inflammatory mediators in the periphery could induce blood brain barrier permeability, penetrate into the brain, and stimulate the microglia to promote a neuroinflammatory response (Safavynia and Goldstein, 2018; Subramaniyan and Terrando, 2019). The findings from three meta-analyses strongly demonstrate that elevation of blood inflammatory markers such as CRP, IL-S, and 100 calcium-binding protein B (S-100β) might be associated with incidence of post-operative cognitive dysfunction (POCD) and post-operative delirium (POD), particularly in an aging population. According to a meta-analysis by Peng et al. (2013), the pooled results from case-control studies showed that incidence of POCD was positively correlated to concentrations of peripheral inflammatory markers, particularly IL-6 (SMD = 1.61, 95% CI [0.60, 2.62], $I^2 = 90.9\%$) and S-100β (SMD = 1.38, 95% CI [0.42, 2.33], $I^2 = 94.9\%$) (Peng et al., 2013). Similarly, a meta-analysis by Liu et al. (2018), evaluating the inflammatory biomarkers related to POD and POCD in observational studies, found that CRP and IL-6 inflammatory markers were associated with the occurrence of POCD and POD (Liu et al., 2018). Recent meta-analysis by Fu et al. (2022) showed consistent results with higher levels of systemic cytokines including CRP (SMD 0.83, 95% CI [0.49–1.18], $I^2 = 86.6\%$), IL-6 (SMD = 0.41, 95% CI [0.17, 0.64], $I^2 = 62.5\%$ and S-100β (SMD = 0.72, 95% CI [0.26, 1.17], $I^2 =$

Table 2
The association between elevated inflammatory markers and cognitively related diseases/conditions: evidence from meta-analyses.

Authors	Population	Main inclusion criteria	No. Studies	Quality/assessment	Main findings	Putative inflammatory markers related to cognitive decline
Yang et al. (2015)	Non-dementia older adults, >55 years	Prospective longitudinal studies measured blood CRP and its correlation with cognitive decline.	4	High quality, Newcastle-Ottawa scale (NOS)	Blood CRP levels were weakly associated with global cognitive decline after 2–5 years of follow-up.	CRP
Bradburn et al. (2017)	Non-dementia older adults, >55 years	Prospective longitudinal studies measured blood IL-6 and cognitive function.	7	High quality, NOS	Higher blood IL-6 levels were more likely to develop cognitive decline at follow-up over 2–7 years.	IL-6
Feng et al. (2023)	Non-dementia older adults, 65–80 years	A cross-sectional or longitudinal cohort assessed the relationship between inflammatory markers and cognitive decline.	17	High quality, NOS and low to moderate risk of bias, the Quality in Prognosis Studies tool	Higher levels of peripheral inflammatory markers may have more chance to develop cognitive decline after 2–7 years of follow-up.	IL-6, CRP, TNF-α
Long et al. (2023)	Non-cognitive impairment adults, >45 years	The cohort study measured the link between blood CRP and cognitive function or dementia outcomes.	13	Moderate -high quality, NOS	High CRP levels were not related to future cognitive decline but associated with an increased risk of conversion to dementia.	CRP
Su et al. (2019)	AD and MCI	Study measured blood inflammatory markers in AD and MCI compared to healthy controls.	88	NA	Elevated inflammatory markers were found in AD and MCI compared to healthy controls.	**AD:** IL-1β, IL-2, IL-6, IL-12, IL-18, MCP-1, MCP-3, IFN-γ, IP10 **MCI:** MCP-1
Shen et al. (2019)	AD and MCI	Observational-longitudinal trials measured blood and CSF markers in AD and MCI compared to controls.	170	High quality, NOS	Inflammatory markers either in the periphery or CSF significantly increased in AD and MCI patients than controls.	**AD:** hs-CRP, IL-6, IL-1β, MCP-1, sTNFR1-2, sCD40L, α1-ACT, TGF-β1, YKL-40 **MCI:** MCP-1, sTNFR2, IL-6, sTNFR2, YKL-40
Lai et al. (2017)	AD	Studies measured the peripheral inflammatory markers in AD compared with healthy controls.	175	NA	Elevated blood inflammatory markers found in AD. IL-6 levels were inversely linked to MMSE scores.	**AD:** IL-1β, IL-2, IL-6, IL-18, IFN-γ, homocysteine, hs-CRP, CXCL10, VCAM-1, TNF-α, sTNF R1-2
Liu et al. (2018)	Alzheimer's and MCI	Case-control and cohort studies measured sTREM2 proteins in CSF or blood in preclinical AD, MCI and AD dementia compared to control.	8	NOS, high quality	sTREM2 concentrations significantly increased in the earlier course of AD, and slightly attenuated in dementia stage.	sTREM2
Leonardo and Fregni (2023)	AD and MCI, >70 years, non-cognitive decline adults, >25 years	Prospective longitudinal and cross-sectional studies evaluated the relationship between inflammation and cognitive functions	79	Moderate-high quality, NOS	Elevated several blood inflammatory markers were found in AD and MCI. IL-6 levels significantly increased the chance of cognitive impairment at follow-up over 2–7 years.	**AD:** CRP, IL-6, IL-1β, TNF-α, sTNFR1 **MCI:** IL-6, IL-1β, TNF-α, sTNFR1
Lozano-Vicario et al. (2023)	Delirium patients, ≥65 years	The case–control, cohort study or case series assessed inflammatory markers in delirium patients compared with non-delirious controls.	6	High quality, NOS	An increase in serum inflammatory markers was found to be consistent among patients with delirium.	IL-6, CRP, TNF-α
Saleem et al. (2015)	MCI	Studies measured blood inflammatory markers in MCI compared to controls.	22	NA	No significant differences in inflammatory markers between subjects with MCI and healthy controls.	-
Kim et al. (2022)	Post stroke cognitive impairment (PSCI), >18 years	Study measured inflammatory proteins related to brain damage and cognitive impairments in PSCI compared to non-PSCI.	40	NA	The serum CRP levels were significantly higher in patients with PSCI than in the non-PSCI.	CRP
Wang et al. (2023)	Acute ischemic stroke	Case–control studies and cohort studies measured inflammatory markers and cognitive function in acute Ischemic stroke patients.	9	Moderate to high quality, NOS	Higher CRP levels were associated with an increased risk of cognitive impairment following an acute ischemic stroke.	CRP
Tack et al. (2023)	PSCI	Cohort or case–control studies measured blood or CSF inflammatory markers in PSCI compared to non-PSCI.	28	Low-high risk of bias, NOS	Increased inflammatory response related to lower cognitive scores, however, individual inflammatory indicators did not differ significantly between PSCI and non-PSCI patients.	–
Peng et al. (2013)	Post-operative cognitive	Case-control study measured peripheral	13	High quality, NOS	Incidence of POCD correlated to the elevated IL-6 and S-100β	IL-6, S-100β

(*continued on next page*)

Table 2 (*continued*)

Authors	Population	Main inclusion criteria	No. Studies	Quality/assessment	Main findings	Putative inflammatory markers related to cognitive decline
	dysfunction (POCD)	inflammatory markers in POCD compared to non-POCD patients.			levels, but not for TNF-α and IL-1β.	
Liu et al. (2018)	Post-operative delirium (POD)/ POCD underwent cardiac surgery	Case-control or cohort study measured inflammatory biomarkers in POD and POCD compared to non-POD/POCD.	54	Medium to high quality, NOS	Blood and CSF inflammatory markers, including CRP and IL-6 were associated with incidence of POCD and POD after cardiac surgery.	CRP, IL-6
Fu et al. (2022)	POCD undergoing total hip arthroplasty (THA)	Cohort study measured inflammatory markers in POCD compared to non-POCD.	11	High quality, NOS	The elevated CRP, IL-6, S-100β levels, but not for TNF-α and IL-1β were found correlation with the occurrence of POCD after THA.	CRP, IL-6, S-100β
Anita et al. (2022)	T2DM, >50 years	Study measured blood inflammatory markers in T2DM patients with/ without cognitive impairment.	40	Low-high risk of bias, NOS and the Cochrane Collaboration's Risk of Bias assessment tool	Cognitive impairment among T2DM people was associated with elevated systemic inflammatory markers and lower BDNF concentrations.	IL-6, CRP, sVCAM-1
Du et al. (2023)	T2DM	Observational study assessed the correlation between systemic inflammation and cognition.	29	Moderate-high quality, 11-item cross-sectional research checklist by the Agency for Healthcare Research and Quality	Higher IL-6, CRP, and TNF-α levels were associated with lower Montreal Cognitive Assessment scores in T2DM. CRP and TNF-α levels positively associated to glycated hemoglobin (HbA1c).	IL-6, CRP, TNF-α

NA: not available.

75.1%) correlated with the occurrence of POCD in patients undergoing total hip arthroplasty (Fu et al., 2022). In POCD and POD, the evidence strongly confirms that elevated acute inflammatory markers during the surgical process are associated with cognitive dysfunction, particularly in older patients. Peripheral IL-6, CRP, and S-100β might be considered as potential inflammatory markers for detecting the impairment of cognitive function in elderly people undergoing surgery.

Type 2 diabetes mellitus (T2DM) is a chronic disease closely linked to inflammation and cognitive impairment. Epidemiological studies have demonstrated that patients with T2DM may increase their high risk of developing either vascular dementia or AD (Arvanitakis et al., 2004; Janson et al., 2004). The impairments of blood glucose control and brain insulin signaling in T2DM may contribute to the development and pathogenesis of AD and the risk of cognitive decline (Barbagallo and Dominguez, 2014). In a meta-analysis by Anita et al. (2022), the researchers assessed peripheral blood inflammatory markers in T2DM with or without cognitive impairment. They used medical diagnoses, mainly dementia, AD, and MCI, to classify T2DM patients into levels of cognitive impairment. The cognitive impairment among people with T2DM was significantly associated with elevated systemic inflammatory markers such as IL-6 (SMD = 0.74; 95% CI, [0.07, 1.42], I^2 = 98.1%), CRP (SMD = 0.80, [0.50, 1.11], I^2 = 94.6%), sVCAM-1 (SMD = 1.64, 95% CI, [0.21, 3.07], I^2 = 95.2%), and lower BDNF concentrations (SMD −0.67; 95% CI, [−0.99, −0.35], I^2 = 89.2%) (Anita et al., 2022). Another meta-analysis found that elevated blood CRP (r = − 0.43, 95% CI [−0.53, −0.32]), IL-6 (r = − 0.54, 95% CI [−0.76, −0.18]), and TNF-α (r = − 0.53, 95% CI [−0.79, −0.11]) were negatively associated with decline in cognition in T2DM patients (Du et al., 2023). These studies provided important data that cognitive impairment is related to higher blood inflammatory markers in T2DM patients.

However, there are some limitations to consider in these findings. Most studies assessed the association between inflammation and cognitive function in populations with health conditions such as aging, AD, MCI, and T2DM, and these populations are likely to be undertaking interventions which may affect the levels of inflammatory markers such as underlying medical conditions, anti-inflammatory drugs, antivirus, and anti-hyperglycemia medicines. Furthermore, additional key issues influencing the relationship between inflammatory status and cognitive performance, such as the modulation of gut microbiome, diet, lifestyle, and physical activities, were not addressed here. Moreover, the majority of studies reported high heterogeneity without identifying the sources of heterogeneity of the inflammatory markers related to cognitive impairment. Clarifying the potential source of heterogeneity might provide more understanding about the factors related to the interaction of inflammation and cognitive decline. Another consideration is that the specific domain of cognitive function affected by elevated inflammatory status has not been clearly identified by research to date. Most studies primarily used global cognitive function tests and/or a clinical diagnosis as criteria to classify the impairment of cognition; for example, the mini-mental state exam (MMSE), the Montreal cognitive assessment (MoCA), the dementia rating scale, European Alzheimer's Diseases Consortium, National institute on aging Alzheimer's association diagnostic guidelines, and Peterson's criteria for MCI. Exploring which domains of cognition are affected by inflammatory status might provide a better understanding of the role of cognition and inflammation in individuals. Finally, it is difficult to identify cause and effect regarding the interaction between inflammation and cognitive function given that the meta-analyses predominately included case-control or cross-sectional designs. However, three meta-analyses assessing the relationship between inflammatory markers and cognitive decline in prospective cohorts, and these implied that elevated IL-6, CRP and TNF-α may be the cause of cognitive dysfunction in non-dementia population (Lai et al., 2017; Liu et al., 2018; Leonardo and Fregni, 2023). In light of the mentioned limitations, the interpretation and implications of this information for individuals should be carefully considered in the context of specific factors which might affect the relationship between inflammation and cognitive performance.

In summary, the described evidence indicates that elevated inflammatory markers are strongly associated with cognitive impairment in older population and several health conditions, including AD, MCI, POCD, stroke, and T2DM. The elevation of individual inflammatory markers linked to cognitive dysfunction shows variation depending on population conditions as well as the study methodologies. For example, AD patients showed upregulation of several inflammatory markers compared to MCI patients due to the severity of cognitive impairment and the pathology of diseases. In addition, some markers may be

specified by specific diseases or health conditions such as the increase of S-100β related to the occurrence of POCD and the up-regulation of sTREM2 demonstrated in AD. However, based on available evidence from systematic reviews and meta-analyses, the elevation of CRP and IL-6 was demonstrated consistently across the study populations, so they might be considered as a potential inflammatory marker connecting with cognitive impairment in humans. Due to the involvement of inflammation and cognitive impairment, the reduction of inflammatory status in various populations may prevent or delay the decline of cognitive function and the progression of neurodegenerative diseases.

5. Role of nutraceuticals in cognitive function related to inflammation

A number of studies are still being undertaken on the relationship between inflammation and cognition in order to benefit people suffering from neurodegenerative diseases and to prevent cognitive decline in the elderly. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen have been investigated for their ability to prevent or reduce the development of inflammation-related neurodegenerative diseases, including AD and MCI (Hayden et al., 2007; Kang and Grodstein, 2003). Long-term investigations have shown benefits in reducing Alzheimer's disease and cognitive decline in the older population, despite some contradictory findings (Grodstein et al., 2008; Arvanitakis et al., 2008). Nutraceutical refers to natural or processed substances which provide health benefits or therapeutic properties to prevent chronic diseases. Various nutrient and non-nutrient bioactive compounds such as vitamins, omega-3 fatty acids, amino acids, polyphenols, prebiotics and probiotics have been extensively studied for their anti-inflammatory properties, which might have therapeutic impacts on brain function and cognitive abilities.

- Folic acid

A recent meta-analysis indicated that supplementation with folic acid may have a substantial influence on the lowering of inflammatory markers and the improvement of cognitive performance in elderly with cognitive impairment (Wang et al., 2024). Daily intake of 1.25 mg of folic acid may improve global cognitive function and reduce plasma TNF-α cytokines in AD patients (Chen et al., 2016). Ma et al. (2016) showed consistently that daily consumption of 400 μg of folic acid can improve working memory and attenuate the serum TNF-α and IL-6 in patients with MCI (Ma et al., 2016). Moreover, the combination of folic acid with vitamin B12 may decrease serum IL-6, TNF-α, and MCP-1 concentrations and improve intelligence and cognitive ability in elderly with MCI (Ma et al., 2019). Similarly, a study by Chen et al. (2021) reported that folic acid plus vitamin B12 supplements showed the improvement of MoCA scores, and reduction of serum TNFα levels in AD patients (Chen et al., 2021). Another study by Li et al. (2021) found that daily consumption of 800 μg of folic acid, 800 mg of DHA and their combination may reduce plasma IL-1β and IL-6 concentration and increase cognitive performance in older adults with MCI (Li et al., 2021). Thus, folic acid and its combination had significant effects on the interplay between inflammation and cognition in neurodegenerative disease patients. The lowering of pro-inflammatory cytokines following folic acid administration may be responsible for cognitive improvement.

- Amino acids and peptides

Amino acids and peptides have been found to have anti-inflammatory properties which may be beneficial for cognitive improvement. Supplementation with the chicken hydrolysate intake for 8 weeks may decrease plasma hsCRP level and improve verbal short- and long-term memory as well as spatial working memory in healthy middle-aged people under mild stress (Wu et al., 2020). In addition, 500 mg of anserine/carnosine supplementation for 3 months might preserve delayed recall verbal memory via the reduction of serum MCP1, IL-8, and IL-5 concentrations in healthy middle aged-older subjects (Hisatsune et al., 2016). Masuoka et al. (2021) reported similarly that the consumption of 750 mg of anserine and 250 mg of carnosine for 12 weeks can decrease blood CRP and improve MMSE scores in MCI patients (Masuoka et al., 2021). These studies suggested that supplementation with specific amino acids and peptides may improve cognitive function via an anti-inflammatory mechanism in individuals with inflammatory-related cognitive impairment. The effects of amino acids/peptides on the interaction between inflammation and cognitive function and its molecular mechanism require more investigation.

- Omega 3 fatty acids

Long chain omega-3 fatty acids demonstrated the prominent effect in reducing inflammatory markers while also improving brain function and cognitive ability. Many studies have supported the role of omega-3 fatty acids in decreasing the progression of AD under the anti-neuroinflammatory mechanism. Previous evidence has shown that consuming additional omega-3 and omega-6 fatty acids may reduce the risk of cognitive impairment in older individuals. Bo et al. (2017) found that consuming 480 mg of DHA and 720 mg of EPA for 6 months reduced plasma TNF-α and IL-6 concentrations while improving cognition in seniors with MCI (Bo et al., 2017). Tang et al. (2020) found that ingesting 360 mg of EPA and 240 mg of DHA for 12 weeks reduced plasma CRP, IL-6, and TNF-α while improving memory function in schizophrenia patients with metabolic syndrome (Tang et al., 2020). Furthermore, Kuszewski et al. (2020) demonstrated that consuming 2000 mg of DHA and 400 mg of EPA for 16 weeks enhanced processing speed and decreased CRP levels in male participants (Kuszewski et al., 2020). However, there were contradictory findings reported that long-term consumption of omega-3 fatty acids had no advantage on cognitive performance and inflammatory status in older individuals and Alzheimer's patients (Danthiir et al., 2018; Lin et al., 2022). Additional research will be required to validate the beneficial effects of omega-3 fatty acids on the interplay between inflammation and cognition, particularly in patients with neurodegenerative conditions.

- Polyphenols

Polyphenols are naturally occurring non-nutritional plant compounds that have been extensively studied for impacts on the brain and cognitive ability, as well as anti-inflammation. A recent systematic review and meta-analysis in human randomized controlled trials reported that long-term (≥5 weeks) polyphenols consumption significantly reduces IL-6 while improving verbal memory and executive function. Additionally, the potential of polyphenols appears to be more obvious in elderly people with obesity or MCI rather in healthy individuals (Mekhora et al., 2024). The findings consistent with Farag et al. (2024) that chronic flavonoid intake had a beneficial effect on cognitive function in the elderly and obesity is a risk factor for cognitive deterioration (Farag et al., 2024). Therefore, polyphenols' anti-inflammatory properties may be associated with cognitive enhancement. Among polyphenols, anthocyanins have been shown to have considerable anti-inflammatory properties, particularly in people with chronic inflammatory disorders (Fallah et al., 2020; Song et al., 2023). Furthermore, curcumin has been shown to have pharmaceutical properties that can delay the progression of cognitive impairment in patients with AD by reducing inflammatory markers and amyloid β accumulation. However, there have been limited clinical trials investigating polyphenols effects on inflammation and cognitive function, particularly in the neurodegenerative population, as well as the inconsistency findings. Further research will be required to investigate the specific polyphenols and their molecular targets for preventing cognitive decline among individuals with chronic inflammatory conditions.

- **Probiotics**

The gut-brain axis involves gut microbiota, inflammation, and cognitive function. Alteration in the gut microbiota may contribute to the pathophysiology associated with brain function and neurodegenerative diseases (Liang et al., 2022). Supplementing with probiotics demonstrated the favorable effect on cognitive performance as well as modulating immune function and reducing inflammation. Lew et al. (2019) found that *Lactobacillus plantarum* P8 intake increased cognitive function and lowered IFN-γ levels in stressed individuals, with stronger results in females than males (Lew et al., 2019). In addition, supplementation with *Lactobacillus plantarum* DR7 reduced IFN-γ, transforming growth factor-α result in improving cognitive and memory functions in adults (Chong et al., 2019). Tamtaji et al. (2019) reported that probiotics plus selenium may improve MMSE scores and decrease serum hsCRP compared to placebo or selenium alone (Tamtaji et al., 2019). Moreover, probiotic supplementation prior surgery reduced the incidence of POCD and global cognitive dysfunction though the reduction of plasma IL-6 levels in elderly patients undergoing surgery (Wang et al., 2021). As a result, probiotic intake may alter the gut-brain axis, underlined their anti-inflammatory properties.

6. Conclusion

The literature reviewed highlights the role of inflammatory status in the exacerbation of cognitive impairment in humans as well as cellular mechanistic pathways and the impact of nutraceuticals. At the molecular level, suppressing microglia activation, attenuating cytokine expression, and inhibiting upstream signaling molecules may be suggested as primary targets to manipulate neuroinflammation-related cognitive impairment. In the context of humans, either acute or chronic inflammatory status showed an association with cognitive decline. For acute inflammatory responses, more than half of the RCTs evaluating the role of endotoxin-induced inflammation on cognition demonstrated that elevated pro-inflammatory markers such as IL-6, TNF-α, and IL-1RA are associated with the impairment of cognitive function, particularly in the domain of memory. In addition, higher acute inflammatory markers such as CRP, IL-6, and S-100β in patients undergoing surgery show a consistent correlation with an increased incidence of POCD. These findings confirm that an acute inflammatory status may lead to worse cognitive function in humans. Regarding low-grade inflammation, the evidence from meta-analyses supports the involvement of sustained inflammation in cognitive impairment. Elevated inflammatory biomarkers, either in the brain or periphery, have been reliably demonstrated to be associated with a decline in global cognitive function in several health conditions. Due to the large number of inflammatory markers and various study populations, the pattern of inflammatory mediators varied across studies. However, higher blood CRP and IL-6 concentrations may be considered potential biomarkers connected with cognitive impairment in humans because their elevation is found consistently in various conditions. The impairment of cognition might not be the only consequence of inflammation; cognitive decline can be accelerated by various factors, including the severity of pathology, medical conditions, genetics, behavior, and diet. These factors likely contribute to the variation of outcomes. Even though there have been some inconsistencies, this review strongly suggests that elevated inflammatory status is associated with cognitive dysfunction in humans. Therefore, to reduce the likelihood of impairment of cognitive function, anti-inflammatory interventions, either drug-based or other alternative approaches, such as nutrients, non-nutrient bioactive compounds, and exercise, could be considered to prevent the development of inflammation related to brain pathologies. In addition, further studies investigating specific domains of cognition and cut-offs for concentration of inflammatory markers related to cognitive decline would be of use for better understanding this field and for developing targeted interventions to prevent cognitive decline and cognitive-related degenerative diseases.

CRediT authorship contribution statement

Chusana Mekhora: Writing – original draft, Formal analysis, Data curation. **Daniel J. Lamport:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Jeremy P.E. Spencer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that I have no significant competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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Data availability

No data was used for the research described in the article.

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