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Research paper

Anti-inflammatory effects of flavonoids in neurodegenerative disorders

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ABSTRACT

Neuroinflammation is one of the main mechanisms involved in the progression of several neurodegenerative diseases, such as Parkinson, Alzheimer, multiple sclerosis, amyotrophic lateral sclerosis and others. The activation of microglia is the main feature of neuroinflammation, promoting the release of pro-inflammatory cytokines and resulting in the progressive neuronal cell death. Natural compounds, such as flavonoids, possess neuroprotective potential probably related to their ability to modulate the inflammatory responses involved in neurodegenerative diseases. In fact, pure flavonoids (e.g., quercetin, genistein, hesperetin, epigallocatechin-3-gallate) or enriched-extracts, can reduce the expression of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β and COX-2), down-regulate inflammatory markers and prevent neural damage. This anti-inflammatory activity is primarily related to the regulation of microglial cells, mediated by their effects on MAPKs and NF-κB signalling pathways, as demonstrated by *in vivo* and *in vitro* data. The present work reviews the role of inflammation in neurodegenerative diseases, highlighting the potential therapeutic effects of flavonoids as a promising approach to develop innovative neuroprotective strategy.

1. Introduction

Neurodegeneration is characterized by a slow and progressive loss of neuronal cells in specified regions of the brain and spinal cord. It represents the pathological condition of various neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) [1]. The main cellular and molecular events that cause neurodegeneration are oxidative stress, deposition of protein aggregates, neuroinflammation, impaired mitochondrial function, induction of apoptosis and alteration of autophagy [1]. Polyphenols can be considered potential neuroprotective compounds for their ability to influence and modulate these key cellular processes implicated in neurodegeneration. Particularly interesting are the class of flavonoids, the most abundant subgroup of polyphenols, widely present in foods and beverages [2,3]. Numerous reviews are present in literature reporting the neuroprotective effects of these compounds, since the early 2000s [4].

Several observational and epidemiological studies suggest that a flavonoids-rich diet improves cognitive function and prevents neurodegenerative disorders in humans [5,6]. For example, it has been reported that drinking green and black tea, rich in flavonoids, may protect brain from ageing; spinach, or strawberry retards age-related neuronal signal-transduction, cognitive and motor behavioral deficits [7]. Daily consumption of wild blueberry juice ameliorates in older adults several aspects of memory and learning, reduces depressive symptoms and lowers glucose levels [8].

Numerous studies examined the neuroprotective activity of flavonoids, suggesting that these compounds are able to exert anti-inflammatory effects throughout different modes of action [3,9].

Considering the important role of neuroinflammation in the onset and development of neurodegenerative pathologies, the present review highlights the key inflammatory processes involved in neurodegeneration and the potentiality of specific flavonoids to inhibit neuroinflammation in the central nervous system (CNS). We select the most recent and relevant data on the promising anti-inflammatory role of flavonoids related to neuroprotection.

2. Neuroinflammation

Neuroinflammatory process is a defense mechanism aimed to

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List of abbreviations

AD	Alzheimer disease
PD	Parkinson disease
MS	multiple sclerosis
HD	Huntington disease
ALS	amyotrophic lateral sclerosis
BBB	blood-brain barrier
CNS	central nervous system
NF-κB	nuclear factor-κB
TNF-α	tumor necrosis factor-α
COX-2	cyclooxygenase 2
LPS	lipopolysaccharide
IL-1	interleukin-1
TLR-4	toll-like receptor
ROS	reactive oxygen species
NO	nitric oxide
iNOS	inducible nitric oxide synthase
MAPK	mitogen-activated protein kinase
Aβ	Amyloid β

protect the CNS from tissue damage or viral insult [10]. In human body, the inflammatory process is a physiological response that involves several cellular types and mediators, resulting in the formation of a scar of the injured part, in order to separate it from the surrounding healthy tissue. However, the brain is considered "an immunologically privileged organ", whose immune response is strictly controlled in relation to the periphery, in case of viral infections or systemic damage, by the passage through the blood-brain barrier (BBB) of immune cells and inflammatory markers in the blood stream [11,12]. Following induction of inflammation, the infiltration of leukocytes into the CNS is due to the increased permeability of the BBB, also promoted by pro-inflammatory mediators [11].

However, an acute inflammatory process, following a cerebral trauma or a stroke, may lead to the formation of an extended lesion, resulting in a massive neuronal death. Furthermore, a sustained inflammatory process in the CNS can cause serious damages to neuronal system compromising functional integrity and the balance between pro-inflammatory and reparatory system, ending with CNS injury [13].

Numerous scientific studies showed that sustained inflammatory state promotes the progression of neurodegenerative diseases, such as PD, AD, MS and ALS [10,11,13–17]. Therefore, considering that inflammation is one of the basic mechanisms involved in the progression of several neurodegenerative diseases, an interesting approach consists in studying the link between inflammation and CNS neurodegeneration, in order to identify possible therapeutic targets [11,18]. Despite inflammation is not a direct inducer of neurodegenerative diseases, it is not surprising that prolonged inflammation interferes with disease progression by different mechanisms [19] that involve inducers, sensors, transducers and effectors contributing to neuronal dysfunction and death.

2.1. The role of microglia in neurodegenerative diseases

Neuroinflammation is characterized by activation of glial cells, including astrocytes and microglia, that represent the primary immune cells in the brain [10,11]. Therefore, once activated, microglial cells are involved in the inflammatory response, promoting the release of cytokines and chemokines, nuclear factor-κB (NF-κB) proteins, tumor necrosis factor-α (TNF-α), TNF-β, adhesion molecules and enzymes, such as 5-lipoxygenase (5-LOX), 12-LOX and cyclooxygenase 2 (COX-2) [20]. It is worthwhile to note that neuroinflammation is regulated by the activation of microglia, which represents the critical point between neurotoxic or neuroprotective effect [20].

As reported above, microglia generally promotes brain defences against injury, even if a recently emerging role is related to its ability to trigger the pathological processes, releasing neurotoxic molecules. The controversial role of microglia activation concerning neurotoxic or neuroprotective effects can result in a neurodegenerative outcome, or evolve in neuroprotection by the release of inflammatory mediators and neurotrophic factors [19]. An example of microglia cytotoxic effect regards the reaction to bacterial lipopolysaccharide (LPS), by the increased expression of Major Histocompatibility Complex (MHC) Class II antigens and upregulation of pro-inflammatory cytokine production, TNF-α and monocyte chemoattractant protein-1 (αMCP-1). Emerging evidences highlighted the interaction of LPS with toll-like receptor (TLR-4), involved in TLR-4 signalling pathways and activation of NF-κB [20].

Furthermore, a sustained inflammatory stimulus is responsible for the activation of uncontrolled microglia mediated by the involvement of NF-κB pathway, resulting in reactive oxygen species (ROS) production, pro-inflammatory cytokines, interferon-γ (INF-γ), and glutamate, whose excessive formation induces neuronal damage [10]. In details, microglia stimulates nitric oxide (NO) by inducible nitric oxide synthase (iNOS), whose uncontrolled activation is crucial in triggering neurodegenerative mechanisms. Moreover, NO is responsible for blocking ATP synthesis of neuronal mitochondrial respiration at the level of cytochrome C oxidase, resulting in an increase of ROS production. It has been demonstrated that superoxide is also generated by NADPH oxidase, whose activation is probably related to increased iNOS expression [21]. The neuronal damage occurs by inhibition of mitochondrial respiration, apoptosis caspase-mediated and release of glutamate, which are associated with the formation of neurotoxic peroxynitrite (ONOO) from superoxide and NO [10]. New insights into the controversial role of microglia may open novel perspectives to clarify its role in pathological conditions [14].

One of the most significant example about the cross-link between inflammation and neurodegeneration is clearly represented by the activation of reactive glial and the infiltration of lymphocytes in the CNS parenchyma, resulting in the production of antibodies against myelin sheath and consecutive neuronal damage in MS [17,22].

The hypothesis that neuronal damage is related to the inflammatory state through a simultaneously cause-effect relationship, is also considered for other non-primary inflammatory neurological diseases, like PD, AD and ALS, characterized by a reactive morphology of astrocytes and microglia [17].

Numerous studies highlighted the role of inflammation in the aetiology of the most common forms of PD, confirmed by the presence of reactive microglial cells expressing human leukocyte antigen (HLA)-DR in the *substantia nigra* of patients, or elevated serum levels of pro-inflammatory cytokines and inflammatory agonists [16]. Therefore, it should be definitely considered the possibility to regulate the progression of neuronal cell death in PD, modulating inflammatory mediators, since the LPS-mediated inflammatory state interacts at the level of dopaminergic neurons [19]. The increase of ROS production and other inflammatory mediators is also involved in the neuronal death of dopaminergic neuron in PD. In this respect, other proteinopathies, e.g., AD, are characterized by abnormal accumulation of specific proteins that affect neuroimmune response, resulting in mitochondria dysfunction and apoptosis [12,15].

It has been reported an increased activation of microglia and

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