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Fucosterol inhibits the cholinesterase activities and reduces the release of pro-inflammatory mediators in lipopolysaccharide and amyloid-induced microglial cells

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Abstract
According to the cholinergic hypothesis, memory impairment in patients with Alzheimer's disease (AD) is associated with the deficit of cholinergic function in the brain. In addition, microglial activation plays an important role in AD by producing pro-inflammatory cytokines, nitric oxide (NO), and prostaglandin E_2 (PGE_2). It was noted that lipopolysaccharide (LPS) and β-amyloid (Aβ) induced microglial activation leading to neuroinflammation and ultimately neuronal cell death. Fucosterol, a plant sterol found in brown algae, has been reported to exhibit several bioactivities. This study aimed to investigate the anti-cholinesterase activities of fucosterol and its effects on the release of pro-inflammatory mediators by LPS- and Aβ-induced microglial cells. Cholinesterase inhibition was determined using the modified Ellman colorimetric method. Expression of pro-inflammatory mediators was determined using RT-PCR and ELISA. The NO content was determined using the Griess test. Fucosterol exhibited dose-dependent inhibitory activities against both acetylcholinesterase and butyrylcholinesterase. It significantly inhibited the production of cytokines, namely interleukins (IL-6, IL-1β), tumor necrosis factor-α (TNF-α), NO, and PGE_2 in LPS- or Aβ-induced microglial cells. Fucosterol provided protective effects against Aβ-mediated neuroinflammation by inhibiting the production of pro-inflammatory mediators. These findings provided insights into the development of fucosterol as a potential drug candidate for AD, a multifactorial neurodegenerative disorder.

Keywords Alzheimer · Anti-inflammatory · Brown algae · *Padina* · Neurodegeneration · Neurotoxicity · Pro-inflammatory cytokines

Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disease that is characterized by progressive cognitive decline that begins with failure of forming recent memories, thus inexorably affecting all intellectual and bodily functions, leading to complete reliance on caregivers for basic daily functions and ultimately death (Alloul et al. 1998). As suggested by the cholinergic hypothesis, memory impairment in AD patients was associated with the deficiency of brain neurotransmitter acetylcholine (ACh) (Francis et al. 1999; Terry and Buccafusco 2003; Craig et al. 2011; Hampel et al. 2017). This has led to the development of cholinesterase inhibitors such as tacrine, donepezil, rivastigmine, and galantamine for the treatment of AD (Amenta et al. 2001; Gauthier 2002; Terry and Buccafusco 2003; Williams et al. 2003; Tan et al. 2014). These drugs inhibit cholinesterase enzymes that breakdown ACh and preserve the presence of ACh in the synaptic cleft, thus allow greater diffusion and half-life of ACh which result in improved cholinergic neurotransmission.

In addition, the amyloid cascade hypothesis proposes that the dysregulation in amyloid precursor protein (APP) results

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