MICROBIOTA-DRIVEN CXCL10-RHOA SIGNALLING IN *LACTIPLANTIBACILLUS PLANTARUM* LAB12-INDUCED NEUROPROTECTION AGAINST ALZHEIMER'S DISEASE

Alzheimer's disease (AD), which is the most prevalent cause of dementia in the world, is characterised by severe deficits in memory, cognition and motor functions. The burden of AD and other dementias accounts for an estimated 0.7% of the global population, translating to 51.6 million people worldwide [1]. In Malaysia, there are currently about 50,000 people living with AD. These are, however, underestimated figures as there are still many who remain undiagnosed, assuming that AD is a normal ageing process [2]. The causes of AD varied and not entirely understood [3].

Existing anti-AD drugs, which revolve around four major drugs that have been approved by the Food and Drug Administration (FDA) for AD treatment [i.e., three acetylcholinesterase (AChE) inhibitors (i.e. donepezil, galantamine and rivastigmine) and an N-methyl-D-aspartate (NMDA) antagonist (i.e. memantine)], are symptomatic-based [3]. Clinical administration of these drugs is also associated with several side effects. There is no evidence that these treatments are curative to limit the progression of cognitive symptoms and behavioural and psychological symptoms of dementia (BPSD) [4].

The major gaps in the knowledge of AD pathogenesis raise the need of reassessment from a different perspective. Emerging evidence on the microbiota-gut-brain axis suggests that ageing is associated with changes in the gut microbiota that increase susceptibility to chronic and degenerative diseases like AD [5]. It appears that gut microbiota alterations precede the development of key pathological features of AD, including amyloidosis and plaque-localized neuroinflammation [6]. It was postulated that ageing can increase intestinal inflammation and change bacterial taxa to a level that pro-inflammatory bacteria's abundance becomes higher than anti-inflammatory bacteria [7].

The emerging role of gut microbiota in pathogenesis of AD raises the possibility of nutritional interventions with food rich in antioxidants to prevent AD. Probiotics are one of the functional foods that contain high level of antioxidants and can therefore potentially act as anti-inflammatory as well as neuroprotective agents [8]. As part of the effort in uncovering superior probiotic strain with beneficial effects, we have explored the neuroprotective potential of locally isolated lactic acid bacteria (LAB) [9]. Our preliminary study found supplementation of adult zebrafish fed with high fat diet with *Lactiplantibacillus plantarum* LAB12 to be associated with improved spatial learning and memory [10].

The mechanisms underlying the LAB12-induced neuroprotection, however, remain to be fully elucidated. Our other preliminary findings implied LAB12-derived CFS as a potent RhoA inhibitor [11]. It was reported that CXCL10, a promising potential as blood-based chemokine biomarkers for AD [12], may activate RhoA and trigger migration of cancer cells [13]. In yet another preliminary study of ours, caecal content of LAB12-fed memory impaired (LPS-challenged) rats was presented with increased Bacteriodetes and decreased Firmicutes, indicating the potential of LAB12 in reverting dysbiosis of colonic microbiota [14].

We therefore hypothesise that the neuroprotection of LAB12 could be mediated through inhibition of microbiota-driven CXCL-10-RhoA signalling along the microbiota-gut-brain-axis. Our experiments are designed to unveil microbiota changes and the accompanying CXCL10-RhoA-related molecular events underlying neuroprotection of LAB12. Our studies will involve the use of cell-based (microglia and neuroblastoma cells) in vitro assays as well as Aβ-induced rats that mimic neuroinflammation and Aβ plaque aggregation in AD. It is our hope that the significant outputs from this study will yield important insights into current efforts of expediting development of natural LAB12 for use in prevention and management of AD.

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