Biomedicine & Pharmacotherapy 89 (2017) 396–413

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Biophenols pharmacology against the amyloidogenic activity in Alzheimer's disease

Syed Haris Omar

School of Biomedical Sciences, Faculty of Sciences and Graham Centre for Agricultural Innovation, Charles Sturt University, Wagga Wagga, NSW 2678, Australia

ARTICLE INFO

Article history:
Received 11 November 2016
Received in revised form 15 February 2017
Accepted 15 February 2017

Keywords:
Alzheimer's disease
Amyloidosis
Amyloid beta
Oxidative stress
Biophenols
Nutraceuticals

ABSTRACT

Alzheimer's disease characterized by misfolding, aggregation, and accumulation of amyloid fibrils in an insoluble form in the brain, is often known as amyloidosis. The process of aggregation follows a mechanism of seeded polymerization. For decades, a great number of failures in Alzheimer's disease (AD) drug development, with both small molecules and immunotherapies failing to establish a drug/placebo difference or having an unacceptable toxicity have led to the therapeutic research interest towards a group of anti-amyloidogenic compounds originated from plants called biophenols. A number of *in vitro* and *in vivo* studies have demonstrated that the plant biophenols bind with amyloid beta (Aβ) toxic oligomers and reducing the fibril formation and toxicity. The exact mechanism of biophenols action against Aβ toxicity is unknown, while studies have suggested the amyloid-binding affinity of biophenols affecting Aβ on various levels, e.g. by direct inhibiting fibril formation or steering oligomer formation into unstructured, inhibiting Aβ aggregation, and promoting nontoxic pathways. Furthermore, biophenols involved in the inhibition of Aβ progression (e.g., oxidative stress and neuroinflammation) and effecting the amyloid precursor protein processing through the direct or indirect inhibition of β-secretase (BACE-1), γ-secretase and/or activation of α-secretase. This critical review account for the biophenols as magic bullet targeting against Aβ, and simulation the results on how biophenols interact with the Aβ monomers and oligomers, highly desirable knowledge for predicting new efficient nutraceutical drugs.

Contents

E-mail address: syedharisomar@gmail.com (S.H. Omar).

http://dx.doi.org/10.1016/j.biopha.2017.02.051
0753-3322/

1. Introduction

At present, ageing population around the cosmos having a profound impact on the emergence of the widespread syndrome of neurodegenerative disorders, such as dementia, Alzheimer's disease (AD) and Parkinson's disease. According to the published World Alzheimer Report in 2014, a well-known syndrome, dementia commonly caused by neurodegeneration, represented by a primary cause of dependence, disability and mortality [1,2], which becomes one of the major health concerns of the twenty-first century and likely to get doubles in frequency every five years thereafter. These disorders all have in common caused by protein misfolding a protein accumulates in an insoluble form in the affected tissue. AD, recognised as one of the most frequent age related and protein misfolding disease [1], in which extracellular and intra-neuronal protein deposits in the form of plaques and neurofibrillary tangles.

The extracellular protein deposits are generally formed by the proteolytic (beta and gamma-secretase) cleavage of amyloid precursor protein (APP), which produces amyloid beta (Aβ) peptides of 36–43 amino acids [2]. Moreover, the intra-neuronal protein deposits in the form of neurofibrillary tangles are formed by the microtubule-associated protein called tau [3]. These intra- or extra-cellular aggregates cause toxicity and impair a number of cell functions including synaptic transmission and plasticity to cell membrane permeability, mitochondria functioning, ER homeostasis, nuclear transcription and cell signalling, eventually leading to cell death by apoptosis or, less frequently, by necrosis [4,5]. A number of factors and conditions, including oxidative stress, inflammation and imbalance metal homeostasis are directly or indirectly associated with the increase in the amyloid-induced cellular toxicity [6,7]. The clinical confirmation of AD is usually based on the histopathologic examination of Aβ deposits in the brain and the amyloid imaging, which are the valuable tools for diagnosis. The positron-emission tomography (PET) or single-photon emission computed tomography (SPECT) with the radiotracers are used to quantify the pathological changes in the human brain that were previously restricted to post-mortem studies. For detection of Aβ deposits and plaques formation in the brain of small animal studies, Congo red and Thioflavin are generally used as common amyloid binding dyes. For the PET imaging, the criteria for the Aβ radiotracers includes: (1) effectively image brain Aβ deposition; (2) have good reproducibility across many subjects and clinical settings; and (3) be widely accessible and appropriate for the particular task [8]. In the development of ^{18}F-labeled amyloid PET tracers, such as ^{18}F-florbetapir, ^{18}F-florbetaben, ^{18}F-flutemetamol [all three US Food and Drug Administration (FDA) and *European Medicines Agency* (EMA) approved] and ^{18}F-AZD4694 has contributed to a widespread use of amyloid PET imaging [9]. Moreover, PET/CT imaging with this agent showed high (7–10% ID/g), rapid brain uptake and fast washout of the agent from normal mice brains and delayed washout from transgenic Alzheimer's mice [10]. The fluorinated stilbene derivatives, [18F]3e and [18F]4e, showed the high binding affinities for Aβ plaque and are suitable candidates as Aβ plaque imaging agents for studying patients with AD as well as *in vivo* plaque labelling in APP/PS1 or Tg2576 transgenic mice [11]. An interesting study [12], showed the first time *in vivo* functional imaging of biophenol (resveratrol) metabolism by means of PET. In the line of same investigation, further studies are warranted to investigate the quantitative information on physiological effects of biophenols *in vivo* using the PET imaging.

The US Food and Drug Administration (FDA) have approved limited clinically relevant drugs to the AD patients, such as cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and memantine, but so far none of them have shown promising benefits and therapy for AD [13]. A great number of failures in AD drug development have occurred, with both small molecules and immunotherapies failing to show a drug/placebo difference or having unacceptable toxicity [14,15]. The evidence provided by the epidemiological researches which suggested a number of risk factors for cognitive decline are likely to be modifiable, including individuals' risk of cognitive decline may either increase or decrease depending on environmental factors, including those related to diet and lifestyle [16,17]. There is a relationship between lifestyle factors, e.g. diet and nutrition, and cognition in the elderly have been suggested by a number of observational and clinical studies [18,19]. Mediterranean diet (MeDi) have received a much higher attention than the other antioxidant diet, widely used to describe the traditional dietary habits of people in Crete, South Italy and other Mediterranean countries [20]. The Mediterranean dietary pattern is generally characterized by abundance of plant foods, including fruits, vegetables, legumes, nuts, seeds, moderate amounts of dairy products, low to moderate amounts of fish and poultry, red meat in low amounts, wine consumed modestly, and olive oil serves as a principal source of fat [21,22]. A number of studies have shown an association between the MeDi and improved cognitive function, and a decreased risk of cognitive impairment or decreased risk of dementia or AD [19,23,24]. Study (observational studies and randomized controlled trial) showed the relationship between MeDi and AD, comprised a total of 2258 non-demented individuals who were prospectively evaluated for a median time of 4 years of follow-up [25]. There were 262 incident cases of AD and it has been reported that a higher adherence, was associated with a lower risk for AD, resulted to be reduced by 40% [25]. Furthermore, in a case-control study [26], led by the same group of subjects nested within the original cohort, were analysed the possible association between a greater adherence to MeDi and AD by taking into account the influence of vascular variables that could explain the manifestation of the disease. After comparison a population of 194 patients who developed AD during the course of follow-up with the remaining 1790 non-demented subjects, the association between the adherence to MeDi and the occurrence of AD was confirmed, with a reduction of 68%, thus suggesting that the association was not mediated by vascular comorbidities [26]. An association between higher adherence to the MeDi and mild cognitive impairment (MCI) in a population of 1393 cognitively normal participants, among whom 275 developed a mild cognitive