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Review

Resveratrol and Alzheimer's disease. From molecular pathophysiology to clinical trials

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1. Introduction

More than 100 years ago Alois Alzheimer examined the brain of Auguste Deter – the first patient described with Alzheimer's disease (AD). Microscopic observation revealed loss of brain weight with massive degeneration of neurons and two specific anomalies – neurofibrillary tangles and amyloid plaques. Since then, successive generations of scientist are still searching for answers that fully explain all the mechanisms of this disease and come up with effective treatment. The World Health Organization defines dementia as a syndrome – usually of a chronic or progressive nature – in which there is deterioration of cognitive functions (i.e. the ability to process thoughts) above what might be expected from the normal aging process. Cognitive impairment is usually accompanied by behavioral and emotional alterations. The severity of symptoms gradually increases over time. According to Alzheimer's Disease International, dementia affected 46.8 million people worldwide in 2015, in which Alzheimer's disease accounted for 60 to 80% of dementia cases (Alzheimer Association, 2018) Furthermore, the number of patients is expected to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050. (Prince et al., 2016) Dementia is expected to be the one of the most problematic diseases in the developed countries, causing huge social and economic impact (Jia et al., 2018). Aggregated global costs of dementia in 2015 are estimated at 818 billion US dollars (Wimo et al., 2017). Therefore, effective treatment should be investigated and implemented as soon as possible.

The complex mechanism of dementia warrants at least several different therapeutic approaches. Current attempts mainly focus on inhibiting amyloid production and reducing the negative effects of amyloid and neurofibrillary tangles accumulation (Kálai et al., 2011). Clinical treatment also comprises of administration of anti-inflammatory drugs to patients with advanced AD. Scientific research indicates that patients treated with non-steroidal anti-inflammatory drugs (NSAIDs), e.g. in the case of cardiovascular diseases, have a lower prevalence of dementia and AD (Nevado-Holgado and Lovestone, 2017). Other AD treatment strategies include administration of cholinergic drugs (Fernandes et al., 2017). However, the most optimal strategy would be to use a substance that would alleviate the disease on multiple pathways related to its complicated pathomechanism. Thus, resveratrol (RSV) has been recently introduced into the research on the treatment of AD.

RSV is a polyphenol present in a variety of plants, such as grapes, peanuts, berries as well as red wine (Inglés et al., 2014; Liu et al., 2003). In the recent years, RSV has gained widespread attention due to its vast therapeutic potential. It has been demonstrated to have many beneficial properties such as anti-inflammatory, anti-steatotic, anti-proliferative and anti-oxidative properties (Hu et al., 2017; Peiyuan et al., 2017). Moreover, RSV has been shown to enhance insulin sensitivity and affect lipid metabolism, which can modify a dysregulated insulin/IGF-1 pathway in signal transduction and gene expression. These abnormalities are likely to contribute to the development of AD (Charytoniuk et al., 2017; de la Monte, 2017). Some studies also provide information on RSV neuroprotective properties (Clark et al., 2012; Gao et al., 2010; Mancuso et al., 2014; Wang et al., 2018a). RSV has been shown to induce mechanisms that reduce β-amyloid production and thereby reduce the progression of AD. Recent studies have shown that protective mechanism of RSV activity may be associated with mitophagia. Furthermore, it is believed that its positive effects in dementia are achieved specifically by modulating expression of SIRT1, a protein modulating post-transcriptional protein activity of cAMP-binding protein. Other

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Table 1
Clinical trials including treatment of patients with AD.

ClinicalTrials.gov search results

No.	Title	Recruitment	Study results	Conditions	Interventions	Locations
1	Resveratrol for Alzheimer's disease	Completed	Has results	•Alzheimer's disease	•Drug: resveratrol •Drug: placebo	•Banner Alzheimer's Institute, Phoenix, Arizona, United States and 25 more
2	Pilot study of the effects of resveratrol supplement in mild-to-moderate Alzheimer's disease	Withdrawn	No results available	•Alzheimer's disease	•Dietary supplement: Longevinex brand resveratrol •Dietary supplement: placebo	
3	Randomized trial of a nutritional supplement in Alzheimer's disease	Completed	No results available	•Alzheimer's disease	•Dietary supplement: resveratrol with glucose and malate •Dietary supplement: placebo	•James J. Peters VA Medical Center, Bronx, NY, Bronx, New York, United States
4	BDPP treatment for mild cognitive impairment (MCI) and prediabetes or type 2 diabetes mellitus (T2DM)	Recruiting	No results available	•Mild cognitive impairment •Alzheimer's disease	•Drug: grape seed polyphenolic extract, resveratrol	•Johns Hopkins University, Baltimore, Maryland, United States

studies report further effects including a reduction in intracellular matrix metalloproteinase (MMP) levels (Malhotra et al., 2015).

That is why RSV, with its pharmacodynamics potential, has been introduced into a various clinical trials, some including treatment of patients with AD (Table 1). However, the main shortfall of RSV usage in the clinical trials is its extremely low bioavailability related to very low water solubility and fast metabolism in liver (Charytoniuk et al., 2017; Krasnow and Murphy, 2004). That is why numerous preclinical research focus on the methods leading to increase its water and oil solubility. The most noteworthy, within investigated strategies, are: formulation of polyethylene-polycaprolactone-glycol polymeric micelles, nanoemulsions, nanoliposomes or solid self-nano-emulsifying systems. (Balata et al., 2016; Ganesan et al., 2015; Herneisey et al., 2016) Moreover, other stilbenoids or RSV derivatives with an extra hydroxyl or methyl group and characterized by higher solubility, and bioavailability are also being introduced to preclinical trials. (Akinwumi et al., 2018) Nevertheless, none of them has been investigated as a potential treatment of AD neither in preclinical studies nor clinical trials. Therefore, due to significant research conducted in the field of RSV supplementation in AD in the last few years, our paper is a current review of the results obtained from most recent preclinical studies and a comparison between them and the first published reports from clinical trials.

2. Pathophysiology of Alzheimer disease

Loss of brain function and reduction of brain nerve tissue in AD are closely related to neurofibrillary tangles (NFTs) and amyloid plaques in a course of the disease. It is known that the loss of the volume of the cerebral cortex, which is the most severe in the temporal and parietal lobes as well as in the limited regions of the frontal cortex and cingulate gyrus, is observed. The degeneration of the above-mentioned areas may explain specific aspects of dementia associated with the development of AD (Wenk, 2003).

Advanced neuron loss is also a cause of compensatory enlargement of ventricles. Amyloid plaques, characteristic for AD, are formed by the concentration of dystrophic neuritis, often localized around the β-amyloid core (Aβ) of dystrophic neuritis, often located around amyloid core built of amyloid (Aβ). The plaques are surrounded by microglial cells and astrocytes, forming dense and insoluble conglomerates that aggregate in brain tissue. Deposits of Aβ without neuritis constitute diffuse plaques (or preplaques) and can be an early stage of plaque development and dementia. (Albertoni and Schor, 2015; Balata et al., 2016) On the other hand, large deposits of Aβ are typical for the advanced stage. However, even a small aggregation of Aβ is neurotoxic and results in loss of synapses. In addition, the presence of Aβ promotes hyperphosphorylation of the neuronal microtubule binding protein tau, which cause the re-distribution of this protein from axons to dendrites and nerve cell bodies. Abnormally hyperphosphorylated tau proteins accumulate in neurons to form NFTs made of paired helical filaments (Nisbet et al., 2015). Predominantly, first the plaques and tangles are placed in the entorhinal cortex, subsequently they occupy hippocampus and isocortex, and in the most advanced stage also neocortex (Balata et al., 2016; Perry et al., 2017; Teune et al., 2014).

It has been shown that the level of cognitive retardation, characteristic for AD, is significantly correlated with the inherence of NFTs (Braskie et al., 2010).

3. Amyloid synthesis

Amyloid precursor protein (APP) is a transmembrane protein with an extracellular N-terminal domain and a short C-terminal cytoplasmic domain counting of 59 amino acid resides. Aβ peptide synthesis is an effect of amyloidogenic converting process of the APP (Dawkins and Small, 2014). APP gene is located on chromosome 21q21.3 and consists of 18 exons, which are responsible for alternative splicing creating few isoforms of APP protein. The N-terminal part of APP is highly conservative and creates 88% of APP_{695} isoform. Longer isoforms e.g. APP_{770} or APP_{771} contain additional domains like E1 domain, which is responsible for the binding exogenous heparin with APP (HBD – heparin-binding domain). This induces the process of shaping the protein and remove amyloid-generative agent.

Another domain present in a longer isoforms of APP is Kunitz protease inhibitor (KPI), which inhibits serine proteases – trypsin and chymotrypsin. The KPI domain is common in isoforms present in non-neuronal cells (Rohan de Silva et al., 1997). Interestingly, long isoforms with the Kunitz domain create amyloid peptide more often than short like APP_{695} (Dawkins and Small, 2014).

All APP isoforms may undergo a cleavage process both on physiological - non-amylogenic pathway and pathological - amylogenic pathway (Fig.1). In the first mechanism two groups of secretases – α and γ split the APP into soluble components in a two-step reaction. At the beginning, a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), which belongs to the group of α-secretases, liberates sAPPα a neurotrophic and neuroprotective protein. Subsequently, the γ-secretase converts remaining fragment of APP into a soluble p3 protein (Murphy and LeVine, 2010).

On the other hand, the first stage of an amylogenic pathway is metabolized by β-secretase (BACE1) creating sAPPβ – proapoptotic protein (Lichtenthaler, 2011). The final stage is the same as in physiological pathway leading to the creation of insoluble Aβ however, it is not the only way to generate new Aβ peptide, hence the first discovered pathway is known as the classic, secretase-dependent as opposed to the more recently discovered secretase-independent pathways (Kummer