THE OBJECTIVE OF THE PROJECT: Alzheimer's disease (**AD**) is the most common type of dementia manifested by memory decline and cognitive dysfunction. It affects nearly 50 million people worldwide and is projected to triple by 2050. Current anti-AD therapies are used to increase concentration of acetylcholine at synapses (acetylcholinesterase inhibitors) and reduce overactivated excitatory glutamatergic neurotransmission (glutamate receptor antagonist). However, these therapeutics provide only moderate symptomatic relief without affecting disease progression. Due to ineffective treatment and great socio-economic impact in the worldwide community, there is an urgent need to search for new and effective therapies. Many studies indicated that dysregulated peroxisome proliferator-activated receptor gamma (**PPARγ**) expression in the brains of individuals with AD may contribute to AD's onset and progression. Although its main functions are lipid homeostasis and insulin sensitivity, in the central nervous system, PPARγ governs the expression of various genes, including these related to cell proliferation, differentiation, metabolism and inflammatory responses. Studies showed that PPARγ agonists, thiazolidinediones (**TZDs**), inhibit neurotoxicity, but they are hepatotoxic, cardiotoxic, and carcinogenic, leading to their partial withdrawal from pharmaceutical market. We postulate that selective PPARγ modulators (**SPPARγMs**), which transactivate the expression of PPARγ-dependent reporter genes as partial agonists, could be safer alternatives to PPARγ full agonists. An interesting candidate for experimental research is a novel SPPARγM isolated from *Amorpha fruticosa* - **amorfrutin B**. *In vitro* and *in vivo* studies indicated that amorfrutin B activates a subset of genes under PPARγ control in a selective way, avoiding side effects typical of TZDs. Therefore, we propose an innovative approach to the treatment of sporadic AD brain injury that is based on the use of a novel SPPARɣM, amorfrutin B. The basic research hypotheses assume that: **A.** A selective modulation of PPARγ by amorfrutin B elicits neuroprotective effect in mouse and human models of sporadic form of AD. **B.** The mechanism of neuroprotection is associated with normalization of PPARγ signaling that is accompanied by an inhibition of neurotoxicity (referred to apoptosis, autophagy, oxidative/nitrosative stress) and microglia-related neuroinflammation, as well as restoration of endothelium integrity and normalization of miRNA/lncRNA expression profiles in brain neurons.

AIM OF THE PROJECT: The aim of proposed research is to identify a new therapy against sporadic form of AD, which possess neuroprotective capacity *via* selective modulation/activation of PPARγ signaling. The project focuses on the use of a new SPPARγM, amorfrutin B, which will be applied as the post-treatment therapy in mouse and human models of sporadic form of AD. The research assumes to check the effectiveness of the compound in relation to apoptosis, autophagy, oxidative/nitrosative stress and inflammation. The study also includes the use of cutting edge technologies to determine miRNA and lncRNA profiles in neuronal cells that would undoubtedly impact the development of modern therapy.

REASONS FOR CHOOSING THE RESEARCH TOPIC: AD is a main cause of dementia among adults aged 65 or above and the number of people living with clinical AD increases dramatically. Currently, there are no disease-modifying therapies available for AD and for that reason it is extremely important to search for new and safe compounds that could provide a breakthrough for pharmaceutical industry. Nowadays, researchers are moving towards a new hypothesis linking AD to a metabolic impairment and ischemia. Targeting brain insulin signaling through anti-diabetic drugs may represent a new therapeutic approach in the field of AD drug discovery. Emerging evidence shows that PPARγ, a key regulator of glucose and lipid metabolism, has an ability to exert neuroprotection in models resembling AD. Despite many positive effects in preclinical research, clinical trials have shown that TZDs have many side effects, which contributed to their partial withdrawal. A novel plant-derived SPPARɣM, amorfrutin B, activates the receptor in a distinct way by modulating interaction of PPARγ with the transcriptional activators or repressors avoiding side effects typical for full PPARɣ agonists, such as hepatotoxicity, however no attempts have been made to utilize amorfrutin B to protect from AD-induced damage.

THE MOST IMPORTANT EXPECTED RESULTS: Due to the lack of effective therapy, AD is globally problematic disease. Our novel therapy applied as a post-treatment will focus on targeting the dysregulated PPARγ signaling. The treatment with amorfrutin B, may be the basis of novel, safe and effective treatment. The breakthrough of the project would rely on providing evidence that selective modulation of PPARγ by amorfrutin B will effectively protect mouse and human neurons, does not elicit severe side effects, and is effective when applied long after the Aβ/AD-induced injury. To address a Precision Medicine' approach, in addition to sex-dependence, the vulnerability of microglia and endothelial cells to the therapy will also be assessed. We expect that insightful and multidirectional characteristic will strongly support the position of amorfrutin B among the most promising anti-AD therapeutics.