SIRTUINS IN THE PATHOGENETIC THERAPY OF NEURODEGENERATIVE DISEASES

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ABSTRACT

The progressive decline in the physiological functions during aging leads to various diseases that place a heavy burden on patients, their families and the society as a whole. Due to the increasing average life expectancy, the problems of prevention and treatment of age-related diseases are becoming more and more relevant. As a part of the research on the regulation of the aging program, considerable attention has been focused on a small family of NAD^+-dependent deacetylases and deacylases called sirtuins. These proteins are involved in the regulation of numerous intracellular processes, and disruption of their functions plays an important role in the development of various diseases, such as metabolic disorders, pathologies of the cardiovascular system and other organs, musculoskeletal diseases, and neurodegeneration. It is interesting to note that the activity of sirtuins can be modulated to some extent under the influence of pharmacological agents, which makes them promising targets for the prevention and therapy of age-related diseases. The aim of the current review is to summarize the effects of sirtuins on the development and pathogenesis of neurodegenerative diseases, taking into account the reported clinical trials on the pharmacologic agents affecting the sirtuins' activity.

Keywords: *sirtuins; Alzheimer's disease; Parkinson's disease; resveratrol; quercetin; NAD.*
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INTRODUCTION

Sirtuins (**sir two** prote**in**s) are a family of nicotinamide adenine dinucleotide (NAD+)-dependent deacylases, found in all observed organisms (including bacteria and vertebrates), that have acquired their name based on the first representative discovered, a Sir2 protein of a yeast fungi *Saccharomyces cerevisiae* that is responsible for the suppression of transcription through the deacetylation of histones [1]. There are seven sirtuin proteins known in humans and mammals. Their size varies from 250 to 750 amino acid residues marked as SIRT1–SIRT7 [2]. The conservative core unit of the sirtuin proteins includes an active center, a big domain with the Rossmann fold responsible for the binding of NAD+, and a small domain consisting of the zinc-binding and spiral modules [3]. The terminal ends of the proteins define their binding to

substrates, differ in their length and structure, and also may include signals of cell localization and posttranslational modifications [4]. Human sirtuins demonstrate different cell localization, which led to classifying sirtuins into nuclear (SIRT1/6/7), cytoplasmic (SIRT2) and mitochondrial ones (SIRT3/4/5) [5]. However, sirtuin cell localization may differ based on the stage of the cell cycle, cell type and external influence [6–8]. Moreover, new splice-isoforms are being discovered that may have no signals of cell localization and possess specific functions [9, 10].

The main function of sirtuins is the removal of posttranslational modifications of the lysin residues in proteins. At the same time all sirtuins except for SIRT5, demonstrate activity towards the acetylic modification [11]. Unlike other proteins SIRT5 specialises on the removal of the malonyl, succinyl and glutaryl lysin modifications, which makes this protein a deacylase [12, 13]. The SIRT4 protein also demonstrates deacylase activity and is able to remove the biotin, glutaryl, the lypoil residues, etc. [14, 15]. Similarly, the SIRT6 protein can remove the myristyl and palmytil modifications in proteins [16, 17]. There is also a description of the ADP-ribosyltransferase activity for the SIRT4/6/7 sirtuins, which results in adenosine diphosphate ribose from NAD+ being transferred to the arginine residues in target proteins [18–20]. One can find more detailed information on the structure and intracellular functions of the sirtuin proteins in a number of detailed reviews [21, 22].

The family of sirtuin proteins plays an important role in controlling metabolism, inflammation, stress response, apoptosis and proliferation, influences the epigenetic mechanisms of gene expression regulation as well as other processes that are disrupted during aging [23]. Considering their part in the regulation of such a number of processes, it is not a surprise that sirtuins take part in the pathogenesis of different diseases such as cancer, pathologies of the cardiovascular system and other organs, metabolic disorders, musculoskeletal diseases, and neurodegeneration [22]. As a rule, protective properties are attributed to sirtuins, although SIRT2 is an exception [24–28]. It is important to note that the activity of sirtuins changes with age, and in a number of cases the assessment of the level of their expression is also offered as a marker of aging and certain neurodegenerative pathologies. For example, a lower level of SIRT1 may serve as a diagnostic criterion for early diagnostics of Alzheimer's disease [29]. Moreover, levels of SIRT1 and SIRT3 in a serum are significantly lower in patients with senile asthenia [30]. At the same time, SIRT2 can serve as a marker of cell aging, as its level rises in cells in case of the irreversible loss of their ability to divide [31].

In the present review we summarize the role of sirtuins in the pathogenesis of such common neurodegenerative diseases as Alzheimer's and Parkinson's disease. As the results of experiments in model systems show, the change in sirtuin activity is considered a promising direction in preventing and treatment of such diseases. That is why we are also going to analyze the current state of research aimed at a possible pharmaceutical correction of sirtuin activity in the therapy of the above-mentioned diseases.

THE ROLE OF SITRTUINS IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

Alzheimer's disease is a widespread neurodegenerative disease which manifests itself in the weakening of cognitive functions and is connected with misfolding, neuroinflammation and disruption of signaling pathways [32]. Pathological changes in brain cells during Alzheimer's disease include amyloid beta (Aβ) peptide accretion outward of neurons (i.e. senile ones or Aβ-plaques) and intraneural accumulation of an abnormal form of the tau protein (i.d. neurofibrillary tangles, NFT) [33, 34]. Four main competing hypotheses have been offered to explain the possible reasons of the disease: an amyloid, a cholinergic, an infectious and a tau-hypothesis.

According to the amyloid hypothesis, the main cause of the disease is Aβ accretions. Toxic peptides of 37-49 amino acids or Aβ arise as a result of proteolytic cleavage by β- and γ-secretases of a large transmembrane glycoprotein called amyloid precursor protein (APP) [35]. At the same time, the transmembrane glycoprotein APP is constantly present in neurons, but its cleavage does not always lead to the production of amyloidogenic peptides. The SIRT1 protein activates a retinoic acid receptor β (RARβ) in the mouse neuroblastoma cell line in N2a, disintegrin and metalloprotease ADAM10, which is an α-secretase that cleaves APP to form non-amyloidogenic soluble APPα (sAPPα) [36, 37]. In contrast, SIRT2 plays a negative role in the pathogenesis of Alzheimer's disease. SIRT2 has been shown to deacetylate and cause the induction of reticulon-4B RTN4B, which is required for β-secretase 1 activation and is involved in amyloid production [38]. On the other hand, SIRT2 deacetylates APP protein at lysines 132 and 134, enhancing its amyloidogenic properties [40]. In turn, inhibition of SIRT2 reduces Aβ production and cognitive deficit in the Alzheimer's disease model in mice [38, 39].

Phosphorylation and acetylation of the tau protein plays an important role in tau-induced neurodegeneration in Alzheimer's disease [37, 40]. Acetylation prevents the degradation of the phosphorylated tau protein and therefore promotes its accumulation and toxicity growth [41-44]. SIRT1 protein can suppress the accumulation of the hyperphosphorylated tau protein by its deacetylating in tauP301S transgenic mice [45]. Another study showed that SIRT1 deacetylates Beclin-1, a protein of the cellular autophagy system, which in turn stimulates autophagy in Alzheimer's disease [46]. In addition to SIRT1, SIRT6 also prevents tau protein hyperphosphorylation through increased activation of GSK3α/β kinase [47]. It has been shown that overexpression of SIRT1 can reduce mitochondrial dysfunction and neuronal damage by regulating the activity of Rho-associated kinase ROCK1 and reducing Aβ accumulation [48]. Meanwhile, SIRT2 deacetylates α-tubulin, thereby increasing tau protein phosphorylation and reducing autophagy in Alzheimer's disease [49]. Therefore, it would be logical to use SIRT1 activators and SIRT2 inhibitors to reduce the severity of symptoms in Alzheimer's disease. For example, resveratrol has been shown to suppress Aβ-induced neuronal apoptosis through SIRT1 activation [48]. In another study, resveratrol treatment improved learning and memory and suppressed nerve cell apoptosis in the Alzheimer's disease mouse model of [50]. Similarly, it was found that resveratrol reduces Aβ levels and improves learning and memory in APP/PS1 AD mice [51]. Moreover, it was demonstrated that SIRT1 activation promotes Aβ degradation in primary astrocytes [52].

It is assumed that numerous factors contribute to the concrection and progression of Alzheimer's disease, but oxidative stress has recently been considered one of the most important etiological and pathogenetic factors of aging in general and the development of neurodegenerative diseases and Alzheimer's disease in particular [53]. In many cases, oxidative stress contributes to the upregulation of genes related to mitochondrial metabolism, and the generated reactive oxygen species (ROS) cause damage to mitochondrial DNA and other mitochondrial components, causing mitochondrial dysfunction [54]. Other molecular pathways, such as protein synthesis and folding [55] or autophagy [56], may also be associated with disturbances in redox homeostasis. Thus, oxidative stress as a part of neuroinflammation is actively involved in the development of Alzheimer's disease [57, 58]. For example, a tumor suppressor protein and transcription factor p53 translocates into the inner mitochondrial matrix under normal conditions and in response to DNA damage [59, 60]. Mitochondrial p53 forms an inhibitory complex with Bcl2 and Bcl-xL, resulting in the release of cytochrome from mitochondria into the cytosol and activation of caspases [61], and translocation of p53 into mitochondria alters the mitochondrial membrane potential [62]. However, Aβ hyperactivates p53 transcriptional activity in Alzheimer's disease, making normal cell signaling of the p53 cascade pathogenic [63]. This is counteracted by the mitochondrial SIRT3, which is prevalent in the brain and has a number of effects on mitochondrial function, the most significant of which is

suppression of oxidative stress [64, 65]. Using the system of co-culture of microglia and neural stem cells, it was demonstrated that Aβ-induced activation of microglia leads to AFC accumulation due to the suppression of SIRT3 and antioxidant enzyme manganese superoxide dismutase (MnSOD) in neural stem cells. Overexpression of SIRT3 in neural stem cells provides protection against microglial cytokinin-induced neuronal death [66]. In addition, reduced SIRT3 levels lead to p53-mediated mitochondrial dysfunction and neuronal damage in Alzheimer's disease [58]. Also, SIRT3 protects neurons from Aβ pathology and excitotoxicity, probably by deacetylating numerous proteins and normalizing mitochondrial functional activity [25]. SIRT1 and SIRT3 proteins can also counteract oxidative stress through deacetylation of the transcription factor FOXO3A, which leads to activation of the antioxidant activity of MnSOD [67, 68].

ROLE OF SIRTUINS IN THE DEVELOPMENT OF PARKINSON'S DISEASE

Parkinson's disease is a common age-related movement disorder. It is characterized by a progressive loss of central dopaminergic neurons of the substantia nigra and the appearance of Lewy bodies, which are cytoplasmic eosinophilic inclusions of abnormal protein aggregates of presynaptic alpha-synuclein protein [69]. Both genetic and environmental factors are considered to be etiological prerequisites for Parkinson's disease [70]. Studies in recent decades have identified several proteins associated with the pathogenesis of Parkinson's disease, including SNCA(PARK1), LRRK2 (PARK8), parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7), and ATP13A2 (PARK9) [71, 72]. Mutations of genes encoding these proteins in Parkinson's disease are closely associated with mitochondrial abnormalities and cellular oxidative stress leading to neuronal damage in in vitro and in vivo experiments [72]. However, genetic forms of Parkinson's disease account for only about 10% of all cases [73, 74]. At the same time, environmental exposure is recognized as an important factor contributing to the development of idiopathic Parkinson's disease. According to the epidemiological data, the influence of environmental factors correlates with an increased risk of Parkinson's disease [75].

We suppose that mitochondrial dysfunction and oxidative stress may play a central role in neurodegeneration and death of dopaminergic neurons caused by external factors [76]. The mechanism may be based on the inhibition of complex I of the electron transport chain, which in turn increases the amount of AFC [77, 78]. The substantia nigra compared to other brain regions is more prone to mitochondrial complex I dysfunction, which results from the generation of AFC in dopaminergic neurons [79]. Consequently, mitochondrial function, especially its preservation or enhancement, is of particular interest as a potential therapeutic target in Parkinson's disease.

Among all vertebrate sirtuins, SIRT3 plays the most significant role in mitochondrial biogenesis [64, 65]. SIRT3 protein is expressed at relatively high levels in tissues with high oxidative capacity, including brain tissues [64, 65]. SIRT3 activation has neuroprotective effects in Parkinson's's disease and other neurodegenerative diseases [80, 81]. Thus, SIRT3 activated by icariin (ICA), a natural flavonoid glucoside, exerts neuroprotective effects on dopaminergic neurons in rotenone-induced rat and cellular models of Parkinson's disease [82]. Pharmacologically elevated levels of SIRT3 may counteract alpha-synuclein-induced mitochondrial dysfunction by reducing the number of alpha-synuclein oligomers and normalizing mitochondrial bioenergetics [83]. In addition, age-dependent increase in the mitochondrial oxidative stress is one of the main factors in the loss of dopaminergic substantia nigra neurons in Parkinson's disease, including the pathway through increased acetylation and decreased MnSOD activity, which is associated with decreased SIRT3 function [81].

SIRT1 protein regulates the activity of the transcriptional coactivator PGC-1α, which is one of the key regulators of mitochondrial biogenesis [84]. In addition, SIRT1 activation protects SH-SY5Y neuroblastoma cells from the toxic effects of rotenone through the suppression of the transcription factor NF-κB [85]. Activation of SIRT1 by resveratrol also leads to deacetylation of

the microtubule-associated protein LC3, which in turn causes degradation of alpha-synuclein by autophagy in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of Parkinson's disease [86]. At the same time, alpha-synuclein accumulation contributes to the dysregulation of mitochondrial function and decreased SIRT1 expression [87, 88]. In contrast to the neuroprotective effects of SIRT1 and SIRT3 described above, the SIRT2 protein deacetylates alpha-synuclein at lysine residues 6 and 10, causing increased toxicity, and inhibition of SIRT2 protects from the death of dopaminergic cells in the Parkinson's disease model [89, 90].

The involvement of sirtuins in the pathogenesis of Parkinson's disease is also confirmed by molecular genetic data. Thus, there was a study of the association of SIRT1 and SIRT2 gene polymorphisms with the risk of Parkinson's disease in the Chinese Han population [91]. Two polymorphisms, rs12778366 and rs2015, were associated with the risk of Parkinson's disease, and the rs2015 polymorphism disrupted the recognition site of miR-8061 regulatory miRNA in the 3'UTR of SIRT2 and was associated with the increased expression of SIRT2.

SIRTUIN MODULATORS IN CLINICAL STUDIES FOR ALZHEIMER'S AND PARKINSON'S DISEASES

Taking into account that human sirtuins are involved in the regulation of a wide range of processes responsible for the development of many pathological conditions, the attention of researchers all over the world is focused on the search for methods of pharmacological modulation of these proteins. On the one hand, since sirtuins are NAD+-dependent enzymes, their activity can be changed by modulating NAD+ metabolism. On the other hand, since all reactions carried out by sirtuins result in the cleavage of NAD+ with the release of nicotinamide, this compound may serve as a non-competitive inhibitor of sirtuins. Finally, over the past 20 years, nearly four dozen small molecules have been discovered that can modulate sirtuin activity and have potential therapeutic value. Sirtuin modulators are the subject of many review articles [92, 93], so in order to reflect the success achieved in the field of clinical significance of sirtuins in the treatment of Alzheimer's and Parkinson's diseases, we will analyse only those ones that have been investigated in clinical trials for these diseases and registered in the international database *ClinicalTrials.gov* (Table 1) [94].

Nicotinamidadenine dinucleotide (NAD+) is a substrate in all reactions mediated by sirtuins. At the same time, this compound is known, first of all, as the most important coenzyme of redox reactions [95]. It has been shown that the concentration of NAD+ in cells decreases with age, and such a decrease leads to a drop in the activity of sirtuins in tissues of model animals [96-98]. A decrease in NAD+ levels during aging has been described in several human tissues, including brain and cerebrospinal fluid [99-101]. This provides a mechanistic basis for explaining the role of sirtuins in the pathogenesis of neurodegenerative diseases. Not surprisingly, replenishing NAD+ by supplementing the diet with its precursors, such as nicotinamidriboside (NR) and nicotinamide mononucleotide (NMN), is considered as a possible strategy in the treatment of Alzheimer's and Parkinson's diseases. As of December 2023, there are seven clinical trials registered on *ClinicalTrials.gov* testing the safety and efficacy of NR in patients with these neurodegenerative diseases (see Table 1). Of these, 3 trials have been completed, but only one has reported results in a publication and concluded a potential neuroprotective function of HP in Parkinson's disease [102]. Moreover, a drug called MIB-626, a peroral form of microcrystalline β-nicotinamide-mononononucleotide (a chemical variant of NMN [103]), is being investigated for pharmacokineticss and physiologic effects in patients with Alzheimer's disease, but is not expected to be completed until 2024.

Resveratrol (3,5,4'-trihydroxy-stilbene) [104] is a natural plant polyphenol discovered when the cardioprotective effects of moderate wine consumption were investigated [105]. Pioneerstudies demonstrated the ability of resveratrol to activate SIRT1, and its effects were later

extended to SIRT3 and SIRT5 [104, 106, 107]. However, there is an ongoing debate as to whether sirtuins are direct targets of resveratrol in humans and animal models [108]. Although no consensus has been reached, it is important to note that the synergistic activation of sirtuins by resveratrol effects may be achieved through multiple independent mechanisms. For example, in addition to sirtuins, resveratrol acts on a wide range of proteins, including the nuclear factor NF-kB, which is a native target of SIRT1 [109]. Be that as it may, despite the controversy, resveratrol continues to be considered as a modulator of sirtuin activity. As of December 2023, 209 clinical trials of resveratrol have been registered on *ClinicalTrials.gov,* of which 17 continue to enroll patients [94]. As for neurodegenerative diseases, three phase II and III clinical trials tested the safety and efficacy of long-term (up to 1 year) daily administration of high doses (up to 1.5 g/day) of resveratrol in patients with diagnosed Alzheimer's disease. The key finding is that resveratrol is safe and well tolerated. In addition, in the clinical trial NCT01504854 (up to 1.5 g of resveratrol daily for a year) it was possible to show that the drug reduces the level of metalloproteinase MMP9 - a marker of neurodegeneration - in the cerebrospinal fluid, modulates neuroinflammation and induces adaptive immunity [110]. A key disadvantage of resveratrol is its low bioavailability, as the compound is poorly absorbed when taken perorally. This problem has been addressed, in particular, by combining it with various supplements or using a purified trans-isoform of resveratrol (commercial name BIA 6-512). The latter option was considered for compatibility and pharmacokineticss in five phase I clinical trials in which the drug was used in conjunction with drugs against Parkinson’s disease. Unfortunately, in none of the studies are the results publicly available. Since these studies were conducted almost 20 years ago, it can be assumed that there is no significant effect of trans-resveratrol in the therapy of Parkinson’s disease.

Quercetin (3,3',4',5,7-pentahydroxyflavone, Q) is a natural flavonoid present in many types of fruits and vegetables. Quercetin was described as an activator of SIRT1 almost simultaneously with resveratrol [104]. The SIRT1-related effects of quercetin have been found to counteract renal fibrosis, intervertebral disc degeneration, and diabetic encephalopathy [111-113]. As of December 2023, 97 clinical trials of quercetin have been registered. However, the research on neurodegenerative diseases has focused on the senolytic properties of quercetin, i.e., its ability to reduce the viability of old (senescent) cells that are unable to divide and produce pro-inflammatory factors [114]. The combination of quercetin with dasatinib, another drug approved by the U.S. Food and Drug Administration (FDA) as an antitumor agent for chronic myeloleukemia and acute lymphoblastic leukemia [115], has been shown to selectively eliminate old cells and has shown promising results in a number of clinical trials [116]. The treatment with senolytics is specific in such a way that old cells accumulate slowly, so the drugs are administered in short courses with a relatively long break. As shown in Table 1, clinical trials of the combination of quercetin and dasatinib in patients with Alzheimer's disease are currently underway. The use of senolytics in this case is motivated by studies linking the accumulation of hyperphosphorylated tau protein to the process of cell aging [117]. Of the three clinical trials, NCT04063124, which tested the safety and pharmacokineticss of quercetin with dasatinib, has been completed. The researchers claim good tolerability of the compounds, however, the experimental group included only 5 subjects [118]. However, it is important to note that although sirtuins are considered to be targets of quercetin, its senolytic properties are most likely due to pleiotropic effects rather than a specific action on sirtuins [116], although some studies show that the ability of quercetin to inhibit aging and induce the death of old cells is associated with an increase in the SIRT1 activity [111, 119].

CONCLUSION

Recent studies show the important role of individual sirtuins in the development of Alzheimer's and Parkinson’s diseases. SIRT1 and SIRT3 proteins have pronounced

neuroprotective functions, while SIRT2 acts as their antagonist. The involvement of sirtuins in the regulation of key enzymes and cellular processes involved in the production and degradation of aberrant proteins in neurons makes sirtuins an attractive target for therapy. Despite considerable efforts to find compounds capable of controlling sirtuins' activity, only a few types of drugs have reached clinical trials. It is important to note that all compounds under investigation have a distinct pleiotropic mechanism of action, so at this point it is difficult to conclude on the contribution of sirtuins to their effects. It can be assumed that the potential of sirtuin activity modulation in approaches to the therapy of neurodegenerative diseases has not been exhausted yet, since most clinical trials have not been completed, and an active search for new sirtuin senolytics and inducers is conducted.

ADDITIONAL INFORMATION

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Table 1

Clinical trials of sirtuin modulators in Alzheimer's disease and Parkinson's disease trials registered at ClinicalTrials.gov as of December 2023

Compound	Identificator	Start date/ end date	Phase	Status	State	Goal	Sample size; age (*n*; y.o.)	Treatment regimen	Results
Nicotinamide riboside	NCT03568968	2020-05-15/ 2024-12-31	Phase 2	Participants enrolment	PD	Slowing down of PD	400; >35	500 mg 2 times a day 52 weeks	Not delivered
	NCT02942888	2017-11-30/ 2021-08-16	Not attributed	Finished	Mild cognitive impairment	HR influence on NAD+ levels and brain function in patients with mild cognitive impairment	46; >65	250 mg–1 g a day 10 weeks	Not delivered
	NCT05589766	2023-01-23/ 2024-12-31	Phase 2	Participants enrolment	PD	Defining of the optimal biological dose of NR in patients with PD	80; 40–100	1–2 g a day 12 weeks	Not delivered
	NCT04430517	2022-03-02/ 2025-04-30	Early phase 1	Participants enrolment	Mild cognitive impairment/ mild case of AD	To study the influence of NR on the brain energy metabolism, oxidative stress and cognitive functions in people with mild cognitive impairment and mild dementia connected with AD	50; 55–89	250 mg NR 2 times a day 12 weeks	Not delivered
	NCT05344404	2022-04-29/ 2022-07-01	Not attributed	Finished	PD	Defining safety and tolerability of NR with PD	20; >35	3000 mg a day 4 weeks	Not delivered
	NCT03816020	2019-03-09/ 2020-02-10	Not attributed	Finished	PD	NR intake effect on symptoms connected with PD	30; >18	500 mg 2 times a day 4 weeks	NR intake is a potential neuroprotective therapy of PD [102]
	NCT05617508	2022-11-22/ 2024-12-31	Not attributed	Participants enrolment	AD	Defining the optimal dose of NR in patients with AD	80; 50–85	1-3 g daily for 12 weeks	Not delivered
Nicotinic acid (niacin, viatamin B3), nicotinamide	NCT03061474	2017-07-12/ 2022-08-30	Phase 2	Finished	AD/ mild cognitive impairment	To check whether B3 can decrease tau phosphorylation in	46; >50	1,5 g 2 times a day up to 47	Published openly

precursor						people with mild cognitive impairment or mild AD		weeks	
	NCT00580931	2008-01/ 2014-07	Phase Phase 2	Finished	AD	To study safety and effectiveness of B3 for AD treatment	50; 50–95	1,5 g 2 times a day 6 weeks	Not published openly
	NCT03808961	2020-01-01/ 2024-04-01	Not attributed	Active; no recruiting	PD	To study the effect of 18-month B3 intake on inflammation and non-motor symptoms in patients with PD	7; >35	100 mg 2 times a day up to 18 months	Not delivered
Resveratrol	NCT01504854	2012-05/ 2014-03	Phase 2	Finished	AD	To study the influence of resveratrol on AD development markers	119; >50	0,5–1,5 g 1 time a day up to 12 months	Resveratrol decreases the level of MMP9 in cerebrospinal fluid, modulates neuroinflammation and induces adaptive immunity [110]
	NCT00743743	2008-09/ 2010-12	Phase 3	Finished due to the principal investigator's employment termination	AD	Assessment of resveratrol influence on cognitive functions and behavior in patients with mild and moderately severe AD	No data; 50–90	215 mg daily 52 weeks	Not delivered
	NCT00678431	2008-01/ 2011-06	Phase 3	Finished	AD	Slowing down AD progression with a mixture of resveratrol, glucose and malate	27; 50–90	Mixture of 5 g dextrose, 5 г malate and 5 mg resveratrol + a glass of 8 oz. grape juice 2 times a day 1 year	Low peroral doses of resveratrol are safe and well tolerated. Interpretation on the influence on the trajectory of clinical outcomes stays undefined [120]
Trans-resveratrol (BIA 6-512)	NCT03093389	2005-05-11/ 2005-07-29	Phase 1	Finished	PD	To study tolerability and safety of intake of multiple dose of BIA 6-512 in healthy	40; 18–45	25 mg, 50 mg, 100 mg and 150 mg 6 times a day	Not delivered

						volunteers			
	NCT03095105	2006-01-24/ 2006-03-02	Phase 1	Finished	PD	Comparison of the pharmacokinetics BIA profile 6-512 in healthy senior and young people after a single peroral dose and redosing	25; >40	From 1 to 8 doses of 200 mg BIA 6-512 every 8 hour	Not delivered
	NCT03094156	2006-04-26/ 2006-07-11	Phase 1	Finished	PD	Studying the influence of multiple BIA 6-512 dose on levodopa pharmacokinetics	39; 18–45	25? 50? 75 or 100 mg (3 times a day for 5 days) + single 200/50 mg dose of levodopa/benserazide combined with 200 mg entacapone	Not delivered
	NCT03095092	2005-05-23/ 2005-07-07	Phase 1	Finished	PD	Studying the influence of food intake on the pharmacokinetics of a single 400 mg BIA 6-512 dose in healthy volunteers	24; 18–45	400 mg single dose after overnight fasting or after breakfast	Not delivered
	NCT03097211	2006-07-17/ 2006-10-20	Phase 1	Finished	PD	Studying the influence of a multiple BIA 6-512 dose on levadopa pharmacokinetics	38; 18–45	25, 50, 75 or 100 mg (3 times a day for 5 days) + a single 200/50 mg dose of levodopa/benserazide combined with 150 mg nebicapone	Not delivered
	NCT03091543	2004-05-04/ 2004-07-23	Phase 1	Finished	PD	Studying tolerability, safety and pharmacokinetics of a	20; 18–45	A single dose of 25, 50, 100 or 200 mg	Not delivered

						BIA 6-512 single dose and their influence on levodopa pharmacokinetics during combined administration		BIA 6-512 + 100/25 mg of levodopa/ benserazide	
β-nicotinamide mononucleotide (MIB-626)	NCT05040321	2021-12-01/ 2024-12-01	Phase 1 Phase 2	Participants enrolment	AD	Defyining pharmacokinetics and physiological effects of the MIB-626 sirtuin activator in AD	50; 55–85	500 mg of MIB-626 2 times a day perorally	Not delivered
Quercetin (Q)	NCT04063124	2020-02-14/ 2023-01-30	Phase 1 Phase 2	Finished	AD	Studying dasatinib + Q pharmacokinetics	5; >65	6 cycles of dasatinib + Q intake for 2 days with 14-day break	Patients tolerate dasatinib + quercetin treatment well[118]
	NCT04785300	2022-07-06/ 2023-12	Phase 1 Phase 2	Enrolment on invitation	AD/ mild cognitive impairment	Assessment of safety and possibility of combined usage of dasatinib and Q in patients with mild cognitive impairment or AD	20; >55	6 cycles 100 mg dasatinib + 1000 mg Q intake for 2 days in a row with a 13-day break	Not delivered
	NCT04685590	2021-12-22/2023-01	Фаза 1 Phase 2	Participants enrolment	Early-onset AD/ mild cognitive impairment	Assessment of safety, usability and effectiveness of dasatinib and Q combination in elderly people with mild amnestic and cognitive imparities or an early DA stage with the tau-positive PET result	48; >65	6 cycles of dasatinib + Q intake for 2 days with a 13-day break	Not delivered

Note. PD — Parkinson’s disease; AD — Alzheimer's disease; NR — nicotinamidriboside; PET — positron emission tomography; Q – quercetin.