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Inhibition of α-Synuclein Aggregation by Polyphenols

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder marked by intracellular Lewy bodies, composed mainly of amyloid fibrils formed by α-synuclein (αSyn). Native αSyn is a soluble intrinsically disordered protein, but in PD it misfolds into a pathological β-sheet structure that aggregates, impairs mitochondrial function, triggers inflammation, and ultimately leads to neuronal death. Because αSyn aggregation proceeds through multistep nucleation and rapid fibril elongation, inhibiting this process – particularly by blocking fibril growth at the ends – is a promising therapeutic strategy. This review focuses on polyphenols as inhibitors of αSyn amyloid fibril aggregation. Polyphenols modulate aggregation through diverse mechanisms, including stabilization of monomers, redirection into non-toxic off-pathway oligomers (e.g., EGCG, Resveratrol), disruption of existing fibrils (Baicalein), and covalent modification of αSyn lysine residues (Quercetin, Hydroxytyrosol). Importantly, gut microbiota-derived metabolites of dietary polyphenols (such as 3-HPPA) can cross the blood-brain barrier and strongly attenuate αSyn seeding, underscoring their therapeutic potential in PD.

Keywords: α-synuclein, Parkinson's disease, amyloid fibril, polyphenols.

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting more than 6 million people worldwide. Approximately 4% of individuals aged 80 and over are suffering from it (de Rijk et al., 1995).

The classic signs of Parkinson's disease are motor symptoms. These include resting tremor, bradykinesia, postural instability, and rigidity. It usually manifests as unilateral tremor, with tremor usually observed in one limb (sometimes involving only one finger) (Haaxma et al., 2007). Bradykinesia is a slowing of movement and simplification of complex motor tasks. The number of spontaneous movements is reduced, the frequency of blinking decreases and the eyes become more open, spontaneous swallowing decreases and swallowing mechanics are impaired, leading to sialorrhea (Raza et al., 2019).

Parkinson's disease is characterized by the presence of pathological inclusions – Lewy bodies – and a decrease in the number of dopaminergic neurons in an area of the brain called the substantia nigra (Raza et al., 2019). Amyloid fibrils formed by αSyn are the main components of Lewy bodies – spherical formations in the cytosol of cells of people with Parkinson's disease and other neurodegenerative disorders (Rocha Cabrero & Morrison, 2024).

α-synuclein (αSyn) is a 140 amino acid neuronal protein encoded by the SNCA gene. In its native form it is soluble monomeric intrinsically disordered protein that contains almost no stable intramolecular hydrogen bonds. It can bind to membranes forming a helix oriented parallel to the membrane surface and is believed to play a role in synaptic vesicle trafficking (Burre et al., 2010). Folding into a pathological parallel β-sheet amyloid form occurs with the formation of many new hydrogen bonds between neighboring protein molecules in the fibril. Under certain conditions, native αSyn can misfold into amyloid fibrils (Spillantini et al., 1997). They are long protein aggregates consisting of thousands αSyn molecules, all in the same β-sheet rich conformation stabilized by intermolecular hydrogen bonds along the fibril axis (Fig 1. A, B)

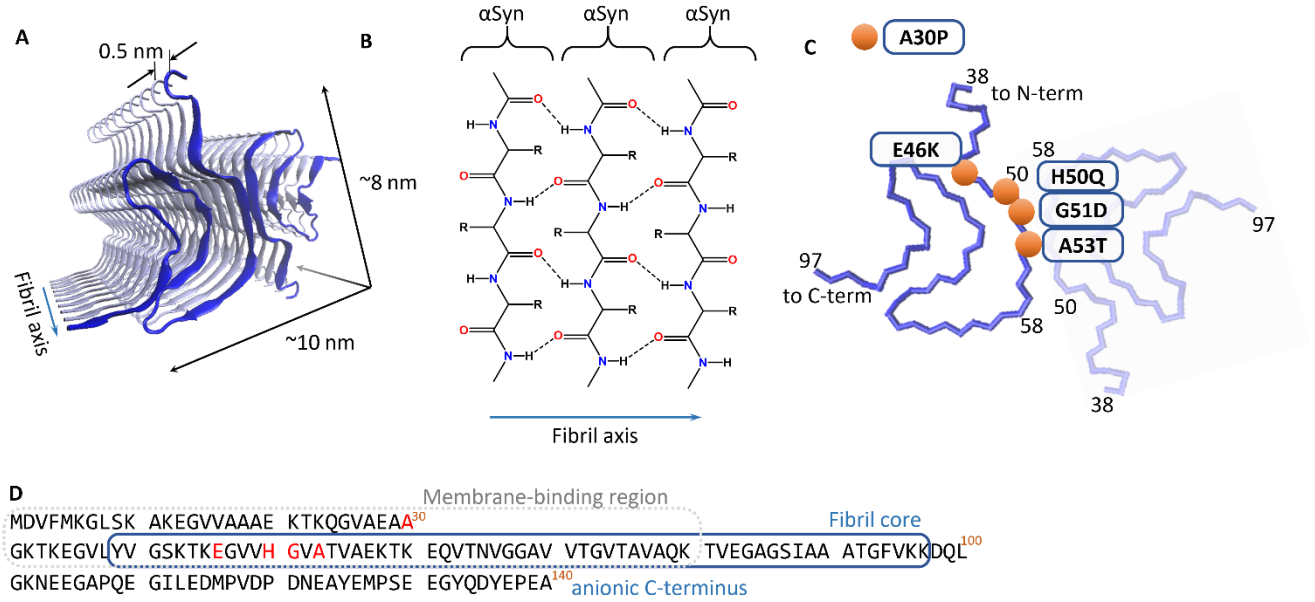

Fig. 1. A) Structure of αSyn fibril core drawn based on CryoEM (PDB ID: 6CU7) (B. Li et al., 2018) B) mode of interaction between αSyn molecules in it C) location of sites of disease-related mutations (A30P, E46K, H50Q, G51D, A53T/E) in respect to fibril core, two αSyn monomers per cross-section are shown in light and dark blue, respectively, D) αSyn sequence with outlined membrane-binding region, fibril core, and anionic C-terminus.

Although most PD cases are idiopathic and the mechanism of disease initiation remains elusive, a fraction of cases (10–15%) are familial and can be connected to particular genome mutations (Chai & Lim, 2013). The first gene found to be associated with familial PD is SNCA, which encodes αSyn. Its duplication and triplication lead to an increase in αSyn expression as well as several point mutations in αSyn sequence (Fig1. C) (A30P, E46K, A53T, G51D, H50Q), results in early development of the disease (Jellinger, 2022). This correlation highlights the significant role of the αSyn protein in the disease. However, several mutations in genes that encode other proteins (GBA, MAPT, LRRK2, PRKN, DJ1, PINK1, and ATP13A2) were also reported to be related to PD cases (Klein & Westenberger, 2012).

The accumulation of αSyn aggregates (in particular fibrils) disrupts mitochondrial function, induces inflammatory processes, and leads to neuron death. Therefore, treatment aimed at stopping

the growth of oligomers and/or αSyn fibrils may reduce the development of neurodegeneration, which is a promising therapeutic strategy for Parkinson's disease (Dehay et al., 2015).

αSyn fibrils are associated with the development of inflammation of the nervous tissue through the involvement of microglia, astroglia, and lymphocytic cells (Zella et al., 2019). α-synuclein oligomers can also cause toxicity by damaging mitochondria (Hsu et al., 2000), causing lysosomal leakage (Hashimoto et al., 2004), or destroying microtubules (Alim et al., 2004). Toxic forms of αSyn interfere with the axonal transport of synaptic proteins such as synapsin-1, leading to synaptic dysfunction and ultimately neurodegeneration (Scott et al., 2010).

Although Parkinson's disease is the second most common neurodegenerative disorder, current therapeutic strategies are mainly symptomatic and do not alter the cause of the illness. Most available treatments aim to elevate dopamine levels in the brain to counteract the decline in dopaminergic neurotransmission (Muller, 2012). While the precise mechanisms leading to dopaminergic neuron loss remain uncertain, αSyn aggregation is thought to trigger a cascade of events that ultimately causes neuronal death. Consequently, inhibiting the formation and growth of αSyn amyloid fibrils is viewed as one of the most promising fields for halting PD progression and developing truly disease-modifying therapies (Ono & Yamada, 2006).

2. TARGETING A-SYNUCLEIN AGGREGATION

In vitro, under physiological conditions, αSyn fibrillization occurs within several days at concentrations of 50 μM (Marotta et al., 2015). It is a multistep process with a slow assembly of monomers into initial fibrils (primary nucleation) and much faster further elongation of the fibrils (Fig. 2).

Upon growth, fibrils break, yielding new fibril ends that serve as templates for αSyn misfolding (Shvadchak et al., 2015). Such an event, so-called fragmentation or secondary nucleation, makes the process autocatalytic and leads to the rapid increase of the fibrillization rate (Fig. 2). There are several strategies to stop formation of amyloid fibrils.

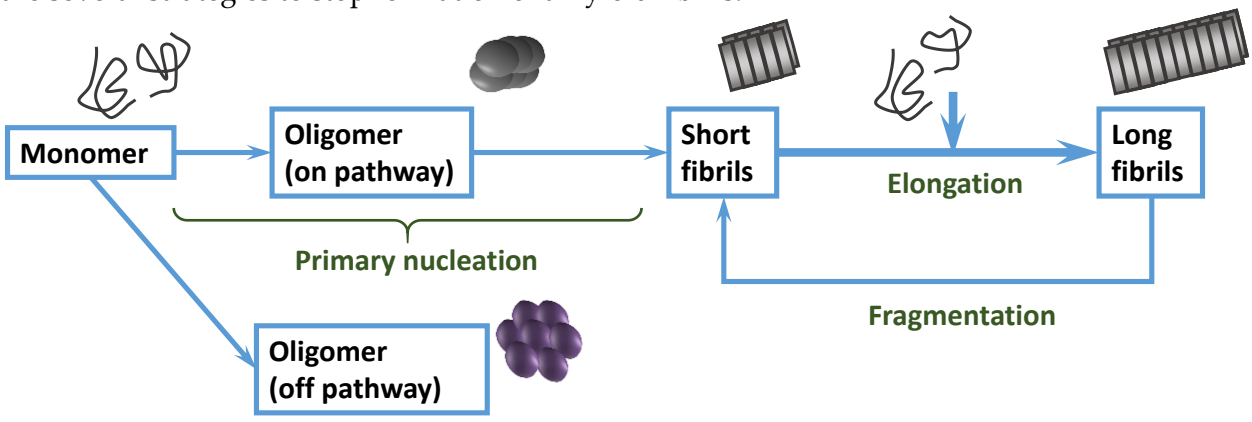

Fig. 2. Schematic representation of αSyn aggregation process. Bold arrows show the elongation process by which most of fibril mass is formed.

Stabilization of monomeric α-Synuclein. The most direct approach to preventing amyloid formation is to target the native monomeric form of αSyn and stabilize it in a non-aggregating conformation (Galkin et al., 2024). However, this approach is challenging for a couple of reasons. First of all, αSyn is an intrinsically disordered protein (IDP) and lacks well-defined stable secondary structure, meaning it does not contain typical hydrophobic pockets suitable for small-molecule drug targeting. Furthermore, because the αSyn concentration in presynaptic terminals is high (up to 20 μM), inhibitors targeting the monomer must be administered at high, stoichiometric ratios. There is also a risk that targeting the native monomer could disrupt its physiological functions. Despite these challenges, the monomeric form was historically the most studied target for inhibition due to

its structural characterization as reviewed in (Oliveri, 2019). The most popular strategy involves developing compounds capable of binding to αSyn, stabilize the monomer and prevent fibrillation. Majority of them were reported to target so-called NAC (Non-amyloidal Component) region (residues 61−95) (Fig.1 D) that was considered to be responsible for fibril formation until 2017 when structure of fibrils was determined by CrioEM (B. Li et al., 2018). Other researchers have focused on binding to the N-terminus (Fig.1 D) (residues 1−60) (Horsley et al., 2022). An alternative method involves diverting the aggregation away from the fibril pathway toward the formation of stable, off-pathway oligomers. This approach, reported for several polyphenols, also requires a stoichiometric amount of the modulator (Szego et al., 2021).

Preventing formation of fibrils from oligomers. The initial step in aggregation is the interaction of several αSyn molecules to form oligomers, which makes them an essential target. Oligomers are frequently viewed as highly toxic species in PD, many of them are reported to have membrane-disrupting activity. Currently, there is no consensus in the field regarding the precise structure and composition of αSyn oligomers, which complicates the investigation of their properties. However, from mechanistic and point of view, they can be classified into two major groups: (i) "on-pathway" oligomers that can be further transformed into amyloid fibrils and (ii) "off-pathway" oligomers that are stable species incapable of further conversion to amyloids (Alam et al., 2019). The key challenge in targeting oligomers is their huge variety and the absence of reliable structural data. Second, because fibril elongation primarily occurs via the binding of monomers, not oligomers, toxic oligomers do not accumulate to high concentrations. Consequently, research focusing on compounds that selectively target oligomers must be evaluated carefully, keeping in mind the concentration and stability of the target species (Bell & Vendruscolo, 2021).

Preventing fibril elongation. The main process by which αSyn molecules misfold into amyloid is the sequential addition of monomeric protein to the fibril ends (Fig. 2). Blocking or capping these fibril ends prevents elongation, thereby stopping the misfolding process (Galkin et al., 2024). Fibril ends are a particularly promising target because they are pathological species not present in healthy neurons and are relatively rare - their concentration is always orders of magnitude lower than the total αSyn concentration (Buell et al., 2014). Furthermore, αSyn within the fibril core adopts a distinct, rigid conformation whose structure is now known, which facilitates the rational, structure-based design of inhibitors (Guerrero-Ferreira et al., 2020). Inhibitors in this class demonstrate the lowest IC_{50} values, working at nanomolar concentrations with a 1:1000 inhibitor-to-αSyn ratio. However, inhibitors that target fibril ends have to be highly potent, requiring strong binding to compete with the monomeric αSyn and to recognize structural fragments as distant as 3-4 nm to be selective towards αSyn fibrils. As a result, almost all representative of this class are protein and peptides with molecular weight of ≥ 3 kDa (Galkin et al., 2024). Smaller mimicking the sequence of amyloid fibril core, such as RGAVVTGR-NH2 and VAQKTmV (Madine et al., 2008) are much less active.

Preventing secondary nucleation. Secondary nucleation is the process responsible for the autocatalytic acceleration of fibril formation, making it a critical target for stopping αSyn aggregation. This process involves the formation of new fibril growth centers, either through fibril breaking or on the fibril surface (branching) (Horne et al., 2024). Inhibitors of secondary nucleation often work by inducing the sticking of multiple fibrils into clamps. This action makes the fibrils less prone to breaking and renders their surface less accessible for the formation of branching centers (Lam et al., 2016). The most known inhibitor of this type is anle138b that intercalates into the fibrils (Levin et al., 2014).

Fibril disassembly. Reversing the formation of pathological species by disassembling amyloid fibrils back into monomeric αSyn is a highly attractive therapeutic goal. and Many compounds, including SynuClean-D (Pena-Diaz et al., 2023) were reported to act by this mechaniusm. However, αSyn amyloid fibrils are thermodynamically more stable than the monomeric form at concentrations above 500 nM. To induce disassembly, a compound must stoichiometrically react with αSyn monomers and possess an affinity stronger than the affinity of the monomer for the fibril end (Afitska et al., 2019).

To sum up there are three major types of inhibitors of αSyn fibrillization: (i) protein and peptide inhibitors that tightly bind fibrillar or monomeric αSyn, (ii) planar organic molecules that intercalate into amyloid fibrils hindering their elongation and secondary nucleation, (iii) polyphenols, for which the acting mechanism is not understood yet. This review aims to cover recent results of the studies of polyphenol inhibitors of αSyn fibrillization in attempt to clarify their acting mechanism.

3. POLYPHENOL INHIBITORS OF A-SYNUCLEIN AGGREGATION

Natural phenolic compounds, including flavonoids and non-flavonoids, are widely studied for their ability to interfere with αSyn aggregation, oligomerization, and subsequent cellular toxicity. However, their mechanism of action against PD can be more complex and include prevention of oxidative damage (Aktas et al., 2025).

An extensive search among other natural polyphenols has identified a number of compounds that are capable of reorganizing or disassembling αSyn aggregates (Pena-Diaz et al., 2023), including baicalein, myricetin (Ardah et al., 2014), and ferulic acid (Ono & Yamada, 2006). These inhibitors function primarily by modulating the kinetic pathway of aggregation, either by stabilizing the functional monomeric state, promoting the redirection of assembly into non-toxic species, or destabilizing preformed toxic aggregates (Ono & Yamada, 2006; Raza et al., 2019).

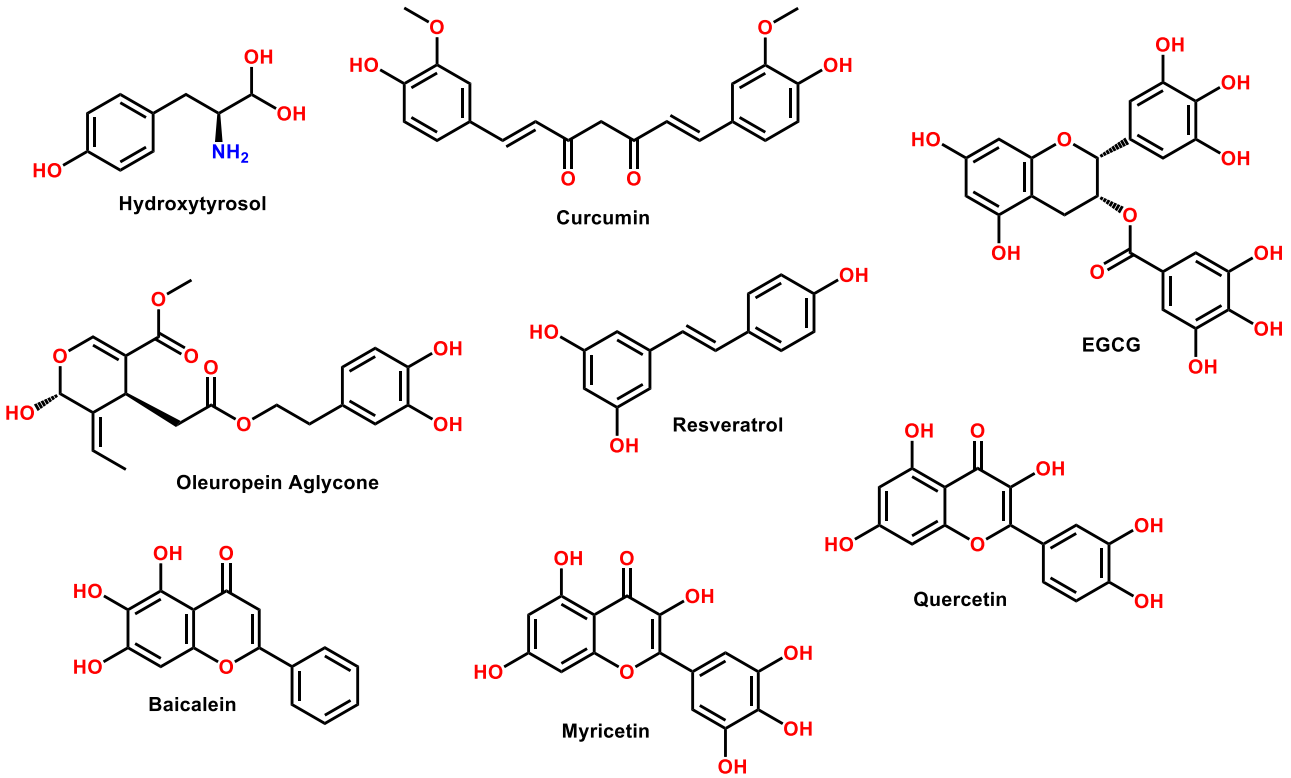

Fig. 3. Most known polyphenol inhibitors of αSyn fibril growth.

3.1 Dopamine derivatives

Catecholamines, namely L-dopa and dopamine are closely related to the pathogenesis of Parkinson's disease as most αSyn aggregates are formed in dopaminergic neurons. These two compounds were first polyphenols reported to disaggregate inhibit αSyn fibril formation and dissociate already formed fibrils (Breydo et al., 2016; J. Li et al., 2004).

Hydroxytyrosol (HT) and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), disrupt αSyn oligomers and disaggregate preformed fibrils (Fongaro et al., 2022). The inhibitory effect is linked to the catechol group (ortho-dihydroxyl structure). These catechol-containing compounds were reported to interact with αSyn through both non-covalent and covalent bonds (Inciardi et al., 2025). Non-covalent interactions are vital as they alter the balance between soluble and insoluble αSyn species. Although catechols initially bind non-covalently to the N-terminal and NAC regions, subsequent covalent modification (covalent bond formation) due to proximity and chemical reactivity may occur, which further disrupts long-range electrostatic interactions, enhancing the inhibitory effect (Di Rosa et al., 2020).

3.2 Flavonoids

(-)-Epigallocatechin-3-gallate (EGCG), the primary polyphenol in green tea, redirects amyloidogenic polypeptides, including αSyn, into unstructured, off-pathway oligomers that are incapable of further conversion into amyloid fibrils. EGCG can also remodel existing mature αSyn and amyloid-beta (Aβ) fibrils, significantly reducing cellular toxicity. Specifically concerning the structure of αSyn, EGCG has been shown to destabilize the αSyn fibril by disrupting salt-bridge between amino acid residues and the inter-protofibril interface (Mirzaei-Behbahani et al., 2024).

Baicalein was reported to inhibit αSyn oligomer formation and suppressing subsequent fibrillation (Wu et al., 2021), as well as to disaggregate pre-existing fibrils (Yao et al., 2022). Researchers hypothesized that its primary mechanism involves the destabilization of α-synuclein fibrils due to remodeling the inter-protofilament interface caused by aromatic stacking interactions with residues Y39 and F94 and strong hydrophobic interactions (Yao et al., 2022). It is important to note that the disruptive effects of baicalein on α-synuclein fibrils are polymorphism-dependent, meaning the exact molecular targets shift when dealing with familial PD-associated mutants (E46K and H50Q) (Hu et al., 2016).

Myricetin inhibits αSyn aggregation and effectively disaggregates preformed protein aggregates (Zhytniakivska et al., 2025). Mechanistic studies show that myricetin inhibits αSyn oligomerization and conversion of the secondary structure by directly binding to the N-terminal region of the protein (Inden et al., 2021). This action is critical for the resulting amelioration of α-synuclein-induced synaptic toxicity (King et al., 2022).

Quercetin, a widely available naturally occurring flavonoid found in fruits, vegetables, and red wine, has been shown to inhibit αSyn. The group of Anthony Fink found that the inhibition is connected to the formation of covalent quercetin - αSyn adducts and is enhanced by quercetin oxidation. (Zhu et al., 2013). This covalent interaction leads to the formation of covalently modified αSyn oligomers and aggregates that exhibit increased hydrophilicity and higher stability compared to toxic species (Jimenez-Aliaga et al., 2011). Furthermore, quercetin was reported to stabilize αSyn oligomers. More recent research showed that primary inhibition mechanism involves interrupting the growth phase of the amyloid structure (Alvarez-Berbel et al., 2022). However, some works report quercetin to be capable of disaggregating preformed fibrils (Kumar et al., 2019), also.

A comparative analysis of αSyn inhibition kinetics indicates that the ortho-dihydroxyl group in the quercetin structure is crucial for its activity against fibril inhibition (Alghamdi et al., 2022). This aligns with observations that flavonoids possessing catechol moieties, such as quercetin and myricetin, are generally more active inhibitors of protein fibrillation. The high amyloid suppression potential of such compounds is often connected to a site-specific inhibition mechanism requiring the initial autooxidation of the catechol moiety into o-quinone, which subsequently forms a covalent

adduct targeting lysine residues on amyloid proteins, disrupting the aggregation pathway (Abioye et al., 2022).

3.3 Other polyphenols

To different extend the ability to inhibit αSyn fibrillization was shown to many other polyphenolic compounds ranging from ferulic acid (Ono & Yamada, 2006) and protocatechuic acid(Hornedo-Ortega et al., 2016) to curcuminoids (Pena-Diaz et al., 2023). Ono and Yamada found that structures containing two motives of ferulic acids (symmetrically bound 3,4-dihydroxyphenyl rings), for example, rosmarinic acid or curcumin, in general show strong inhibition than smaller compounds, and hypothesized that it is connected to stronger interaction with NAC region of αSyn (Ono & Yamada, 2006).

Resveratrol (trans-3,5,4'-trihydroxy-trans-stilbene, Fig. 3) acts as a modulator of αSyn aggregation. Investigations using pulsed Hydrogen-Deuterium Exchange Mass Spectrometry (HDX-MS) and kinetic modeling revealed that in the presence of resveratrol, the aggregation pathway differs markedly from the uninhibited pathway (Zhang et al., 2018). The resulting aggregated particles possess a strong inhibitory-like behavior, suggesting that resveratrol either destabilizes intermediate aggregates or interacts directly with αSyn , leading instead to the formation of off-pathway oligomers (Illes-Toth et al., 2024). Morphological studies corroborate this, showing that in the presence of resveratrol, αSyn forms small oligomers and amorphous deposits rather than the long, large fibrils typical of uninhibited aggregation. Spectroscopic analyses further indicate that the resulting aggregates formed with resveratrol exhibit a tendency toward a more α-helical conformation rather than the characteristic β-sheet structure seen in canonical amyloid formation. Resveratrol have been demonstrated to directly disassemble αSyn oligomers and fibrils in vitro (Chau et al., 2021).

Curcumin is a polyphenolic natural compound derived from *Curcuma longa* reported to have versatile therapeutic activities. It was reported to prevent αSyn aggregation and reduce amyloid-induced cytotoxicity. Curcumin inhibits the aggregation of αSyn in a dose-dependent manner and increases αSyn solubility in cell models. A key action of curcumin is its ability to enrich the population of non-toxic "off-pathway" soluble oligomers and prefibrillar aggregates of α-synuclein and Aβ (Rezaei Kamelabad et al., 2021). It strongly inhibits both αSyn oligomer and fibril formation. Curcumin exerts its anti-amyloid effect primarily through a non-covalent binding mechanism (Radbakhsh et al., 2021). It was reported to bind specifically to αSyn oligomers and fibrils, but not monomers (Liang et al., 2017). The binding targets the hydrophobic NAC region of the protein. This interaction significantly alters the morphology of the protein oligomers and modifies the α-synuclein morphology without fully disintegrating them to monomers. Molecular dynamics simulations reveal that curcumin reduces the structural stability of αSyn oligomers by disturbing their β-sheet structure, this structural perturbation is attributed to van der Waals and electrostatic interactions. By binding to the hydrophobic core, curcumin facilitates a faster reconfiguration rate of αSyn, which prevents aggregation (Tavanti et al., 2020).

Furthermore, curcumin dose-dependently destabilizes preformed amyloid fibrils and reduces the exposed hydrophobic surface of the fibrillar structure. The efficacy in disaggregating preformed structures is enhanced when curcumin is used in an optimized cocktail with β-cyclodextrin (Gautam et al., 2014).

Oleuropein Aglycone (OA), the deglycosylated form of oleuropein, was reported to stabilize the monomeric α-synuclein and promote the formation of non-toxic aggregates (Manzanza et al., 2021). Computational investigations indicate that OA strongly binds and stabilizes the αSyn monomer structure, subsequently reducing long-range hydrophobic interactions between the NAC and C-terminal regions necessary for aggregation (Basellini et al., 2025). Studies suggest OA interacts with the αSyn structure across multiple domains, including the N-terminal amphipathic region, the central NAC domain, and the C-terminal acidic region (Canuelo, 2025).

3.4 The influence of gut microbiota on inhibitory efficacy

The efficacy and neuroprotective action of polyphenols are profoundly influenced by the gut-brain axis, particularly the metabolism carried out by the gut microbiota (Wu et al., 2024). Since most dietary polyphenols are consumed as glycosides, they are not completely absorbed in the upper gastrointestinal tract, requiring microbial action for conversion into bioactive metabolites that can cross the blood-brain barrier (BBB) (Kemperman et al., 2010). Gut microbes transform polyphenols into various phenolic acid metabolites, whose concentrations and bioactivity depend significantly on the individual's microbiota composition (Yamasaki et al., 2020).

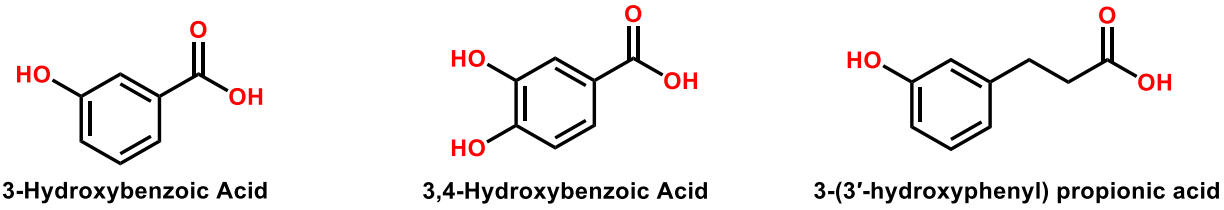

Fig. 4. Gut microbiota metabolites inhibitors of αSyn fibril growth.

Following oral administration of a polyphenol-rich preparation in mice, three specific microbial metabolites were found to accumulate in the brain: 3-hydroxybenzoic acid (3-HBA), 3,4-dihydroxybenzoic acid (3,4-diHBA), and 3-(3′-hydroxyphenyl) propionic acid (3-HPPA) (Fig.4) (Takahashi et al., 2015). In vitro assays confirmed that these metabolites (3-HBA, 3,4-diHBA, and 3-HPPA) inhibit α-synuclein aggregation, particularly suppressing the formation of low-order oligomers such as dimers and trimers (Wang et al., 2015). Crucially, these metabolites were found to significantly attenuate intracellular αSyn seeding aggregation in a cell-based system, a finding confirmed using insoluble αSyn aggregates extracted from post-mortem Multiple System Atrophy (MSA) and PD brain specimens. This highlights the essential role of microbiota-derived metabolites in modulating αSyn pathology in neurodegenerative conditions (Foscolou et al., 2018).

Polyphenols, therefore, function as multi-modal inhibitors, utilizing diverse molecular strategies - from structural deformation via hydrophobic and stacking interactions (Baicalein, OA) to redirecting the assembly pathway (EGCG, Resveratrol) and generating potent metabolites in the gut (3-HPPA, 3,4-diHBA) - to interfere with the fundamental pathological process of αSyn misfolding (Siracusa et al., 2020). Studies of structural activity have shown that for phenolic acids, inhibition increases with an increase in the number of hydroxyl groups located in sequence. Based on data on fibrillation inhibition by a set of different polyphenols, (Ono & Yamada, 2006) suggested that polyphenols with two symmetrically linked 3,4-dihydroxyphenyl or 4-hydroxy-3-methoxyphenylene rings (rosmarinic acid, curcumin) are most suitable for interacting with the NAC region of αSyn (Lashuel et al., 2013).

4. CONCLUSION

Parkinson's disease is fundamentally linked to the misfolding and aggregation of α-synuclein into pathological parallel β-sheet amyloid form. The accumulation of such aggregates disrupts mitochondrial function, induces inflammation, and leads to the characteristic loss of dopaminergic neurons. Therefore, the inhibition of αSyn oligomer and fibril formation is a promising therapeutic strategy for mitigating neurodegeneration in PD. Polyphenols is the only distinct class of small molecules know to inhibit α-synuclein misfolding. They have been extensively studied as multi-modal inhibitors capable of modulating the kinetic pathway of αSyn aggregation by diverse mechanisms:

• Redirection of αSyn assembly from the fibril pathway into non-toxic, unstructured, off-pathway oligomers that was reported for compounds like (-)-Epigallocatechin-3-gallate (EGCG) and Resveratrol.

• Disaggregation of amyloid fibrils reported for Baicalein and several other compounds.

• Covalent Modification of αSyn monomer. This mechanism is possible for certain catechol-containing flavonoids, such as Quercetin and Hydroxytyrosol, and is linked to oxidation of the catechol moiety into o-quinone, which forms a covalent adduct targeting lysine residues on αSyn, stabilizing the resulting aggregates and inhibiting fibril growth.

The neuroprotective efficacy of dietary polyphenols is profoundly influenced by the gut-brain axis**.** The gut microbiota converts non-absorbable dietary polyphenols into much smaller bioactive phenolic acid metabolites that are capable of crossing the blood-brain barrier (BBB). These microbiota-derived compounds are vital as they significantly attenuate intracellular αSyn seeding aggregation, a finding confirmed using pathological aggregates extracted from post-mortem PD brain specimens. This highlights that successful PD therapy using polyphenols may depend not just on the compound itself, but also on the metabolic activity of the individual's gut microbiome.

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Author contributions. Conceptualization: AS and VS. Methodology, data collection, and referencing: AS. Writing – original draft preparation: AS. Writing – review and editing: VS.

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Declarations

Conflict of interest. The authors have no competing interests to declare relevant to this article's content.

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Штурмак А.В, Швадчак В.В, (2025) Інгібування агрегації α-синуклеїну поліфенолами. *Журнал Прикарпатського національного університету імені Василя Стефаника. Біологія* 12: 87-100.

У роботі розглянуто сучасні уявлення про роль фібрилізації α-синуклеїну в патогенезі хвороби Паркінсона та можливості її гальмування природними поліфенольними сполуками. Проаналізовано механізми агрегації α-синуклеїну, зокрема утворення олігомерів, ріст фібрил, вторинну нуклеацію та фактори, що сприяють нейродегенерації. Особливу увагу приділено поліфенолам (EGCG, ресвератрол, баікалеїн, мірицетин, кверцетин, куркумін та ін.) як перспективним інгібіторам, здатним стабілізувати мономерний білок, перенаправляти агрегацію в нетоксичні форми або дестабілізувати вже сформовані фібрилярні структури. Обговорено вплив метаболітів поліфенолів, утворених мікробіотою кишечника, які також проявляють виражений антіфібрилогенний ефект. Поліфеноли розглядаються як багатофункціональна та перспективна платформа для створення нових терапевтичних засобів проти хвороби Паркінсона.

Ключові слова: α-синуклеїн, хвороба Паркінсона, амілоїдні фібрили, поліфеноли.