Inhibition of alpha-synuclein fibrillation using epigallocatechin-3-gallate for treatment of Parkinson's disease

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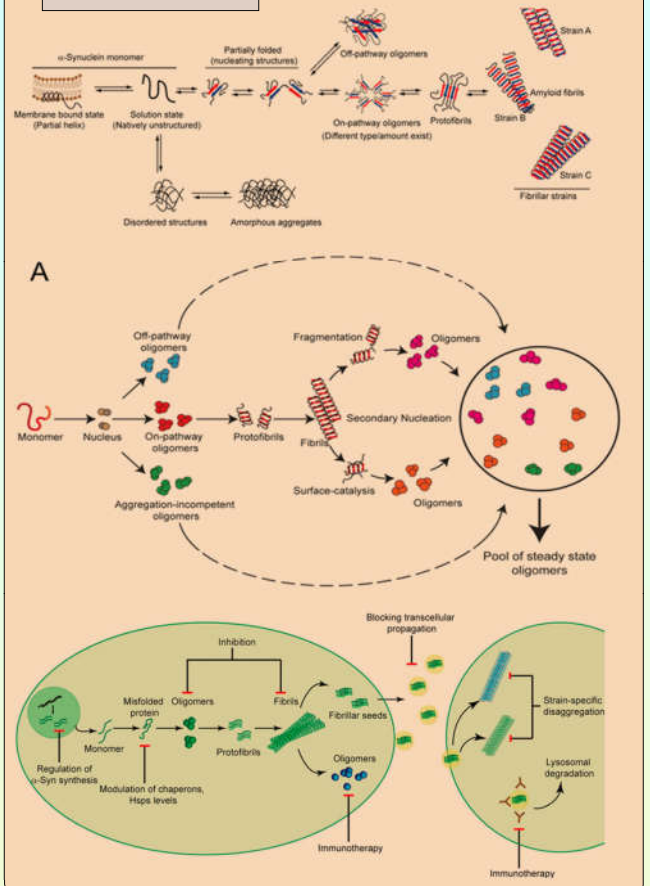
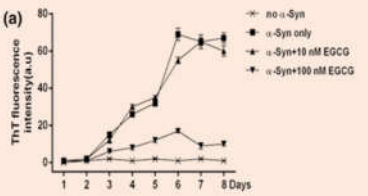
Abstract

pakinson's disease is the second most common neurodegenerative disease in the world. A pathological feature of Parkinson's disease is the accumulation of intracellular filamentous aggregates of alpha-synuclein. Alpha-synuclein protein is a 15 kD disordered protein that forms beta-sheets under specific conditions and creates oligomers, protofibrils, and fibrils step by step. Cells that produce dopamine are killed by toxic aggregates of alpha-synuclein. In this regard, many compounds have been tested for their ability to inhibit the fibril formation of alpha-synuclein. Among them, polyphenols, which are found in large amounts in plants and herbal remedies including green teas, are beneficial in preventing protein aggregation. Green and black teas are rich sources of polyphenols, the most abundant being epigallocatechin-3-gallate (EGCG) and theaflavins.

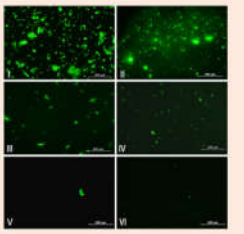
Introduction



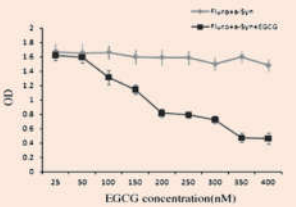
Results



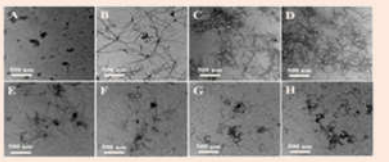
Unfolded monomer WT human SNCA was incubated in vitro under conditions that result in fibril formation in the absence or presence of 10 and 100 nM of EGCG



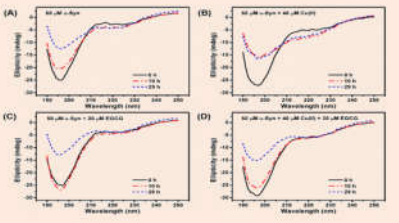
I(α-S without EGCG, II(α-S +10 nM EGCG, III) α-S +100 nM EGCG, IV) α-S +200 nM EGCG, V) α-S +300 nM EGCG, VI) α-S +500 nM EGCG



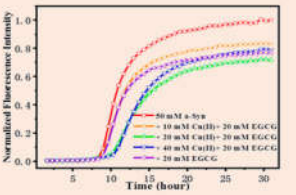
α-Syn-HiLyte488 binding with α-Syn in the presence of EGCG using ThT fluorescence. According to the result, the ED50 of the blocking activity by EGCG was 250 nM.



0 h (A), 29 h (B). 50 μM α-Syn incubated in the presence of (C) 20 μMCu(II), (D) 40 μM Cu(II), (E) 20 μM EGCG, (F) the mixture of 10 μM Cu(II) and 20 μM EGCG, (G) the mixture of 20 μM Cu(II) and 20 μM EGCG, and(H) a mixture of 40 μM Cu(II) and 20 μM EGCG.



EGCG hindered Cu(II)-induced conformation transition of α-Syn from random coil to β-sheet state.



EGCG interacts with Cu(II), forming a complex which played a vital role in inhibiting the aggregation of α-Syn.

Method

Different methods such as circular dichroism, fluorescence spectroscopy and peptide array as well as electron microscopy images were used to study the interaction between EGCG and alpha-synuclein.

Conclusion

Inhibition of a-syn aggregates is a promising approach for treating PD. In this study, it is suggested that EGCG could be a potent remodeling agent of a-syn aggregates and the potential disease modifying drug for the treatment of PD.

Refrences

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