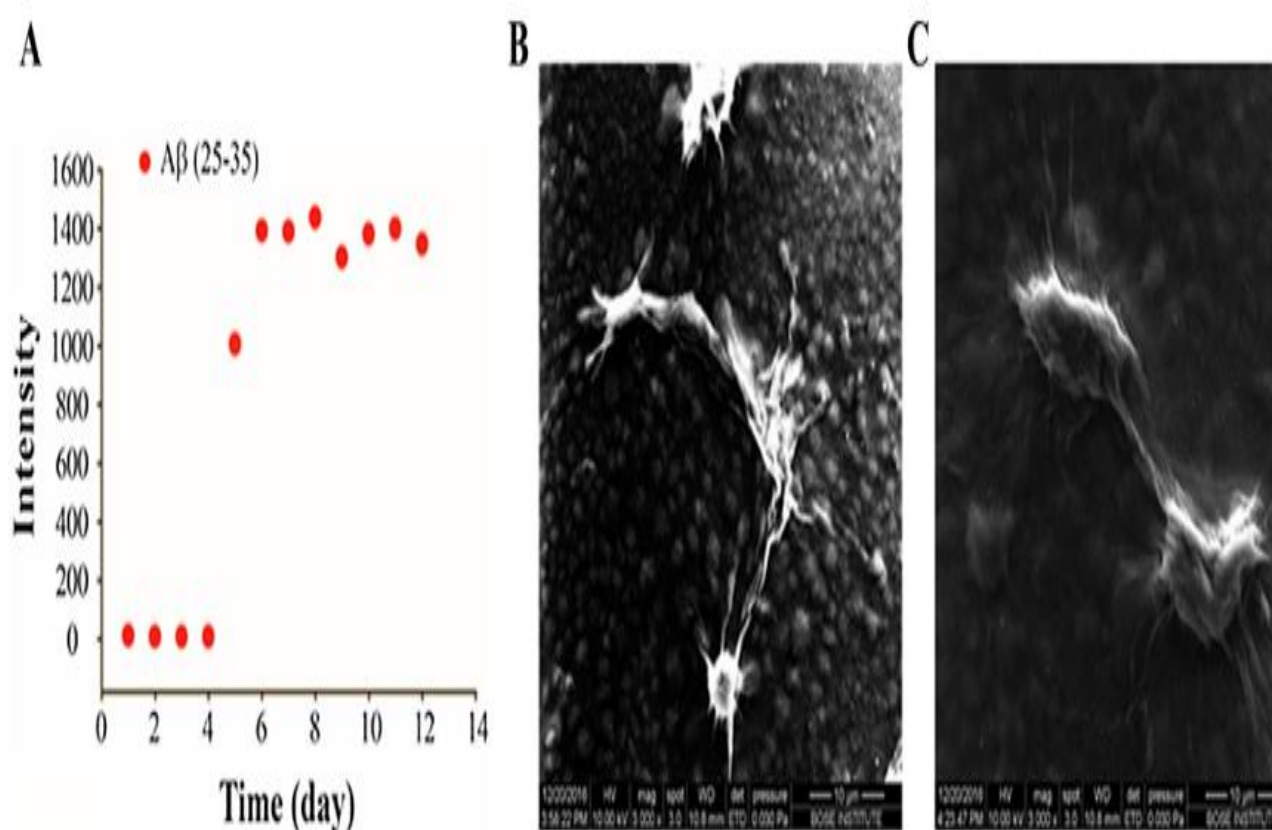
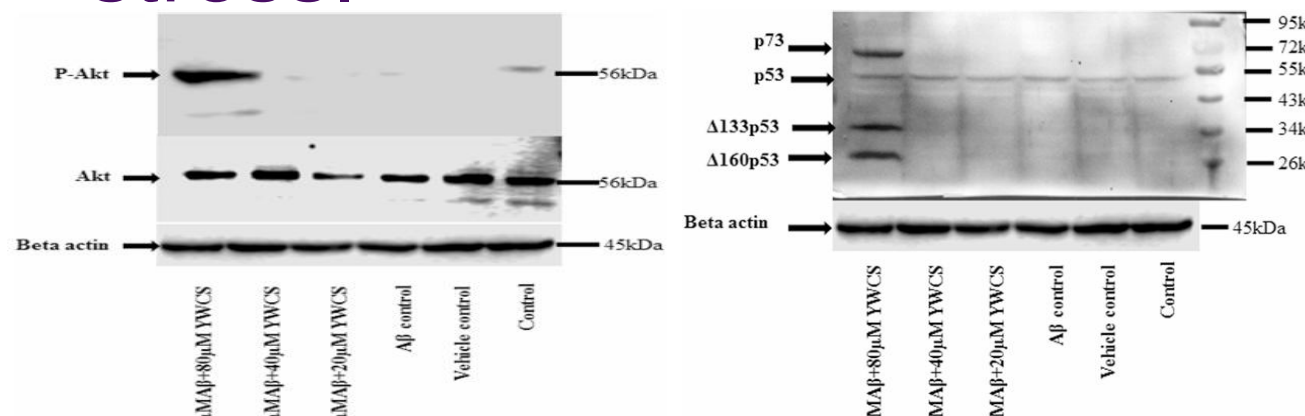
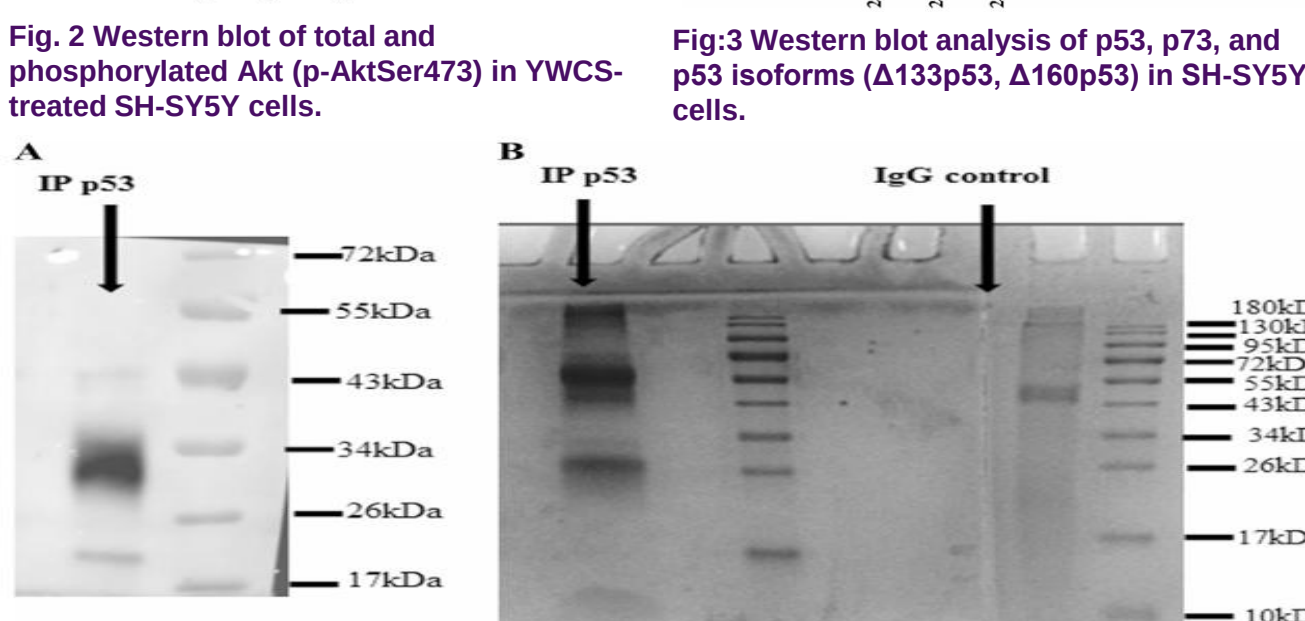
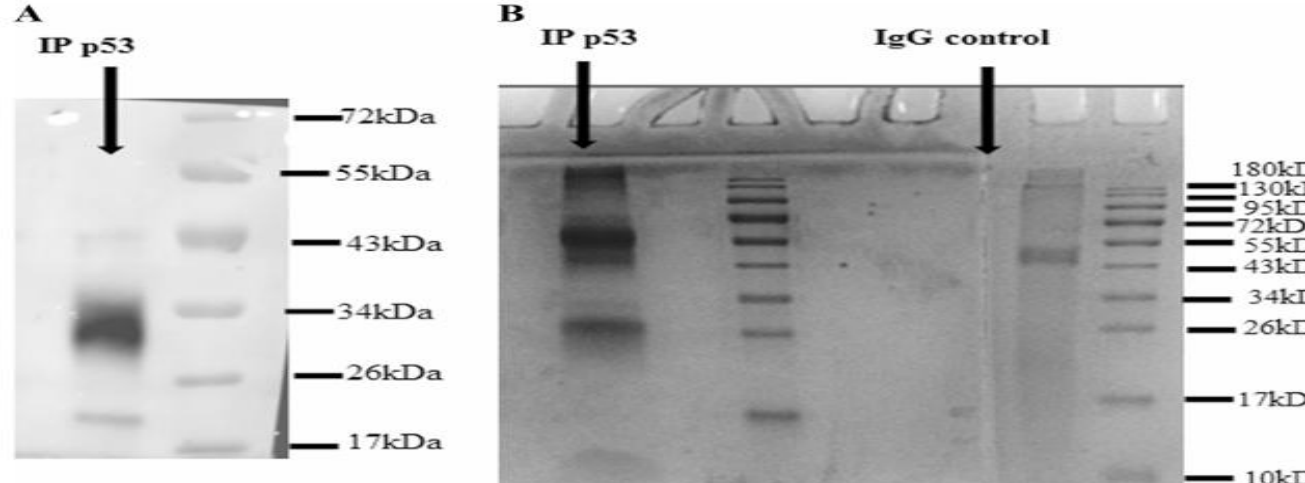
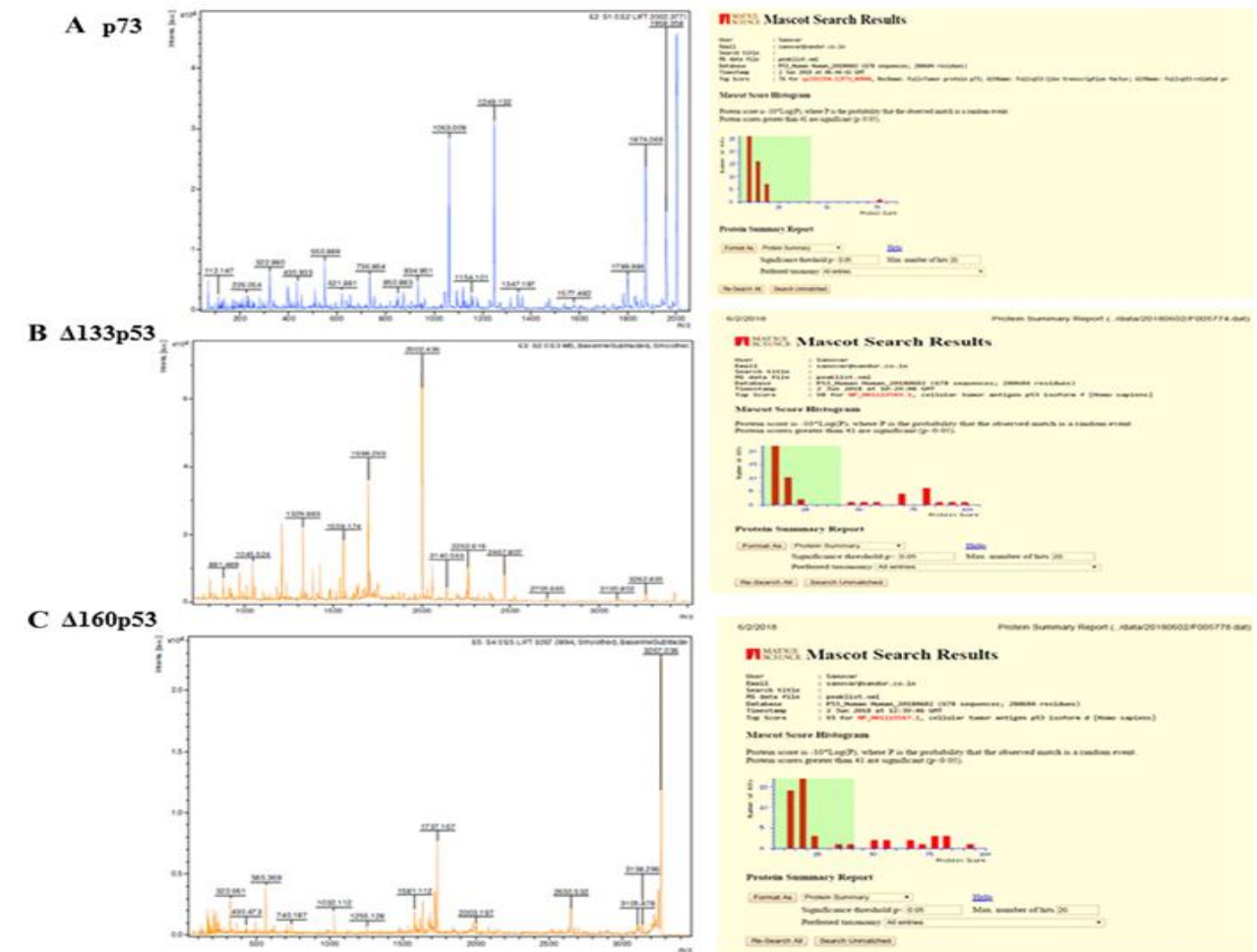


5-Lipoxygenase inhibition activates p53 isoforms and PI3K/Akt signaling to protect neurons from amyloid-β–induced toxicity

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Alzheimer’s Disease (AD), Neuroinflammation, 5-Lipoxygenase, Amyloid-beta, Neurotoxicity.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Alzheimer's Disease (AD) Pathology: Driven by Aβ accumulation, tau hyperphosphorylation, oxidative stress, neuronal loss, and neuroinflammation. Targeting the inflammatory enzyme 5-lipoxygenase (5-LOX) modulates these pathologies. The Premise: A peptide 5-LOX inhibitor YWCS is known to reduce Aβ-induced neurotoxicity, but its exact molecular mechanisms remain unknown. This study Investigates how YWCS provides neuroprotection, specifically looking at the PI3K/Akt signaling pathway and p53 family isoforms in cell survival and DNA damage repair.	➤ Model: Differentiated SH-SY5Y cells treated with aggregated Aβ 25–35 (20 μM) for 72 hours. ➤ Treatment: Co-administered with 5-LOX inhibitor YWCS (20, 40, 80 μM). ➤ Methods: Analysis via Western blot, immunoprecipitation, and mass spectrometry to identify downstream signaling and protein interactors.  Fig. 1 Aβ25–35 peptide aggregation. (a) Significant increase in fluorescence intensity after 4 days of incubation. Electron micrographs of Aβ25–35 (b) prior to aggregation and (c) post-aggregation.	➤ YWCS activates the PI3K/Akt survival pathway by selectively upregulating p-Akt. Additionally, 80 μM YWCS induces three p53-lane protein bands, identified by IP-MS as isoforms p73, Δ133p53, and Δ160p53, which mediate DNA double-strand break repair and cell survival during oxidative stress.  Fig. 2 Western blot of total and phosphorylated Akt (p-AktSer473) in YWCS-treated SH-SY5Y cells.  Fig. 3 Western blot analysis of p53, p73, and p53 isoforms (Δ133p53, Δ160p53) in SH-SY5Y cells.  Fig. 4 Immunoprecipitation (IP) of p53. a Immunoblot of IP samples. b SDS page of immunoprecipitate. IgG was used as negative control.	➤ This study identifies a novel neuroprotective mechanism mediated by 5-LOX inhibition in Aβ-induced neurotoxicity. Activation of the PI3K/Akt pathway and induction of p53 isoforms involved in DNA damage repair collectively contribute to neuronal survival. ➤ Targeting 5-LOX may represent a promising therapeutic strategy for Alzheimer’s disease.  Fig. 5 Mass spectroscopy of bands from IP. a Identified as p73, b identified as Δ133p53 and c identified as Δ160p53 isoforms of p53.	Shekhar S, Yadav SK, Rai N, Kumar R, Yadav Y, Tripathi M, Dey AB, Dey S. 5-LOX in Alzheimer's Disease: Potential Serum Marker and In Vitro Evidences for Rescue of Neurotoxicity by Its Inhibitor YWCS. Mol Neurobiol. 2018 Apr;55(4):2754-2762. doi: 10.1007/s12035-017-0527-1. Epub 2017 Apr 27. PMID: 28451886.

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