The *Crocus sativus* compounds *trans*-crocin 4 and *trans*-crocetin modulate the amyloidogenic pathway and tau misprocessing in Alzheimer disease neuronal cell culture models

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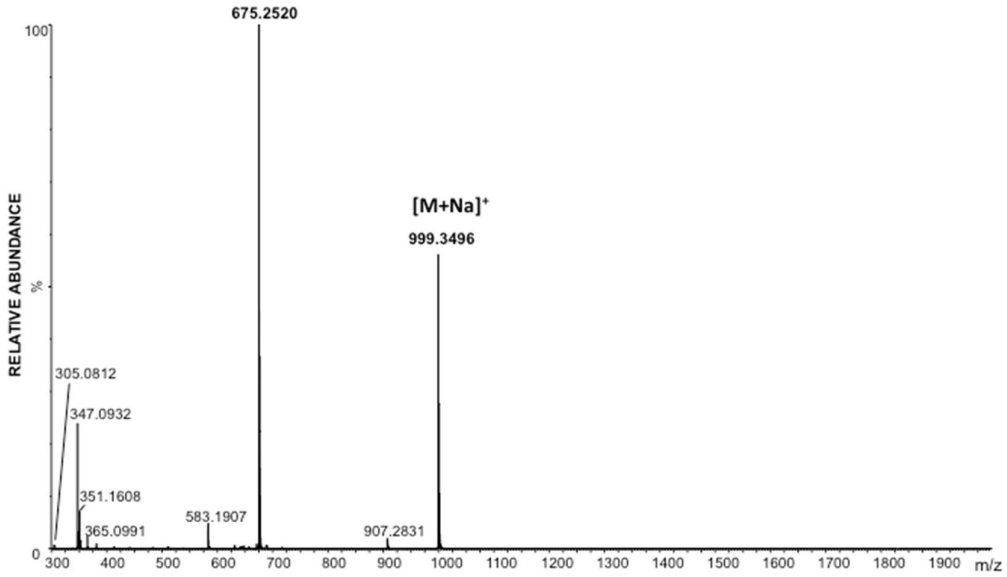
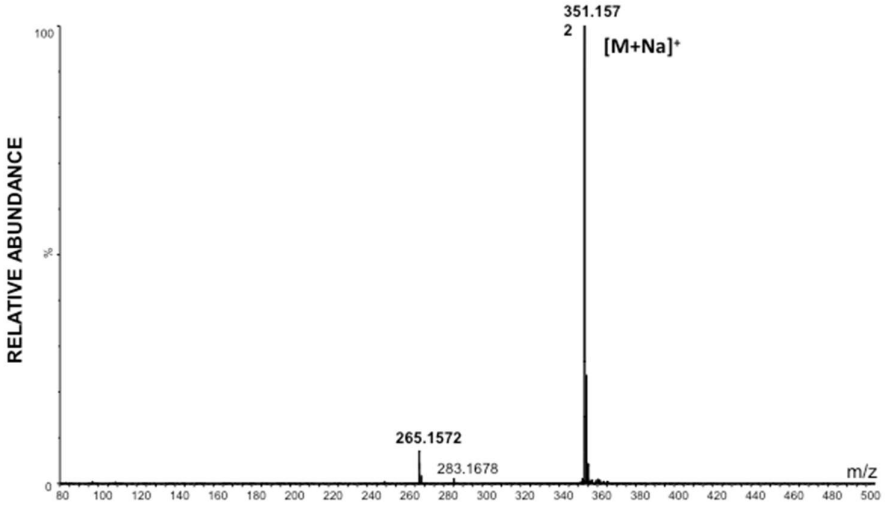
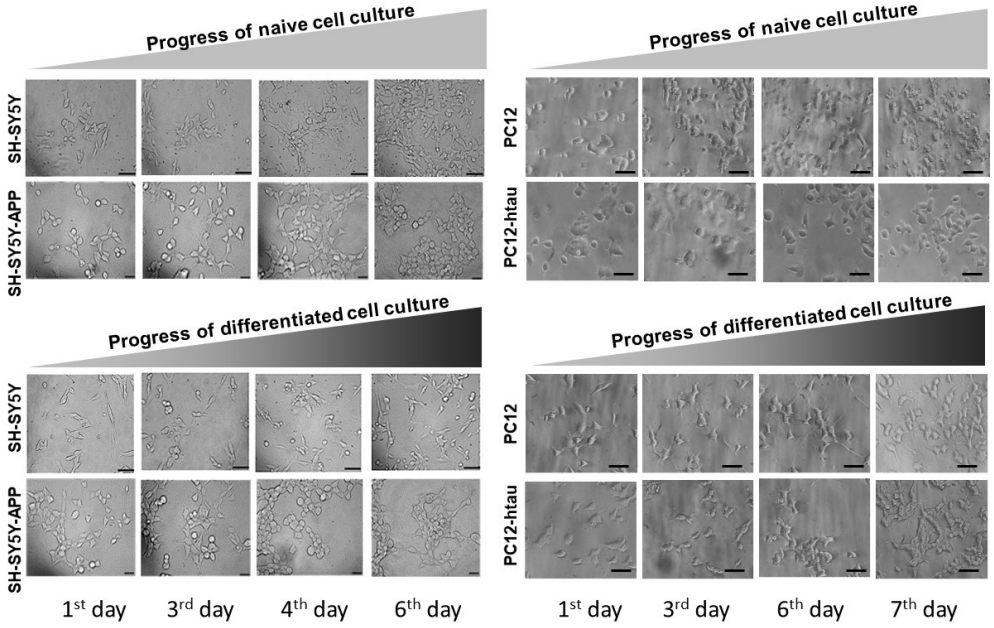


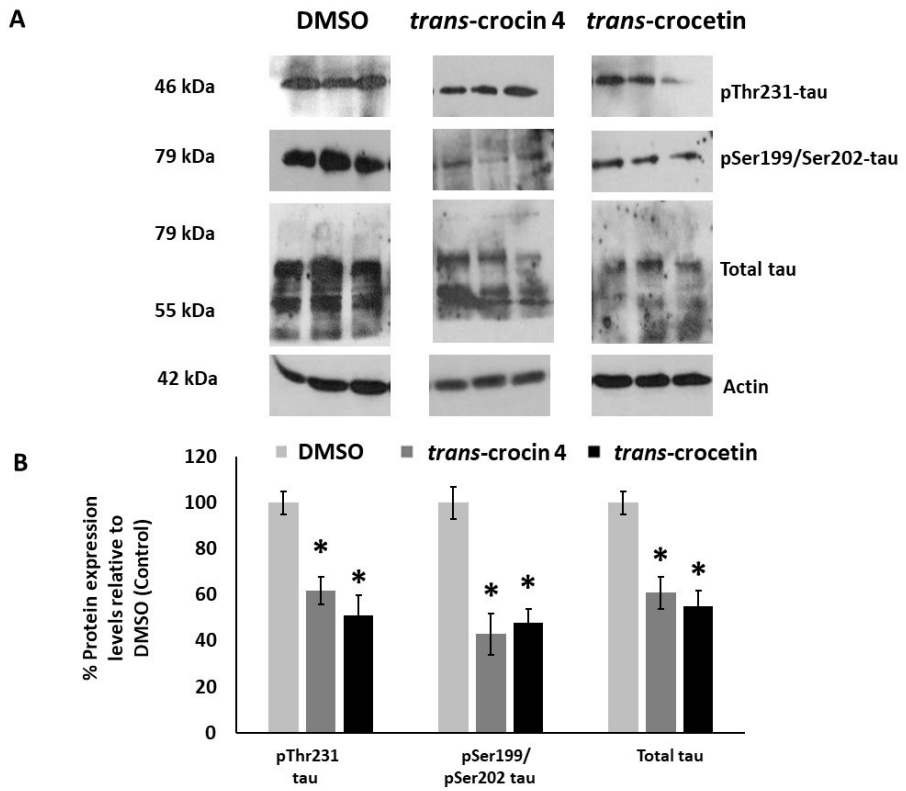
Supplementary Figure 1: Positive-ion ESI product ion spectrum of the $[M+Na]^+$ precursor ions of *trans*-crocetin utilizing a Waters Premier quadrupole reflectron time-of-flight (QqRTOF) mass spectrometer.



Supplementary Figure 2: Positive-ion ESI product ion spectrum of the $[M+Na]^+$ precursor ions of *trans*-crocin-4 utilizing a Waters Premier quadrupole reflectron time-of-flight (QqRTOF) mass spectrometer**.**



Supplementary Figure 3: Differentiation of SH-SY5Y, SH-SY5Y-APP, PC12 and PC12-htau to neuron-like cells. Representative photos of SH-SY5Y and SH-SY5Y-APP (A), PC12 and PC12-htau naive cells (B) at 6 and 7 days, respectively, of proliferation and differentiation (C and D). Differentiated cells exhibit decreased proliferation, and increased dendritic and neuritic-like projections compared to naive cells.



Supplementary Figure 4: Immunoblotting assessment of the tau levels and phosphorylation after treatment of differentiated PC12 cells with *trans*-crocin 4 or *trans*-crocetin. (**A**) Immunoblotting detection of pThr231-tau, pSer199/Ser202-tau, total tau, with actin as internal control of protein expression. (**B**) Diagrammatic presentation of quantified protein expression (* $p<0.05$, when compared test treatment versus DMSO in post-hoc one-way ANOVA, n=3).

Supplementary Table 1: Primary antibodies and electrophoresis conditions

Protein	Catalogue number	Company	MW	Host	Gel
Cellular APP	R1(57)	By Prof. Efthimiopoulos Lab	~110 kDa	Polyclonal anti-rabbit	10% Tris-Glycine
APP-C99	R1(57)	By Prof. Efthimiopoulos Lab	12 kDa	Polyclonal anti-rabbit	4-12% Bis-Tris
APP-C83	R1(57)	By Prof. Efthimiopoulos Lab	10 kDa	Polyclonal anti-rabbit	4-12% Bis-Tris
sAPPα	SIG-39320	Covance	~100 kDa	Monoclonal anti-mouse	16.5% Tris-Tricine
beta-amyloid	SIG-39320	Covance	4 kDa	Monoclonal anti-mouse	16.5% Tris-Tricine
BACE1	MAB5308	Chemicon Millipore	56 kDa	Monoclonal anti-mouse	10% Tris-Glycine
PSEN1	AB5308	Chemicon Millipore	Multiple forms	Polyclonal anti-rabbit	10% Tris-Glycine
PSEN2	2192	Cell Signaling	Multiple forms	Polyclonal anti-rabbit	10% Tris-Glycine
Total tau (Tau5 antibody)	ab80579	Abcam	79 kDa	Monoclonal anti-mouse	10% Tris-Glycine
pSer199/Ser202-tau	AB9674	Chemicon Millipore	79 kDa	Polyclonal anti-rabbit	10% Tris-Glycine
pThr231-tau	ab151559	Abcam	46 kDa	Monoclonal anti-rabbit	10% Tris-Glycine
pERK1/2	4370	Cell Signaling	44/42 kDa	Monoclonal anti-rabbit	10% Tris-Glycine
ERK1/2	4695	Cell Signaling	44/42 kDa	Monoclonal anti-rabbit	10% Tris-Glycine
pSer9-GSK3β	9323P	Cell Signaling	46 kDa	Monoclonal anti-rabbit	10% Tris-Glycine
GSK3β	9315S	Cell Signaling	46 kDa	Monoclonal anti-rabbit	10% Tris-Glycine

Actin	MAB1501	Chemicon Millipore	42 kDa	Monoclonal anti-mouse	
GAPDH	SC-365062	Santa Cruz	37 kDa	Monoclonal anti-mouse	