PL-05

Morin Hydrate Ameliorates Endoplasmic Reticulum Stress-Induced Apoptosis and Mitophagy in Huntington's Disease- an Experimental Neuroprotective Approach

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INTRODUCTION

Huntington's disease (HD) is a rare dominant autosomal neurodegenerative disease resulting from a gene mutation that creates a mutant version of the huntingtin protein (mHtt). HD is characterized by the progressive loss of neurons in the striatum and cortex, resulting in a triad of motor dysfunction, cognitive decline, and psychiatric symptoms.

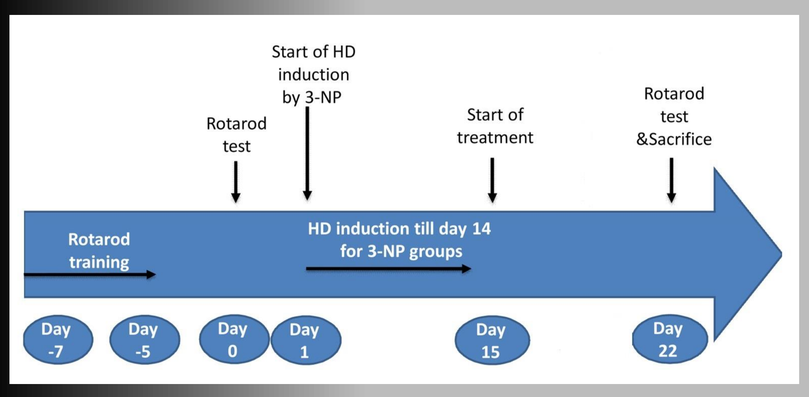
Notably, many proteinopathies originate from the aggregation of misfolded proteins such as mHtt leading to endoplasmic reticulum stress (ERS). Under harsh ERS conditions, inositol-requiring protein-1α (IRE-1α)/ spliced form of X-box binding protein 1 (XBP1s) are provoked following the activation of the mammalian target of rapamycin complex 1 (mTORc1) to drive apoptosis. Meanwhile, mitophagy is activated and encourages the mitochondria endoplasmic reticulum contact (MERC). Moreover, mitochondrial dysfunction leads to the activation of caspase-3.

Morin hydrate (MH), a potent antioxidant flavonoid was found to mitigate HD-3-nitropropionic acid (3-NP) model. Herein its impact on combating the ERS/MERC, mitophagy, and apoptosis was investigated.

EXPERIMENTAL DESIGN

Male Sprague Dawley rats were divided randomly **into 6 groups** (n= 9 each except for CN+MH n= 6). The **control rats** (n=15) received saline for 14 days and then nine of them received **saline with 0.5 % CMC-Na/saline** while the other six received **MH (10 mg/kg/day; i.p.) with 0.5 % CMC-Na/saline** for 7 days. The rest of animals (n=36) were subjected to 3-NP **(10 mg/kg/day; i.p.)** for 14 days, then divided among 4 subgroups. Rats in the 1st one received **daily saline and 0.5 % CMC-Na/saline** to serve as the **HD group**, whereas those in the other three groups were administered **MH and/or the ERS inducer WAG-4S (1 mg/kg/day; i.p.)** for 7 days.

On day 22, the animals underwent a rotarod test and then were euthanized. The rats' body weight was assessed on days 1 and 22. Disease progression was determined by striatal biochemical (mTOR, IRE1-α, XBP1s, *p*-PGC-1α, and *p*-Mfn2), histopathological, and transmission electron microscopical (TEM) examinations.



RESULTS

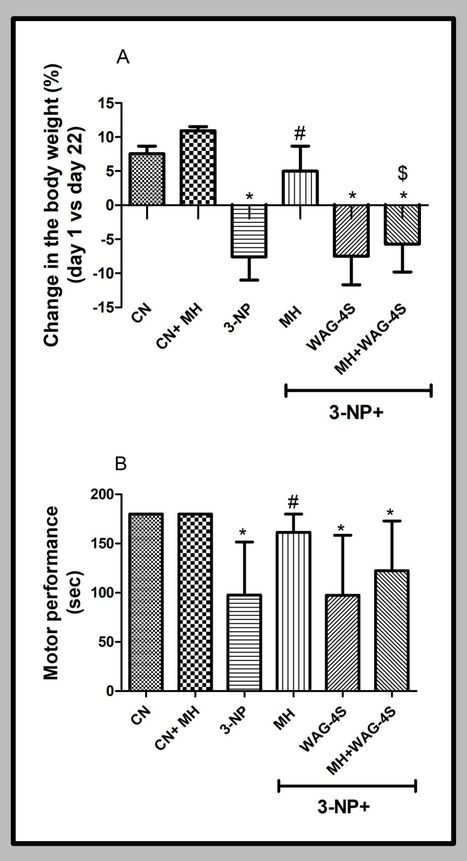


Fig. 1. Effect of MH with or without WAG-4S on (A) the percentage of change in the body weight and (B) motor performance in HD rats. Data are presented as mean ± S.D. As compared with (*) CN, (#) 3-NP, and ($) 3-NP+MH at $p<0.05$.

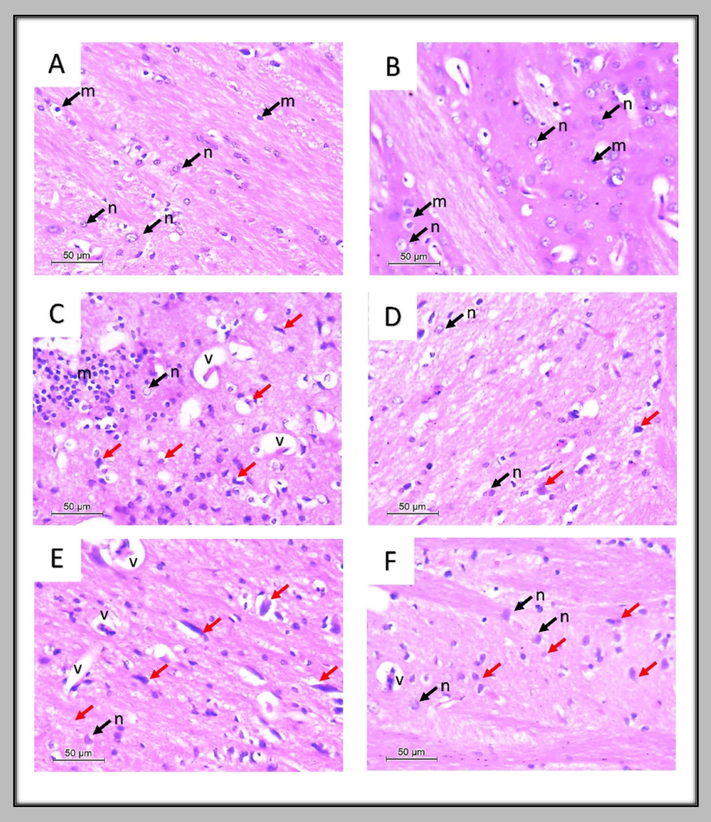


Fig. 2. Histopathologic changes of MH striatum with or without WAG-4S in HD rats.
A= CN, B= CN+MH, C= 3-NP, D= 3-NP+MH, E= 3-NP+WAG-4S, and F= 3-NP+MH+WAG-4S.
n= normal neurons, red arrows = degenerated neurons, v= vascular edema, and m= microglial cells

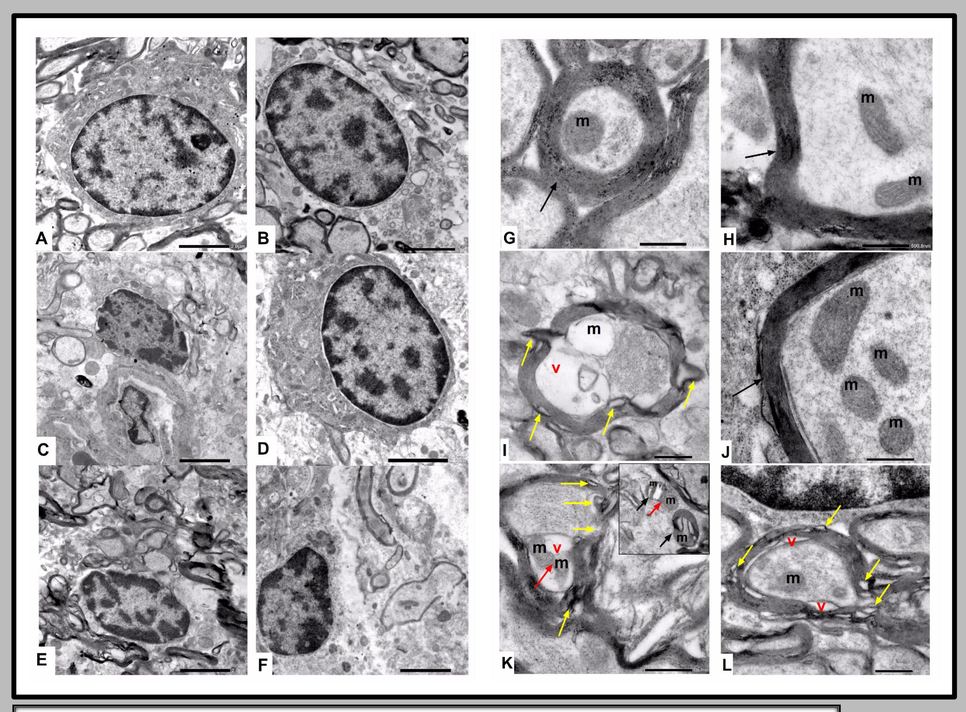


Fig. 3. Striatal TEM images of nuclei, mitochondria, and myelination of MH with or without WAG-4S in HD rats (scale bar for nuclei (2 µm), mitochondria/ myelination (500 nm).
A & G= CN, B & H= CN+MH, C & I= 3-NP, D &J= 3-NP+MH, E & K= 3-NP+WAG-4S, and F & L= 3-NP+MH+WAG-4S.
m= mitochondria, v= autophagic vacuoles, Black arrows in G, H, and J= normal myelination, Black arrows in K inset= damaged mitochondria, yellow arrows= vacuolated myelin sheath, and red arrows= mitochondrial fission

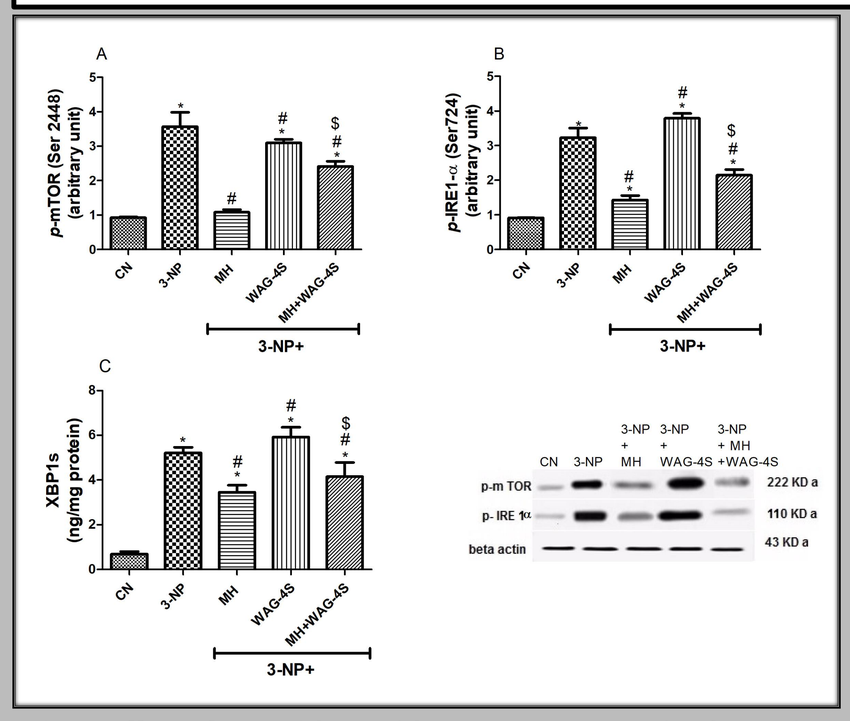


Fig. 4. Effect of MH with or without WAG-4S on striatal protein expression/content of (A) *p*-mTOR, (B) *p*-IRE1-α, and (C) XBP1s in HD rats. Data are presented as mean ± S.D. As compared with (*) CN, (#) 3-NP, and ($) 3-NP+MH at $p<0.05$.

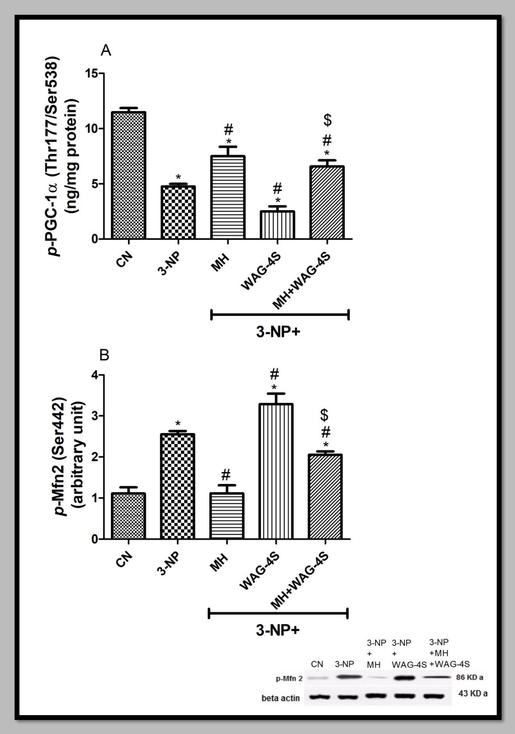


Fig.5. Effect of MH with or without WAG-4S on striatal protein expression/content of (A) *p*-PGC-1α and (B) *p*-Mfn2 in HD rats. Data are presented as mean ± S.D. As compared with (*) CN, (#) 3-NP, and ($) 3-NP+MH at $p<0.05$.

CONCLUSION

MH alleviated HD-associated ERS-, MERC-, mitochondrial fission- induced apoptosis, and heightened mitophagy. This is mainly achieved by combating the mTOR/IRE1-α signaling and *p*-Mfn2, effects that were ameliorated by WAG-4S pre-administration, indicative of a novel MH anti-ERS mechanism.

Acknowledgement

Thanks to **Assoc. Prof. Dr. Ahmed M. El Kerdawy** (Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Cairo University) and **Assoc. Prof. Dr. Wagdy M. Eldehna** (Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kafrelsheikh University) for supplying the study with WAG-4S.