Dimethyl fumarate ameliorates experimentally induced Huntington's disease *via* its antioxidant and anti-apoptotic potentials

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ABSTRACT

Background: Huntington's disease (HD) is a rare progressive neurodegenerative disease that is characterized by a triad of symptoms, namely of uncontrolled movements, cognitive impairment, and emotional disturbance. Dimethyl fumarate (DMF), a fumaric acid methyl ester, has been a subject of experimental studies due to its beneficial properties in treatment of multiple sclerosis. **Aim:** This study aimed to audit the role of DMF post-treatment on HD by targeting oxidative stress (OS) and apoptosis in a 3-nitropropionic acid (3-NP) HD model. **Methods:** Adult male Wistar rats were divided into 4 groups; control (saline or DMF), HD, HD+DMF. Behavioral testing was conducted, including open field and beam walk tests, biochemical investigation was carried out to assess striatal OS and apoptotic markers as well as its dopamine (DA) content. Additionally, histopathological analysis of the striatum was performed. **Key findings**: In HD animals, DMF ameliorated behavioral deficits indicated by enhanced locomotion in the open field test as well as beam walk paradigm. Indeed, structurally it improved the striatal architecture where it hampered pyknotic neuronal cell bodies shrinkage, as well as the mild blood vessel congestion and focal glial cells infiltrate induced by 3-NP. At the cellular level, DMF reduced striatal OS as indicated by the decline in both its ROS and malondialdehyde contents, while boosting glutathione. Meanwhile, it was able to decrease the striatal caspase 3 content associated by an increment in its DA content. **Conclusion:** This study features a focal point on DMF therapeutic ability to reduce HD manifestations via its antioxidant and anti-apoptotic potentials to preserve dopaminergic neurons.

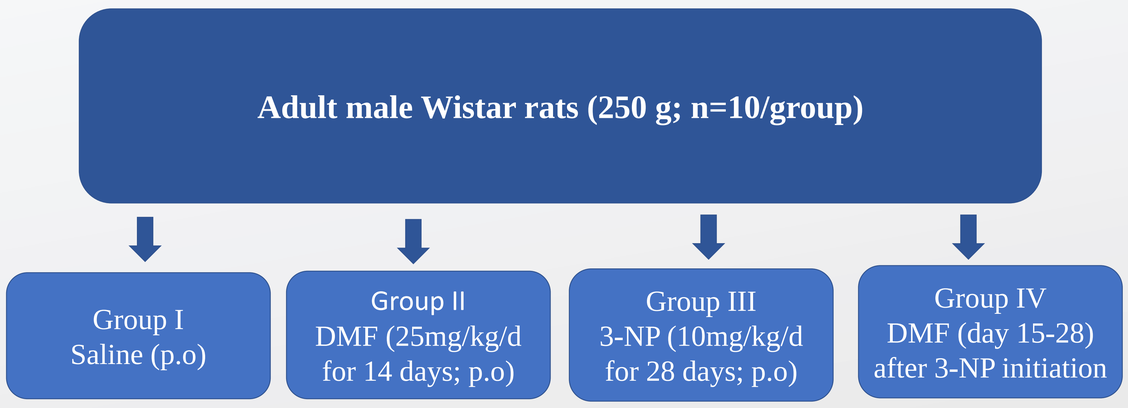
INTRODUCTION

Huntington's disease (HD) is characterized by locomotion, cognitive, and emotional deficits. This rare progressive neurodegenerative disease is caused by a CAG triplet repeat expansion to form mutant huntington (mHTT) associated by significant damage of medium spiny neurons located in striatum (Cepeda, Murphy, Parent, & Levine, 2014). One of the main pathogenic mechanisms in HD is the increased burden of reactive oxygen species (ROS) that off set the equilibrium between antioxidants and oxidants leading to cellar disruption or death (Kumar & Ratan, 2016).

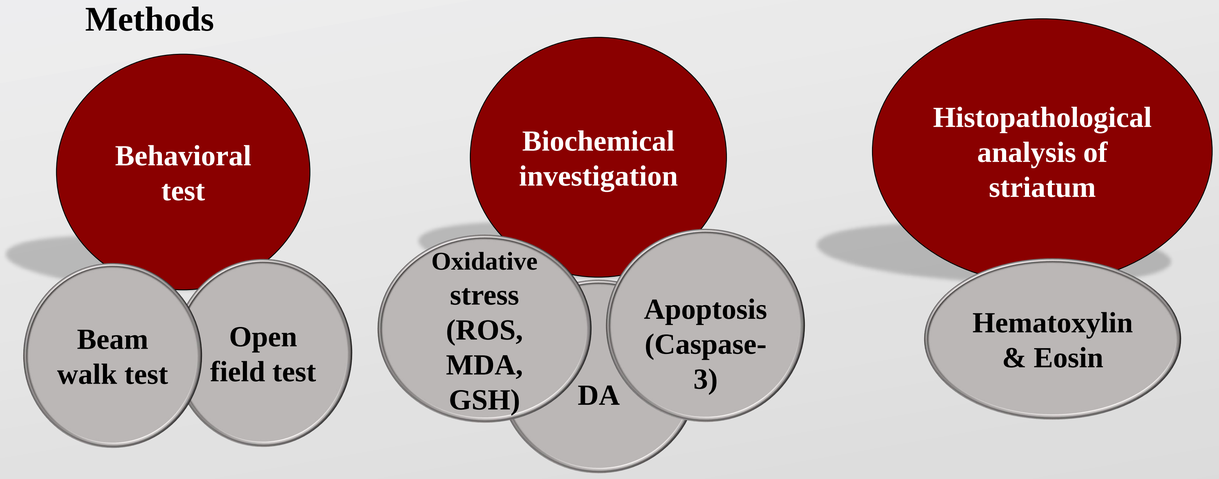
Dimethyl fumarate (DMF) is a fumaric acid methyl ester that is used in the treatment of multiple sclerosis. It has potent antioxidants with anti-inflammatory and immuno-modulatory potentials that has been subjected to experimental studies (Saidu et al, 2019)

MATERIALS & METHODS

Experimental design



Methods



DA; dopamine, GSH; glutathione, MDA; malodialdehyde, ROS;reactive oxygen species

RESULTS

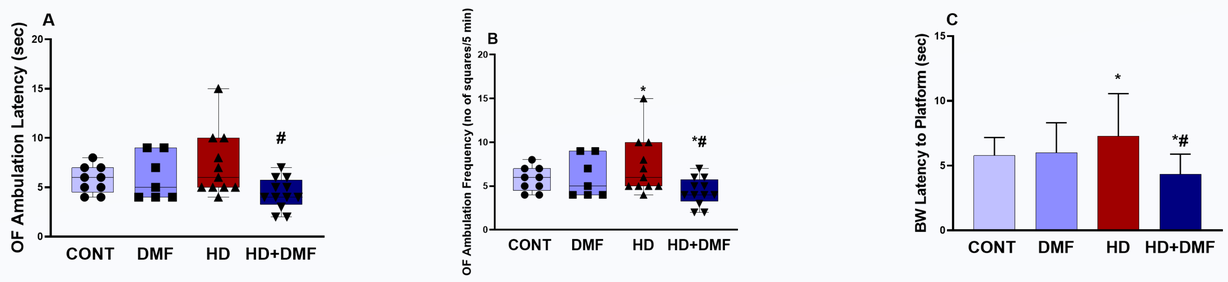


Fig.1. Effect of DMF on (A) OF ambulation latency and (B) OF ambulation frequency, as well as(C) BW latency to platform in HD rats. Non-parametric data were analyzed by Kruskal-Wallis test followed by Dunn's Multiple Comparisons test, whereas for parametric data were analyzed using one-way ANOVA followed by Tukey's post-hoc test; P < 0.05, * vs CONT and # vs HD. BW; beam walk test, CONT; control, DMF; dimethyl fumarate, HD; huntington disease, OF; open field test

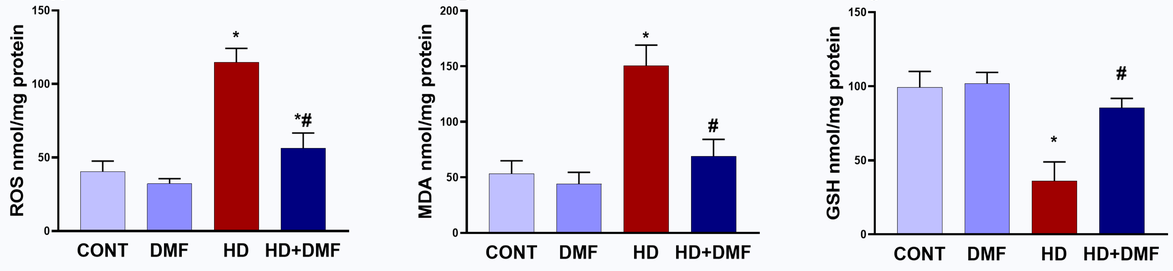


Fig.2. Effect of DMF on striatal content of (A) ROS, (B) MDA, and (C) GSH in HD rats. Each bar with a vertical line represents mean ± SD; P<0.05, * vs CONT, # vs HD. CONT; control, DMF; dimethyl fumarate, GSH; glutathione, HD; huntington disease, MDA; malondialdehyde, ROS; reactive oxygen species

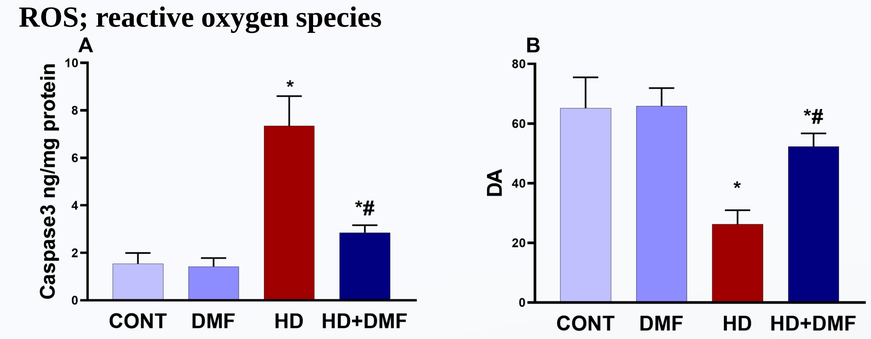


Fig.3. Effect of DMF on striatal content of (A) caspase 3 and (B) DA in HD rats. Each bar with a vertical line represents mean ± SD; P<0.05, * vs CONT, # vs HD. CONT; control, DA; dopamine, DMF; dimethyl fumarate, HD; huntington disease

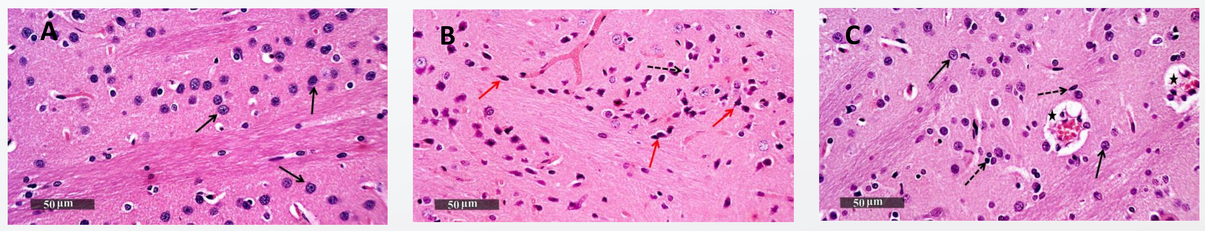


Fig.4.Illustrative photomicrographs of the striatum isolated from (A) CONT showing ordinary histopathological architecture (arrow); (B) HD showing bountiful degeneration of neurons with contracted pyknotic neuronal cell bodies (red arrow) and mild focal glial cells infiltrates (dashed arrow); (C) HD+DMF showing marked renovation of morphological features with intact neurons (arrow) and few congested blood vessels (star). CONT; control, DMF; dimethyl fumarate, HD; huntington disease

CONCLUSION

- DMF post-treatment ameliorated 3-NP-induced neurotoxicity resembling the late HD stage.
- DMF improved locomotion and dampened microscopic alterations of the striatum.
- DMF mediated OS inhibition to enhance glutathione abating thus ROS formation in the striatum.
- DMF restored DA and attenuated apoptosis via deactivating caspase 3 to maximize the chances of neuronal survival in HD rats.
- The study sheds light at the possibility of using DMF for treatment of HD through its anti-apoptotic and antioxidant features, besides DA augmentation.

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