EUR REV MED PHARMACOL SCI
2025; 29: 443-451

DRUG REPURPOSING OF DIMETHYL FUMARATE IN PARKINSON'S DISEASE: A PROMISING DISEASE-MODIFYING STRATEGY

M. SALVADÈ[1,2], F. GARDONI[1]

• • •

[1]Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", University of Milan, Milan, Italy
[2]School of Advanced Studies, Center for Neuroscience, University of Camerino, Camerino, Italy

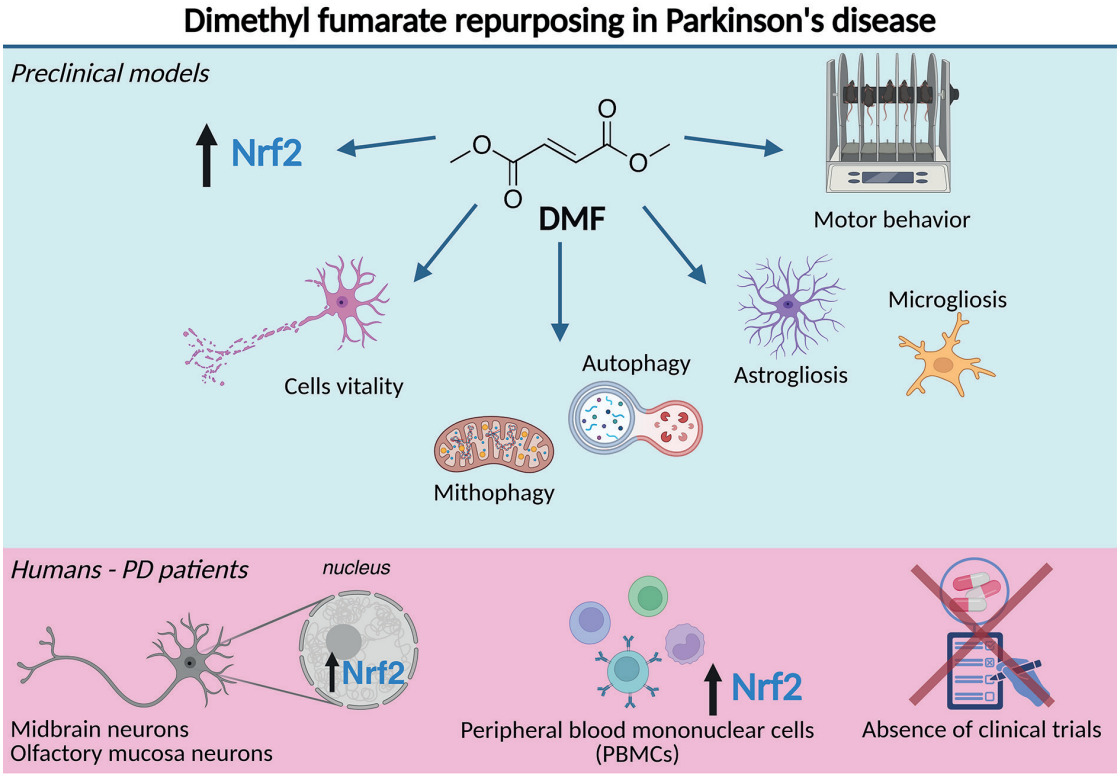
Corresponding Author
Fabrizio Gardoni, Ph.D; e-mail: fabrizio.gardoni@unimi.it

ABSTRACT – Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of nigrostriatal dopaminergic neurons and pathological aggregation of α-synuclein. Despite advancements in symptomatic treatment, there is a critical unmet need for disease-modifying therapies capable of halting or slowing disease progression. Drug repurposing offers an efficient, cost-effective strategy to identify new treatments by leveraging the established safety and pharmacokinetic profiles of existing compounds. Dimethyl fumarate (DMF), an FDA-approved drug for multiple sclerosis and psoriasis, has recently emerged as a promising neuroprotective agent in PD research. Preclinical studies consistently demonstrate that DMF exerts beneficial effects in both *in vitro* and *in vivo* PD models, primarily *via* activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Through this mechanism, DMF counters oxidative stress, reduces neuroinflammation, promotes mitochondrial quality control, and impedes pathological protein aggregation. These biological effects translate into the preservation of dopaminergic neurons and improvements in motor behavior in animal models. Although direct clinical evidence of DMF's efficacy in PD patients is currently very limited, early mechanistic human studies provide indirect support for the targeting of the Nrf2 pathway in PD. Furthermore, DMF's neuroprotective properties extend to other neurodegenerative diseases, underscoring its broader therapeutic potential. In conclusion, the strong preclinical foundation, combined with an established clinical safety record, makes DMF an attractive candidate for repurposing as a disease-modifying therapy for PD. Future clinical trials will be essential to validate these preclinical promises and define DMF's role in the management of PD.

KEYWORDS: Dimethyl fumarate, Drug repurposing, Nrf2 pathway, Neuroprotection, Oxidative stress, Neuroinflammation.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) and aggregation of α-synuclein into Lewy bodies. Several drugs have been approved in the last decades for the treatment of PD patients[1]. However, no disease-modifying therapy is currently available to halt or prevent disease progression[2]. Current treatments primarily address symptoms through dopamine replacement strategies, thus providing only symptomatic relief. This significantly impairs patients' quality of life, burdens healthcare systems, and creates an urgent need for disease-modifying therapies.



Graphical Abstract. Dimethyl fumarate repurposing in Parkinson's disease.

Interestingly, a high percentage of drugs used for PD therapy were not originally introduced in the market for PD patients but derive from a drug repurposing strategy[3]. In addition, drug repurposing still represents a promising alternative strategy in PD research[4-6], being a faster and more cost-effective alternative to traditional drug development. Accordingly, pharmaceutical companies and research institutions, including The Michael J. Fox Foundation, emphasize repurposing to capitalize on existing safety and pharmacokinetic data, reducing development timelines.

Drug repurposing approaches in the PD field leverage epidemiological insights and preclinical models, though challenges persist—particularly with neurotoxin-based animal models that inadequately replicate disease progression and exhibit high variability. Gaps remain in translating preclinical findings to clinical efficacy, necessitating improved biomarker strategies and more representative disease models. Despite uncertainties, the integration of artificial intelligence and multi-omics data holds promise for identifying novel repurposing candidates, potentially bridging the gap between symptomatic relief and disease modification[7].

Drugs investigated for their possible repurposing for PD include several compounds targeting PD-associated pathological mechanisms, including oxidative stress, neuroinflammation, mitochondrial dysfunction, and impaired protein degradation systems[3]. Among these drugs, dimethyl fumarate (DMF), an FDA-approved drug for multiple sclerosis and psoriasis[8], has emerged in preclinical studies as a promising anti-inflammatory, antioxidant, and neuroprotective agent primarily associated with the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway[9]. This review comprehensively examines the preclinical and clinical evidence supporting DMF as a repurposed therapeutic for PD, mainly focusing on molecular and cellular mechanisms correlated to DMF's neuroprotective effects.

PRECLINICAL EVIDENCE SUPPORTING DMF REPURPOSING FOR PARKINSON'S DISEASE

An increasing number of studies explored the efficacy of DMF in *in vivo* preclinical models of PD. Specifically, DMF has been evaluated mostly in neurotoxin-based PD models, including MPTP-treated mice[10,11], 6-OHDA-lesioned mice[12], and rotenone-treated mice[13] (Table I). Some of these studies integrated data obtained in mice with findings from cells lines exposed to neurotoxins[11,12]. Only very few studies investigated DMF effects also in α-synuclein-based PD models, using hip-

Table I. Effects of DMF oral chronic treatment on PD *in vivo* preclinical models. Reported effects do not distinguish between different DMF dosages.

	PD model	*SNpc MPP⁺-injected mice*[11]	*Rotenone-induced PD in mice*[13]	*MPTP-induced PD model in mice*[10]	*SNpc unilateral overexpression of hα-syn in mice*[15]	*Intrastriatal 6-OHDA-lesioned mice*[12]
DMF treatment	Duration	21 days	14 days	7 days	1, 3 and 8 weeks	7 days
	Dose	15, 30 or 60 mg/kg	15, 30 or 60 mg/kg	10, 30, 100 mg/kg	100 and 300 mg/kg	50 mg/kg
Nrf2	mRNA	nr	↑	nr	↑ ctx	↑
	protein	↑	↑	↑	↑ ctx	↑
Nrf2 PW genes		nr	nr	↑ HMOX1 (protein)	↑ HMOX1 and Nqo1 (mRNA)	↑ HMOX1 and Nqo1 (mRNA, protein)
Other molecular/ cellular events	DA neurons	↑ TH	↑ TH	↑ TH and histological score	↑ TH	↑ TH
	α-syn inclusions	↓	↓ p-ser129 inclusions	↓	nr	nr
	Apoptosis	nr	Bax↓, Bcl-2↑, active casp-3 ↓, ↓ Cathepsin D	nr	nr	nr
	Autophagy	↑ BNIP3, ↓ LC3	*Nrf2-TIGAR-LAMP2/Cathepsin D axis* ↑ LC3, ↓ p53, ↑ LAMP2	nr	↓ LC3, ↑ p62 co-loc α-syn	nr
	Mitophagy	NRF2/BNIP3/PINK1 axis	nr	nr	nr	nr
Inflammation	Factors	nr	↓TNFα, ↓IL-1β, ↓IL-6, ↑IL-4	↓IL-1β	nr	nr
	Microgliosis, Astrogliosis	nr	nr	↓ Iba1, ↓ CD11b, ↓ GFAP	↓ Iba1 ↓ GFAP	↓ CD11b ↓ GFAP
Motor Behavior		Improved	Improved	Improved	Improved	Improved

↑: increased compared to PD condition; ↓: decreased compared to PD condition; nr: not reported.

pocampal neurons from A53TSyn mice[14] or by viral vector-mediated unilateral overexpression of human α-synuclein into SNpc in mice[15]. Currently, no studies are available investigating the effects of DMF in α-synuclein models obtained by stereotaxic injections of α-synuclein aggregates such as oligomers or fibrils.

The heterogeneity of the above-mentioned preclinical PD models offers a unique advantage by allowing the testing of the efficacy of drugs to counteract different pathological features of the disease. However, this situation also introduces an additional layer of complexity, adding to the variability already present in the literature regarding drug dosage, timing, and routes of administration relative to neurotoxin injection, especially in *in vivo* models. Given these considerations, we will critically review the available studies, focusing on the key effects of DMF treatment on PD pathological features, namely motor behavior, oxidative stress, dopaminergic neuronal loss and neuroinflammation.

Behavioral effects modulated by DMF in Parkinson's disease models

Assessing the effects of candidate compounds on motor-related PD deficits is an essential step for preclinical evaluation of drug repurposing[3]. DMF has demonstrated efficacy in counteracting MPTP-induced bradykinesia in mice[11]. In this model, MPTP-treated animals exhibited motor impairments in both open field and rotarod tests, which were significantly attenuated by DMF administration in a dose-dependent manner. Campolo et al[10] further corroborated the ability of DMF to improve MPTP-induced motor dysfunctions, though noted that DMF treatment did not alleviate emotional behavior alterations.

DMF treatment prevented deficits in the elevated body swing test in mice unilaterally injected with α-synuclein[15]. Similarly, DMF significantly alleviated both locomotor and motor coordination impairments in rotenone-induced PD mice[13]. Notably, the authors highlighted that doses above 30 mg/kg did not confer further benefit and could potentially reduce treatment efficacy. Furthermore, in the 6-OHDA model, DMF reduced apomorphine-induced contralateral rotational behavior, further supporting its protective role in this model of nigrostriatal degeneration[12]. Together, these findings demonstrate that DMF consistently ameliorates motor deficits across diverse preclinical PD models, underscoring its potential for mitigating the motor symptoms associated with PD.

DMF activates Nrf2 pathway, regulates oxidative stress, and mitochondrial activity

The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), the main cellular target of DMF, plays a pivotal role in the maintenance of cellular homeostasis[9]. In physiological conditions, the repressor protein KEAP1 retains Nrf2 in the cytoplasm. DMF disrupts this interaction, inducing the release of Nrf2 and its subsequent translocation into the nucleus. Increased Nrf2 protein levels have been reported after chronic oral DMF treatment in a variety of neurotoxin-based models of PD[10-13]. Interestingly, a specific and acute effect of oral DMF on Nrf2 pathway has been observed also in α-synuclein-related model[15]. Interestingly, the authors also tested the specificity of DMF effects on the Nrf2 pathway by replicating the experiments in Nrf2-deficient mice ($Nrf2^{-/-}$)[15]. Nrf2 activation levels are correlated to DMF dosage, with higher doses leading to greater Nrf2 upregulation compared to controls[10,11]. Moreover, some studies demonstrated the increase of both protein and mRNA levels of Nrf2 further supporting its activation by DMF treatment[12,13,15]. Interestingly, increased Nrf2 levels following acute DMF treatment have also been observed *in vitro* in SH-SY5Y cells[12].

In the nucleus, Nrf2 promotes the transcription of numerous cytoprotective and anti-inflammatory genes, particularly those under the control of Antioxidant Response Elements (AREs)[16]. Specifically, Nrf2 binds to AREs located in the promoter region of target genes, which mainly encode antioxidant and detoxifying enzymes[17]. *Hmox1* represents one of the best-characterized genes upregulated by DMF treatment. *Hmox1* encodes HO-1, a key enzyme involved in the cellular response to oxidative stress. An upregulation of HO-1 following DMF treatment has been reported in PD models, both *in vivo*[10,12] and *in vitro*[12,14], and this event has been described as critical for mediating the antioxidant effects of DMF. Interestingly, Lastres-Becker et al[15] observed increased mRNA levels of *Hmox1* only in the cortex after the treatment with the highest dose (300 mg/kg).

Glutamate-Cysteine Ligase Catalytic subunit (GCLC) and Glutamate-Cysteine Ligase Modifier subunit (GCLM) of Glutamate-Cysteine Ligase (GCL) are needed for the maintenance of the antioxidant environment mediated by glutathione[18]. Upregulation of both GCLC and GCLM following DMF treatment has been reported in both 6-OHDA-treated SH-SY5Y cells and the corresponding mouse model[12]. Interestingly, GCLC mRNA is also upregulated by DMF in A53TSyn hippocampal neurons[14].

Lastly, NQO1, also regulated by the ARE promoter, contributes to maintaining cellular redox balance[19]. Upregulation of NQO1 has been observed

following DMF treatment in 6-OHDA-treated cells and lesioned mice[12], whereas only mRNA levels increase in A53TSyn mouse neurons[14]. In addition, acute oral treatment with DMF in α-synuclein-injected mice induces an increase in *Nqo1* mRNA levels in the cortex, whereas this upregulation is not observed in striatal samples[15].

Mitochondrial dysfunction represents a central pathogenic event that contributes to neurodegeneration in PD[20]. Among the multiple pathways modulated by DMF, the restoration of mitochondrial functionality plays a key role in ensuring an ultimate neuroprotective effect. Indeed, DMF significantly promotes mitophagy by increasing the modulation of BNIP3/PINK1 axis in the *substantia nigra* of MPTP-induced PD mice[11]. The importance of DMF effects on mitochondrial functioning was further confirmed in hippocampal neurons A53TSyn by Brandes et al[4]. Specifically, their study revealed that DMF decreases the deficit in mitochondrial bioenergetic profile by reducing mitochondrial ROS. Coherently, DMF reduced ROS production and enhanced mitochondrial function in both SH-SY5Y cells and animals exposed to 6-OHDA[12].

Cell viability and apoptosis and Parkinson's disease-related damage

The evaluation of the ability to counteract dopaminergic neuron loss in the SNpc and the effect on α-synuclein inclusions represent two crucial issues for *in vivo* PD preclinical drug repurposing studies[3]. DMF treatment counteracts neuron loss induced *in vivo* by MPTP[10,11], 6-OHDA[12], and rotenone[13] administration as well as in mice overexpressing α-synuclein[15]. Moreover, Jing et al[12] also reported restored dopamine levels after DMF treatment in the 6-OHDA mouse model. Moreover, *in vivo* DMF treatment exerts neuroprotective effects by reducing α-synuclein levels in both MPTP[10,11] and rotenone-induced[13] models. Lastly, DMF pre-treatment reduced 6-OHDA-induced cell death in SH-SY5Y cells[12].

Interestingly, Brandes et al[14] focused on the neuroprotective effects of DMF treatment. Specifically, hippocampal neurons isolated from an A53TSyn mouse model of synucleinopathy showed reduced neuronal arborization, which was restored following DMF treatment[14]. Moreover, DMF treatment significantly increased spine density, which is markedly impaired in A53TSyn neurons compared to controls. Notably, the authors tested the specificity of these effects and confirmed their dependence on Nrf2 activation. Coherently, Campolo et al[10] also observed increased nuclear Nrf2 levels specifically in the neuronal nucleus after DMF treatment. Since Nrf2 is predominantly expressed in astroglia cells, the upregulation of Nrf2 signaling in neurons further supports an additional neuron-specific mechanism of action that may contribute to its neuroprotective properties.

Interestingly, recent studies further highlighted the protective potential of Nrf2 pathway activation in PD, using drugs other than DMF. For instance, Jahan et al[21] demonstrated that emodin exerts protective effects in MPTP-induced PD mouse models by enhancing Nrf2 signaling and its downstream antioxidant targets. Similarly, another study[22] reported that epalrestat alleviates MPTP-induced toxicity by targeting the KEAP1/Nrf2 axis in both *in vivo* and *in vitro* models. Together, these findings emphasize the relevance of the Nrf2 pathway in modulating oxidative stress and promoting neuronal survival in PD models.

Finally, Khot et al[13] proposed a novel mechanism by which DMF could exert its neuroprotective effects, at least against rotenone-induced dopaminergic neurodegeneration. Specifically, they showed that DMF reversed apoptotic (Cathepsin D, Bax, Caspase 3) and anti-apoptotic (Bcl-2) protein expression.

DMF ameliorates autophagic impairments in Parkinson's disease models

Impaired autophagy has been described as one of the main factors negatively affecting neuronal functionality in PD[23]. Interestingly, Khot et al[13] demonstrated that DMF modulation of TP53-inducible glycolysis and apoptosis regulator (TIGAR) pathway also promotes autophagosome formation. Notably, in the midbrain of rotenone-treated mice, DMF administration led to an increased expression of LC3, a key marker and mediator of the autophagic process, further supporting its neuroprotective role. A modulation of LC3 expression as a result of DMF treatment was also observed in MPTP-injected[11] and α-synuclein-overexpressing mice[15]. Additionally, Lastres-Becker et al[15] further supported the DMF modulation of the autophagic process through the possible involvement of the p62/SQSTM1 pathway. Coherently, p62 is an autophagosome cargo protein whose expression is regulated by Nrf2[24,25]. However, additional quantitative analyses are needed to support these observations.

DMF attenuates neuroinflammation *via* NF-κB and cytokine modulation in Parkinson's disease models

DMF exerts anti-inflammatory activity in PD mouse models[9]. In addition to the Nrf2 pathway, DMF also induces these effects through the mo-

dulation of the NF-κB signaling pathway. In contrast to Nrf2, nuclear translocation of the NF-κB p65 subunit promotes the transcription of pro-inflammatory genes. Consistently, DMF treatment has been shown to suppress NF-κB nuclear translocation and to reduce the expression of downstream targets involved in neuroinflammation in the MPTP-induced PD model[10].

The modulation of cytokines IL-1β, IL-4, IL-6, and TNF-α has been explored as a key target modulated by DMF treatment. Notably, a reduction in the pro-inflammatory cytokine IL-1β has been reported in both rotenone-[13] and MPTP-induced[10] PD models after DMF treatment. Nevertheless, IL-6 and TNF-α downregulation has been observed only in DMF-treated rotenone-injected mice, as well as an increase in the anti-inflammatory cytokine IL-4[13]. Campolo et al[10] further investigated the dose-dependent effects of DMF on IL-1β modulation, emphasizing the importance of dosage in achieving anti-inflammatory outcomes. In this study, the authors reported that DMF treatment also significantly reduced COX-2 expression in the substantia nigra of MPTP-treated mice[10].

In addition to cytokine regulation, DMF modulates glial cell activation. Specifically, analysis of microglial marker Iba1 and CD11β revealed increased microglial activation in MPTP-treated mice, which was significantly reduced following DMF administration[10]. These results agree with earlier findings from Jing et al[12], who reported a reduction in CD11β expression in 6-OHDA-treated mice after DMF treatment. Furthermore, in the same models, DMF reduced the expression of GFAP, a marker of astrocytic reactivity, suggesting a broader anti-inflammatory effect on both microglia and astrocytes. Lastly, the attenuation of both microgliosis and astrogliosis after DMF treatment was observed also in a-syn-overexpressed mice[15].

Human studies supporting DMF repurposing for Parkinson's disease

While the above-described preclinical data are robust and overall indicate the efficacy of DMF in rescuing PD-associated detrimental behavioral, molecular, and cellular events in several experimental models, clinical evidence showing DMF therapeutic effects in PD remains quite limited. Similarly, only a few studies clearly indicate that the Nrf2 signaling pathway represents an ideal target for treatment of PD patients.

An early report showed that Nrf2 has higher nuclear localization in the substantia nigra of autopsy brain tissue from PD patients, compared with age-matched controls in which Nrf2 staining was predominantly cytoplasmic, thus suggesting a PD-associated activation of Nrf2 signaling pathway[26]. Interestingly, this modification of Nrf2 subcellular localization in neurons was specific for PD patients and not detected in tissues from Alzheimer' disease (AD) and Lewy body variant of AD patients.

More recently, an increased Nrf2 nuclear localization was detected in post-mortem PD midbrain in the presence of Lewy related α-synuclein pathology[27]. This event was correlated with an augmented Nrf2 phosphorylation on Ser40, a robust post-translational modification known to be associated with the nuclear accumulation of the protein.

Conversely, another very recent study observed a stage-specific functional impairment of the Nrf2 pathway in PD olfactory mucosa neurons (ONs) obtained by nasal brush[28]. In PD *de novo* patients, Nrf2 mostly presented in the inactive cytosolic localization in ONs compared with healthy controls whereas in PD under treatment the Nrf2 active nuclear fraction increased. In agreement with these observations, SOD-1 expression, one of the final products of Nrf2 nuclear translocation, was reduced in PD de novo patients of the same neurons and increased in PD treated patients[28].

Another cross-sectional study attempted to outline the peripheral profile of the Nrf2 pathway in the blood of PD patients[29]. Interestingly, the authors demonstrated a significant increase in Nrf2 protein and mRNA levels and in its target products GCL and glutathione reductase (GR) in leukocytes of PD patients compared with controls.

Finally, analysis of molecular markers of Nrf2 activation in post-mortem samples of PD patients suggested that some dopaminergic neurons in the SNpc up-regulate the Nrf2 response to protect from α-synuclein toxicity[15].

Unfortunately, literature is almost lacking data related to clinical trials or case reports describing the pharmacological effect of DMF in PD patients. Only one study showed a marked improvement in parkinsonian clinical symptoms after two months administration of DMF for management of psoriasis in a 51-year-old patient[30].

DMF repurposing for other brain disorders

Preclinical evidence about the possible repurposing of DMF for its use in brain disorders extends beyond PD, showing DMF efficacy in experimental models of brain disorders such as AD, Huntington's disease, and amyotrophic lateral sclerosis, suggesting broad neuroprotective applications[31]. Moreover, clinical trials have been performed to test DMF efficacy in a variety of human diseases, including T-cell lymphoma, glioblastoma, and rheumatoid arthritis[31].

In AD research, DMF has been shown to reduce neuroinflammation and cognitive impairment by modulating microglial activation and oxidative stress, key contributors to neurodegeneration. Chronic oral administration of DMF attenuated neuroinflammation, particularly in astrocytes, and reversed cognitive dysfunction presumably by activating the Nrf2-dependent pathway in App-KI mice. Furthermore, DMF modulated astrocyte–microglia crosstalk by regulating C3-STAT3 signaling in the AD mouse model[32]. Interestingly, DMF has been evaluated not only in AD but also in preclinical models of other dementias. DMF treatment mitigated neurodegenerative features in a frontotemporal dementia (FTD-TAU) mouse model, reducing TAU hyperphosphorylation, neurodegeneration, neuroinflammation, and oxidative stress[33]. Similarly, DMF chronic oral treatment from pre-symptomatic stages improved cognitive function in a TDP-43-related FTD mouse model. Cognitive enhancement correlated with the neuroprotection observed in the dentate gyrus and a reduction in astrogliosis[34].

Finally, recent studies have started to consider DMF as an alternative strategy for other brain disorders, such as epilepsy. Administration of DMF following status epilepticus increased Nrf2 activity, attenuated status epilepticus-induced neuronal cell death, and decreased seizure frequency and the total number of seizures compared to vehicle-treated rats. Moreover, DMF treatment reversed epilepsy-induced behavioral deficits[35].

CONCLUSIONS

The body of preclinical evidence accumulated over the past decade strongly supports the therapeutic potential of DMF as a repurposed agent for PD. DMF consistently improved motor behavior in several *in vivo* PD models and demonstrates robust neuroprotective properties, effectively mitigating oxidative stress, neuroinflammation, and mitochondrial dysfunction—hallmarks of PD pathology. These multimodal actions are primarily related to the activation of the Nrf2 pathway and set DMF apart from most conventional symptomatic therapies, raising hope that it may bridge the gap between basic neuroprotection and true disease modification.

However, it is important to acknowledge the inherent limitations in preclinical research that may affect the translatability of these findings. The most widely used animal models of PD—predominantly neurotoxin-based models—fail to fully recapitulate the progressive and multifactorial nature of human PD, especially with respect to α-synuclein pathology and the gradual neurodegenerative timeline. Moreover, variability in study design, including differences in dosing, administration routes, timing of treatment, and behavioral assessment protocols, introduces methodological biases that complicate cross-study comparisons and interpretation of results. The lack of standardized protocols and insufficient reporting of negative findings also raise the risk of publication bias, potentially inflating the perceived efficacy of DMF.

In addition, despite encouraging advances in experimental models, clinical translation remains in its infancy and important questions remain unanswered. It is still uncertain whether the dosing regimens effective for autoimmune disorders will be suitable—or optimal—for neuroprotection in PD. The timing of intervention is also a critical consideration, as the efficacy of DMF may depend on early treatment before irreparable neuronal loss has occurred. Furthermore, the identification and validation of reliable biomarkers will be vital to accurately track target engagement and drug efficacy in upcoming clinical trials. However, the extensive clinical experience with DMF in other indications, such as multiple sclerosis and psoriasis, provides reassurance regarding its safety profile and general tolerability, supporting the rationale for its exploration in neurodegenerative settings.

The potential impact of DMF repurposing extends beyond PD. Preclinical studies have demonstrated beneficial actions in other neurodegenerative contexts, including Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, and even experimental epilepsy, suggesting a broad neuroprotective profile that warrants further investigation across neurological diseases.

Moving forward, rigorously designed clinical trials will be essential to determine whether DMF's neuroprotective promise can translate into clinically meaningful benefits for people living with Parkinson's disease. The hope is that DMF, either as monotherapy or in combination with existing interventions, may finally offer patients a treatment that not only alleviates symptoms but also slows or halts disease progression. Continued interdisciplinary research will be crucial to address outstanding questions and to position DMF - and the broader paradigm of drug repurposing - at the forefront of neurodegenerative disease therapeutics.

Conflict of Interest

The authors declare no conflict of interest.

Funding

This work has been supported by Fondazione Regionale per la Ricerca Biomedica (FRRB, Regione Lombardia), Linking Park, ID 3433068.

Authors' Contributions

Michela Salvadè: writing – review and editing, writing – original draft. Fabrizio Gardoni: writing – review and editing, writing – original draft, conceptualization.

ORCID ID

Michela Salvadè: 0009-0008-2476-8539
Fabrizio Gardoni: 0000-0003-4598-5563

Ethics Approval and Informed Consent

Not applicable.

REFERENCES

1) Pardo-Moreno T, García-Morales V, Suleiman-Martos S, Rivas-Domínguez A, Mohamed-Mohamed H, Ramos-Rodríguez JJ, Melguizo-Rodríguez L, González-Acedo A. Current Treatments and New, Tentative Therapies for Parkinson's Disease. Pharmaceutics 2023; 15: 770.
2) Mahlknecht P, Poewe W. Pharmacotherapy for Disease Modification in Early Parkinson's Disease: How Early Should We Be? J Parkinsons Dis 2024; 14: S407-421.
3) Salvadè M, DiLuca M, Gardoni F. An update on drug repurposing in Parkinson's disease: Preclinical and clinical considerations. Biomed Pharmacother 2025; 183: 117862.
4) Hernández-Parra H, Cortés H, Avalos-Fuentes JA, Del Prado-Audelo M, Florán B, Leyva-Gómez G, Sharifi-Rad J, Cho WC. Repositioning of drugs for Parkinson's disease and pharmaceutical nanotechnology tools for their optimization. J Nanobiotechnology 2022; 20: 413.
5) McFarthing K, Buff S, Rafaloff G, Pitzer K, Fiske B, Navangul A, Beissert K, Pilcicka A, Fuest R, Wyse RK, Stott SRW. Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update. J Parkinsons Dis 2024; 14: 899-912.
6) Bashir B, Vishwas S, Gupta G, Paudel KR, Dureja H, Kumar P, Cho H, Sugandhi VV, Kumbhar PS, Disouza J, Dhanasekaran M, Goh BH, Gulati M, Dua K, Singh SK. Does drug repurposing bridge the gaps in management of Parkinson's disease? Unravelling the facts and fallacies. Ageing Res Rev 2025; 105: 102693.
7) Shaker B, Ahmad S, Lee J, Jung C, Na D. In silico methods and tools for drug discovery. Comput Biol Med 2021; 137: 104851.
8) Valencia-Sanchez C, Carter JL. An evaluation of dimethyl fumarate for the treatment of relapsing remitting multiple sclerosis. Expert Opin Pharmacother 2020; 21: 1399-1405.
9) Bresciani G, Manai F, Davinelli S, Tucci P, Saso L, Amadio M. Novel potential pharmacological applications of dimethyl fumarate-an overview and update. Front Pharmacol 2023; 14: 1264842.
10) Campolo M, Casili G, Biundo F, Crupi R, Cordaro M, Cuzzocrea S, Esposito E. The Neuroprotective Effect of Dimethyl Fumarate in an MPTP-Mouse Model of Parkinson's Disease: Involvement of Reactive Oxygen Species/Nuclear Factor-κB/Nuclear Transcription Factor Related to NF-E2. Antioxid Redox Signal 2017; 27: 453-471.
11) Pinjala P, Tryphena KP, Kulkarni A, Goswami PG, Khatri DK. Dimethyl Fumarate Exerts a Neuroprotective Effect by Enhancing Mitophagy via the NRF2/BNIP3/PINK1 Axis in the MPP+ Iodide-Induced Parkinson's Disease Mice Model. J Alzheimers Dis Rep 2024; 8: 329-344.
12) Jing X, Shi H, Zhang C, Ren M, Han M, Wei X, Zhang X, Lou H. Dimethyl fumarate attenuates 6-OHDA-induced neurotoxicity in SH-SY5Y cells and in animal model of Parkinson's disease by enhancing Nrf2 activity. Neuroscience 2015; 286: 131-140.
13) Khot M, Sood A, Tryphena KP, Pinjala P, Srivastava S, Singh SB, Khatri DK. Dimethyl fumarate ameliorates parkinsonian pathology by modulating autophagy and apoptosis via Nrf2-TIGAR-LAMP2/Cathepsin D axis. Brain Res 2023; 1815: 148462.
14) Brandes MS, Zweig JA, Tang A, Gray NE. NRF2 Activation Ameliorates Oxidative Stress and Improves Mitochondrial Function and Synaptic Plasticity, and in A53T α-Synuclein Hippocampal Neurons. Antioxidants (Basel) 2021; 11: 26.
15) Lastres-Becker I, García-Yagüe AJ, Scannevin RH, Casarejos MJ, Kügler S, Rábano A, Cuadrado A. Repurposing the NRF2 Activator Dimethyl Fumarate as Therapy Against Synucleinopathy in Parkinson's Disease. Antioxid Redox Signal 2016; 25: 61-77.
16) Hybertson BM, Gao B, Bose SK, McCord JM. Oxidative stress in health and disease: the therapeutic potential of Nrf2 activation. Mol Aspects Med 2011; 32: 234-246.
17) He F, Ru X, Wen T. NRF2, a Transcription Factor for Stress Response and Beyond. Int J Mol Sci 2020; 21: 4777.
18) Lu SC. Regulation of glutathione synthesis. Mol Aspects Med 2009; 30: 42-59.
19) Dinkova-Kostova AT, Talalay P. NAD(P)H:quinone acceptor oxidoreductase 1 (NQO1), a multifunctional antioxidant enzyme and exceptionally versatile cytoprotector. Arch Biochem Biophys 2010; 501: 116-123.
20) Henrich MT, Oertel WH, Surmeier DJ, Geibl FF. Mitochondrial dysfunction in Parkinson's disease - a key disease hallmark with therapeutic potential. Mol Neurodegener 2023; 18: 83.
21) Jahan S, Ikram M, Siraj S, Ullah S, Zakria M, Ahmad N. Emodin, a Potent Anthraquinone Mitigates MPTP-Induced Parkinsons' Disease Pathology by Regulating Nrf2 and Its Downstream Targets: In Silico and In Vivo Approach. Mol Neurobiol 2025; 62: 8103-8120.
22) Jia H, Liu M, Jiang H, Qiao Z, Ren K, Du X, Chen X, Jiao Q, Che F. Repurposing of epalrestat for neuroprotection in parkinson's disease via activation of the KEAP1/Nrf2 pathway. J Neuroinflammation 2025; 22: 125.
23) Nechushtai L, Frenkel D, Pinkas-Kramarski R. Autophagy in Parkinson's Disease. Biomolecules 2023; 13: 1435.
24) Jain A, Lamark T, Sjøttem E, Larsen KB, Awuh JA, Øvervatn A, McMahon M, Hayes JD, Johansen T. p62/SQSTM1 is a target gene for transcription factor NRF2 and creates a positive feedback loop by inducing antioxidant response element-driven gene transcription. J Biol Chem 2010; 285: 22576-22591.
25) Komatsu M, Kurokawa H, Waguri S, Taguchi K, Kobayashi A, Ichimura Y, Sou YS, Ueno I, Sakamoto A, Tong KI, Kim M, Nishito Y, Iemura S ichiro, Natsume T, Ueno T, Kominami E, Motohashi H, Tanaka K, Yamamoto M. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. Nat Cell Biol 2010; 12: 213-223.
26) Ramsey CP, Glass CA, Montgomery MB, Lindl KA, Ritson GP, Chia LA, Hamilton RL, Chu CT, Jordan-Sciutto KL. Expression of Nrf2 in neurodegenerative diseases. J Neuropathol Exp Neurol 2007; 66: 75-85.

27) Delaidelli A, Richner M, Jiang L, van der Laan A, Bergholdt Jul Christiansen I, Ferreira N, Nyengaard JR, Vægter CB, Jensen PH, Mackenzie IR, Sorensen PH, Jan A. α-Synuclein pathology in Parkinson disease activates homeostatic NRF2 anti-oxidant response. Acta Neuropathol Commun 2021; 9: 105.

28) Maftei D, Di Certo MG, Maurizi R, Veltri F, Rosina M, Bissacco J, Mascioli D, Bovenzi R, Simonetta C, Mancini M, Buttarazzi V, Viola S, Gravina A, Maglie MG, Rinaldi AM, Gabanella F, Saso L, Stefani A, Passali FM, Di Girolamo S, Pierantozzi M, Valle C, Ferri A, Mercuri NB, Lattanzi R, Severini C, Schirinzi T. α-Synuclein-Related Mitochondria-Nrf2 Dysfunction in Parkinson's Disease Olfactory Mucosa. Ann Neurol 2025; Online ahead of print.

29) Petrillo S, Schirinzi T, Di Lazzaro G, D'Amico J, Colona VL, Bertini E, Pierantozzi M, Mari L, Mercuri NB, Piemonte F, Pisani A. Systemic activation of Nrf2 pathway in Parkinson's disease. Mov Disord 2020; 35: 180-184.

30) Filippi F, Zengarini C, Sacchelli L, Bardazzi F. Unexpected improvements of Parkinson's symptoms in a psoriatic patient during dimethyl fumarate therapy. Ital J Dermatol Venerol 2022; 157: 106-107.

31) Kourakis S, Timpani CA, de Haan JB, Gueven N, Fischer D, Rybalka E. Dimethyl Fumarate and Its Esters: A Drug with Broad Clinical Utility? Pharmaceuticals (Basel) 2020; 13: 306.

32) Wang T, Sobue A, Watanabe S, Komine O, Saido TC, Saito T, Yamanaka K. Dimethyl fumarate improves cognitive impairment and neuroinflammation in mice with Alzheimer's disease. J Neuroinflammation 2024; 21: 55.

33) Cuadrado A, Kügler S, Lastres-Becker I. Pharmacological targeting of GSK-3 and NRF2 provides neuroprotection in a preclinical model of tauopathy. Redox Biol 2018; 14: 522-534.

34) Silva-Llanes I, Martín-Baquero R, Berrojo-Armisen A, Rodríguez-Cueto C, Fernández-Ruiz J, De Lago E, Lastres-Becker I. Beneficial Effect of Dimethyl Fumarate Drug Repositioning in a Mouse Model of TDP-43-Dependent Frontotemporal Dementia. Antioxidants (Basel) 2024; 13: 1072.

35) Sandouka S, Singh PK, Saadi A, Taiwo RO, Sheeni Y, Zhang T, Deeb L, Guignet M, White SH, Shekh-Ahmad T. Repurposing dimethyl fumarate as an antiepileptogenic and disease-modifying treatment for drug-resistant epilepsy J Transl Med 2023; 21: 796.