Musa Mustapha, Che Norma Mat Taib: MPTP-Induced Mouse Model of Parkinson’s disease

MPTP-induced mouse model of Parkinson’s disease: A promising direction of therapeutic strategies

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ABSTRACT

Amongst the popular animal models of Parkinson’s disease (PD) commonly used in researches are those that employ neurotoxins, especially the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). MPTP neurotoxin exerts its neurotoxicity by causing a barrage of insults such as oxidative stress, mitochondrial apoptosis, inflammation, excitotoxicity, and formation of inclusion bodies acting singly and in concert. All of this ultimately leads to dopaminergic neuron damage in substantia nigra pars compacta and striatum. The selective neurotoxicity induced by MPTP in the nigrostriatal dopaminergic neuron of the mouse brain brought a new dawn in our perspectives about PD. For decades now MPTP-induced mouse model of PD has become the gold standard in PD research despite its shortcoming in fully recapitulating PD symptomatology. It has the advantage of easy practicability, affordability, less ethical consideration, and more clinical correlation over the other toxin models of PD. The model has rejuvenated researches in PD and has also opened new frontiers in the quest for more novel therapeutic and adjuvant agents for PD. Hence, this review summarizes the MPTP’s role in producing Parkinson-like symptoms in mice, the MPTP-induced mouse model’s experimental role, and the recent development in PD therapeutics using this model to enrich our existing knowledge on this neurotoxin. Furthermore, our review promotes the use of this model by researchers for developing more promising therapeutic strategies.

KEYWORDS: Parkinson’s disease; MPTP; C57BL mouse; MPTP-induced PD mouse
INTRODUCTION

Parkinson’s disease (PD) is an insidiously progressive and irreversible neurodegenerative disease that mainly affects the ageing population [1]. Though the disease can appear at any age, the average age of onset is 60 [2]. Garza-Ulloa [3] have reported PD as the second most popular neurodegenerative disease in the world after Alzheimer disease. PD is now the fastest growing neurological disorder and the leading source of disability globally with a total population of patients from 1990 to 2016 at over 6 million [4]. This number is expected to double to over 12 million by 2040 [5]. Studies have shown that factors such as increasing life expectancy, increasing industrialization and declining smoking rates could raise the burden of the disease [6,7]. This rising incidence and prevalence of the disease globally make it a disease of huge economic, social and public health importance [8].

Based on current thinking two forms of PD exist; sporadic/late-onset and familial/early-onset cases [9]. Epidemiological studies have reported that the familial form of PD only accounts for a few of the PD subjects while the overwhelming majority of the PD subjects fall under the sporadic type [10]. The etiology of the PD is complex due to the heterogeneity of the disorder [11]. However, PD is believed to begin principally by degeneration of dopaminergic nigrostriatal neurons in the brain and secondarily by complex pathological mechanisms including mitochondrial dysfunction, oxidative stress, apoptotic cell death, protein aggregation and misfolding, inflammation, excitotoxicity, loss of trophic factors and other cell death pathways [12]. The PD patient presents with a myriad of symptomatology including the four cardinal motor manifestations viz tremor, rigidity, akinesia and postural reflexes [13] and non-motor symptoms such as dementia, anxiety, somnolence, urinary symptoms, attention deficit, hyposmia and restless leg syndrome as the disease progresses [2,14]. The pathognomonic signs of PD are loss of dopaminergic neurons in the substantia
nigra pars compacta (SNpc) and the formation of intraneuronal protein inclusions termed Lewy bodies (LB), composed primarily of α-synuclein [15]. Jagmag et al. [16] have also reported some neuronal losses in other parts of the brain such as in thalamic subnuclei and amygdala, serotoninergic neurons of the raphe nucleus and the cholinergic nucleus basalis of Meynert as the disease progresses.

Regardless of the tremendous advancement in the understanding of the disease mechanism, the present approved PD treatments only provide circumscribed therapeutic benefits [17]. This unmet clinical need to develop new therapeutic strategies have triggered further research clarification into the pathology of the disease. As a result, efforts have been made to emulate human PD using animal models as studies have shown that they can mimic various aspects of the PD features and thus gives us the leverage to study the disease pathophysiology and explore treatments possibilities [18].

The experimental animal models so far are of two main types; toxin models and genetic models. The transgenic models only simulate the familial form of PD and the final neuropathological and behavioural features reminiscent of human PD are not fully recapitulated in this model [19]. The transgenic models also use transgenic technology which makes it pretty expensive and thus not commonly used in PD researches [19]. The toxin models now commonly used make use of some neurotoxins such as paraquat, rotenone, 6-hydroxydopamine (6-OHDA), methamphetamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce dopaminergic neurodegeneration in brain of animals [10, 20, 21]. The extent to which these neurotoxins phenocopy the salient features of PD and their related mechanisms varies greatly especially in the sporadic type of PD [22]. Though PD-toxin models have played a significant role in defining critical disease-related
mechanisms and have been at the forefront of evaluating novel therapeutic approaches, they also cannot fully mirror symptoms reminiscent of the human PD [23].

However, for decades now, mouse models using MPTP are among the most extensively used in PD researches because it has the advantage of easy practicability, affordability, less ethical consideration and more clinical correlation compared to the other toxin models [10, 24]. Worthy of note, the PD neurotoxic potentials of MPTP on human, monkeys, rodents, zebrafish and C. elegans have also been documented [1, 25]. Though studies have shown that MPTP intoxicated monkey demonstrates the best results of PD pathology such as LB like inclusions, the MPTP mouse model is still more popular because of its practicability and feasibility [10, 16]. Now researches involving the MPTP-induced mouse model of PD are in vogue and have been on the increase to date [18]. Amongst the mice, different strain or same strain from another source shows strikingly different sensitivity to the MPTP concerning the loss of DA neurons in SNpc and striatum [10]. The most sensitive of the mouse strain to MPTP intoxication is the C57BL/6, followed by CD-1 and BALB, with the least being the Swiss Webster [26, 27]. Therefore, to get the best reproducible PD results from one experiment to another, a male mouse of at least 8 weeks of age, the average weight of 22 g and same mouse strain must be obtained from the same source [28].

MPTP-mouse models of PD have provided more insight into the etiology and pathophysiology of this debilitating disease, PD [29]. Its relevance in providing researchers with a unique model platform for testing the efficacy of novel neuroprotective drugs cannot be underscored. Thus, in this review the use of MPTP in mouse to recapitulate PD symptoms will be highlighted i.e., the pharmacokinetics and pharmacodynamics of MPTP, MPTP administration dynamics, mechanisms of MPTP-induced neurotoxicity, laboratory findings in MPTP-induced PD mouse model to enrich our understanding of this neurotoxin. To further
promote the use of MPTP-induced mouse model of PD by researchers for developing more promising therapeutic strategies, the light will also be shaded on its merits and demerits, models experimental role and the recent development in PD therapeutics using the model. Using the following keywords; Parkinson’s disease, MPTP, C57BL/6 mice, and MPTP-induced PD mouse, all the relevant literature used in this review were searched and collected from credible scientific databases such as Science Direct, Scopus, PubMed, and Google Scholar. The search on laboratory findings in MPTP-induced mouse model of PD and the recent development in PD therapeutics using this model were restricted to published papers from 2019 to date.

**Structure, pharmacokinetics and pharmacodynamics of MPTP**

MPTP is structurally a meperidine analogue produced as a by-product in the process of synthesizing 1-methyl-4-phenyl-propionoxy-piperidine (MPPP). This toxin once injected into the body of mice, it traverses the blood-brain barrier (BBB) into the central nervous system (CNS) with ease because of its lipophilicity [10]. In the CNS, monoamine oxidase type B (MAO-B) enzyme secreted by glial cell (astrocytes) converts the MPTP to an intermediate metabolite 1-methyl-4-phenyl-2,3-dihydropyridine (MPDP+, Fig. 1) and subsequently to the final toxic metabolite 1-methyl-4-phenylpyridinum (MPP+, Fig. 1) [30]. Cohen et al. [31] and Heikkila et al. [32] noticed striatal MPP+ depletion following treatment with MAO-B inhibitor such as seleginine and this proves that inhibition of this enzyme significantly prevents the formation of this toxic metabolite. MPP+, the active neurotoxin is a polar compound and as such, it cannot cross back the BBB, thus it acts at the cellular level [28]. It selectively enters norepinephrine (NE) and dopaminergic (DA) neurons via the special transporters NE transporter (NET) and DA transporter (DAT) respectively [33]. Studies by Takahashi et al. [34] proved that mice deficient in DAT were resistant to MPTP toxicity.
Therefore, excessive expression of DAT will enhance MPTP neurotoxicity. Once in the NE/DA nerve cell, MPP+ forms a complex with neuromelanin in the axoplasm and is subsequently transported by vesicular monoamine transporter type 2 (VMAT-2) and stored in synaptosomal vesicles. This was confirmed by Gainetdinov et al. [35] experiment in which mice deficient of VMAT-2 showed a strikingly increased toxicity to MPTP. Therefore, selective toxicity of MPTP is directly related to the amount of DAT [36] and inversely to the amount of VMAT-2 [37]. MPP+ continues to accumulate in synaptosomal vesicles to a point when the threshold is surpassed and cell death of DA nigrostriatal neurons occurs in the SNpc and striatum (Fig.1).

**Mechanisms of MPTP-induced neurotoxicity**

Once the toxic metabolite of MPTP (MPP+) continues to accumulate and aggregates in synaptosomal vesicles of DA neuron, it gets to a point where it becomes too much in the cytoplasm and eventually triggers cell damage in the striatum and SNpc via the following pathways (refer Fig. 2):

**Mitochondrial Apoptotic Pathway**

MPP+ inhibits COMPLEX 1 in the mitochondria and induces less expression of anti-apoptotic proteins like Bcl2 [38, 39]. This inhibition hinders the electron transport chain (ETC) and thus blocks ATP synthesis and increases ROS production leading to the opening of mitochondrial transition pores [28]. Cytochrome C is then released from the mitochondrion and it forms a complex with pro-caspase-9 and apoptosis protease activating factor-1 [40]. The complex now formed activates caspase 9 and downstream caspases resulting in apoptosis and finally DA nigrostriatal cell death in SNpc and striatum [41].
Oxidative Stress Pathway

MPP+ inhibits NADH dehydrogenase in the mitochondria and allows excessive reactive oxygen species (ROS) production such as hydrogen peroxide (H$_2$O$_2$), nitric oxide (NO), hydroxyl (OH) radicals [42, 43]. These ROS overwhelm cellular antioxidant defense mechanism and causes DA nigrostriatal cell damage in SNpc and striatum through lipid peroxidation, DNA damage, protein cross-linkage [42, 44, 45].

Alpha Synuclein Pathway

Increase in ROS causes the production of alpha synuclein monomers [46]. As the level of these monomers increase, they aggregate together to form toxic alpha synuclein oligomers. Oligomers of this kind can also be produced by mutation of alpha synuclein gene [47, 48]. The oligomers inhibit ubiquitin proteasome system (UPS) and autophagy system (ATGS) which are responsible for maintaining biochemical balance in the neuron [49, 50]. Failure of UPS leads to development of Lewy bodies, one of the pathological hallmarks of PD [28].

Inflammation Pathway

MPP+ triggers an inflammatory process which is characterized by T cells infiltration into the striatum and SNpc and also microglia activation [33, 51]. Activated microglia releases proinflammatory factors such as TNF-α, PGE2, IFN-γ and ROS like NO and H2O2 which are all toxic to the neuron [52]. Nagarajan et al. [17] documented that activated microglia performs an intrinsic role in MPTP-induced neurotoxicity because it up regulates inducible nitric oxide synthase (iNOS) and nicotinamide adenine dinucleotide oxidase (NADPH- oxidase). These two enzymes produce SO$_4^{2-}$ and NO and being ROS they cause oxidative stress thus leading to death of DA nigrostriatal neurons in the SNpc and striatum [13].
Glutamatergic Pathway

MPP+ causes an increase in extracellular glutamate in SNpc and striatum (53). Glutamate binds to ionotrophic and metabotropic receptors (52). Increase in glutamate causes excessive and prolonged activity at the synaptic cleft. This causes an increase in the entry of ions especially Ca2+ (33). The influx of these ions increases the production of ROS which leads to oxidative stress (44). Also, an increase in glutamate can impair the function of the mitochondria resulting in a series of events that converts non-toxic levels of glutamate into higher levels that are cytotoxic (28).

MPTP administration dynamics

Different MPTP dosing regimen has been used by researchers to produce mouse model features that closely recapitulate PD in humans (33). The time course of any regimen used will determine the degree of apoptosis, striatal dopamine loss and dopaminergic cell loss in substantia nigra [54]. Repeated administration of a particular regimen for a longer period produces more robust and irremediable neurodegeneration compared to an administration. Based on the literature, when more than one injection is given in 24 hours, it said to be an acute administration regimen while when a single injection is given daily for several consecutive or non-consecutive days or week, it is said to be a subacute or chronic administration regimen [13]. However, controversy still trails the subacute and chronic regimen of administration because of the rapid toxicokinetics of the neurotoxin. For this reason, the commonest regimen used irrespective of the aforementioned nomenclatures will be considered. The first of this regimen involves single MPTP injection given 2 hourly for a total of four doses over 24 hours. In this regimen, striatal dopamine diminution can range from 40% (14 mg/kg per dose x4) to roughly 90% (20 mg/kg per dose x4) 7 days after the last MPTP dose depending on the doses given (Fig. 3) [54]. Another regimen that is also
popularly used is the one developed by Tatton and Kish (55). Here a single injection of MPTP free base, 30 mg/kg is given daily for five consecutive days (Fig. 3). In this method, 40–50% striatal dopamine depletion (Fig. 3) and apoptosis is seen especially in young adult C57/BL mice, and by day 21, the dopaminergic lesion stabilizes after the administration of MPTP [54].

As regards the administration site, many studies have agreed on the intraperitoneal route as the ideal administration site because several MPTP administered via this route remarkably impairs motor function and induces DA neuronal damage [13,35]. There are conflicting reports regarding the appearance of Lewy body-like cytoplasmic inclusion when MPTP is administered intraperitoneally. To confirm this, Alvarez-Fischer et al. [56] and Shimoji et al. [57] and found that the 28 day chronic intraperitoneal MPTP administration (23 mg/kg/day), 7 day subacute intraperitoneal injection (20 mg/kg/day), and 28 day subcutaneous infusion (23 mg/kg/day) did not produce or trigger the formation of Lewy body neuronal inclusions. However, studies by Gibrat et al. [58] and Giráldez-Pérez et al. [59] demonstrated that chronic intraperitoneal infusion of MPTP (46 mg/kg/day) for 14 days with osmotic minipumps reproduced the formation of neuronal inclusions as observed by the alpha-synuclein expression within the cytoplasm of dopaminergic neurons in SNpc. It could be inferred that low dose MPTP may not be adequate to facilitate the formation of Lewy body. According to Jiang et al. [60], increase lactate level in the brain is associated with the formation of inclusion body simply because it can activate AMP-activated protein kinase and promote a-synuclein accumulation and phosphorylation.

**Laboratory findings in MPTP-induced mouse model of PD**

MPTP neurotoxin is the gold standard employed for studying and understanding the processes involved in the DA nigrostriatal neuron death in PD [61]. Studies have revealed
usage of different MPTP dosing regimen in mouse over the years and similar findings were reported in virtually all the studies i.e., significant motor impairment and damage to nigrostriatal DA pathway with marked loss of DA neurons in SNpc and striatum [62, 63].

This explicit and reproducible neurotoxic effect on the nigrostriatal system is the exclusive asset of this model and it bears semblance to that seen in PD patients [64]. It is important to note that Lewy body which is one of the pathological hallmarks of PD was not studied in the articles used for this section probably because this model seldom shows it [21]. Since studies have shown MPTP to be selectively more toxic to the C57BL/6 mouse strain [28], in this section only findings on this mouse strain will be reported. Table 1 is a summary of some laboratory findings in MPTP-induced C57BL/6 mouse model of PD.

Merits of MPTP-induced mouse model of PD

1. The ability of the MPTP mouse model to almost mirroring the parkinsonian symptoms as seen in human PD is the main reason for its usage [13, 27].
2. It has helped to improve our knowledge of the molecular and cellular mechanism behind PD [18, 72, 73].
3. This model is cheap, easy to handle and requires less ethical consideration in contrast to other toxin-induced animal models [19, 74].
4. This model has brought to light the non-motor symptoms of PD [75].
5. In electrophysiological studies, Wallace et al. [76] reported the role of MPTP mouse models in aiding in the treatment for deep brain stimulation related therapy.
6. It has also helped in developing promising therapeutic strategies for neuroprotection and neurorestoration [77].
7. The model has helped advance our understanding of the role played by mitochondrial dysfunction in PD [33, 78].
8. The model has better enhanced our knowledge on the role of autophagy in PD pathogenesis [79, 80].

9. According to Filograna et al. [81], MPTP mouse Model is now showing some light at the end of the tunnel for clinical research in PD.

**Demerits of MPTP-induced mouse model of PD**

1. The commonest drawback of this model is that it rarely induced Lewy body formation in most of the studies [19].

2. Behavioural features reminiscent of human PD is difficult to demonstrate in this model [82].

**Recent development in therapeutics regarding PD using MPTP-induced mouse model of PD**

Efforts channeled at developing anti-parkinsonian therapeutics have shown promising and encouraging results in preclinical MPTP neurotoxic mouse model [23, 29, 65, 69, 83, 84, 85]. These therapeutics have proven their efficacy in aiding diagnosis and their ability to slow down or reverse or prevent PD symptoms out rightly in this preclinical model. However, whether these preclinical findings can be translated into clinical trials or not is a million-dollar question. The good news is that these therapeutics can excite translational research towards their neuroprotective adjuvant potentials in human PD. Table 2 presents a summary of the recent development in PD therapeutics using the MPTP-induced C57BL/6 mouse model of PD in the year 2019 and 2020.

**CONCLUSION**

Transgenic and neurotoxin models have been used to mimic parkinsonian symptoms that are reminiscent of human PD. Though they all have the limitation of not fully recapitulating the
PD symptomatology, the MPTP-induced mouse model of PD now stands out amongst the other toxin models in PD researches. This model is cheap to acquire, easy to handle, less ethical consideration, more practicable and with good clinical correlation. Despite its shortcoming, this model has enhanced our understanding of the cellular and molecular mechanisms behind DA neuron death in SNpc and striatum and have also provided researchers avenue for exploring the neuroprotective and neurorestorative potentials of more novel therapeutic and adjuvant agents for PD. We believe that this model can further be perfected under the unrelenting efforts of researchers so that all the pathological and phenotypic features reminiscent of human PD can be recapitulated. If a cocktail of miRNA or siRNA is introduced into the MPTP mouse model system, a more robust and precise PD model showing all the symptoms of human PD is likely to be formed. Also, an improved model can be produced by combining MPTP neurotoxin and a genetic mouse model so that the progressive neurodegeneration associated with PD can fully be appreciated. Based on this premise, the MPTP-induced mouse model of PD could likely write a good end in the story of PD.

ACKNOWLEDGEMENTS
Special acknowledgement to the Ministry of Education, government of Malaysia for their financial assistance throughout the research grants under IPTA Fundamental Research Grant Scheme (FRGS), FRGS/1/2019/STG03/UPM/02/15. We like to thank the anonymous reviewers for their insightful comments (PDF) MPTP-Induced Mouse Model of Parkinson's Disease: A Promising Direction of Therapeutic Strategies
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TABLES AND FIGURES

**TABLE 1:** Laboratory findings in MPTP-induced C57BL/6 mouse model of PD.

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<th>Authors</th>
<th>MPTP Dose</th>
<th>Neuropathological Findings</th>
<th>Neurobehavioural Findings</th>
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<tr>
<td>[22]</td>
<td>30 mg/kg bwt</td>
<td>TH proteins ↓↓&lt;br&gt;GFAP proteins ↑↑</td>
<td>Invert screen test ↓↓&lt;br&gt;Cross beam test ↓↓&lt;br&gt;Lifting on hind legs ↓↓</td>
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<td>[65]</td>
<td>25 mg/kg bwt</td>
<td>Dopaminergic neurons in SNpc ↓↓&lt;br&gt;TH positive cells/proteins in striatum ↓↓&lt;br&gt;Anti-Iba1 activated microglia in SNC ↑↑&lt;br&gt;CRMP2 phosphorylation ↑↑</td>
<td>Rotarod test ↓↓</td>
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<td>[66]</td>
<td>25 mg/kg but</td>
<td>Dopaminergic neurons in SNpc ↓↓&lt;br&gt;TH positive cells in striatum ↓↓&lt;br&gt;5-HT in SNpc ↓↓</td>
<td>Vertical and Horizontal grid test ↓↓</td>
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<td>[67]</td>
<td>20 mg/kg bwt</td>
<td>Dopaminergic neurons in SNpc ↓↓</td>
<td>Pole test ↓↓</td>
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<tr>
<td>Reference</td>
<td>Dose</td>
<td>Effects</td>
<td>Additional Tests</td>
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<tr>
<td>[68]</td>
<td>20 mg/kg bwt</td>
<td>TH positive cells in striatum ↓↓ Dopaminergic neurons in SNpc ↓↓ TH positive cells in striatum ↓↓ Microglial cells ↑↑</td>
<td>Rotarod test ↓↓</td>
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<tr>
<td>[69]</td>
<td>20 mg/kg bwt</td>
<td>Dopaminergic neurons in SNpc ↓↓ TH positive cells in striatum ↓↓ pAMPK, SIRT1 and PGC1α ↓↓</td>
<td>Not studied</td>
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<tr>
<td>[70]</td>
<td>22 mg/kg bwt</td>
<td>Dopaminergic neurons in SNpc ↓↓ TH positive cells in striatum ↓↓ GFAP and Iba1 ↑↑</td>
<td>Rotarod test ↓↓</td>
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<tr>
<td>[71]</td>
<td>25 mg/kg bwt</td>
<td>Dopaminergic neurons in SNpc ↓↓ TH positive cells in striatum ↓↓ α-syn aggregation ↑↑</td>
<td>Rotarod test ↓↓ Beam walk test ↓↓ Novel object recognition test ↓↓</td>
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TABLE 2: Recent development in PD therapeutics using MPTP-induced mouse model of PD.

<table>
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<tr>
<th>S/N</th>
<th>Paper Title</th>
<th>Benefits of the research paper</th>
<th>MPTP-induced PD mouse Model application</th>
<th>References</th>
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<tbody>
<tr>
<td>1.</td>
<td>Effect of Valerenic acid on neuroinflammation in a MPTP-induced mouse model of PD</td>
<td>In this article, the authors demonstrated the usefulness of valerenic acid as a co-treatment in PD because it prevents neuroinflammation in MPTP-induced PD mouse which may reflect the neuroprotection of DA neurons with recovery of motor ability. There may be a positive promise if used on human PD.</td>
<td>Test symptomatic therapy</td>
<td>[22]</td>
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<td>2.</td>
<td>Anti-inflammatory activity of ursolic acid in MPTP-induced parkinsonian mouse model</td>
<td>This model has clearly demonstrated that the neuroinflammation and neurodegeneration along with impairments in biochemical and behavioural parameters in PD can be reversed by ursolic acid. Thus, its usage in human PD may be a game changer.</td>
<td>Test symptomatic therapy</td>
<td>[85]</td>
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<td>3.</td>
<td>Lanthionine ketamine ester (LKE) improves outcome in</td>
<td>The authors suggest that LKE usage in PD may represent a novel strategy for slowing its progression via its ability</td>
<td>Test symptomatic therapy</td>
<td>[65]</td>
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<td><strong>4.</strong> Antioxidant and anti-inflammatory effects of dextrazoxane on dopaminergic neuron degeneration in rodent models of Parkinson's disease.</td>
<td>The authors have unraveled the neuroprotective potential of dextrazoxane in MPTP intoxicated mouse model and concluded that dextrazoxane could positively change the future of PD therapy in human if applied in clinical trials.</td>
<td>Test symptomatic therapy [29]</td>
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<td><strong>5.</strong> Gami-Chunggan formula prevents motor dysfunction in MPTP/p-induced and A53 T α-Synuclein overexpressed Parkinson's disease mouse model though DJ-1 and BDNF expression.</td>
<td>The authors demonstrated the neuroprotective ability of the Gami-Chunggan Formula via expression of DJ-1 and BDNF in the mouse model. Some signaling molecules such as Akt, ERK, CREB, and AMPK, were also found to enhance its neuroprotective activity.</td>
<td>Test symptomatic therapy [86]</td>
<td></td>
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<td><strong>6.</strong> Role of microtubule-associated protein 6 glycosylated with Gal-(β-1,3)-GalNAc in Parkinson's disease</td>
<td>In this study, the authors decipher the intrinsic role played by microtubule-associated protein 6 (MAP6) glycosylated with Gal-(β-1,3)-GalNAc in the pathogenesis of PD. Another potential therapeutic targets for the treatment of PD as well as reliably prognostic biomarkers were discovered in this study.</td>
<td>Gives more insight into the pathogenesis of PD with new potential therapeutic targeting site [66]</td>
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<td><strong>7.</strong> Comparison of the protective effects of Bee Venom extracts with varying PLA2</td>
<td>The authors uncovered the novel role of bee venom PLA2 in improving motor impairment in MPTP-induced mouse by activating regulatory T cells (Tregs) and suppressing neuroinflammation</td>
<td>Test symptomatic therapy and neuroinflammation [67]</td>
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<td><strong>compositions in a mouse model of Parkinson’s disease</strong></td>
<td>inflammatory Thelper (Th) 1 and Th17 cells. This could be a promising therapeutic agent in PD.</td>
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<td><strong>8. The phosphodiesterase 10 inhibitor papaverine (PAP) exerts anti-inflammatory and neuroprotective effects via the PKA signaling pathway in neuroinflammation and Parkinson’s disease mouse models</strong></td>
<td>The strong neuroprotective and anti-inflammatory properties of PAP proved it to be a potential candidate in the treatment of PD.</td>
<td>Test symptomatic therapy and neuroinflammation [69]</td>
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<td><strong>9. Neuroprotective effect of Schisandra chinensis on Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-induced Parkinsonian syndrome in C57BL/6 Mice</strong></td>
<td>According to the authors a high dose of the <em>S. chinensis</em> fruit extract exhibited strong ameliorative and neuroprotective potentials in MPTP intoxicated mouse. Thus, it could be a potential agent to be used in human PD alongside the conventional drug.</td>
<td>Test symptomatic therapy [87]</td>
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<td><strong>10. Embelin averts MPTP-induced dysfunction in mitochondrial bioenergetics and biogenesis via activation of SIRT1</strong></td>
<td>Embelin (10 mg/kg) also conferred protection in vivo in MPTP mouse model of PD, wherein, MPTP-induced loss of TH staining, reduced striatal dopamine and markers of mitochondrial biogenesis pathway were averted by embelin.</td>
<td>Test symptomatic therapy [69]</td>
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<td><strong>11. Nei-like 1 inhibition results in motor dysfunction and promotes inflammation in Parkinson’s disease mice model</strong></td>
<td>The authors were able to demonstrate the relevance of Nei-like factor (NEIF-1) in the pathogenesis of MPTP-induced PD. A decreased level in this factor predisposes to DA neuron death and motor dysfunction by enhancing glial cell activation and neuroinflammatory response. Hence, NEIF-1 could serve as a novel therapeutic target in PD treatment.</td>
<td>Gives more insight into the pathogenesis of PD with new potential therapeutic targeting site [70]</td>
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<td>12.</td>
<td>Novel fatty acid-binding protein 3 ligand inhibits dopaminergic neuronal death and improves motor and cognitive impairments in Parkinson's disease model mice</td>
<td>The authors discovered that MF8 treatment in MPTP-induced PD mouse did not only improved PD symptoms but also improved cognitive symptoms. The drug has proven to have advantage over the conventional L-DOPA that only reverses motor symptoms and as could likely replace it in future.</td>
<td>Test symptomatic therapy and PD-induced cognitive dysfunction</td>
<td>[71]</td>
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<td>13.</td>
<td>RIP1/RIP3/MLKL mediates dopaminergic neuron necroptosis in a mouse model of Parkinson disease</td>
<td>The authors discovered the pivotal role played by RIP1/RIP3/MLKL-mediated necroptosis is the pathogenesis of MPTP-induced PD. Therefore, downregulating the expression of this molecule can significantly improve the MPTP-induced PD symptoms. Targeting necroptosis pathway in future therapies may be a promising option</td>
<td>Gives more insight into the pathogenesis of PD with new potential therapeutic targeting site</td>
<td>[61]</td>
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<td>14.</td>
<td>A mouse model of 1-Methyl-4-Phenyl-1,2,3,6 Tetrahydropyridine (PTP)-induced Parkinson disease shows that 2-aminoquinoline targets JNK phosphorylation</td>
<td>The authors discovered the neuroprotective ability of 2-aminoquinoline in the MPTP mouse model of PD i.e., it improved motor deficiencies, regulated the Bax/Bcl-2 ratio by targeting p-JNK and inhibited MPP+ activated astrocyte apoptosis.</td>
<td>Test symptomatic therapy and gives more insight into the molecular pathways in PD pathogenesis</td>
<td>[88]</td>
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<td>15.</td>
<td>Neuroprotective effect of β-Lapachone in MPTP-induced Parkinson’s disease mouse model: involvement of astroglial</td>
<td>The authors demonstrated the neuroprotective potential of β-Lapachone in MPTP intoxicated mice via upregulation of the p-AMPK/Nrf2/HO-1 signaling pathways. This could be a novel target site for future therapy.</td>
<td>Test symptomatic therapy and gives more insight into the molecular pathways in PD pathogenesis</td>
<td>[89]</td>
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<td>p-AMPK/Nrf2/HO-1 signaling pathways</td>
<td>Schisandrin A ameliorates MPTP-induced Parkinson’s disease in a mouse model via regulation of brain autophagy</td>
<td>Schisandrin exerted its neuroprotective potentials by decreasing the markers of inflammation such as the IL-6, IL-1β, and TNF-α, increasing the antioxidant defenses and activation of autophagy related proteins including LC3-II, beclin1, parkin, and PINK1 and increased mTOR expression in MPTP induced mice. Schisandrin could serve as a therapeutic drug to ameliorate PD.</td>
<td>Test symptomatic therapy, demonstrate neuroinflammation and autophagy in PD</td>
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FIGURE 1. Structure, pharmacokinetics and pharmacodynamics of MPTP in the CNS. Upon injection of MPTP, it crosses the BBB and is converted to the toxic metabolite MPP+ by MAO-B. This metabolite is transported into the dopaminergic neuron by DAT. In the cytoplasm, MPP+ is further transported into vesicles by VMAT. Consequently, further concentration of MPP+ in the cytoplasm leads to a cascade of reactions that results in cell death. **Abbreviations**: BBB: blood-brain barrier; CNS: central nervous system; DAT: dopamine transporter; MAO-B: monoamine oxidase type B;
MPDP+: 1-methyl-4-phenyl-2, 3-dihydropyridine; MPP+: 1-methyl-4-phenylpyridinum; MPTP: 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; VMAT: vesicular monoamine transporter type 2.
FIGURE 2. Summary of the neurotoxic pathways of MPTP. MPP+ causes inhibition of COMPLEX-1 in the mitochondria which leads to the opening of transitional pores and then release of cytochrome C which causes a cascade of reactions that leads to cell death (Mitochondrial apoptotic pathway). Inhibition of COMPLEX 1 also causes an increase in ROS which leads to cell damage and eventually cell death (Oxidative stress pathway). Further excessive production of ROS leads to formation of AS monomers, and the monomers then form toxic oligomers which then inhibits UPS and ATGS and eventually leads to cell death (Alpha synuclein pathway). MPP+ causes excessive binding of glutamate at the synaptic cleft. This causes Ca influx that leads to excessive production of ROS, which damages the cell and cell death occurs finally (Glutamatergic pathway). MPP+ activates microglia cell and induces release of proinflammatory cytokines/enzymes leading to excessive ROS production, then cell damage and eventually cell death (Inflammation pathway). **Abbreviations:** APAF-1: apoptosis protease activating factor 1; AS: Alpha synuclein; ATGS: autophagy system; iNOS: Inducible nitric oxide synthase; LB: Lewy body; MPP+: 1-methyl-4-phenylpyridinium; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Mt: Mitochondria; ROS: Reactive oxygen species; UPS: ubiquitin-proteasome system; (-): downregulates; (+): upregulates; (↑): Activates.
FIGURE 3. Schematic diagram of the commonest MPTP dosing regimen and route.