Review

Promising drug targets and associated therapeutic interventions in Parkinson's disease

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Abstract

Parkinson's disease (PD) is one of the most debilitating brain diseases. Despite the availability of symptomatic treatments, response towards the health of PD patients remains scarce. To fulfil the medical needs of the PD patients, an efficacious and etiological treatment is required. In this review, we have compiled the information covering limitations of current therapeutic options in PD, novel drug targets for PD, and finally, the role of some critical beneficial natural products to control the progression of PD.

Key Words: dopamine; epigenetics; gene therapies; glutamate receptor; levodopa; molecular chaperones; monoamine oxidase B; mucuna alpha-synuclein; Parkinson's disease; striatum; substantia nigra

Introduction

To date, a number of molecules have been reported for their therapeutic potential against Parkinson's disease (PD) pathogenesis and some of them have been proven to be promising in the preclinical studies using laboratory animal models with more or less associated side effects (Duty and Jenner, 2011). For example, levodopa is the gold standard drug which provides symptomatic relief from the motor problem but exerts some side effects (Jankovic and Aguilar, 2008). Ubiquinone, PYM50028, and creatine are some other drugs that show limited efficacy for PD patients (Visanjiet al., 2008; Mo et al., 2017; Zhu et al., 2017b). The reasons for such unwanted results remain unclear, which shows our incomplete understanding of the PD pathogenesis. The complex etiology and overdependence on the toxin-induced model are responsible for the limited success in clinical trial designs in PD. Till now, no potential drug has been developed against PD dementia; however, the relation between cognitive decline, tau, and amyloid-β deposition as evident through the rising pathological, genetic and biochemical pieces of evidence, further opens up new possibilities for therapeutic interventions (Athauda and Foltynie, 2015). Two effective strategies can work to improve the situation of therapeutic development for PD. The first includes L-Dopa mediated specific therapies for the disease symptoms associated with PD; that is either passive or protective. The symptomatic treatments of locomotory impairments such as dyskinesia and non-motor symptoms-based therapy need to be explored more to fulfil the therapeutic strategy (Lawson et al., 2014; Charvin et al., 2018; Magrinelli et al., 2018; Carrarini et al., 2019). The other strategy is the involvement of safe and effective neuroprotective agents to retard the progression of the disease. As the patients undiagnosed at their preliminary stages of disease development, mostly face the risk of these problems, while diagnosis and treatment of the disease at the early stage may prevent the patients from developing additional PD features which do not respond to the current therapies. It is evident that the motor symptoms are easier to quantify than nonmotor symptoms; therefore, research has been mainly focused on preserving motor function in PD patients even though some of the nonmotor symptoms, specifically cognitive dysfunction, have been recognized which adversely impacts the quality of life (Duncan et al., 2014; Sarkar et al., 2016). Nonmotor symptoms remain largely obstinate to current interventions, and dopaminergic therapy does not satisfactorily rescue them (Duncan et al., 2014; Lawson et al., 2014).

The lack of resources, including appropriate model animals, well known biomarkers and limitation in clinical trial design restrict the complete understanding of PD pathogenesis, which in turn obstructs the development of its potential neuroprotective therapies (Bezard et al., 2013). Advancement and testing of effective disease-modifying treatments are facilitated by novel transgenic animal models, adaptive trial designs, and detection of potential serum, cerebrospinal fluid, and neuroimaging biomarkers (Emamzadeh and Surguchov, 2018; Merchant et al., 2019). The key protein in the pathogenesis of PD, such as α-synuclein (α-Syn), can be targeted to inhibit its accumulation either by blocking its aggregation directly or by antibody based therapy against α-Syn and improving its lysosomal degradation (Emamzadeh and Surguchov, 2018). In the previous studies of preclinical trials, targeting the inhibition and clearance of α-Syn has shown potential results in blocking the progression of PD (Dehay et al., 2015; Fields et al., 2019). Since 50% of PD patients share common symptoms concomitant with Alzheimer's disease (AD) pathology thus, targeting tau and amyloid-β might also give a new direction to retard the progression of cognitive dysfunctions (Valera et al., 2016). Disease-modifying therapies that are under exploration in

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AD might also benefit in PD; further investigation of existing therapeutic molecules might require more attention (Athauda and Foltynie, 2015).

L-Dopa discovery is the breakthrough in the symptomatic treatment of PD. It has been proven the most efficacious drug even after the three decades of extensive research in finding out a suitable drug for PD therapy (Tambasco et al., 2012). The drug is highly efficient in the initial years of treatment that the period is termed as L-Dopa "honeymoon." But the prolonged use of L-dopa imposes debilitating side effects and hence is not an adequate drug for long-term management of PD (Salat and Tolosa, 2013). Despite the initial outstanding results from dopaminergic therapy, effectiveness dampens in long-term treatment in PD patients. L-dopa therapy has limitations such as 1) Motor dysfunction in PD does not get improved; 2) it has various side effects like increased toxicity, inflammatory response, nausea, loss of appetite, hypotension; and (3) the disease progression does not halt through its usage (Barbeau, 1969; Jankovic and Aguilar, 2008; Dorszewska et al., 2014). In current scenario, therapeutic interventions, based on catechol-o-methyl transferase and monoamine oxidase B inhibitors, dopamine agonists, and invasive methods such as deep brain stimulation, are being used to reduce the shortcomings of L-dopa therapy. However, these therapies are quite helpful but are not entirely beneficial. Therefore, further study is required to confirm the efficacy of these treatments (Rascol et al., 2003; Jankovic and Aguilar, 2008).

To date, only symptomatic therapies with the minimum satisfactory effects are known against PD, and no treatment has been known to deaccelerate the disease progression (Jankovic and Aguilar, 2008). Symptomatic therapy causes severe physical disabilities in PD patients in the later stages of their lives (Goldenberg, 2008). The biochemical, pathological, and genetic evidences from different studies have suggested that α-Syn and tau are involved in the pathogenesis of PD and also can promote cognitive impairment in PD patients (Irwin et al., 2013). New targets are most likely to be identified with the discovery of these convergent pathways. The efficacy of PD treatments can be increased by involving a blend of agents targeting multiple pathways involved in disease pathogenesis. The new neuroprotective agents that are advised for long-term use should be evaluated for adverse side effects such as an increased inflammation and reduced immunosurveillance in the peripheral tissue. Thus, these parameters are expected to be monitored while following-up on the process of treatment (Kempuraj et al., 2016; Maiti et al., 2017). This article discusses novel therapeutic targets and associated strategies, along with phytochemicals based therapy for PD.

Search Strategy

PubMed, SCI, Web of Science, Scopus, Google Scholar were employed to conduct the literature search of original articles, review articles, mete analysis between year 1969 to 2020. The common search terms that were employed for this manuscript are novel targets in Parkinson's disease, novel signaling in Parkinson's disease, and novel molecular pathways of Parkinson's disease.

Potential Drug Targets for Parkinson's Disease

α-Syn

PD is a neurodegenerative disease that belongs to synucleinopathy, which gradually develops, and there is nocompetent method for the early diagnosis and treatment (Xu and Pu, 2016). Dopaminergic neurodegeneration and intracellular accumulation of insoluble α-Syn protein (encoded by the SNCA gene) as Lewy bodies and Lewy neuritis are the major pathological hallmarks of PD progression (Stefanis, 2012). The SNCA gene undergoes duplications, triplications, and point mutations (Konno et al., 2016). However, the specific mechanism of α-Syn in PD is yet to be understood. Oligomerization of α-Syn form toxic aggregates which propagate from one to other cell. Propagation of α-Syn oligomers damages certain brain part in PD patient (Xu and Pu, 2016). Four common ways have been documented so for to prevent the production of toxic effects of α-Syn, i.e., decreasing α-Syn aggregation, increasing its clearance, controlling its propagation, and stabilizing its existing circumstances (Lashuel et al., 2013; Zhang et al., 2018). A proteostasis has a central role in maintenance of the nervous system (Hetz and Glimcher, 2011).There are numerous factors involved in the production of neurotoxicity in synucleinopathies. For instant, the inflammatory protease caspase-1 proteolyze C-terminal of α-Syn which promotes aggregation of α-Syn *in vitro* and *in vivo* as well (Games et al., 2014). Caspase-1 inhibitor reduces α-Syn cleavage that limits its aggregation and ultimately provides neuroprotective effects in PD (Ganjam et al., 2019). The passive or active immunization approaches, or gene-silencing technologies might suppress the aggregation (Eisele et al., 2015).

The α-Syn aggregation has been reported to extend across the cell types and cell populations in brain (Lee et al., 2010; Brück et al., 2016). Two major cellular mechanisms have been reported in degradation of these toxic aggregate accumulations: autophagy and the ubiquitin-proteasome system (UPS). A few studies suggest that UPS might contribute to the degradation of misfolded proteins, indicating that its downregulation might enhance PD pathogenesis (Dennissen et al., 2012; Ciechanover and Kwon, 2015). Furthermore, it has been reported that the major risk factor for the development of neurodegenerative diseases, such as AD, Huntington's disease, and etc., is also associated with a progressive decline of the UPS and accumulation of toxic proteins (Maheshwari et al., 2014; McKinnon and Tabrizi, 2014; Singh et al., 2017, 2018a). Various studies have documented the development of powerful tools and models focusing on these two systems to scale-up the removal of toxic α-Syn. In the future, this might come out to be an efficient treatment for PD. Besides, plenty of researches are emphasizing on the strategies which uplift the clearance of pathogenic aggregates through innate and adaptive immunization, which suppress the proteotoxic mechanisms and inflammation induced by α-Syn (Reish and Standaert, 2015). The aggregation of the C-terminal domain truncated α-Syn (CTD-syn) can be suppressed by immunotherapy (Tran et al., 2014). Also, axonal and motor deficits can be rescued by blocking the formation of the CTD-Syn (Ulusoy et al., 2010; Games et al., 2014). Moreover, it is speculated that cell-to-cell propagation of α-Syn could be minimized using the antibodies which inhibit C-terminal truncation. Immunotherapies targeting CTD-syn, the nitration and oxidation of α-Syn, and enhancing aggregate clearance might have potential therapeutic approach utilized not only as agents that induce the degradation of aggregation proneα-Syn, but also as blockers of α-Syn oligomerization (Games et al., 2014). The mechanism involving a sufficient amount of antibodies reaching the brain and recognizing its intracellular target protein and subsequently promoting its intracellular toxicity is still not known. It has been noticed that the pathogenicity of α-Syn can be reduced by the small molecules which stabilize its physiological tetramer (Xu and Pu, 2016). The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is well known to regulate cell proliferation, differentiation, apoptosis, immune response, hematopoietic cell generation, and to share a variety of biological functions in tumorigenesis and neural development (Nicolas, 2013). Thus, cytokines such as interleukin, interferon, and epidermal growth factor may involve in protecting the nervous system through this pathway and provide new insights into the future therapy of PD (Himpe and Kooijman, 2009). α-Syn based PD therapy is beneficial for the PD patients as shown by randomized single-blinded phase 1 trial (Volc et

al., 2020). Reduce Lewy bodies' accumulation is found in PD patients that shows lesser aggregation of α-Syn (Teil et al., 2020).

Glutamate receptors

Ionotropic and metabotropic glutamate receptors potentially modulate neural transmission in basal ganglia. This ability of glutamate receptors may be utilized as possible targets for PD treatment (Crupi et al., 2019). In dopamine replacement therapy, the modulated activity of these receptors leads to the alleviation of primary motor symptoms of PD along with some side effects. Additionally, ligands antagonizing these receptors might reduce the progression of PD by delaying the neurodegenerative processes (Johnson et al., 2015). In preclinical PD models, N-methyl-D-aspartate receptors antagonist reversed the motor symptoms, levodopa-induced side effects along with neurodegeneration (Johnson et al., 2015). Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors show potential for neuroprotection, whereas its antagonist demonstrates effectiveness in treating levodopa-induced dyskinesias (Freudenberg et al., 2015). Metabotropic glutamate receptors (mGluRs) can regulate neurotransmission, and the studies reveal that its pharmacological modulation may hold even more potential for the treatment of PD (Niswender and Conn, 2010). In multiple animal models of PD, the antagonists of mGluR5, as well as activators of group II mGluRs and mGluR4 have been reported to show promising results (Conn et al., 2005; Johnson et al., 2009; Crupi et al., 2019; Zhang et al., 2019). These drugs not only treat motor dysfunctions, but they also protect against neurodegeneration. In conclusion, we can say that glutamate receptors can be promising drug targets for PD (Duty, 2010; Crupi et al., 2019). Therapeutic targeting of glutamate receptors slows down the processes of PD symptoms, as observed in the clinical trial study too (Finlay and Duty, 2014). Clinical research also shows that striatal metabotropic glutamate receptor type 5 can also be targeted for PD therapy (Vallano et al., 2013).

Molecular chaperones and autophagic pathways

The definitive pathological hallmark of PD is the development of Lewy bodies, which are intraneuronal protein aggregates found in the nigral neurons (Fields et al., 2019). The processes of cellular proteostasis become dysfunctional in both idiopathic and familial PD if any mutation or environmental agents hamper the normal functioning of molecular chaperones (Kalia et al., 2010; Lehtonen et al., 2019). This molecular chaperones and co-chaperones regulate the cellular proteostasis by balancing the folding and misfolding processes during redox imbalance (Kaliaet al., 2010; Niforou et al., 2014). The chaperone system corrects the misfolded proteins and contributes in proteostasis by eliminating them through its association with UPS and autophagy (Ciechanover and Kwon, 2017). Apart from their proteostasis role, some chaperone molecules also modulate cell death pathways (Dong and Cui, 2018). Heat shock protein (Hsp) 70, Hsp90, Hsp40, and Bcl-2-associated athanogene (BAG) family members such as BAG5, carboxyl terminus of Hsc70-interacting protein (CHIP), and Hsp70 interacting protein (Hip) play an essential role in the regulation of neuronal death by targeting the nigrostriatal pathway (Dimant et al., 2012). Thus, further study should be needed to target the different components of molecular chaperones to combat this progressive disease and to find an effective cure.

Autophagic pathways are significantly dysregulated in the PD brain. PD-related genes are also involved in the autophagic pathways that affect the disease phenotype. For the early diagnosis of PD, autophagic proteins might be considered as important biomarkers (Zhang et al., 2012). Oxidative stress and neuroinflammatory are the most commonly affected pathways during autophagic impairment. These two factors cause significant mitochondrial dysfunction that promotes the degeneration of dopaminergic neurons in substantia nigra pars compacta (He et al., 2020). For example, neuroinflammation along with oxidative stress is alleviated by valeric acid that protects the progression of this disease by modulating the autophagic pathways (Jayaraj et al., 2020). Mitophagy is a vital component of autophagy that selectively removes damaged mitochondria and promotes quality control (Ding et al., 2012). The identification of healthy and damaged mitochondria is very crucial, which is mediated by priming of the damaged one by the Parkin-Pink1 pathway or by the mitophagy receptors (Liu et al., 2019). For example, for the protection of dopaminergic neurons, mitophagy is regulated by one very important receptor called sigma-1 which prevents progressive neurodegeneration in PD by promoting mitophagy. The agonist (2-morpholin-4-ylethyl 1-phenylcyclohexane-1-carboxylate) of the sigma-1 receptor also exhibits a similar activity and prevents the PD progression. The knockdown model of the sigma-1 receptor shows the progressive death of dopaminergic neurons in SH-SY5Y DA cells. The knockdown of this receptor is also responsible for the reduced expression of some autophagic components like p-ubiquitin, TANK binding kinase 1, and Unc-51 like autophagy activating kinase 1. This further promotes the progression of PD. In the experimental model of PD, autophagic impairment leads to the microglial mediated degeneration of dopaminergic neurons by regulating the activation of NLRP3 inflammasome (Qin et al., 2020). In addition, the toxicity generated by aggregated α-Syn is also mediated via lysosomal pathways. The fibrillar α-Syn is very toxic inside the lysosome. Thus, prevention of the uptake of these aggregates by lysosomes might be a preventive therapy for PD (Guiney et al., 2020). Furthermore, lysosomal dysfunctions cause the impairment in autophagic processes in neuroblastoma SH-SY5Y cells (Nascimento et al., 2020). In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxicated PD model, the autophagic process was promoted by Ghrelin that protects the dopaminergic neuronal death by regulating the activity of α-Syn. Ghrelin also inhibits endoplasmic mediated apoptosis (Wang et al., 2020a). α-Syn clearance via autophagic activation is also seen in the PD rat model by fasudil (Yang et al., 2020b). The level of α-Syn is also ameliorated in the paraquat model of PD via autophagic activation mediated by Vasicinone that also protects the dopaminergic cells from mitochondrial damage (Huang et al., 2020). In mitochondrial Rho GTPase 1 neurons of PD, impaired autophagic process and dysfunctional interaction between endoplasmic reticulum and mitochondria were also observed (Berenguer-Escuder et al., 2020). In the mouse model of PD, disease symptoms appear after inflammasome activation as a result of autophagic impairment mediated by microglial cells (Cheng et al., 2020).

Synaptic vesicle glycoprotein 2c

Synaptic vesicles in nigrostriatal pathway function in two ways: packaging neurotransmitters required for neural-transmission and sequestering cytosolic dopamine. Abnormal function of synaptic vesicle glycoprotein 2c (SV2C) might impose the adverse impact on the cell (Goldstein et al., 2013; Dunn et al., 2017; Lohr et al., 2017). It was shown in mice model; the abnormal packaging and sequestration of dopamine were responsible for progressive neurodegeneration which enhanced the vulnerability towards dopaminergic toxicants (Taylor et al., 2014; Rai et al., 2018). Infantile Parkinsonism arises as a result of mutations in the vesicular monoamine transporter-2 forming gene, which causes enhanced expression of vesicular monoamine transporter-2 that is linked with decreased risk for PD (Brighina et al., 2013; Rilstone et al., 2013; Lohr and Miller, 2014). The primary reason for PD progression is abnormalities in the dopaminergic neurons, resulting in the impairment of the functioning of dopamine vesicles, which in turn is due to the genetic mutations taking place in other vesicular- proteins, such as α- synuclein,

synaptojanin and leucine-rich repeat kinase 2 (Cirnaru et al., 2014; Pifl et al., 2014; Hunn et al., 2015; Xiong et al., 2017; Hur et al., 2019). Novel mediators of vesicular function could offer additional advantages regarding disease pathogenesis caused by disrupted dopamine vesicles (Lohr et al., 2017). Proteins residing within synaptic vesicle glycoprotein 2 families are considered to regulate vesicular function positively in a different way. This regulation might happen probably by aiding in vesicular trafficking and exocytosis and further by interacting with synaptotagmin-1 or with other stabilizing stored transmitters (Harlow et al., 2013; Dunn et al., 2017; Rai et al., 2018). However, the complete understanding of each member of the SV2 family is yet to be known. However, studies reported that SV2A might be a specific pharmacological target for the antiepileptic levetiracetam (Lynch et al., 2004; Löscher et al., 2016; Bartholome et al., 2017). On the other hand, maximum expression of SV2C is found in the basal ganglia and mostly inside dopaminergic cells (Dardou et al., 2011; Dunn et al., 2017, 2019; Rai et al., 2018). However, PD risk due to excessive nicotine use was mediated by SV2C genetically as reported by the study (Hill-Burns et al., 2013).The sensitivity of the PD patients' towards L-DOPA can also be predicted by finding the mutation within the SV2C gene (Altmann et al., 2016). Therefore, SV2C might crucial in neuronal activity in the basal ganglia, although there is no direct link between SV2C and dopaminergic function (Dunn et al., 2017, 2019; Rai et al., 2018).

Lately, in a study by Dunn et al. (2017), the role of SV2C was described in dopamine neurotransmission and PD by confirming the expressions of SV2C on the vesicles of dopamine-producing neurons. It was also seen that reduction in the synaptic release of dopamine was caused by the genetic deletion of SV2C. This reduction in dopamine causes a decrease in motor activity. Moreover, SV2C respond against action of nicotine in SV2C knockout mice. Thus, SV2C is supposed to mediate the neuroprotective effects of nicotine. Ultimately, it was reported that PD patients and those mice which expressed mutated α-Syn specifically demonstrated disrupted expression of SV2C. Together, these studies emphasize that SV2C mediates the dopamine homeostasis and a potentially contributes to PD pathogenesis (Dunn et al., 2017, 2019; Rai et al., 2018). Finally, SV2C might be a novel and potential drug target for PD which should be targeted by the researchers.

Non-receptor tyrosine kinase Abelson

Non-receptor tyrosine kinase Abelson (c-Abl; also known as ABL1) is tyrosine kinase which is distributed in the cytoplasm and nucleus as well. Expression of c-Abl is found in most of the cells and is an integral part of protein interaction network and phosphorylation events (Hantschel and Superti-Furga, 2004; Lindholm et al., 2016). c-Abl also plays an important role in the regulation of cell growth and motility. In addition, the dynamics of cytoskeleton, receptor-mediated endocytosis, repair of DNA, cell survival, and autophagy processes are also regulated by the c-Abl (Hantschel and Superti-Furga, 2004; Lindholm et al., 2016). Normally c-Abl present in the cell in the inactive form and its activity is strongly regulated by intramolecular interactions as well as its binding to protein complexes, and linkage to membranes via an amino-terminal myristoyl group (Hantschel, 2012). c-Abl is activated by autophosphorylation and also by the action of other kinases like Lyn and Fyn kinases (Plattner et al., 1999). Studies showed that any injury in DNA or increased production of reactive oxidative species (ROS) during cell stress causes the activation of c-Abl that in turn, leads to cellular degeneration (Rojas et al., 2015).

Latest preclinical information reveals the protective role of c-Abl inhibitors in PD that encourages the application of these compounds should be tested in clinics as well (Lindholm et al., 2016; Wyse et al., 2016; Van Bulck et al., 2019). A small study shows the efficacy of c-Abl inhibitor Nilotinib in PD patients for 24 weeks (Pagan et al., 2016). However, a large-scale study will be required to validate the findings of Nilotinib in PD. It is observed that not all the c-Abl inhibitors have the ability to penetrate the blood-brain barrier, and the permeability might also change during the disease progression (Imam et al., 2013). Thus, for more promising results, the different routes for the delivery of these inhibitors must be considered, such as the intranasal application is being analyzed for the same. However, when the treatment of PD standardized using c-Abl inhibitors, the adverse reactions and side effects of it must be considered. p53-dependent impairment of autophagic processes was also seen in α-Syn linked activation of c-Abl (Karim et al., 2020). Clinical studies show that c-Abl is a potential target for PD treatment (Brahmachari et al., 2017). c-Abl might be a novel and effective therapeutic target that reduces PD progression (Imam et al., 2013; Abushouk et al., 2018).

GPR109A

GPR109A (also known as hydroxycarboxylic acid receptor 2, niacin receptor 1, HM74a in humans and PUMA-G in mice) is a G protein-coupled anti-inflammatory receptor. The highest levels of expression of GPR109A are found in macrophages along with neutrophils as compared to other human organs and tissues, and its anti-inflammatory role is well-established (Digby et al., 2012; Giri et al., 2019). The physiological agonist of GPR109A is beta-hydroxybutyrate (BHB). On the other hand, the level of BHB is not enough to show the anti-inflammatory response in the inflammatory conditions (Wakade et al., 2014). GPR109A shows a strong affinity towards niacin which acts as an agonist ofGPR109A and plays a vital role in suppressing the inflammatory conditions (Offermanns, 2006). Niacin showed potent anti-inflammatory activity through GPR109A (Giri et al., 2019). In PD, GPR109A mediates the inflammatory processes by microglia activation in the substantia nigra (Wakade et al., 2014). Even though GPR109A plays an important role in inflammation, their exact mechanism through microglia activation in PD is yet to be investigated (Giri et al., 2019). The upregulation of GPR109A is found in both macrophages and microglia which is a very good sign of its anti-inflammatory activity. Supplementation with niacin exhibits the ability to reduce the inflammation by inhibiting the active contribution of these activated microglia and macrophages (Giri et al., 2019). The nicotinamide adenine dinucleotide is derived from niacin which potentially affects the sleep-wake cycle through circadian rhythm and ultimately responsible for the oxidative pathways in mitochondria (Cantó et al., 2015; Yang and Sauve, 2016; Pehar et al., 2018). Therefore, abnormal sleep or low niacin reduces the nicotinamide adenine dinucleotide level (Wakade et al., 2014; Sancar and Brunner, 2014). Niacin acts through GPR109A but nicotinamide does not. On the other hand, niacin dose as a vitamin supplement is much less as compared to what is required to act on GPR109A as an anti-inflammatory mediator (Wakade et al., 2014). Interferon-gamma, a cytokine stimulates GPR109A in macrophages and signals a cascade of proinflammatory events (Schaub et al., 2001). On the contrary, in the gut, agonists of GPR109A suppress lipopolysaccharide (LPS)-induced inflammation via the nuclear factor-κB (NF-κB) pathway (Wakade et al., 2014). GPR109A plays an anti-inflammatory role in the retinal pigment epithelium (Martin et al., 2009). BHB is the physiological agent of GPR109A and is also utilized by neurons as an energy source. Against 1-methyl-4-phenylpyridinium (MPP^+) toxicity, BHP exhibited neuroprotective activity in mesencephalic neurons (Kashiwaya et al., 2000). The actual function of BHB in mitochondrial energy generation is independent of GPR109A. There is a strong need to explore the role of GPR109A in the Parkinsonian model and established a connection between them. Some clinical trials also showed convincing findings

associated with targeting GPR109A in PD (Wakade et al., 2014).

Metals

Metal homeostasis is crucial for the regular activity of CNS (Chen et al., 2016). Disturbance in the homeostasis of metals causes progressive neurodegeneration of the CNS (Aizenman and Mastroberardino, 2015). Impaired metal homeostasis is also seen in PD. For example, impaired regulation of copper, iron, and calcium has been seen in PD (Double et al., 2000; Zaichick et al., 2017; Bisaglia and Bubacco, 2020). These metals can also be targeted for effective PD therapy. The data from epidemiological studies suggested that cadmium exposure causes neurotoxicity and neurodegeneration in PD (Forcella et al., 2020). In the PD model, cadmium uptake was enhanced by α-Syn that causes neurotoxicity via apoptotic and oxidative stress-mediated pathways (Chong et al., 2017). Significant differences were seen at genome-wide alterations, morphology, and electrophysiology level in Manganese and MPTP induced idiopathic PD (Mythri et al., 2017). In the brain, an elevated level of Parkin and accumulation of iron is observed in transgenic mice that overexpress the divalent metal transporter 1 (Zhang et al., 2017). In the iron-induced unilateral model of PD, significant alterations were seen of tetrahydrobiopterin in the striatum (Aryal et al., 2014). In the mitochondria of the brain, protein aggregation was enhanced after an elevated level of magnesium, calcium, and ferric ion (Alleyne et al., 2012). Vinylic telluride protects the death of dopaminergic neurons in Manganese induced neurotoxicity (Avila et al., 2010). Similarly, 6-hydroxydopamine (6-OHDA) lesion-induced neurotoxicity was also observed as a result of the enhanced level of extracellular potassium ion in the subthalamic nucleus (Strauss et al., 2008). Elevated extracellular potassium is also seen in MPTP-induced neurotoxicity in the striatum (Hollinden et al., 1998).

Metal chelation therapy is a very effective strategy to manage PD progression. Selective chelation therapy of metals shows a favorable response in PD (Tosato et al., 2019). For example, CN128 is an iron chelator that inhibits the formation of the oxidized product of dopamine. Therefore, CN128 inhibits PD progression (Sun et al., 2020). In recent years, iron chelation therapy shows a robust therapeutic response against PD progression (Nunez and Chana-Cuevas, 2019). Commination of iron chelator and monoamine oxidase B inhibitor suggest synergistic and effective response for PD (Youdim, 2018). A review article published by Singh et al. (2019) suggested the therapeutic potential of iron chelators in PD and AD. In mild iron and α-Syn induced mouse model, behavioral deficits were rescued by deferiprone (Carboni et al., 2017). Deferiprone mediated iron chelation also shows a good response in phase II clinical trial for PD (Martin-Bastida et al., 2017).

Similar to iron, altered homeostasis is also overserved for calcium in PD (Chan et al., 2009). Calcium dysregulation causes severe pathological alterations that are ultimately responsible for cell death. Disruption in calcium homeostasis is also caused by α-Syn aggregation (Rcom-H'cheo-Gauthier et al., 2016; Leandrou et al., 2019). Calcium affects the ROS mediated neurodegeneration of dopaminergic neurons via the mitochondrial pathway. Mitochondria regulate the level of calcium spatiotemporally in various locations with neurons (Calì et al., 2012). An elevated level of calcium in mitochondria is responsible for the production of ROS. ROS changes the permeability of the membrane of mitochondria that ultimately results in cell death (Adam-Vizi and Starkov, 2010). Therefore, the calcium level might be targeted for effective PD therapy.

Gene therapy and gene editing

Gene therapy in both animals and humans shows convincing findings for PD treatment in which testing has been performed on both disease-modifying and non-disease modifying transgene levels (Axelsen and Woldbye, 2018). Growth derived neurotrophic factor, brain-derived neurotrophic factor, cerebral dopamine neurotrophic factor, and neurturin are some of the example disease-modifying transgene that slows down the PD progression at the preclinical level (Huttunen and Saarma, 2019). On the other hand, dopamine and gamma-aminobutyric acid synthesis are an example of non-disease modifying therapy for PD that also shows its effectiveness at both clinical and preclinical levels (Axelsen and Woldbye, 2018). Mutation in mitochondrial genes also responsible for the progression of the familial form of PD. Targeting these genes that lead to dysfunctional mitochondrial dynamics, reduced electron transport system activity, impaired mitochondrial permeability, and membrane potential might be a potential gene therapy for PD. Parkin and Pink1 are the crucial examples of mitochondrial genes for which gene therapy might show convincing results (Choong and Mochizuki, 2017). α-Syn and mitochondrial apoptotic associated gene also can be tested for PD gene therapy (Valdés and Schneider, 2016). Brain activity is reorganized by gene therapy that leads to reduced PD symptoms (Niethammer et al., 2018). Enhanced glucocerebrosidase activity and improved α-Syn clearance observed by gene therapy in the non-human primate model (Pignataro et al., 2018). Human gene therapy is quite successful in PD patients. In these PD patients, neuromodulation, enhanced expression of different vital growth factors, and dopamine activity were found by gene therapy (Hitti et al., 2019). α-Syn accumulation is also linked with a reduced concentration of miR-7 in clinical studies. The gene therapy that replaces the miR-7 activity also slows down the progression of PD (Titze-de-Almeida and Titze-de-Almeida, 2018). Thus, it can be concluded that gene therapy for PD might be beneficial for PD patients and offers a potential target for the treatment.

Gene editing has recently emerged as a novel therapy and efficient target in the treatment of human diseases, including PD (Li et al., 2020a). Clustered regularly interspaced short palindromic repeats (CRISPR) system shows a revolution in the field of biomedical research that transformed the thinking of researchers about treatment processes (Deshpande et al., 2015). The CRISPR system is very effective in identifying gene-gene interaction, novel pathways in PD research (Luo et al., 2019). CRISPR-Cas9 Gene Editing System reduced the oxidative stress and neuroinflammatory load and reduces the speed of PD progression in a significant way (Maiti et al., 2017; Caobi et al., 2020). In Gaucher disease modelling, the CRISPR-Cas9 system shows a positive response (Pavan et al., 2020). CRISPR/Cas9 mediated gene editing provides a powerful tool to visualize and trace the abnormalities in dopaminergic neurons and also may be helpful in the generation of knockout cell lines to explore disease in depth (Überbacher et al., 2019). Therefore, along with gene therapy, gene editing might also be a potential tool for PD therapy.

Multi-target approach for PD

Despite targeting one component, a multi-target approach is more beneficial for any treatment process with certain limitations (Talevi, 2015). For example, the multi-receptor approach for the sigma receptor shows the efficient outcome for PD and other neurodegenerative diseases (Brimson et al., 2020). In PD, modulation of misfolded α-Syn was achieved by using mesenchymal stem cells with the help of a multi-target disease-modifying approach (Shin et al., 2020). For the prediction of the effectiveness of monoamine oxidase A and B drug, the multi-target approach is very useful for PD (Concu et al., 2020). Dopaminergic receptors and human monoamine oxidase both are targeted by Bromophenols for the potential PD treatment (Paudel et al., 2020). Deep brain stimulation by a multi-target approach is also vital for PD treatment (Parker et al., 2020). Dual-acting monoamine oxidase and acetylcholinesterase inhibitors might also be employed as a

multi-target approach for PD (Mathew et al., 2019). Targeting whole adenosine signaling for PD is also a part of the multi-target approach (Nazario et al., 2017). The monoaminergic and histaminergic system both can also be targeted by the multi-target approach for PD (Di Giovanni et al., 2016). Therefore, a multi-target approach is also can be employed for the potential treatment of PD.

Transcription factor

Many transcription factors such as NF-κB, nuclear factor erythroid 2-related factor 2 (Nrf2), transcription factor EB (TFEB), etc. are involved in the pathogenesis of PD. These factors can also be targeted for an effective treatment for PD. Multiple pieces of evidence have suggested the role of these transcription factors in PD progression and treatment. Some recent studies signify the pivotal role of these transcription factors. An *in vitro* study shows the importance of tripartite motif 8 (TRIM8) in PD. This study demonstrated that 20 μM MPP^+ was well enough to induce the PD pathology in PC12 cells. The regulation of TRIM8 was performed by lentiviruses. The expression of TRIM8 was induced by the MPP^+. MPP^+ is responsible for the upregulation of proinflammatory cytokines like IL-1β and TNF-α through the NF-κB pathway. TRIM8 inhibits the activation of NF-κB through IκBα ubiquitination. Thus, the upregulation of the IL-1β and TNF-α was inhibited by TRIM8 through suppression of NF-κB activation. Therefore, TRIM8 silencing can be utilized to prevent PD pathogenesis (Pang et al., 2020). Mucuna pruriens (Mp) show anti-inflammatory activity by inhibiting the activation and nuclear translocation of NF-κB in the MPTP-induced Parkinsonian mouse model (Rai et al., 2017). Similarly, Tinospora cordifolia suppresses the neuroinflammatory processes by inhibiting the activity of NF-κB (Birla et al., 2019). Ursolic acid and Chlorogenic acid also exert its neuroprotective potential by inhibiting the NF-κB pathway in PD (Singh et al., 2018b; Rai et al., 2019b).

A study showed that ferulic acid alleviates PD pathology by ERK1/2-dependent Nrf2 Activation in both MPTP intoxicated mouse model and SH-SY5Y cells. Biochemical abnormalities were considerably improved by FA treatment in both *in vitro* and *in vivo* models. Thus, FA exerts its neuroprotective activity through the ERK1/2/Nrf2 pathway (Li et al., 2020b). Similarly, Oxidative Stress and inflammatory response were suppressed by Bruceine D in PD which enhances the activation of Nrf2 (Yang et al., 2020a).

Activation of TFEB was induced by the derivatives of curcumin *in vitro*. Curcumin derivatives prevented the neurotoxicity induced by MPP^+. A further detailed study will be needed to confirm the activity of these curcumin derivatives (Wang et al., 2020b). TFEB-mediated autophagy shows a favorable response in the Parkinsonian mouse model (Decressac et al., 2013; Torra et al., 2018). The pharmacological enhancement of TFEB prevents the PD progression in 6-OHDA/ascorbic acid (6-OHDA/AA) induced PD model. Thus, pharmacological enhancement of TFEB might be utilized as novel strategies to combat this disease (Zhuang et al., 2020). Transcription factors might also be used as an efficient marker for cell death in PD progression (Wang et al., 2017). In PD, neurotrophic factors based clinical trial also shows an interesting result that might be utilized to fill a gap between basic science and clinical studies (Chmielarz and Saarma, 2020). In the animal model of PD, the activity of several transcription factors like Nurr1, Otx2, Foxa1/2, and Lmx1a/b has been tested. These transcription factors might also be targeted for the treatment of PD (Blaudin de Thé et al., 2016). Hematopoietic transcription factor GATA-1 also regulates the activity of α-Syn and affect disease progression. GATA-1 might also be targeted for the PD treatment (Scherzer et al., 2008). **Table 1** shows the novel molecular pathways as promising targets for PD treatment.

Table 1 | The novel molecular pathways as promising targets for PD treatment

Target molecular pathway	Significance	Reference
Mitochondrial calcium pathway	Mitochondrial dysfunction responsible for the overload of calcium (Ca^{2+}) inside dopaminergic neurons. This overload of Ca^{2+} generating severe oxidative stress. Thus, any agent that effectively targets these mitochondrial calcium pathways or buffering its activity might have the potential to inhibit the progressive neurodegeneration in PD.	Lee et al. (2018); Jung et al. (2019); Zhao et al. (2019); Ricke et al. (2020)
Wnt/beta-catenin pathway	Wnt/beta-catenin pathway offers a potential target in PD. Various agents' exhibits the therapeutic activity by targeting these pathways. Thus, this pathway has the ability to inhibit the progression of PD.	Yang et al. (2018); Cao et al. (2019); Mishra et al. (2019); Adusumilli et al. (2020); Gong et al. (2020); Jiang et al. (2020); Li et al. (2020c); Yue et al. (2020); Zhang et al. (2020)
Akt/Nrf2/Erk/glutathione pathway	Akt/Nrf2/Erk/glutathione pathway also plays very pivotal role and presents a novel targets for PD treatment.	Gunjima et al. (2014); Rai et al. (2019a)
JAK-STAT signaling pathway	Various pharmacological agents, herbal plants, isolated compounds shows potent Anti-parkinsonian activity through JAK-STAT signaling pathway. Therefore, this pathway might be a novel one for PD.	Qin et al. (2016); Zhu et al. (2017a); Porro et al. (2019)
PTEN/AKT/mTOR signaling pathway	This pathway also has potential to combat with PD progression. Targeting this pathway might have promising response as suggested by several researchers.	Li et al. (2018); Wang et al. (2018); Ge et al. (2019); Ba et al. (2020); Zhao et al. (2020)

Akt: Protein kinase B; Erk: extracellular signal-regulated kinase; JAK/STAT: Janus kinase/signal transducer and activator of transcription; mTOR: mammalian target of rapamycin; Nrf2: nuclear factor E2-related factor 2; PD: Parkinson's disease; PTEN: phosphatase and tensin homolog.

Conclusion

Multiple drug targets have been identified recently, which can be utilized to treat PD. α-Syn, glutamate receptors, molecular chaperones, SV2C, c-Abl, GPR109A, and transcription factors are some of the examples of novel drug targets in PD. A broader level study is needed to confirm the efficiency of these drug targets in PD. Autophagy mediated pathways might also be targeted for effective PD treatment. Gene therapy, gene editing, and various metal chelators also exhibit potent therapeutic activity and offer novel drug targets for PD. Also, a multi-target response shows better efficiency for the treatment of PD.

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