Experimental and Molecular Pathology 129 (2022) 104846

Contents lists available at ScienceDirect

Experimental and Molecular Pathology

journal homepage: www.elsevier.com/locate/yexmp

Review

The PI3K-AKT pathway: A plausible therapeutic target in Parkinson's disease

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ARTICLE INFO

Keywords:
Neurodegeneration
Signaling pathway
Parkinsonism
PI3K
AKT

ABSTRACT

Parkinson's disease is a common progressive and multifactorial neurodegenerative disease, characterized by the loss of midbrain dopaminergic neurons. Numerous pathological processes including, inflammation, oxidative stress, mitochondrial dysfunction, neurotransmitter imbalance, and apoptosis as well as genetic factors may lead to neuronal degeneration. With the emergence of aging population, the health problem and economic burden caused by PD also increase. Phosphatidylinositol 3-kinases-protein kinase B (PI3K-AKT) signaling pathway regulates signal transduction and biological processes such as cell proliferation, apoptosis and metabolism. According to reports, it regulates neurotoxicity and mediates the survival of neurons. Accumulating evidences indicate that some natural products can play a neuroprotective role by activating PI3K-AKT pathway, providing an effective resource for the discovery of potential therapeutic drugs. The current review provides an overview of the PI3K-AKT signaling pathway and review the relationship between this signaling pathway and PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by gradual loss of neurons in the region of substantia nigra pars compacta (SNpc) with simultaneous dopamine loss from the striatum leading to motor imbalance (Varshney et al., 2019; Garabadu and Agrawal, 2020). According to estimates, the frequency of PD will increase as the population ages and the mortality risk for PD patients has risen by 1.5–2.2 times (Macleod et al., 2014; Ng, 2018). We discovered that the bulk of PD cases are sporadic, and the precise pathomechanics of PD is still unknown. Although there has been a lot of study on PD for decades, there are currently no effective treatments other than those that temporarily relieve symptoms, making the management of PD more challenging than it first appears (Chen et al., 2017). Several physiological processes, such as mitochondrial malfunction, oxidative stress, and abnormal protein folding, have been posited in the onset and progression of PD (Maries et al., 2003). Scientists have often proposed theories about the pathophysiology of PD, such as mitochondrial damage, excitatory amino acid toxicity, inflammatory response, increased reactive oxygen species (ROS) generation, activation of associated caspase pathways, and aberrant synuclein deposition. The majority of the pathogenic variables, meanwhile, are still under investigation. The aberrant accumulation of fibrillation and α-synuclein is currently thought to be the primary cause of the series of degenerative events in PD(Omura et al., 2013; Gorelenkova Miller et al., 2016; Campolo et al., 2017). In recent years, neurodegenerative disorders (NDs) have gained attention as a major public health issue (Garabadu et al., 2019). Numerous signaling pathways are involved in the therapy of NDs. Recently, PI3K-AKT has also received considerable research attention for its role in central nervous system physiological processes such as neurogenesis, autophagy, neuronal proliferation and differentiation, and synaptic plasticity (Matsuda et al., 2019). In addition, research has demonstrated that PI3K-AKT is one of the key pathways important in the management of various brain disorders (Hevner, 2015; Rai et al., 2019).

The PI3K-AKT pathway is an intracellular signaling system that, in response to external cues, encourages metabolism, proliferation, cell survival, growth, and angiogenesis. Interestingly, the role of PI3K-AKT has been viewed in a variety of ways. For example, PI3K-AKT mediates growth factor signals during organismal growth and crucial cellular activities including glucose homeostasis, lipid metabolism, protein synthesis, and cell proliferation and survival. Through controlling cell survival, growth, cardiac contractility, apoptosis, and even the transcription of related genes, PI3K-AKT is also involved in controlling the occurrence, progression, and pathological formation of cardiac fibrosis (Abeyrathna and Su, 2015; Qin et al., 2021a, 2021b). Furthermore, many natural compounds have been shown to protect dopaminergic

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https://doi.org/10.1016/j.yexmp.2022.104846
Received 1 September 2022; Received in revised form 14 November 2022; Accepted 19 November 2022
Available online 24 November 2022

neurons, hippocampal neurons, and cortical neurons, and suppress the activation of microglia *via* the PI3K-AKT signaling pathway, which may help with the prevention and treatment of like Alzheimer's disease (AD) and PD (Garabadu and Verma, 2019; Long et al., 2021). Therefore, in this review, the authors discuss the possible role of the PI3K-AKT pathway, as a therapeutic target in the treatment and management of PD.

2. Methods

Relevant studies were identified through electronic searches of Pubmed and Google scholar. The search used the terms "PI3K" "AKT" or "PI3K-AKT" paired with "Parkinson" "dopamine" "oxidative stress" "apoptosis" "mitochondrial dysfunction".In addition, we searched the bibliographies of relevant studies and reviews between 2000 and 2022 for articles in English.

2.1. AKT: The central site of the pathway

One of the most significant effector kinases found downstream of PI3K and at the center of the PI3K-AKT signal pathway is Protein Kinase B (PKB), a serine/threonine kinase. AKT1/PKBα, AKT2/PKBβ, and AKT3/PKBγ are three highly similar subtypes of AKT that are encoded by distinct genes. Each isoform has a conserved central segment, a plekstrin homology (PH) domain at the N-terminus, and a regulatory domain at the C-terminus (Brazil et al., 2004). The PH domain mediates membrane translocation during AKT activation, and its loss or mutation reduces AKT activity. AKT1-Thr308, AKT2-Thr309, and AKT3-Thr305, the required phosphorylation site for AKT activation, are located in the catalytic domain's structure together with an ATP binding site (Linnerth-Petrik et al., 2016). Additionally, a variety of external signals, including growth hormones, cytokines, oncogenes, and cell stress conditions, activate AKT kinase (Sivertsen et al., 2006; Manning and Cantley, 2007). The wide network of cellular proteins that the phosphorylated AKT influences *via* PI3K result in a variety of cellular consequences (Brazil et al., 2004; Missiroli et al., 2009; Payrastre and Cocco, 2015). AKT is found in the cytosol prior to activation, and upon cellular stimulation (such as EPO/EPOR contact and PI3K activation), it is moved into the plasma membrane where it attaches to PI (3,4,5) P3. Engagement with PI (3,4,5) P3 alters AKT's conformation, resulting in the development of phosphorylation sites (certain Ser/Thr residues) that, when phosphorylated, activate AKT signaling (Myklebust et al., 2002; Bouscary et al., 2003; Kadri et al., 2005). The three AKT subtypes are also very similar, and they all exert different physiological effects. AKT1 is widely distributed throughout the body's tissues and is primarily responsible for cell growth, proliferation, angiogenesis, and tumor cell invasion (Linnerth-Petrik et al., 2016). AKT2, which is found in skeletal muscle and adipose tissue of mammals, is known to play a role in cell growth and proliferation as well as glucose homeostasis (Garofalo et al., 2003). Also, AKT3 is essential for brain growth and the survival of malignant glioma cells, although very little is known about it (Ghoneum and Said, 2019).

2.2. PI3K: The key component of the pathway

An important component in the route upstream of the PI3K-AKT signaling cascade is the family of intracellular lipid kinases known as PI3Ks. Three subunits make up the PI3K family of plasma membrane-associated lipid kinases: the p85 regulatory subunit, the p55 regulatory subunit, and the p110 catalytic subunit (Donahue et al., 2012). PI3K is classified into three classes: classes I, II, and III, based on the variations in their structural makeup and particular substrates (Katso et al., 2001; Engelman et al., 2006). Class I PI3Ks were divided into classes IA and IB PI3Ks. A heterodimer of the catalytic subunit p110 and the regulatory subunit p58 makes up class IA PI3K (Yuan and Cantley, 2008). However, based on how they are regulated, class I isoforms are further divided into class IA (PI3K, PI3K, and PI3K) and class IB (PI3K) (Thorpe et al., 2015). Class IA is made up of the regulatory subunits p85α, β, c, and the catalytic subunits p110α, β, δ (Pacold et al., 2000). Class IB is made up of the regulatory isoforms p101 or p87 and the catalytic subunit p110γ. The two kinases' methods of activation are different, which is where the discrepancies lie. When external ligands connect to a transmembrane glycoprotein receptor tyrosine kinase (RTK) with enzyme activity, PI3K α, β and δ are activated, whereas PI3Kγ is activated by G protein-coupled receptors (GPCRs) and Ras family GTP enzymes (Dobbin and Landen, 2013). There are three class II isoforms, designated as PI3KC2α, 2β, and 2γ, which may attach to membranes on their own and require additional activation signals. Vacuolar protein sorting 34 (VPS34), the only class III PI3K, is important for membrane traffic from the plasma membrane to early endosomes (Sugiyama et al., 2019).

2.3. Regulation of PI3K-AKT signaling pathway

The PI3K-AKT pathway appears to be a key player in mediating neuronal survival in a range of situations. Several signaling cascades, such as the Ras-mitogen-activated protein kinase (MAPK), the cAMP/protein kinase A (PKA), and PI3K-AKT pathways, are triggered by trophic nutrients such as NGF, insulin-like growth factor I, or BDNF (Schlessinger, 2000). The survival factors activate PI3K recruitment to the region of the plasma membrane by attaching to their corresponding tyrosine kinase receptors (Vanhaesebroeck and Alessi, 2000). Through its SH2 domain, the regulatory component P85 interacts with the active receptor's phosphorylated tyrosine residue. The p110 catalytic subunit is then added to create a fully functional PI3K enzyme. Additionally, the P110 subunit as well as other cohesive molecules like Ras GTP and the insulin receptor substrate could be recruited independently of p85 (IRS). Moreover, G subunit activation could activate PI3k's Src-dependent integrin signal transduction. The second messenger phosphorylated from phosphatidylinositol (4,5)-disphosphate (PIP2) by P110 recruits inactive AKT and PDK1 from the cytoplasm to the cell membrane through their association with the signal protein AKT and phosphatidylinositol dependent protein kinase 1 (PDK1) containing PH domain, Phosphatidylinositol (3,4,5)- trisphosphate (PIP3) (Altomare and Testa, 2005; Wei et al., 2019).

In response to the upstream signal, PI3K-AKT phosphorylates or assembles complexes for a variety of downstream molecules, including members of the FoxO family, GSK-3, mTOR, and actin-related protein (Mirdamadi et al., 2017; Matsuo et al., 2018). PI3K-AKT signal transduction's primary downstream target, mTOR, is also a crucial regulator of cellular metabolism. Furthermore, Bcl-2 family members, the Bax protein, and the Bim protein all exhibit negative regulation of their production or activity by AKT. Through its influence on transcription factors like FOXO and p53, AKT also reduces the production of BH3-only proteins. It's interesting to note that protein phosphatases 2 A (PP2A) and PH domain and leucine-rich repeat protein phosphatase (PHLPP) similarly function as negative regulators, dephosphorylating AKT at Ser473 and Thr308 respectively (Bertacchini et al., 2015).

2.4. PI3K-AKT pathway in neurodegeneration

It has long been understood that aging is a collective process of damage accumulation that causes noticeable disruption of numerous cellular and molecular processes, which in turn results in a variety of chronic illnesses like AD, multiple sclerosis, PD, atherosclerosis, and many others (Adami et al., 2014; Caulfield et al., 2014; Ikehara and Li, 2014). Pharmacological treatments of many NDs like AD, PD, epilepsy, and MS halt the progression of the disease and are limited to damage restriction, these treatments are not sufficient to reverse the consequences or, as a result, heal the ill (Jha et al., 2015). Several roles of PI3K-AKT in neurodegeneration have been seen, which are explained below.

In AD, PI3K-PDK1 dominates the process of phosphorylating the Tau

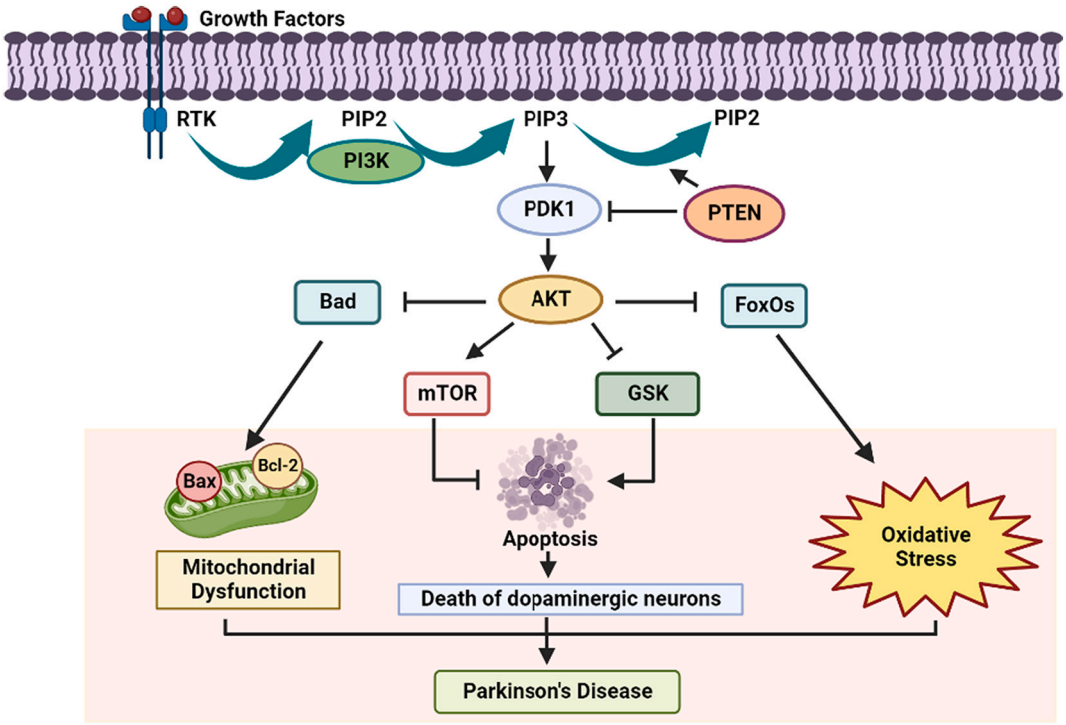

Fig. 1. The relationship between PI3K-AKT signaling pathway and PD.

protein at Tr212 and Ser214, which is mediated by AKT. AKT and PDK1, which has a PH domain, colocalize as a result of elevated amounts of PIP3, the second messenger in the PI3K pathway, stimulating kinase-mediated phosphorylation (Howes et al., 2003). AKT is induced by activated PI3K, which also phosphorylates and inhibits GSK-3β (a multifunctional serine/threonine protein kinase that plays a significant role in increasing Tau phosphorylation; Ksiezak-Reding et al., 2003). Another role of PI3K-AKT in neurodegeneration is seen in HD. In early HD, abnormal muscle twitches such as finger flexion and extension, head nodding, and facial twitching are detected. These movements are followed by matching psychological symptoms, such as depressive mood disorder and varying degrees of personality alterations(Ribeiro et al., 2014). Studies have demonstrated that BDNF, which is essential for the survival and development of neurons, can bind to tropomyosin receptor kinase B (Trkb) and activate the PI3K-AKT pathway, thereby defending neurons and avoiding the onset of HD (Silva et al., 2015). Additionally, HD neurons significantly phosphorylated the Tau protein, which is a pathogenic aspect of HD (Fernández-Nogales et al., 2014). Studies have demonstrated that the PI3K-AKT pathway regulates GSK-3β, which is downstream ofPI3K-AKT, in a manner that is necessary for the hyper-phosphorylation of the Tau protein. The above findings suggest that HD occurrence and progression are influenced by PI3K-AKT signaling, which also controls Tau protein hyperphosphorylation through the downstream component GSK-3β (L'Episcopo et al., 2016). These findings very well emphasize the vital role of the PI3K-AKT signaling pathway in neurodegeneration. Therefore, the potential of PI3K-AKT signaling as a promising target in the treatment of PD has been discussed further.

2.5. PI3K-AKT Pathway in Parkinson's disease

For decades, there has been research on PD, but drugs for successfully inhibiting or reversing the development of this disorder remain an assumption. Researchers have discovered that AKT and phosphorylated AKT are significantly decreased in the SNpc of PD patients (Luo et al., 2019). GSK-3 is broadly expressed in the central nervous system, but unusually in PD (Zhang et al., 2016). Moreover, during the pathogenesis of PD, activation of GSK-3 increases caspase-3 content in the dopaminergic nerve, resulting in the apoptosis of dopaminergic neurons. Experiments revealed that AKT may inhibit GSK-3 activity by phosphorylating Ser21 of GSK-3α or Ser9 of GSK-3β (Yang et al., 2018). Noteworthy, the activation of PI3K-AKT pathway promotes the survival and development of dopamine neurons by suppressing apoptosis. PI3K-AKT pathwaymodulates apoptosis by inhibiting Bad (Bcl2-antagonist of cell death). Furthermore, PTEN knockout contributes to neuroprotection and the fast development of dopaminergic neurons (Wang et al., 2017). Also, oxidative stress leads to neuronal cell death and apoptosis and contributes to the development of PD. The PI3K-AKT pathway regulates oxidative stress by influencing molecular targets like GSK-3, mTOR, and FoxO3a. Reduced mTOR activity may lead to neurodegeneration. Due to the disruption of the PI3K/AKT/FoxO3a pathway in the case of aberrant Parkin gene expression, oxidative stress becomes unbalanced and results in PD (Gong et al., 2018). The relationship between PI3K-AKT pathway and PD is represented in Fig. 1.

Previous studies conducted in cellular and animal models of PD provide evidence for the suggested role of the PI3K-AKT pathway as a therapeutic target in the management of PD. Research has reported that dihydroartemisinin (artemisinin derivative) significantly inhibited LPS-induced inflammation and attenuated LPS-induced behavioral and memory disorders in C57BL6 mice by inhibiting the PI3K-AKT pathway. This suggests the possible role of the PI3K/AKT pathway in neuroinflammation-associated disorders like AD and PD (Gao et al., 2020). Moreover, the findings of an *in vitro* experiment suggested that the activation of the PI3K-AKT pathway is involved in the protective effect of puerarin against MPP^+-induced neuroblastoma SH-SY5Y cell death through inhibiting nuclear p53 accumulation and subsequently caspase-3-dependent programmed cell death (Zhu et al., 2012). Recently, various research has been conducted to explore the relationship between PI3K-AKT pathway and PD. A study demonstrated that miltirone attenuated the reduction in cell viability, ROS production, apoptosis, and increase of caspase-3 activity in MPP^+- induced cell model of PD *via* regulating the PI3K-AKT pathway (Feng and Xi, 2022). Another study suggested that electroacupuncture increased the TH level in serum and SNpc as well as improved the behavioral performance of rotenone-induced mice by up-regulating the activity of GLP-1R/PI3K/

Table 1
Various *in vivo* and *in vitro* studies which investigated the role of PI3K-AKT signaling pathway in PD.

S. No.	Name of Compound/ formulation (Dose used)	Site of administration with the agent used for disease induction	Animal used or Cell culture	Major Outcomes	Ref.
1.	Rifampicin (100 μM)	Cells were treated with 10 μM rotenone	SH-SY5Y cells	Increased cell viability, and phosphorylation of CREB, AKT, and GSK-3β	(Wu et al., 2018a)
2.	*In-vitro* Stellettin B (0.1-100 nM)	Cells were treated with 20 μM 6-OHDA	SH-SY5Y cells	Reduced cell death, reversed downregulation of phospho-Akt, increased SOD activity and HO-1 expression	(Feng et al., 2019)
	In-vivo Stellettin B (1 nM)	Zebrafish larvae were treated with 250 μM 6-OHDA	Zebrafish	Significantly increased TH protein expression	
3.	N-propargylcaffeamide (15 mg/kg; p.o.)	Mice were administered with MPTP (25 mg/kg; i.p.)	Male C57BL/6 N mice	Improved motor function, enhanced the survival of dopaminergic neurons	(Luo et al., 2018)
4.	Low intensity pulsed ultrasound [1 MHz]	Cells were treated with MPP^+ (0.5 mM)	PC12 cells	Inhibited mitochondrial dysfunction and apoptosis	(Zhao et al., 2017)
5.	*In-vivo* Vildagliptin (30 or 50 mg/kg, p.o)	Mice were injected with MPTP (30 mg/kg; i.p.)	Male C57BL/6 mice	Improved motor coordination, alleviated the reduction in TH-positive cells, prevented apoptosis	(Pariyar et al., 2022)
	In-vitro Vildagliptin (5 or 10 μM)	Cells were treated with 200 μM MPP+	SH-SY5Y cells	Inhibited autophagy	
6.	*In-vivo* Echinocystic acid (5 mg/kg; i.g.)	Mice were injected with MPTP (30 mg/kg/day; i.p.)	Male C57BL6 mice	Improved locomotor activity and loss of dopaminergic neurons	(He et al., 2022)
7.	BNN-20 (100 mg/kg; i.p.)	Intercossed weaver heterozygous mice with NGL homozygous mice	Weaver mice both male and female	Increased TH level, luciferase expression and reduced total MDA	(Botsakis et al., 2017)
8.	Acacetin (0.5-10 μM)	Cells were exposed to 200 μM of 6-OHDA	SH-SY5Y cells	Decreased ROS intensity, increased MMP intensity, decreased the cleavage of caspase-9, caspase-3, and PARP	(Kim et al., 2017)
9.	SKP-SC-CM (skin-derived precursors differentiated into Schwann cells)	Cells were treated with 50 μM 6-OHDA	SH-SY5Y cells	Attenuated cytotoxicity and downregulated autophagy, increased ratio of p-mTOR/ mTOR	(Yan et al., 2022)
10.	THIF (2.5–50 μM)	Cells were incubated with 200 μM 6-OHDA	SH-SY5Y cells	Inhibited LDH release, decreased MDA activity and Bcl-2 levels, increased SOD, CAT, Bax, and GSH levels	(Ko et al., 2019)
11.	*In-vivo* Platelet-derived growth factor (PDGF)-BB (50 ng/day; i.c.v.)	Mice were injected with 30 mg/kg MPTP (i.p.)	Pregnant C57BL/6 J mice	Reserved dopaminergic neurons and increased the TH^+ nerve fibers	(Chen et al., 2021a)
	In-vitro Platelet-derived growth factor (50 ng/mL)	Cells were exposed to 250 μM MPP^+	SH-SY5Y cells	Promoted TH expression	
12.	Baicalin (10-100 μM)	Cells were treated with 6-OHDA (10–200 μM)	PC12 cells	Significantly increased cell viability, down-regulated miR-192-5p expression	(Kang et al., 2019)
13.	Tetrahedral framework nucleic acids (62.5, 125, or 250 nM)	PC12 cells were exposed to MPTP (250, 375, 500, or 625 μM)	PC12 cells	Decreased ROS and α-synuclein levels, increased Bax and caspase-3 while decreased Bcl-2	(Cui et al., 2019)
14.	AM1241 (0.75-12 mg/kg, i.p.)	Animals received MPTP (30 mg/kg; i.p.)	Male C57BL/6 N mice	Reversed motor deficits, increased dopamine and serotonin levels	(Shi et al., 2017)
15.	BNN-20 (100 mg/kg, i.p.)	Intercossed weaver heterozygous mice with NGL homozygous mice	Wild type (+/+) and "weaver" (wv/wv) mice	Increased BDNF levels, dopamine levels, DOPAC/DA and HVA/DA ratios	(Panagiotakopoulou et al., 2020)
16.	DJ-1-binding compound B (1 μM)	Cells were treated with 10 μM 6-OHDA	SH-SY5Y cells, 293 T, A549 and PC3 cells	Ameliorated cell death	(Niki et al., 2020)
17.	*In-vivo* FLZ (25, 50 and 75 mg/kg; p.o.)	Mice were injected with MPTP (30 mg/kg; i.p.)	Male C57/BL mice and α-Syn (A53T) transgenic mice	Increased dopamine level and GDNF expression	(Bao et al., 2020)
	In-vitro FLZ-conditioned medium (1, 5, 10 μM)	Cultures were treated with 200 μM MPP^+	Mesencephalic neuron-glia cultures from Sprague-Dawley rats	Increased TH expression and dopamine release	
18.	Cong Rong Shu Jing Compound (0.5, 1, and 2 g/kg, i.g.)	Rats were injected with rotenone-sunflower oil emulsion (1.5 mg/mL; s.c.)	Male Sprague-Dawley rats	Improvedmotor coordination, reduced the loss of TH^+ cells and decreased α-synuclein levels	(Lin et al., 2020)
19.	Adropin (2.1 μg/kg; i.p.)	Rats were injected with rotenone (2.5 mg/kg; i.p.)	Ault male albino rats	Improved motor functions, restored dopamine,decreased MDA levels and caspase 3 activities	(Abo El Gheit et al., 2020)
20.	GDNF (0.3, 1, and 10 ng/mL)	Cultures were exposed to 6-OHDA (150 μM) and rotenone (30 nM)	Midbrain cell cultures from Sprague-Dawley rats	Increased TH levels and dopamine synthesis, release, and reuptake	(Mesa-Infante et al., 2022)
21.	*In-vivo* Dl-3-n-Butylphthalide (100 mg/kg; i.p.)	Mice were injected with MPTP·HCl (30 mg/kg; i.p.)	C57BL/6 male mice	Improved motor impairment, raised DA, DOPAC, and HVA levels, downregulatedexpression of iNOS	(Chen et al., 2019)
	In-vitro Dl-3-n-Butylphthalide (2.5–200 μM)	Cells were treated with LPS (100 ng/mL) or MPP^+ (500 μM)	BV-2 cells and SH-SY5Y cells	Reduced ROS production, downregulatedexpression of IL-1β, IL-6, TNF-α, iNOS, and COX-2	
22.	Morphine (10-200 μM)	Cells were exposed to MPP^+ (0.3 mM)	PC12 cells	Increased TH expression and cell survival	(Fan et al., 2019)
23.	*In-vivo* ZIF-8@PB-QCT (4 mg/kg, i.v.)	Mice were administrated with PBS (100 μL; i.v.)	Male/SD rats and C57BL/6 mice	Increased dopamine, DOPAC and HVA, restored IL-1β, TNF-α, and IL-6 mRNA levels	(Liu et al., 2021a, 2021b)

(*continued on next page*)

Table 1 (*continued*)

S. No.	Name of Compound/ formulation (Dose used)	Site of administration with the agent used for disease induction	Animal used or Cell culture	Major Outcomes	Ref.
	In-vitro ZIF-8@PB-QCT (5–160 μM)	Cells were treated with MPP^+ (2 mM)	ALT cells and SH-SY5Y cells	Decreased apoptosis level	
24.	Fisetin (0.5–50 μM)	Cells were treated with rotenone (100 nM)	SH-SY5Y cells	Increased cell viability, up-regulated Bcl-2, down-regulated Bax and caspases-3	(Rajendran and Ramachandran, 2019)
25.	Platelet-Derived Growth Factor (10–100 ng/mL)	Cells were treated with MPP^+ (10–500 μM)	SH-SY5Y Cells	Enhanced cell viability, reduced apoptotic cells, inhibited ROS production	(Chen et al., 2021b)
26.	(KD5040) (100 mg/kg and 300 mg/kg; included in food intake)	Mice were injected with MPTP (30 mg/ kg; i.p.)	C57BL/6 mice	Improved motor dysfunction, inhibited the loss of TH protein, increased BDNFexpression	(Hwang et al., 2019)
27.	*In-vivo* FTY720 (2 mg/kg; p.o.)	Mice were administered MPTP (20 mg/kg; s.c.)	Male C57BL/6 J mice	Increased dopamine, DOPAC and HVA, lowered apoptosis and necrosis.	(Yao et al., 2019)
	In-vitro FTY720 (0.5 μM)	Cells were treated with MPP^+ (500 μM)	BV-2 and SH-SY5Y cells	Reduced ROS and inflammation, inhibited caspase-1 activation	
28.	*In-vivo Uncariarhynchophylla* (20, 40, or 80 mg/kg; p.o.)	Mice were administered with MPTP (30 mg/kg, dissolved in H_2O)	C57BL/6 mice	Attenuated decrease in the levels of dopamine, prevented the loss of TH^+ cells	(Lan et al., 2018)
	In-vitro Uncariarhynchophylla (5, 10, or 20 mg/mL)	Cells were treated with MPP^+1 mM	SH-SY5Y cells	Significantly increased the cell viability	
29.	Aerobic exercise training	Mice were injected with MPTP (30 mg/kg; i.p.)	Male C57BL/6 J mice	Improved pathogenic characteristics and motor function	(Zhang et al., 2020)
30.	Alpha lipoic acid (0.1–20 mM)	Cells were treated with MPP^+ (0.25–2 mM)	PC12 cells	Decreased MDA, and ROS levels, increased GSH levels	(Liu et al., 2021a, 2021b)
31.	TRIM3 (bilaterally injected into dorsal hippocampus at a rate of 0.2 μL/min)	Mice were injected with MPTP (30 mg/kg; i.p.)	C57BL/6 mice	Improved bradykinesia, increased levels of GSH and SOD, increased dopaminergic neurons	(Dong et al., 2020)
32.	Decoction of Rehmanniae (125–1000 μM)	Cells were treated with MPP^+ (40–160 μM)	SH-SY5Y cells	Increased cell viability, SOD and GPx levels, decreased ROS, MDA and apoptosis, increased Bcl-2 while decreased Bax	(Jiang and Peng, 2021)
33.	Astragalus polysaccharide (50, 100 and 200 μM)	Cells were treated with 100 μM 6-HODA	PC12 cells	Increased cell viability	(Tan et al., 2020)
34.	MicroRNA-185	Rats were injected with 6-OHDA into the medial forebrain bundle at doses of 2.25 mL and 2.7 mL	Male Wistar rats	Increased dopaminergic neurons, decreased neuronal apoptosis and oxidative stress	(Qin et al., 2021)
35.	*In-vivo* Bergenin (40, 80 mg/kg)	Mice were administered with MPTP (30 mg/kg; i.p)	Male C57BL/6 mice	Reduced behaviour disorder, inhibited decrease in TH protein level, suppressed the levels of iNOS, TNF-α, IL-1, and IL-10	(Ji et al., 2019)
36.	Fecal Microbiota Transplantation (p.o.)	Mice were administered with MPTP (30 mg/kg; i.p.)	Male C57BL/6 mice	Enhanced motor performance, reduced α-synuclein expression, greatly increased the TH level	(Zhong et al., 2021)
37.	*In-vivo* Vitexin (50 mg/kg daily, p.o)	MPTP (30 mg/kg; i.p.)	Male C57BL/6 mice	Improved motor activity, reduced Bax/Bcl-2 ratio and caspase-3 activity	(Hu et al., 2018)
38.	*In-vivo* IGF-1 1 μL(injected into the lateral cerebral ventricle)	Mice were injected with MPTP (15 mg/kg; i.p.)	Male C57BL/6 mice	Increased dopamine, α-synuclein protein expression and decreased the protein expression of TH	(Wang et al., 2020a)
39.	Hydrogen-saturated saline (5 mL/kg; i. p.)	Rats were treated with rotenone (3 mg/kg; i.p.)	Male Wistar rats	Improved motor disorders, reduced ROS and α-synuclein levels	(Zhang et al., 2021)
40.	Resveratrol (12.5 μM and 25 μM)	Cells were incubated with 75 μM 6-OHDA	PC12 cells	Increased cell viability, SOD activity and MMP	(Huang et al., 2021)
41.	Uncariarhynchophyllaalkaloids (0.75–3 g/kg, i.g.)	MPTP (30 mg/kg; i.p.) was administered to the mice	Male C57BL/6 mice	Increased the expression of the dopamine transporter and tyrosine hydroxylase, attenuated the cleaved caspase-3 level	(Zheng et al., 2021a)
42.	*In-vivo* Rhynchophylline (30 mg/kg; i. g.)	MPTP (30 mg/kg; i.p.) was administrated to mice	Male C57BL/6 mice	Improved motor behaviour and inhibited loss of TH^+neurons	(Zheng et al., 2021b)
	In-vitro Rhynchophylline (5–50 μM)	Cells were treated with 500 μM MPP^+	PC12 cells	Improved cell viability, decreased ROS levels, apoptosis rate, caspase-3 activation and Bcl-2/ Bax ratio	
43.	Resveratrol (15 and 30 mg/kg, p.o.)	6-OHDA (8 μg/4 μL) was injected unilaterally into the SNpc of the midbrain	Male Sprague-Dawley rats	Increased dopaminergic neurons cells, decreased the Bax/Bcl-2 ratio and activated caspase-3 level	(Huang et al., 2019)
44.	Dapagliflozin (1 mg/kg; p.o.)	Rotenone (1.5 mg/kg; s.c.) was administered to the rats	Male Wistar rats	Reduced expression of α-synuclein, and increased dopamine levels, downregulated Bax and cleaved caspase-3 expression	(Arab et al., 2021)
45.	Crocin (30 mg/kg; i.p.)	Rats were treated with rotenone (1.5 mg/kg; i.p.)	Male Wistar rats	Decreased GSK-3β, FoxO3a, and the downstream caspase-9, increasedTH and dopamine	(Salama et al., 2020)
46.	*In-vivo* Danshensu (15, 30, or 60 mg/ kg; i.g.)	Mice were administered with rotenone (30 mg/kg; p. o.)	Male C57BL/6 mice	Increased GSH, dopamine, DOPAC and HVA expressions, decreased MDA content	(Wang et al., 2020b)
	In-vitro Danshensu (0.1 μM, 1 μM and 10 μM)	Cells were treated with rotenone (10–400 nM)	SH-SY5Y cells	Attenuated cell toxicity and decreased ROS generation	
47.	*In-vivo* Purmorphamine (1 mg/kg, i.p.)	Mice received injection of MPTP (20 mg/kg; i.p.)	Male C57BL/6 mice	Decreased the expression of IL1β and TNF-α mRNA, enhanced survival rate of dopamine neurons	(Shao et al., 2017)

(*continued on next page*)

Table 1 (*continued*)

S. No.	Name of Compound/ formulation (Dose used)	Site of administration with the agent used for disease induction	Animal used or Cell culture	Major Outcomes	Ref.
48.	*In-vivo* Exendin-4 (1.25 μg/kg; i.p.)	AAV-9-A53T-α-synuclein (2 mL) was unilaterally injected into the right SNpc	Female Sprague-Dawley rats	Decreased loss of TH^+ neurons and dopaminergic neurons	(Bu et al., 2021)
	In-vitro Exendin-4 (100 nM)	Cells stably overexpressing hA53T-α-syn were constructed	SH-SY5Y cells	Reduced mutant α-syn accumulation, increased the expression ratio of LC3-II to LC3-I	
49.	Fucoidanfraction sulfatedheterosaccharide (100, 500 and 800 μg/mL)	SH-SY5Y cells were treated with 100 μM MPP^+	SH-SY5Y Cells	Enhanced cell viability and Bcl-2 expression, decreased Bax, GSK3β and Bax/ Bcl-2 ratio	(Liu et al., 2020)
50.	Skin-derived precursors Schwann cells (SKP-SCs)	Cells were incubated with 6-OHDA (0-125 μM)	SH-SY5Y cells	Improved the cell viability, decreased the ratio of cleaved caspase-3/total caspase-3, enhanced mitochondrial activity and Bcl-2/ Bax ratio	(Chen et al., 2020)
51.	Schisandrol A (10, 20, 30 mg/kg; p.o.)	Mice were injected with 6-OHDA (2 μg/μL) into the ipsilateral medial forebrain bundle	Male C57BL/6 J mice	Increased dopamine, SOD and GSK-3β level, reduced the ROS, IL-1 and TNF-α levels	(Yan et al., 2019)
52.	Glutamine (64 μM)	Cells were treated with MPP^+ (113.5, 227, and 454 μM)	PC12 cells	Reduced cell apoptosis and MDA content, increased SOD and GSH-Px activity, decreased the expression levels mTOR	(Zhao et al., 2019)
53.	Berberine (1, 10, and 100 μM)	cells were treated with rotenone (20 μM) for 24 h	SH-SY5Y cells	Increased cell viability, Bcl-2/Bax ratio and caspase-3 protein expression, reduced ROS production	(Deng et al., 2020)
54.	Apelin-36 1 μM	Cells were treated with MPP^+ (250–1000 μM)	SH-SY5Y cells	Enhanced TH expression, lowered apoptotic ratio and increased cell viability	(Zhu et al., 2019)
55.	*In vivo* Oligo-Porphyran (25 and 50 mg/kg; i.p.)	Mice were injected with MPTP (20 mg/kg; i.p.)	Male C57BL/6 mice	Suppressed excessive dopamine metabolism and TH protein levels, inhibited the activation of caspase-3	(Liu et al., 2018)
56.	*In vitro* Chrysoeriol (5, 10 and 20 μM)	Cells were treated with MPP^+ (1 mM)	SH-SY5Y cells	Decreased cell death, decreased cleaved-caspase-3 level and reduced the protein level of α-synuclein	(Limboonreung et al., 2020)
57.	Urothelial carcinoma associated 1-si-RNA (1 μL; i.c.v.)	6-OHDA (2.25 and 2.7 μL; i.c.v.)	Male Wistar rats	Improved behavioral changes, increased dopamine, BDNF and NGF, reduced oxidative stress	(Cai et al., 2019)
58.	Vasicinone (5-20 μM/mL)	Cells were treated with paraquat (100–1000 μM/ mL)	SH-SY5Y cells	Improved cell viability, decreased ROS formation, reduced Bax and caspase, increased Bcl-2	(Ju et al., 2019)
59.	Isorhamnetin (64 μM)	MPP^+ (500 mmol/L) was applied to PC12 cells	PC12 cells	Increased cell viability, lowered rate of apoptosis, boosted the antioxidant action	(Gu et al., 2020)
60.	*In-vivo* Procyanidin (60 mg/kg, p.o.)	Rats were administered with 6-OHDA (4 μL; i.c.v.)	Male Sprague-Dawley rats	Reduced motor impairment, partially reversed the loss of TH-positive neurons	(Zhang et al., 2019)
	In-vitro Procyanidin (0.01–100 μM)	Cells were treated with 75 μM 6-OHDA	PC12 cells	Increased cell viability, increased SOD activity and Akt Ser473 phosphorylation	
61.	Growth differentiation factor-15	Cells were treated with oligomycin (5–50 μM) for 24 h.	Neuronal cell line HT22	Improved cell viability, elevated Mapk14, Syk, Ccl5, and Cav1 and downregulated Ptgs2 and Cx3cl1	(Liu et al., 2019)
62.	Araiostegiaperdurans (5–100 μg/mL)	Rat B35 neuroblastoma cells were treated with 6-OHDA (50 μM).	B35 cells	Enhanced cell survival, reduced apoptosis, ROS, and MDA, restored GSH levels and glutathione peroxidase and reductase activities	(Wu et al., 2018b)
63.	Ang1–7 (240 pg/0.5 μL)	Rats were injected with 6-OHDA (10 μg; i.c.v.)	Male Wistar rats	Improved motor coordination, increased dopamine and decreased inflammatory markers	(Rabie et al., 2018)

Akt protein pathway (Li et al., 2022). Further, WuziYanzong pill was found to protect the loss of dopamine neurons in MPTP-induced PD mice by inhibiting apoptosis and increasing the secretion of neurotrophic factors *via* activating PI3K-AKT signaling pathway (Hang et al., 2022). Furthermore, an *in vivo* study confirmed that nootkatonecould inhibit the expression of MAPK3 by activating the PI3K-AKT signaling pathway and therefore reducing the neuroinflammation and ultimately alleviating the PD symptoms in rotenone-induced rats (Yao et al., 2022). Interestingly, the results of another *in vivo* study suggested that taurine may regulate microglia-mediated inflammatory responses through inhibition of the PI3K-AKT pathway in a paraquat-induced mouse model of PD, thereby reducing the damage of dopaminergic neurons (Wang et al., 2022a). Another study demonstrated that oral administration of chitosan oligosaccharides exerted neuroprotective effects by reducing the α-synuclein overexpression, alleviating neuroinflammation, and activating the PI3K/Akt/Bcl-2 pathway to reduce apoptosis in an MPTP-induced animal model of PD (Wang et al., 2022b). Also, sinomenine improved the motor ability in PD mice, raised the survival of dopaminergic neurons, and inactivated the PI3K/AKT/mTOR pathway in the SNpc of mouse brains (Bao et al., 2022). Moreover, in a 6-OHDA-induced cell model of PD, celastrol attenuated 6-OHDA- induced neurotoxicity by regulating the miR-146a/PI3K/Akt/mTOR pathway (Guo et al., 2022). Collectively, the above findings indicate that PI3K-AKT pathway has a therapeutic potential that can greatly influence the treatment and management of PD.Table 1 summarizes various studies that explored the role of PI3K/AKT signaling pathway in the treatment of PD.

2.6. Clinical approaches

As discussed above, inflammatory response, apoptosis and increased levels of hazardous mediators like ROS may lead to the development of

PD·As a result, the development of novel therapeutic interventions that can target these processes is highly anticipated. Future strategies for new treatments must also consider the involvement of targets, such as PI3K and Akt. Functioning of the PI3K/AKT pathway may assure that neurodefense is engaged, providing neuroprotection by preventing apoptosis, oxidative stress, and neuroinflammation. Furthermore, the involvement of the PI3K-AKT signaling pathway has been observed in neuroprotection *via* reduction of inflammation, oxidative stress, and apoptosis in different trials including clinical studies.

The results of a study on AD patients showed that modulation of the p-Akt/PTEN pathway affected the key players of inflammation and oxidative stress that are involved in AD pathology and led to the alleviation of AD pathological cascade and cognitive decline (Mohamed et al., 2019). Moreover, the potential role of PI3K-AKT pathway has been observed for the survival of patients with neuroblastoma (Smith et al., 2016; Kushner et al., 2017). These studies indicate the clinical relevance of the PI3K-AKT pathway and suggests that this pathway plays a significant role in mediating neuroprotective actions in neurodegenerative disorders such as AD and PD. We believe that deeper knowledge and overall understanding of the molecular details of the nature of the PI3K-AKT signaling pathway may lead to the availability of innovative treatments to strengthen the therapeutic efficacy in the treatment of PD. Furthermore, well-focused future clinical investigations can lead to the development of this pathway into robust and safe clinical treatment strategies.

3. Conclusion

In recent years, the PI3K/AKT signaling pathway has attracted significant interest in search of a promising therapeutic target. This pathway has a role in the onset and progression of a number of neurological illnesses. Therefore, this review provides an overview of the PI3K-AKT pathway and summarizes numerous *in vivo* and *in vitro* studies on PD, which involve the PI3K-AKT signaling pathway as a therapeutic target. Taking these findings into consideration, further investigation of molecules involved in the PI3K-AKT pathway and their interactions will yield fresh insights for the mechanistic examination of PD and related medication development.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Ahsas Goyal: Conceptualization, Methodology. **Anant Agrawal:** Visualization, Investigation, Software. **Aanchal Verma:** Supervision, Writing – review & editing. **Nandini Dubey:** Data curation, Writing – original draft.

Declaration of Competing Interest

The authors confirm that they have no competing interests.

Data availability

No data was used for the research described in the article.

Acknowledgments

The authors acknowledge the support from BioRender for providing the platform to create chemical structures and professional science figures.

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