·综述·

中药调控PI3K/Akt信号通路治疗帕金森病的机制研究进展

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摘　要：帕金森病（PD）是一种以中脑黑质多巴胺能神经元丢失为特征的神经退行性疾病，现有治疗手段难以逆转其神经变性进程，因此迫切需要神经保护治疗。磷脂酰肌醇3-激酶/蛋白激酶B（PI3K/Akt）信号通路作为调控细胞存活的关键通路，已成为PD干预的重要靶点。近年来，中药以其多靶点、整体调节的特色，在基于PI3K/Akt通路的PD神经保护研究中展现出潜力。然而，该领域研究目前多停留于临床前阶段，缺乏将患者临床终点（如UPDRS评分）与通路生物标志物（如p-Akt水平）相关联的高质量临床证据，制约其临床转化。因此，本文对中药通过调控PI3K/Akt通路防治PD的研究进展进行综述，并展望未来“临床表型-通路活性-中药干预”整合研究的方向，旨在为相关基础研究与临床转化提供参考。

关键词：帕金森病；中药；PI3K/Akt；信号通路；作用机制
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Advances of the Mechanisms Underlying Traditional Chinese Medicine Targeting the PI3K/Akt Pathway against Parkinson´s Disease

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain. Current therapeutic strategies are unable to reverse the neurodegenerative process, highlighting an urgent need for neuroprotective interventions. The phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway, as a key pathway regulating cell survival, has emerged as an important target for PD intervention. In recent years, traditional Chinese medicine (TCM), with its distinctive properties of multi-targeted action and holistic regulation, has demonstrated considerable potential in PD neuroprotection research based on the PI3K/Akt pathway. However, most studies in this field are currently limited to the preclinical stage, and there is a lack of high-quality clinical evidence that correlates patients' clinical endpoints [e.g., Unified Parkinson's Disease Rating Scale (UPDRS) scores] with pathway-related biomarkers [e.g., phosphorylated Akt (p-Akt) levels], which hinders its clinical translation. Therefore, this paper reviews the research progress of TCM in the prevention and treatment of PD by regulating the PI3K/Akt pathway, and prospects the future direction of integrated research on "clinical phenotype-pathway activity-TCM intervention", aiming to provide references for relevant basic research and clinical translation.

Key words: Parkinson's disease; traditional chinese medicine; PI3K/Akt; signaling pathway; mechanisms
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帕金森病(Parkinson's disease, PD)是常见神经退行性疾病,发病率仅次于阿尔茨海默病,核心运动症状包括静止性震颤、肌强直、运动迟缓及姿势平衡障碍,同时伴随认知功能损伤、情绪异常等非运动并发症[1]。左旋多巴及多巴胺受体激动剂是PD一线治疗药物,但长期使用易引发疗效减退、异动症等不良反应[2]。因此,挖掘疗效确切、安全性高的替代治疗策略是当前PD领域的研究热点与难点。

PD的标志性改变是中脑黑质多巴胺能神经元进行性丢失伴纹状体多巴胺水平降低[3-4],其发生与发展与氧化应激、神经炎症、α-突触核蛋白(alpha-synuclein, α-Syn)沉积、自噬紊乱等多环节交织相关[5]。近年来,肠道菌群失调介导的"肠-脑轴"功能障碍[6],及以铁代谢紊乱和脂质过氧化为核心的铁死亡[7],也被证实参与神经元丢失过程,与经典病理过程相互作用,共同构成PD复杂的系统性病理网络。磷脂酰肌醇3-激酶/蛋白激酶B(phosphatidylinositol 3-kinase/protein kinase B, PI3K/Akt)信号通路作为调控细胞存活、增殖与代谢的核心枢纽,其功能异常与PD发病密切相关[8]。该通路在PD中扮演着双重角色,适度激活可触发内源性保护机制,功能紊乱则会加剧自噬失调、神经炎症与神经元凋亡,从而推动疾病进展[9-10],故为PD治疗的潜在干预靶点。不同于单一靶点药物的局限,协同激活内源性神经保护系统的多通路干预策略已成为当前研究的前沿[11]。中医药凭借多成分协同、多靶点调控的整体优势,在PD治疗中展现出低不良反应、多维度神经保护的价值[12-13],且其效应与PI3K/Akt通路及其下游靶点的调控密切相关[14]。但目前缺乏对"中药(活性成分、复方、中成药)-PI3K/Akt通路-PD病理环节"关联机制的系统整合。本综述旨在探讨中药通过该通路治疗PD的调控规律,阐明其在抗氧化、抗凋亡、抗神经炎症等关键病理环节中的多靶点协同效应,以期为PD的中西医结合防治与药物研发提供参考。

1 PI3K/Akt信号通路概述

PI3K/Akt信号通路是细胞内一条关键的信号传导通路,主要参与细胞生长、存活、代谢等核心生物学过程,由磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)和其下游效应分子蛋白激酶B(protein kinase B, Akt,又称PKB)构成[8]。PI3K为磷脂酰肌醇3-激酶催化亚基110(phosphatidylinositol 3-kinase catalytic subunit p110)与磷脂酰肌醇3-激酶调节亚基85(phosphatidylinositol 3-kinase regulatory subunit, p85)组成的异源二聚体,可被生长因子、趋化因子等胞外信号激活,这些配体分别与细胞膜上的受体酪氨酸激酶(receptor tyrosine kinasee, RTKs)或G蛋白偶联受体(G protein-coupled receptors, GPCRs)结合,通过磷酸化等机制招募并激活PI3K[9]。活化的PI3K可催化磷脂酰肌醇-4,5-二磷酸二钠(phosphatidylinositol-4, 5-bisphosphate, PIP2)转化为磷脂酰肌醇-3, 4, 5-三磷酸(phosphatidylinositol-3,4,5-trisphosphate, PIP3)[15],后者可将胞质中含PH结构域的Akt募集至细胞膜[16]。Akt被招募至细胞膜后,其Thr308位点可通过3-磷酸肌醇依赖性蛋白激酶1(3-phosphoinositide-dependent protein kinase 1, PDK1)介导发生磷酸化,而丝氨酸473位点(serine 473 site,Ser473)位点的磷酸化则由雷帕霉素靶蛋白复合物2(mammalian target of rapamycin complex 2, mTORC2)催化完成,从而被完全激活[17]。该通路活性受精密负反馈调控,磷酸酶张力蛋白同源物(phosphatase and tensin homolog, PTEN)是核心负调控因子[18],通过催化PIP3去磷酸化逆转为PIP2以终止Akt膜募集及信号传导[19],其基因突变或功能丧失便会导致该通路出现过度激活的情况[20]。在PD的病理背景下,该通路适度激活能够通过抑制糖原合成酶激酶3β(glycogen synthase kinase 3 beta, GSK-3β)、B淋巴细胞瘤-2基因相关启动子(Bcl-2-associated death promoter, Bad)等促凋亡因子,并调控雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)与叉头框蛋白O(forkhead box O, FoxO)等下游节点,发挥关键的神经保护作用[8,21];而持续功能紊乱,则会破坏自噬、加剧炎症并诱导凋亡,最终推动多巴胺能神经元的丢失和疾病进展[22-23]。

2 PI3K/Akt信号通路在帕金森病中的作用机制

2.1 调节氧化应激

在PD中,氧化应激通过产生过量活性氧(reactive oxygen species, ROS)损伤蛋白质、脂质和DNA等生物大分子,进而触发一系列导致细胞功

能衰竭与死亡的病理过程[24]。PI3K/Akt信号通路在此过程中发挥关键的双重调控作用。当细胞遭受ROS攻击时，Akt被迅速激活并通过磷酸化其下游关键靶点GSK-3β的Ser9位点以抑制其活性[25]；该抑制不仅有助于神经元存活，还能通过解除GSK-3β对核因子E2相关因子2（nuclear factor erythroid 2-related factor 2，Nrf2）的负向调控，激活下游抗氧化应答以增强ROS清除能力[26]。研究证实，褪黑素正是通过激活此PI3K/Akt/Nrf2信号轴发挥神经保护作用[27]。同时，该通路下游的mTOR和FoxO可通过调控线粒体自噬与抗氧化基因表达，协同抵御氧化损伤[9]。然而，氧化应激亦可负向调控该通路。研究表明，线粒体来源的过氧化氢可通过激活PTEN抑制Akt信号，进而削弱线粒体自噬，导致多巴胺能神经元死亡[28]，揭示了氧化应激通过PI3K/Akt通路失调加速神经元丢失的重要机制。

2.2　抑制神经炎症反应

在PD中，神经炎症主要由激活的小胶质细胞驱动，是导致多巴胺能神经元损伤的关键环节[29]。PI3K/Akt信号通路异常活化会直接驱动核因子κB（nuclear factor kappa-B，NF-κB）信号，进而间接激活NOD样受体家族含热蛋白结构域蛋白3（NOD-like receptor family pyrin domain containing 3，NLRP3），导致白细胞介素1β（interleukin-1 beta，IL-1β）等炎症因子释放，直接介导神经元损伤[30]。研究证实，通过药物干预抑制PI3K/Akt/NF-κB轴，能够有效减轻神经炎症并保护多巴胺能神经元[23]。此外，PI3K/Akt信号功能减弱会解除对GSK-3β的抑制，而过度激活的GSK-3β可直接促进NLRP3炎症小体活化[25]。因此，恢复Akt功能以抑制GSK-3β对减轻PD神经炎症至关重要。在抗炎方面，PI3K/Akt通路则通过激活Nrf2信号发挥抗炎作用。研究发现，大麻素Ⅱ型受体激动剂通过启动PI3K/Akt/Nrf2信号通路，可促使小胶质细胞由促炎的M1表型向抗炎的M2表型转换，进而发挥神经保护作用[31]。综上，在PD治疗中，调控PI3K/Akt信号通路以协调其抗炎与促炎分支的平衡，是减轻神经炎症损伤的有效策略。

2.3　调控细胞自噬

细胞自噬可通过溶酶体清除受损细胞器及病理蛋白以维持物质稳态[32]，PD中自噬功能障碍会因α-Syn和受损线粒体累积而加速多巴胺能神经元变性[33]。PI3K/Akt信号通路通过其关键下游节点mTOR，对细胞自噬起着核心的负向调控作用。在PD病理状态下，该信号轴的异常过度激活会强烈抑制自噬，导致毒性蛋白清除障碍[34]。研究证实，黄连-肉桂药对可通过抑制PI3K/Akt/mTOR通路，增强自噬流并促进α-Syn清除，进而发挥保护作用[35]。这表明纠正PD中PI3K/Akt/mTOR信号通路的失衡状态，对于神经保护至关重要。除通过mTOR途径外，PI3K/Akt通路还通过FoxO转录因子实现对自噬的精密调控[8]。其中转录因子FoxO3蛋白在PD调控网络中发挥枢纽作用，为PI3K/Akt/FoxO轴在神经元自噬与存活中的核心作用提供了关键证据[36]。此外，最新研究发现，Akt还可通过磷酸化去泛素化酶USP15，促进其从细胞核转位至细胞质，进而恢复自噬水平，揭示了该通路调控自噬的新机制[37]。

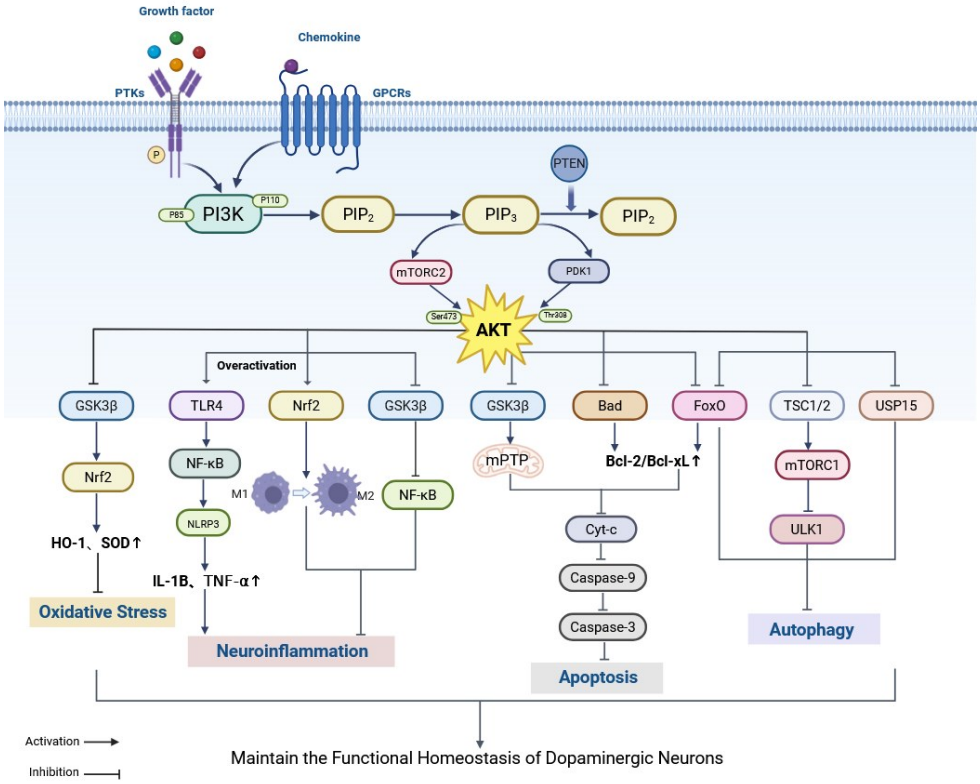
2.4　抑制细胞凋亡

PD的核心运动症状源于中脑黑质多巴胺能神经元的进行性丢失，细胞凋亡是此过程的主要执行途径之一[24]。PI3K/Akt信号通路通过多层次调控在PD中发挥核心抗凋亡作用。程序性细胞死亡因子4（programmed cell death 4，PDCD4）作为该通路的关键上游负调控因子，在PD模型中呈现高表达，敲低PDCD4可激活PI3K/Akt/mTOR信号，改善神经细胞凋亡与线粒体损伤[38]。通路下游活化的Akt可通过磷酸化BAD和抑制FoxO家族分子，恢复并增强Bcl-2/Bcl-xL等促存活蛋白的功能[9]。研究发现，COS2-COS5型壳寡糖单体即通过激活PI3K/Akt/Bcl-2信号通路，有效抑制多巴胺能神经元凋亡[39]。Akt还能够通过磷酸化GSK-3β使其失活以阻断下游促凋亡信号[25]，同时Akt信号的激活也能通过抑制FoxO1的活性以下调半胱氨酸天冬氨酸蛋白酶3（cysteine-aspartic protease-3，caspase-3）的水平，共同发挥神经保护作用[40]。然而，在PD状态下，氧化应激等因素通过抑制PI3K/Akt通路，解除其对下游凋亡信号的关键抑制，最终导致抗凋亡网络失衡，加剧多巴胺能神经元损伤[9]。

2.5　维持神经元功能稳态

PI3K/Akt信号通路是维持多巴胺能神经元功能稳态的核心调控通路，可通过传导神经营养信号、调控神经元微环境等维持神经元正常功能与存活[9]。在神经营养传递方面，该通路是脑源性神经营养因子（brain-derived neurotrophic factor，BDNF）、胰岛素样生长因子-1（insulin-like growth factor-1，IGF-1）等神经营养信号的下游关键节

点。研究发现,BDNF与酪氨酸激酶受体TrkB结合后,可介导PI3K/Akt信号通路的激活并直接促进神经元存活[41]。然而,神经稳态的维持依赖于适度的通路激活。研究表明,短期给予胶质细胞源性神经营养因子(glial cell line-derived neurotrophic factor, GDNF)可通过Ret/PI3K/Akt信号轴发挥神经保护作用,而长期持续刺激则会引发Ret受体及下游Akt信号的脱敏与负反馈调节,进而削弱其保护效应[42],提示过度激活通路会破坏其内在稳态,精准调控通路下游特定节点活性是维持功能稳态的关键。此外,该通路还可通过调节小胶质细胞活性和抑制NLRP3炎症小体,稳定神经元微环境以间接支持神经元存活[43] PI3K/Akt信号通路与多巴胺能神经元功能稳态的调控机制见图1。



PTKs: protein tyrosine kinase; GPCRs: G protein-coupled receptors; P85: PI3K regulatory subunit p85; P110: PI3K catalytic subunit p110; PIP2: phosphatidylinositol 4,5-bisphosphate; PIP3: phosphatidylinositol 3,4,5-trisphosphate; PTEN: phosphatase and tensin homolog deleted on chromosome ten; mTORC2: mammalian target of rapamycin complex 2; PDK1: 3-phosphoinositide-dependent protein kinase 1; Ser473: serine 473; Thr308: threonine 308; GSK3β: glycogen synthase kinase 3 beta; Nrf2: nuclear factor erythroid 2-related factor 2; HO-1: heme oxygenase-1; SOD: superoxide dismutase; TLR4: toll-like receptor 4; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; IL-1β: interleukin-1 beta; TNF-α: tumor necrosis factor alpha; M1: classically activated macrophages; M2: alternatively activated macrophages; mPTP: mitochondrial permeability transition pore; Bad: Bcl-2-associated death promoter; FoxO: forkhead box O; Bcl-2: B-cell lymphoma-2; Bcl-xL: B-cell lymphoma-extra large; Cyt-c: cytochrome C; Caspase-9: cysteine-dependent aspartate-directed protease 9; Caspase-3: cysteine-dependent aspartate-directed protease 3; TSC1/2: tuberous sclerosis complex 1/2; mTORC1: mammalian target of rapamycin complex 1; ULK1: Unc-51 like autophagy activating kinase 1; USP15: ubiquitin-specific protease 15.

图1 PI3K/Akt信号通路与多巴胺能神经元功能稳态(本图采用Biorender绘制)

Fig. 1 PI3K/Akt signaling pathway and functional homeostasis of dopaminergic neurons

3 中药调控PI3K/Akt信号通路治疗PD的研究

PD可归属于中医学中“颤病”“拘病”或“颤拘病”范畴,其病机核心为本虚标实,本虚为肝肾亏虚、气血不足,标实则为肝风、痰浊、瘀血互结[44]。如《内经》所言“诸风掉眩,皆属于肝”,王肯堂强调“肝风内动为颤证之标”,王清任则创立“气虚血瘀”理论,认为“元气既虚,必停留而瘀”。现代研究进一步证实了肝肾阴虚、气虚血虚、肾虚阳亏及风、

瘀、痰相关证型为PD核心辨证类型，为传统病机理论提供了现代实证支持[45]。因此，中药治疗PD以滋补肝肾、益气养血以治本，平肝息风、化痰祛瘀以治标为基本法则[46]。现代研究发现，上述扶正祛邪治则所对应的许多中药及复方，其神经保护作用与精准调控PI3K/Akt信号通路密切相关，为该通路的中医药靶向治疗研究奠定了理论基础。

3.1　中药活性成分调控PI3K/Akt信号通路治疗PD

3.1.1　*黄酮类化合物*　黄酮类化合物为广泛分布于植物体内的天然成分，具抗氧化、抗炎活性。高良姜具有温胃止呕、散寒止痛的功效。Huang等[47]发现其活性成分高良姜素通过激活PI3K/Akt通路并抑制Beclin-1介导的自噬，从而减轻神经炎症和氧化损伤，改善PD小鼠的运动协调能力与多巴胺神经元存活。凌霄花的活性成分芹菜素可提高p-Akt水平，阻断NF-κB通路激活及炎症因子表达并抑制Caspase-3活性与细胞凋亡，实现对多巴胺能神经元的保护[23]。槲皮素是一种天然黄酮类化合物，Li等[48]研究证实，其可通过激活PI3K/Akt/GSK-3β通路并调节Bcl-2/Bax等凋亡相关蛋白平衡，发挥抑制神经炎症与减少细胞凋亡的作用，从平衡、协调性等方面改善小鼠的运动功能。金莲花、竹叶等富含的荭草苷可抑制线粒体过度自噬，减轻氧化应激与钙超载，实现脑保护[49]。Sajini等[50]研究发现，荭草苷能够上调Akt促进CREB/BDNF信号传导，并抑制GSK-3β活性及调控Bcl-2家族蛋白，从而减轻线粒体自噬、氧化应激与致病蛋白沉积，该成分还协同激活Nrf2抗氧化通路并下调IL-6等炎症因子，显著改善PD小鼠的运动协调、自主活动能力并减轻肌肉强直症状。综上，以高良姜素、芹菜素、槲皮素和荭草苷为代表的黄酮类化合物，通过调控PI3K/Akt不同下游靶点，协同发挥抑制神经炎症、减少细胞凋亡、减轻氧化应激及调节自噬等多重作用，最终共同实现保护多巴胺能神经元和改善运动功能的核心目标。

3.1.2　*生物碱类*　中药所含的多种生物碱成分，具有多成分、多靶点的整体调节特点，在PD的细胞及动物模型中均表现出神经保护作用。胡椒碱是中药胡椒的主要活性成分，具有抗炎、抗氧化、调节肠道菌群等药理活性。Yu等[51]发现，胡椒碱通过抑制PI3K/AKT/mTOR信号通路激活自噬，从而促进PD大鼠模型体内α-Syn的降解，减缓多巴胺能神经元丢失，并改善大鼠的综合运动能力及胃肠功能。青风藤具有祛风湿、通络止痛之效，Bao等[52]研究发现，其活性成分青藤碱可抑制PI3K/Akt/mTOR通路磷酸化，上调自噬相关蛋白Beclin1，提高LC3-Ⅱ/LC3-Ⅰ比值并减少p62积累，从而增强多巴胺能神经元自噬，最终改善PD模型的运动协调性、肌力及步态。钩藤具有清热平肝、息风止痉的功效，Zheng等[53]研究表明，钩藤碱通过上调Akt磷酸化，调控Bcl-2/Bax平衡并抑制Caspase-3活化，同时降低ROS与细胞内钙离子水平，从而在MPTP小鼠模型中改善运动功能，并在MPP^+诱导的PC12细胞中增强细胞活力。小檗碱又名黄连素，是黄连的主要活性成分。Deng等[54]研究证实，小檗碱通过恢复Akt磷酸化以激活PI3K/Akt通路，进而上调Bcl-2/Bax比值、抑制caspase-3活化，并通过降低ROS与恢复线粒体膜电位而发挥抗凋亡与抗氧化效应，实现多巴胺能神经保护。综上，多种中药生物碱通过协同调控PI3K/Akt通路，增强自噬以清除致病蛋白，并通过抗凋亡与抗氧化以抵抗神经元损伤，共同实现保护多巴胺能神经元与改善PD模型运动功能的整体效应。

3.1.3　*萜　类*　萜类化合物是由异戊二烯单元构成的一大类天然产物，结构多样，活性广泛。蒿甲醚是青蒿素的重要衍生物，Quan等[55]，网络药理学分析与分子对接验证显示，蒿甲醚可激活PI3K/Akt/GSK-3β通路，通过提高Bcl-2/Bax比值、降低ROS水平、保护线粒体功能及减少细胞凋亡，改善PD小鼠运动和认知功能障碍，并提升黑质与纹状体中多巴胺神经元表达。雷公藤具有祛风除湿、活血通络等功效，在6-OHDA诱导的PC12细胞模型中，其活性成分雷公藤红素通过下调miR-146a激活PI3K/Akt/mTOR通路，有效缓解氧化应激与线粒体损伤，最终抑制细胞凋亡并提升细胞活力[56]。刺囊酸是一种提取自合欢花、皂荚等中药的五环三萜类化合物。He等[57]发现，其在体内外PD模型中均展现出显著的神经保护作用，通过激活PI3K/Akt信号通路并抑制NF-κB和丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）炎症通路，阻止小胶质细胞活化及减少促炎介质产生，显著减轻了神经炎症反应，并逆转MPTP诱导的行为障碍。同为萜类的香茅醇进一步丰富了该类成分的多靶点作用模式。研究表明，香茅醇在6-OHDA诱导的SH-SY5Y细胞中，通过上调p-Akt，进而调节Bcl-2/Bax比值、抑制炎症因子并减轻氧化应激，从多途

径发挥神经保护作用[58]。总结而言，萜类化合物可通过激活PI3K/Akt信号通路，协同发挥抑制细胞凋亡、缓解氧化应激及减轻神经炎症等多重药理活性，展现了其在帕金森病治疗中多靶点、综合调控的独特优势。

3.1.4 酚 类 酚类化合物涵盖简单酚酸与酚醛等类型，具有较强的抗氧化活性。姜黄具有破血行气、通络止痛的功效，Cai等[59]发现，姜黄素通过激活PI3K/Akt通路发挥抗凋亡、抗炎等多重神经保护效应，进而保护PD小鼠的多巴胺能神经元并改善其运动障碍。在细胞模型中则通过抑制PI3K/Akt/mTOR通路上调微管相关蛋白轻链3B-Ⅱ/微管相关蛋白轻链3B-I（microtubule-associated protein light chain 3B-Ⅱ/3B-Ⅰ，LC3B-Ⅱ/LC3B-Ⅰ）以增强自噬，促进α-Syn的清除[60]。这种针对同一核心通路在不同病理环节的差异调控，共同构成了姜黄素多靶点、综合性的神经保护网络。而白藜芦醇则在细胞与动物模型中均表现出一致的保护效应。Huang等[61]发现，白藜芦醇在细胞模型中通过上调p-Akt显著增强SOD活性并降低乳酸脱氢酶（lactate dehydrogenase，LDH）泄漏率，并有效拮抗氧化应激损伤，从而改善小鼠的不对称运动障碍；在动物实验中通过激活PI3K/Akt/GSK-3β通路并抑制Caspase-3表达，实现多巴胺能神经元保护及运动功能改善[62]。杜仲叶具有补肝肾、强筋骨的功效，Huan等[63]通过网络药理学预测和多层次生物学实验验证，证实杜仲叶中的双环氧木脂素可激活PI3K/Akt/GSK-3β/Nrf2通路促进下游抗氧化蛋白的表达，同时显著增强SOD和GPx酶活性，降低ROS水平和LDH释放，从而减轻氧化应激损伤。菊苣酸是一种能够穿越血脑屏障的天然抗氧化剂，研究证实其可显著激活PI3K/Akt通路，增加谷胱甘肽（glutathione，GSH）和SOD水平，协同发挥抗炎、抗氧化应激与抗凋亡作用，进而改善PD小鼠行为学障碍[64]。绿原酸为金银花等中药的关键成分，Sharma等[65]研究发现，其通过激活GPR40/43受体促进GLP-1释放，上调PI3K/Akt通路、抑制GSK-3β和α-Syn，最终有效改善PD小鼠的运动与认知功能并减轻氧化应激，保护多巴胺能神经元。丹参素为丹参的水溶性活性成分，Wang等[66]研究表明，丹参素通过激活PI3K/Akt/Nrf2信号增强抗氧化蛋白表达、减轻脂质过氧化，有效缓解6-OHDA诱导的氧化应激，保护多巴胺能神经元并改善PD小鼠的协调与平衡能力。综上，多种酚类化合物通过调控该通路下游关键靶点，在PD抗氧化应激、抗炎、抗凋亡及增强自噬等核心病理环节中发挥协同或侧重性作用，构成“多靶点、综合性”神经保护网络，有效缓解神经退行性病变，改善运动及认知功能障碍。

3.1.5 苷 类 苷类化合物通过调控PI3K/Akt在不同PD模型中发挥抗炎、抗氧化应激、抗凋亡等多重神经保护作用。三七具有活血定痛、化瘀止血之效。Wu等[67]研究发现，三七茎叶皂苷通过抑制PI3K/Akt/NF-κB信号，降低下游IL-1β等炎症因子的表达，表现出明显的抗炎效应并改善PD小鼠的运动迟缓与协调能力。甘草具有补脾益气、清热解毒之效，其核心成分甘草酸联合脂肪干细胞能够激活PI3K/Akt/mTOR/HIF-1α通路，抑制自噬标志蛋白LC3Ⅱ/LC3I转化与Beclin-1的表达，减轻神经炎症，进而显著改善PD小鼠的运动行为[68]。黄芪甲苷Ⅳ来源于中药黄芪的干燥根部，Liu等[69]研究证实，黄芪甲苷Ⅳ通过CCN3/PI3K/Akt/BDNF轴，抑制神经炎症与α-Syn聚集，实现了抗炎、抗氧化应激及抗凋亡的多效性神经保护。此外，黄芪甲苷Ⅳ可直接高亲和力结合Akt1、Akt2、PIK3CG等通路关键蛋白，促进PI3K/Akt的基因表达与磷酸化，从而有效拮抗MPP^+诱导的PC12细胞损伤与凋亡[70]。芍药具有养血柔肝、缓急止痛之效，研究发现，其活性成分芍药苷通过激活PI3K/Akt/CREB/BDNF信号通路，显著上调线粒体功能、下调氧化应激水平并抑制凋亡，实现PD小鼠综合运动功能的改善[71]。酸枣仁皂苷A和B为中药酸枣仁的主要活性成分，在6-OHDA诱导的神经细胞损伤中，其通过抑制PI3K/Akt通路并调节Bax/Bcl-2比值以抗凋亡，同时增强SOD等抗氧化酶活性以减轻氧化应激，进而协同发挥神经保护作用[72]。Qiao等[73]研究发现，人参皂苷Re通过激活PI3K/Akt/ERK-Nrf2信号轴减少ROS生成与细胞色素c释放，并上调抗氧化防御系统与下调线粒体凋亡通路，从而改善PD模型的行为学缺陷。积雪草微量皂苷CA-1具有优于常见同类成分的神经保护活性。其通过上调Akt、p85及PDK1等关键蛋白，促进SOD1、Bcl-2表达，进而降低ROS水平，发挥抗氧化与抗凋亡作用[74]。除了经典的抗凋亡与抗氧化作用，PI3K/Akt通路的最新研究还揭示其可通过调控转录因子Nrf2来抑制铁死亡。Wang等[75]研究证实，毛蕊花糖苷通过激活

PI3K/Akt信号通路，进而上调下游的Nrf2及其靶基因SLC7A11/GPX4的表达，最终抑制Salsolinol诱导的铁死亡，改善小鼠的运动及焦虑症状。综上所述，苷类化合物通过精准调控PI3K/Akt信号轴下游关键靶点，在PD模型中发挥抗炎、抗氧化、抑制铁死亡等多重神经保护作用，并有效改善模型的行为学缺陷，展现出多维度治疗PD的巨大潜力。

3.1.6　多糖类　多糖类是由多个单糖分子缩合而成的天然大分子，具有免疫调节、神经保护等多种生物活性。五味子具有益气生津、补肾宁心等功效。研究表明，五味子中性多糖SBP-1通过抑制PI3K/Akt/mTOR信号增加LC3-Ⅱ/LC3-Ⅰ比值并下调p62以增强自噬活性，协同降低Bax/Bcl-2比值及Caspase-3表达以抑制细胞凋亡，最终保护多巴胺能神经元，改善小鼠的运动协调能力[76]。枸杞多糖来源于枸杞的干燥果实，在MPP^+诱导的PC12细胞模型中，其通过上调p-Akt以激活PI3K/Akt信号通路，进而提升细胞存活并抑制凋亡，实现对多巴胺能神经元的保护[77]。此外，Wang等[78]研究表明，从黄芪中提取的黄芪多糖通过下调p-Akt、p-mTOR蛋白表达，上调PTEN及LC3-Ⅱ/LC3-Ⅰ比值增强自噬活性，从而保护多巴胺能神经元。综上所述，多糖类成分如五味子多糖与黄芪多糖通过抑制PI3K/Akt/mTOR通路以增强自噬，而枸杞多糖则通过激活PI3K/Akt通路以抑制凋亡，凸显了多糖类药物多靶点、双向调节的治疗潜力。

3.1.7　其　他　除上述活性成分外，苯丙素类、核苷类及萜醌类等多种天然产物也显示出通过调节PI3K/Akt通路实现神经保护的潜力。β-细辛醚是苯丙素类活性成分，研究表明，其通过激活PI3K/Akt/mTOR通路上调p62并抑制Beclin-1介导的自噬，减少α-Syn聚集，进而改善PD合并抑郁模型大鼠的运动与抑郁样行为[79]。虫草素是核苷类天然活性成分，研究发现，虫草素通过协同抑制PI3K/Akt/mTOR与MAPK通路，上调自噬标志物LC3并降低IL-6、iNOS等促炎因子，从而发挥促进自噬与抑制神经炎症的双重保护作用，改善PD小鼠的运动、认知功能及焦虑行为[80]。紫草素是从传统中药紫草中提取的萘醌类活性成分。Anandan等[81]发现，紫草素通过激活IGF1R/PI3K/Akt通路，提升细胞ATP水平、恢复线粒体膜电位，并下调Caspase-8、Caspase-3活性及ROS水平，抑制α-Syn异常聚集，发挥抑制氧化应激和抗凋亡的双重神经保护作用。牛磺酸是一种最初从牛黄中分离得到的含硫条件必需氨基酸，研究发现，外源性牛磺酸可通过抑制PI3K/Akt信号通路，减少小胶质细胞活化及炎症因子表达，同时提升多巴胺能神经元标志物TH及多巴胺水平，从而改善PD小鼠的运动协调、步态以及焦虑与抑郁样行为[82]（附表1）。

3.2　中药提取物调控PI3K/Akt信号通路治疗PD

中药提取物是包含多种活性成分的混合物，体现中药多组分、多靶点协同作用的特点。金盏花具有清热解毒、凉血止血之功效，其富含的黄酮与酚酸类成分具有抗炎、抗氧化及神经保护等药理活性。Zhang等[83]研究发现，在MPTP诱导的斑马鱼和MPP^+诱导的SH-SY5Y细胞模型中，金盏花提取物中的3,4-二咖啡酰奎宁酸、异鼠李素-3-O-葡萄糖苷和金盏花苷E通过靶向分子伴侣Hsp90α，双向调控PI3K/Akt生存通路和ERK死亡通路，通过上调磷酸化PI3K并抑制磷酸化ERK，协同促进多巴胺能神经元存活并抑制细胞凋亡，展现出显著的神经保护作用。艾叶作为传统中药，具有温经止血、散寒止痛的功效，艾叶提取物通过激活溶酶体钙离子通道TRPML1，增强PI3K/Akt/β-catenin细胞生存通路，抑制线粒体分裂蛋白p-DRP1（Ser616）表达，并促进自噬/线粒体自噬过程，有效清除α-Syn、减少活性氧积累，从而改善了PD小鼠的运动协调与平衡及肌力[84]。刺五加具有益气健脾、活血通络的功效。研究表明，刺五加提取物可改善PD小鼠运动功能，其机制与减少α-Syn聚集、提升多巴胺能神经元TH表达，并抑制Bax/Bcl-2-Caspase-3凋亡通路及TLR4/MyD88/NF-κB炎症通路有关[85]。代谢组学分析进一步表明，其可通过回调皮质中多种差异代谢物，并激活PI3K/Akt信号、抑制RAC1表达，协同发挥神经保护作用。综上所述，金盏花、艾叶及刺五加等中药提取物虽作用机制各异，但均能通过调控PI3K/Akt信号通路发挥多巴胺能神经保护作用，并最终改善PD模型的行为学缺陷，充分体现了中药多成分、多靶点、整合调控的治疗优势（附表2）。

3.3　中药复方与中成药调控PI3K/Akt信号通路治疗PD

中药复方在中医药理论指导下，遵循“君臣佐使”配伍理论，呈现出多成分、多靶点整体调节的治疗优势，且安全性良好。天麻钩藤饮由天麻、钩藤、石决明等11味中药组成，具有熄风止痉、柔肝舒筋

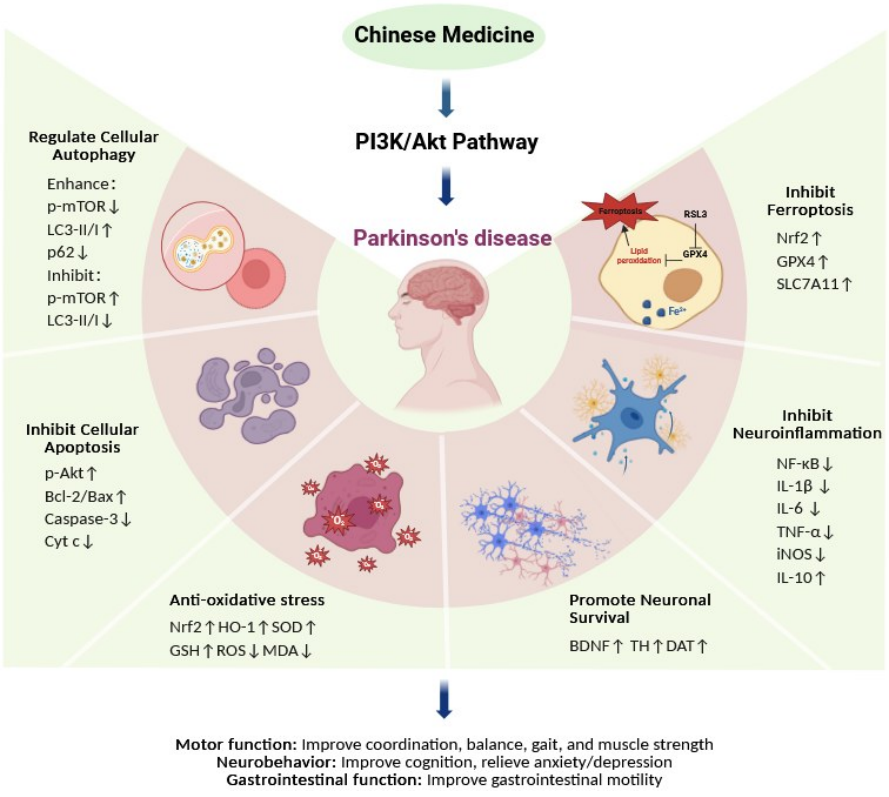
的作用。研究发现,该复方在MPTP诱导的PD小鼠模型中通过激活PI3K/Akt信号通路显著下调Bax/Bcl-2与Caspase-3水平、增加TH表达,从而抑制多巴胺能神经元凋亡并改善PD小鼠的自主运动及探索行为障碍[86]。五味子汤由五味子、麦冬、人参等8味中药组成,具有滋肾填髓之效。Pan等[87]研究证实,五味子汤通过抑制异常自噬发挥神经保护作用,显著改善了PD小鼠的运动功能障碍,其机制为上调p-Akt、p-mTOR及TH蛋白表达,增加LC3 Ⅱ/Ⅰ比值,下调PTEN、p62及α-syn水平,从而抑制异常自噬,改善运动迟缓、平衡协调能力差和自主探索活动减少等PD核心运动症状。芍药甘草汤出自张仲景《伤寒论》,由芍药、甘草组成,具有养血敛阴、柔筋缓急的功效。研究表明,该方通过抑制PI3K/Akt/mTOR通路,上调Beclin1水平并增加LC3-Ⅱ/LC3-Ⅰ比值及自噬小体数量,从而增强多巴胺能神经元自噬能力并显著改善PD大鼠旋转行为[88]。四君子汤出自《太平惠民和剂局方》,由人参、白术、茯苓、甘草组成,具有益气健脾之效。Yang等[89]研究发现,该复方通过激活PI3K/Akt信号通路上调Bcl-2,同时下调Bax与Caspase-3,发挥抗凋亡作用,尽管网络药理学预测其作用涉及IL-6、TNF-α等炎症靶点,但抗炎效应尚待后续实验进一步证实。复方地黄颗粒由熟地黄、白芍、钩藤等组成,具有滋补肝肾、平肝熄风、活血化痰、解毒散结的功效。研究表明,该方通过抑制PI3K/Akt/mTOR通路,上调LC3B-Ⅱ/Ⅰ比值并下调p62,从而激活黑质区自噬、保护多巴胺能神经元,最终改善PD大鼠的运动功能[90]。五子衍宗丸源自唐代著名中医方剂,由枸杞子、菟丝子、覆盆子、五味子及车前子组成,具有补肾益精之功效。Huang等[91]研究发现,该成分通过激活PI3K/Akt通路,调控Bcl-2/Bax/Caspase-3凋亡途径并促进BDNF与CDNF分泌,从而发挥抗凋亡与神经营养的双重保护作用,有效改善小鼠步态、肌力等方面的运动障碍。综上所述,中药复方和中成药治疗PD展现出对PI3K/Akt信号通路独特的双向调节能力,具体表现为激活该通路以抑制神经元凋亡,同时通过抑制其下游的mTOR轴来激活保护性自噬,实现了对PD的多靶点整合治疗。具体机制见附表3。综上,中药可通过多种途径调控PI3K/Akt信号通路治疗PD,其潜在作用机制见图2。

4 总结与展望

PD是常见的神经退行性疾病,其病理机制复杂,当前以西药为主的治疗策略虽能短期缓解症状,却难以阻断疾病进展,且长期应用还会出现药效减退与并发症。近年来,中医药凭借多成分、多靶点的整体调节优势,在PD治疗研究中展现出潜力,其中针对PI3K/Akt信号通路的机制研究尤为突出。本研究系统梳理了黄酮类、生物碱类等中药活性成分及天麻钩藤饮、复方地黄颗粒等中药复方和中成药通过调控mTOR、GSK-3β、Bcl-2/Bax等关键下游因子,在调节自噬、抑制凋亡、减轻氧化应激等方面发挥神经保护作用,并在多种PD临床前模型中显示出疗效。临床研究亦证实熄风定颤汤通过抑制炎症、改善神经递质水平提升UPDRS评分[92]、加味五虎追风散合康复疗法则显著改善运动功能与生活质量[93],为中医药治疗PD临床转化研究奠定实践基础。

然而,该领域研究在向临床转化过程中仍面临诸多挑战。首先,现有机制证据主要来源于细胞及小动物模型,在体研究深度不足,且缺乏大型动物模型的系统验证与独立重复,研究成果的稳健性与外推性有待夯实。其次,中药多成分的特性导致其核心药效物质与精准靶点尚未明晰,且多数研究聚焦于单一成分或单体,对复方中多组分协同调控PI3K/Akt通路的网络化机制解析严重不足。临床研究多局限于症状改善,缺少将临床症状与通路生物标志物动态结合的高质量随机对照试验(RCT),导致“干预-通路-疗效”的实证链条不完整。据此,未来研究应聚焦以下方向:①推动研究范式升级,在加强机制可重复性验证的基础上,开展基于大动物模型的临床前研究,并重点设计实施高质量的RCT,在临床试验中同步采集临床症状与通路相关生物标志物,为中医药的疗效提供高级别循证医学证据。②运用系统药理学与多组学技术,阐明中药复方中多成分协同调控PI3K/Akt信号网络的作用图谱,明确核心效应成分群。③探索中西医结合的协同治疗方案,评估中药在激活内源性保护通路的同时,与常规西药联用的增效减副潜力。通过深化机制研究与创新临床验证模式,有望为PD防治提供机制明确、证据可靠的中医药新策略。

附表
Appendix table



PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; p-mTOR: phosphorylated mammalian target of rapamycin; LC3-Ⅱ/Ⅰ: microtubule-associated protein 1 light chain 3; p62: sequestosome 1; Nrf2: nuclear factor erythroid 2-related factor 2; GPX4: glutathione peroxidase 4; SLC7A11: solute carrier family 7 member 11; p-Akt: phosphorylated protein kinase B; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X protein; Caspase-3: cysteine-dependent aspartate-directed protease 3; Cyt c: cytochrome c; HO-1: heme oxygenase-1; SOD: superoxide dismutase; GSH: glutathione; ROS: reactive oxygen species; MDA: malondialdehyde; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; IL-1β: interleukin-1 beta; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha; iNOS: inducible nitric oxide synthase; IL-10: interleukin-10; BDNF: brain-derived neurotrophic factor; TH: tyrosine hydroxylase; DAT: dopamine transporter.

图2　中药靶向PI3K/Akt通路治疗PD的作用机制（本图采用Biorender绘制）

Fig. 2　The mechanism of TCM targeting the PI3K/Akt pathway in the treatment of PD

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