

# Traditional Chinese Medicine Regulation of the NLRP3 Inflammasome in Parkinson's Disease: An Integrative Framework Based on Fuxie Theory

Xingkun Yang<sup>1</sup>, Xiaoming Shen<sup>2,\*</sup>, Cheng Wu<sup>3</sup>

<sup>1</sup>Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

<sup>2</sup>The First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou 450000, Henan, China

<sup>3</sup>The First Clinical Medical College, Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

\*Correspondence Author

**Abstract:** *Parkinson's disease (PD) has an insidious onset and a relentlessly progressive course. Abnormal  $\alpha$ -synuclein ( $\alpha$ -Syn) accumulation, impaired mitochondrial quality control, and sustained NLRP3 inflammasome activation reinforce one another and together constitute the pathological basis of chronic progression. In traditional Chinese medicine (TCM), Fuxie theory describes a dynamic disease course in which pathogenic factors remain concealed, erupt once triggered, and then persist. This temporal logic maps onto the progression of PD from inflammasome priming through activation to feedback amplification. Focusing on these three stages, we review the evidence linking  $\alpha$ -Syn burden, Parkin-dependent mitochondrial quality control, ASC specks, and gasdermin D to sustained NLRP3 activity. Without equating TCM pathogenesis with any single molecular mechanism, we propose a Fuxie–NLRP3 integrative framework in which declining quality control, accumulating danger signals, and persistent NLRP3 activation form a candidate mechanistic bridge between deficient healthy qi and sustained neuroinflammation. We then appraise the evidence for Chinese herbal formulas, bioactive compounds, and acupuncture as NLRP3-directed interventions in PD. The framework converts the temporal logic of Fuxie theory into testable mechanistic questions; however, current evidence remains largely correlational and requires stronger causal validation.*

**Keywords:** Parkinson's disease, Fuxie theory, NLRP3 inflammasome,  $\alpha$ -synuclein, Neuroinflammation, Traditional Chinese medicine.

## 1. Introduction

Parkinson's disease (PD) is a common chronic, progressive neurodegenerative disorder that evolves through prodromal, clinical, and advanced stages. Recent work indicates that abnormal  $\alpha$ -synuclein ( $\alpha$ -Syn) aggregation, disturbed mitochondrial homeostasis, and neuroinflammation are not independent processes but reinforce one another and form a pathological network. The NLRP3 (NOD-like receptor family pyrin domain containing 3) inflammasome is a key node linking danger-signal recognition to inflammatory output. Fuxie theory in traditional Chinese medicine (TCM) holds that pathogenic factors may remain concealed, erupt upon provocation, and persist once manifest — a temporal pattern comparable to the shift in PD from inflammatory susceptibility through triggered activation to chronic amplification. On this basis, we develop a Fuxie–NLRP3 integrative framework with the aim of informing both the interpretation of PD pathogenesis within TCM and mechanistic research on TCM interventions.

## 2. Fuxie Theory and Parkinson's Disease

### 2.1 Origins and Development of Fuxie Theory

Fuxie theory grew out of the long-standing TCM observation that pathogenic qi may lie dormant before it erupts. Fuxie is not the name of a specific pathogen; it denotes pathogens or pathological products that have entered the body and persist there without immediately producing overt clinical manifestations. They become apparent only when healthy qi is compromised, when the internal milieu becomes imbalanced, or when a new precipitating factor appears, and they may then recur over a prolonged period because they are

never fully eliminated. Fuxie therefore describes a pathogenic state that unfolds over time rather than a static pathological entity. The idea is already present in the Huangdi Neijing: the Suwen chapter of the spirit-convergence theory states that cold injury in winter leads to warm disease in spring, indicating that exposure does not invariably cause immediate illness. Later physicians developed this into the concepts of latent qi and latent pathogen and extended their application from externally contracted disorders to internal and miscellaneous diseases. Contemporary studies emphasize latency, accumulation, eruption after provocation, and persistent non-resolution as characteristic features of Fuxie [1], and use the concept to explain how deficient healthy qi and the long-term accumulation of pathological factors relate to disease emergence in metabolic and inflammatory conditions [2]; in the management of chronic relapsing diseases, attention centers on how prolonged latency interacts with systemic imbalance [3]. Structurally, Fuxie comprises three linked phases: pathological factors are present while clinical signs remain inconspicuous; changes in internal or external conditions convert latent pathology into overt disease; and after emergence, retained pathogen and deficient healthy qi interact so that the disease is difficult to terminate. Deficient healthy qi here refers not merely to constitutional weakness but to an impaired capacity to clear pathological factors, maintain homeostasis, and complete repair. Insufficient healthy qi favors the inward lodging of pathogens, and prolonged retention further depletes physiological function, generating a cycle of deficient healthy qi, latent pathogen, and renewed injury to healthy qi. The value of Fuxie theory lies in this dynamic view of disease: it implies that pathological change precedes symptoms, and it accounts for why a disease may worsen markedly under certain

conditions and continue to progress after it has become clinically evident.

## 2.2 Fuxie Theory and Parkinson's Disease

The core pathology of PD comprises progressive loss of dopaminergic neurons in the substantia nigra pars compacta, abnormal  $\alpha$ -Syn aggregation, and persistent neuroinflammation. By the time cardinal motor features such as bradykinesia, resting tremor, and rigidity appear, the disease has usually evolved over a long period. Hyposmia, rapid eye movement sleep behavior disorder, depression, and autonomic dysfunction may precede typical motor symptoms by many years [4], and constipation — another common early non-motor feature — is associated with gut-brain axis dysfunction [5]. This pattern, in which pathology precedes symptoms, corresponds well to the Fuxie notion of being concealed and unsensed. As  $\alpha$ -Syn accumulates, neuroinflammation intensifies, and dopaminergic neurons are lost, the disease shifts from a relatively silent phase to overt symptomatology, a transition that can be understood as eruption on provocation. The provocation, however, should not be equated with a single infectious episode. Some patients deteriorate markedly after infection [6], which shows that external stress can disturb an existing pathological state but does not establish infection as a direct cause of PD; more commonly, endogenous pathological burden rises progressively, or external stress exceeds residual compensatory capacity, tipping the disease from relative stability into overt imbalance. In terms of TCM pathogenesis, PD typically presents as deficiency at the root and excess at the branch, with intermingled deficiency and excess. Studies describe liver and kidney insufficiency, weakness of the middle burner, and disordered qi dynamics during the course of illness [7], while emotional disturbance may allow qi stagnation, phlegm, and blood stasis to persist [8]. Staging studies report liver-kidney yin deficiency in the early stage, weakening of spleen qi with internal phlegm-dampness as the disease advances, and kidney yang insufficiency with intermingled phlegm, dampness, blood stasis, and toxin in advanced disease [9]. Professor Ji-Xue Ren interpreted the pathogenesis of PD as kidney as the root, spleen as the foundation, and liver as the branch: depletion of kidney essence leaves the sea of marrow unfilled, impaired splenic transportation generates phlegm turbidity, and failure of hepatic free coursing allows phlegm and blood stasis to lodge and damage the sinews, vessels, and cerebral collaterals. Treatment therefore reinforces healthy qi and eliminates pathogens while addressing both the substrate on which latent pathogen forms and the pathological products themselves [10]. This account is consistent with the sequence of deficient healthy qi, latent pathogen, and persistence.

## 3. Activation of the NLRP3 Inflammasome in Parkinson's Disease

### 3.1 Molecular Architecture and Two-signal Activation of the NLRP3 Inflammasome

The NLRP3 inflammasome is a cytosolic multiprotein complex through which innate immunity senses cellular injury and internal disturbance. It consists of the sensor NLRP3, the adaptor apoptosis-associated speck-like protein

containing a caspase recruitment domain (ASC), and the effector precursor pro-caspase-1. NLRP3 contains an N-terminal pyrin domain (PYD), a central NACHT domain, and a C-terminal leucine-rich repeat (LRR) domain, which mediate ASC binding, oligomerization, and maintenance of the resting conformation, respectively; the PYD and CARD of ASC bridge NLRP3 and pro-caspase-1. Cryo-electron microscopy has shown that activation induces conformational rearrangement and oligomerization of the NACHT domain, recruitment of ASC to form ASC specks, and assembly of a catalytically active inflammasome complex [11]. Assembly proceeds in two stages. Priming renders the cell responsive: upstream signals increase NLRP3 and pro-IL-1 $\beta$  expression through nuclear factor kappa B (NF- $\kappa$ B), and additional priming signals can further modulate its activatability [12]. SPARC-related work indicates that JNK/p65 signaling enhances priming [13], whereas aberrant RAC2-PAK1 signaling promotes activation through a distinct intracellular route [14]. During activation, primed cells assemble the inflammasome in response to a danger stimulus. Nigericin-induced ASC speck formation is widely used to assess NLRP3 activation [15], and particle phagocytosis, K<sup>+</sup> efflux, and reactive oxygen species (ROS) generation are important contributors [16]; lipopolysaccharide (LPS) combined with nigericin is commonly used to separate the two stages experimentally [17]. Once assembled, the complex activates caspase-1, which matures interleukin (IL)-1 $\beta$  and IL-18 and cleaves gasdermin D (GSDMD). In microglia carrying the PD-associated LRRK2 (leucine-rich repeat kinase 2) G2019S variant, NLRP3 expression and nuclear ASC specks increase even without a canonical second stimulus, yet full cytosolic ASC speck formation and IL-1 $\beta$  release still require further stimulation [18], indicating that priming and effector output are not the same event.

### 3.2 $\alpha$ -Synuclein as a Driver of Sustained NLRP3 Activation

Misfolding and aggregation of  $\alpha$ -Syn is a hallmark of PD. For the NLRP3 inflammasome,  $\alpha$ -Syn is more than an upstream ligand: it is recognized by microglia and simultaneously burdens protein clearance and disturbs cellular homeostasis, making it a persistent danger signal. Studies in primary microglia show that  $\alpha$ -Syn assemblies of different conformations engage Toll-like receptors TLR2 and TLR5 to modulate NLRP3, and that deletion or inhibition of NLRP3 paradoxically improves the clearance of  $\alpha$ -Syn oligomers [19]; other work implicates TLR4 [20]. Distinct upstream routes therefore converge on NLRP3. What makes the process self-sustaining is that  $\alpha$ -Syn is difficult to clear completely.  $\alpha$ -Syn preformed fibrils (PFFs) suppress Ulk1 transcription through TLR4-STAT1 and impair microglial autophagy, whereas restoring ULK1 activity or deleting Stat1 improves autophagy and reduces both neuroinflammation and dopaminergic neuronal loss [21]; patient-derived  $\alpha$ -Syn fibrils induce a more neurotoxic phenotype in the presence of chronic inflammatory mediators [22]. Dopamine and levodopa inhibit NLRP3 activation through D1/D2 receptors in primary human microglia [23], suggesting that endogenous restraint weakens as dopaminergic neurons are lost. Pharmacological NLRP3 inhibition reduces downstream microglial inflammation and microglial activation in the brain [24], and in paraquat/maneb-induced PD mice,

glibenclamide-mediated NLRP3 inhibition also attenuates  $\alpha$ -Syn accumulation, oxidative stress, dopaminergic neuronal loss, and motor deficits [25]. Together, persistent stimulation, impaired clearance, and diminishing negative regulation converge on NLRP3, positioning it at the interface between abnormal protein homeostasis and chronic neuroinflammation.

### 3.3 Defective Mitochondrial Quality Control and Sustained NLRP3 Amplification

Mitochondrial quality control relies on mitochondrial dynamics, mitophagy, and protein degradation to remove damaged mitochondria promptly. When this system fails in PD, damage signals such as mitochondrial reactive oxygen species (mtROS) and oxidized mitochondrial DNA (mtDNA) accumulate, providing a stable endogenous stimulus for NLRP3. Urolithin A enhances mitophagy, improves mitochondrial function, and reduces NLRP3 activation in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice and LPS-stimulated BV2 cells, and its protection is markedly attenuated when mitophagy is blocked [26]. Parkin links the two processes mechanistically. In neurons, Parkin promotes NLRP3 degradation; loss of Parkin function enhances NLRP3 priming and, through accumulation of PARIS/ZNF746, increases mtROS [27]. In microglia, Parkin promotes NLRP3 degradation via K48-linked polyubiquitination [28] and directs NLRP3 to chaperone-mediated autophagy, alleviating NLRP3-associated PANoptosis and dopaminergic neuronal loss [29]. USP22 promotes NLRP3 degradation through ATG5-dependent autophagy [30], and USP5 also routes NLRP3 to autophagic degradation [31]. Accordingly,  $\alpha$ -Syn increases the clearance burden; as quality control declines, damaged mitochondria and damage-associated molecular patterns (DAMPs) accumulate, providing chronic stimulation for NLRP3. Findings in non-PD models suggest that the association is general: enhancing autophagy or mitochondrial quality control reduces NLRP3 activation [32], mitochondrial ROS are closely linked to NLRP3 [33], enhanced BNIP3-mediated mitophagy accompanies reduced NLRP3-related inflammation [34], disruption of mitochondrial homeostasis alone sustains cellular stress [35], promoting the clearance of damaged mitochondria attenuates inflammation [36,37], and PPAR $\gamma$  activation both enhances mitophagy and suppresses the NLRP3 inflammasome [38]. These observations are informative, but conclusions in PD should rest primarily on direct evidence concerning Parkin, autophagy, and mitochondrial quality control.

### 3.4 A Positive Feedback Loop Between $\alpha$ -synuclein and NLRP3

A one-way model in which  $\alpha$ -Syn activates NLRP3 cannot explain why inflammation persists over a prolonged course in PD. Inflammation-induced changes in the cellular environment also influence  $\alpha$ -Syn clearance and propagation, and ASC specks are the clearest link identified so far.  $\alpha$ -Syn PFFs induce NLRP3 activation and ASC speck formation in microglia, and extracellular ASC specks further amplify inflammation in surrounding cells and aggravate  $\alpha$ -Syn aggregation and propagation; reducing ASC alleviates  $\alpha$ -Syn pathology and dopaminergic neuronal loss in neighboring neurons [39]. ASC specks derived from patients with PD and dementia with Lewy bodies show comparable inflammatory

activity, and the ASC-neutralizing antibody IC100 suppresses these responses and reduces the increase in pS129- $\alpha$ -Syn after PFF stimulation [40]. In PFF models, suppressing microglial responses similarly reduces  $\alpha$ -Syn propagation and protects dopaminergic neurons [41]. These findings point to a multi-node feedback network: abnormal  $\alpha$ -Syn triggers pattern recognition and organelle stress, driving NLRP3/ASC activation; ASC specks and persistent inflammation then impair the handling of abnormal protein, enhancing seeding and propagation; and the additional  $\alpha$ -Syn burden further stimulates the inflammatory system. This network fits the available evidence better than attributing persistent inflammation to a single cytokine.

### 3.5 Downstream Mechanisms Linking NLRP3 Activation to Neuronal Injury

Once the NLRP3 inflammasome assembles, pro-caspase-1 is converted to active caspase-1, which matures pro-IL-1 $\beta$  and pro-IL-18 and cleaves GSDMD. The consequences are twofold: a sustained pro-inflammatory milieu acts on dopaminergic neurons over the long term, and GSDMD pore formation drives inflammatory cell death. In PD animal models, NLRP3 inhibition lowers caspase-1 and mature IL-1 $\beta$  and attenuates microglial reactivity, dopaminergic neuronal loss, and motor deficits [25]. The selective NLRP3 inhibitor Usnolast (ZYIL1) also improves nigrostriatal injury, motor function, and abnormal  $\alpha$ -Syn accumulation in MPTP and 6-hydroxydopamine (6-OHDA) models [42], and Gsdmd deletion reduces microglial activation and dopaminergic neuronal loss, as does pharmacological blockade of GSDMD pore formation [43]. These interventions demonstrate a functional link between downstream NLRP3 signaling and neuronal injury. The role of NLRP3 nevertheless differs between cell types. When Parkin function is lost, dopaminergic neurons themselves assemble NLRP3 and undergo cell-autonomous injury [27], and work on Parkin-dependent chaperone-mediated autophagy (CMA) suggests that the relevant cell death may involve PANoptosis [29], whereas in human brain tissue NLRP3 localizes predominantly to microglia [40]. The most defensible current view is that microglial NLRP3 sustains a pro-inflammatory microenvironment that indirectly harms dopaminergic neurons, while neuronal NLRP3 may also contribute directly to cell death under specific genetic or pathological conditions.

## 4. An Integrative Fuxie–NLRP3 Framework

The preceding discussion shows that inflammation in PD is not constant in intensity. As abnormal  $\alpha$ -Syn accumulates and cellular quality control declines, the response threshold of the inflammatory system shifts; when danger signals increase further, NLRP3 moves from priming into full activation; and as the disease advances, abnormal protein, inflammation, and organelle damage reinforce one another. The Fuxie sequence of latency, eruption, and persistence is comparable to this temporal pattern. The comparison does not imply that Fuxie is NLRP3: TCM pathogenesis describes an overall pathological state, whereas NLRP3 is one key node within the neuroinflammatory network. We use this framework to address three successive questions: why the disease can accumulate for years before symptoms appear, what drives the transition from latent to overt pathology, and why

inflammation becomes self-sustaining once the clinical phase begins.

#### 4.1 Concealed and Unsensed: NLRP3 Priming

Being concealed and unsensed does not mean that no disease is present; it means that pathology exists but has not yet reached the threshold for a typical clinical phenotype, which corresponds closely to the prodromal phase of PD. Hyposmia, constipation, isolated rapid eye movement sleep behavior disorder (iRBD), and autonomic dysfunction may be present for years before motor symptoms appear [4], and  $\alpha$ -Syn seeding activity is detectable at the iRBD stage [44]. The inflammatory system is also not entirely quiescent early on: peripheral blood mononuclear cells from newly diagnosed, untreated patients already show abnormalities in the P2X7 receptor (P2X7R)/NLRP3 axis [45], extracellular ASC specks in blood change in early disease [46], and NLRP3, ASC, caspase-1, IL-1 $\beta$ , and IL-18 do not rise in parallel across disease stages [47]. Describing the latent phase simply as increased NLRP3 expression is therefore inaccurate; it is more appropriate to say that the response threshold and susceptibility of the inflammatory system have shifted.

Microglia carrying LRRK2-G2019S provide a graphic illustration: NLRP3 and nuclear ASC specks are already abnormal in the absence of a canonical second stimulus, whereas full cytosolic ASC speck formation and IL-1 $\beta$  release still require further activation [18]. This state — prepared but not yet committed to effector output — is structurally similar to being latent but not yet erupted. The emphasis for the concealed and unsensed phase should therefore fall on inflammasome priming and the accumulation of pathological burden rather than on identifying a single biomarker that is persistently elevated in all patients.

#### 4.2 Eruption on Provocation: NLRP3 Activation

Eruption on provocation describes the transition from latent to overt pathology once an existing balance is disrupted. In PD, the provocation need not be a specific external stimulus; it is better understood as an event that exceeds residual compensatory capacity, and a rising  $\alpha$ -Syn burden, mitochondrial or lysosomal damage, infection, and metabolic stress can all serve this role. Abnormal  $\alpha$ -Syn itself affects both inflammasome priming and organelle homeostasis: studies in human induced pluripotent stem cell (hiPSC)-derived microglia show that  $\alpha$ -Syn influences TLR2-related signaling and promotes NLRP3 activation [48], and an LRRK2 background amplifies this response [49]. Transition from latency therefore does not require a wholly new external stimulus. As abnormal protein accumulates, the balance that was previously sustainable may be broken at some point, and exogenous inflammation acts more as an amplifier than as a trigger. Some patients deteriorate markedly after infection [6], and viral encephalitis models show that intense inflammation aggravates  $\alpha$ -Syn aggregation and dopaminergic neuronal loss [50], supporting a model of pre-existing pathology plus additional stress without establishing infection as a direct cause of sporadic PD. Peripheral immune studies point in the same direction: peripheral blood mononuclear cells from patients with PD show an abnormal cytokine and chemokine profile even without stimulation, and this profile correlates

with motor and non-motor severity [51];  $\alpha$ -Syn stimulation raises cytokine release in healthy control cells to levels approaching those of patients, whereas patient cells show no comparable further increase, indicating that the individual immune background determines the response to a given danger signal. The relevant question is therefore not which fixed second hit applies, but what allows a primed system to cross its compensatory boundary; that boundary is likely set jointly by genetic background,  $\alpha$ -Syn burden, mitochondrial function, and immune status.

#### 4.3 Protracted and Refractory: Positive Feedback Amplification

Once PD enters a progressive phase, pathological maintenance depends less on the initial stimulus than on mutual reinforcement among abnormal protein, inflammation, and cellular quality control. In Fuxie theory, being protracted and refractory does not simply mean a long course; it emphasizes that once pathological factors persist, lingering pathogen and deficient healthy qi become entangled, so that the disease can no longer resolve on its own. The most direct evidence concerns the reciprocal promotion of abnormal protein and inflammation:  $\alpha$ -Syn PFFs induce NLRP3 activation and ASC speck formation, extracellular ASC specks aggravate  $\alpha$ -Syn pathology [39], and patient-derived ASC specks and related pathological material provide human-level support [40]. Microglial handling of  $\alpha$ -Syn is not uniformly beneficial either: after taking up  $\alpha$ -Syn fibrils, microglia generate truncated  $\alpha$ -Syn with greater seeding activity in a TREM2-dependent manner [52], so cells that normally clear protein may instead propagate pathology. The harder abnormal protein is to clear, the more persistent the inflammatory stimulus becomes, and vice versa. A second line of evidence concerns declining clearance and repair capacity: mitophagy limits the inflammatory input from damaged mitochondria [26], Parkin in both neurons and microglia promotes NLRP3 degradation [27,28], Parkin-mediated chaperone-mediated autophagy extends this regulation [29], USP22 [30] and USP5 [31] indicate that NLRP3 is constrained by the autophagy system, and  $\alpha$ -Syn itself suppresses microglial autophagy [21]. Deficient healthy qi can thus be understood as a progressive decline in the capacity to maintain cellular homeostasis: impaired quality control allows DAMPs and abnormal protein to accumulate, and sustained NLRP3 activation aggravates oxidative stress and organelle damage, creating a cycle of declining clearance, accumulating danger signals, persistent inflammation, and further loss of clearance capacity. Being protracted and refractory is therefore better understood as a self-sustaining state that develops gradually. The  $\alpha$ -Syn–NLRP3/ASC– $\alpha$ -Syn loop continually increases pathological burden while declining mitochondrial, autophagic, and Parkin-related quality control weakens clearance; the two loops drive each other, converting PD from a response to specific stimuli into a pathological state with a degree of self-maintenance.

#### 4.4 Therapeutic Implications of the Framework

The value of these correspondences is not that they identify a molecular counterpart for Fuxie, but that they translate latency, eruption, and persistence into observable mechanistic steps. Within this framework, NLRP3 is best regarded as a

representative node connecting abnormal protein burden, mitochondrial damage, and neuroinflammation, rather than as a biological synonym for Fuxie. The therapeutic emphasis accordingly shifts from simply lowering NLRP3 expression to simultaneously reducing upstream danger signals, improving autophagy and mitochondrial quality control, and limiting inflammasome assembly and downstream injury. This approach aligns well with the multi-target character of TCM: formulas, bioactive compounds, and acupuncture may act separately or together on abnormal protein handling, oxidative stress, organelle homeostasis, and inflammation. The following section appraises the available evidence along the axis of danger signals, cellular homeostasis, NLRP3, and neuronal injury.

## 5. Evidence for Chinese Medicine Interventions Targeting the NLRP3 Inflammasome

Along this pathological chain, Chinese medicine may influence not only NLRP3 itself but also  $\alpha$ -Syn-related inflammasome priming, oxidative stress, mitochondrial homeostasis, the gut–brain axis, and downstream inflammasome effects. Research to date has focused on herbal formulas, bioactive compounds, and acupuncture. When evaluating these findings, the relevant question is not simply whether a given protein decreases, but whether the intervention engages upstream danger signals, alters inflammasome assembly, and is supported by adequate causal evidence. The principal evidence is summarized in Table 1.

### 5.1 Chinese Herbal Formulas

Formula studies generally reveal multi-target effects. Qiji Shuijiang formula improves motor function and dopaminergic neuronal injury in the MPTP/probenecid model and reduces NLRP3, caspase-1, GSDMD-N, and IL-1 $\beta$ ; the study also included an NLRP3 overexpression arm and found that the formula still partially reversed changes related to ROS, malondialdehyde (MDA), and inflammatory cell death [53], which brings it closer to mechanistic validation than pathway-protein measurements alone. Bushen Yisui formula reduces NLRP3, ASC, caspase-1, and inflammatory cytokines while increasing tyrosine hydroxylase (TH) expression [54]. Animal experiments with Bushen Huoxue granules suggest regulation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/NLRP3 axis [55], and a drug-containing serum study further documented changes in the Nrf2/NLRP3/caspase-1 pathway in MPP+-treated PC12 cells [56]; another Bushen Huoxue formula extended the effects to NOX2/ROS and mitochondrial damage [57]. Yiqi Wenyang Sanhan formula showed neuroprotection in PD mice [58], and Congrong Shuijiang granules reduced mitochondrial damage and suppressed PD-related neuroinflammation [59]. These findings suggest that formulas limit NLRP3 indirectly by reducing upstream danger signals and improving cellular homeostasis rather than by targeting NLRP3 alone, and NLRP3-related mechanisms is the more defensible description.

### 5.2 Bioactive Compounds

Bioactive compounds have well-defined structures and allow effects to be assigned to specific upstream nodes. Polysaccharides from *Dendrobium huoshanense* reduce oxidative stress and NLRP3-related indices in SH-SY5Y and BV2 cells and in PD mice, with MCC950 used as a comparator [60]; this supports a role for NLRP3 in their anti-inflammatory effect but does not establish direct targeting. Echinacoside is better localized:  $\alpha$ -Syn pretreatment provides an inflammasome priming signal through TLR2/NF- $\kappa$ B, and echinacoside reduces  $\alpha$ -Syn and inhibits the TLR2/NF- $\kappa$ B/NLRP3 pathway [61]. Baohuoside I regulates NF- $\kappa$ B–NLRP3 signaling through the G protein-coupled estrogen receptor (GPER), and GPER antagonism or knockout attenuates its protective effect [62]. Baicalin acts in concert with the Nrf2 antioxidant system, and Nrf2 knockdown markedly weakens both NLRP3 suppression and neuroprotection [63]. Curcumin improves Drp1-related excessive mitochondrial fission together with NLRP3 inflammation [64], and hyperoside involves pituitary adenylate cyclase-activating polypeptide (PACAP)/cAMP response element-binding protein (CREB) signaling [65]. There is thus no single NLRP3-suppressive mechanism shared by these compounds; they act on abnormal protein recognition, receptor signaling, oxidative stress, mitochondrial dynamics, and neuropeptide regulation. Studies using defined compounds are better suited than formula studies to determine which upstream change actually drives the reduction in NLRP3 activity.

### 5.3 Acupuncture

Acupuncture research initially focused on nigral neuroinflammation and has more recently extended to intestinal inflammation and the gut–brain axis. Electroacupuncture regulates intestinal thioredoxin-interacting protein (TXNIP)/NLRP3 signaling [66], and a further study documented changes in the NIMA-related kinase 7 (NEK7)/NLRP3 pathway [67]; in the rotenone model, electroacupuncture also increased nigral Nrf2 and reduced NLRP3, caspase-1, GSDMD, and inflammatory cytokines [68], suggesting effects on both the central inflammatory environment and upstream oxidative stress. Gut–brain axis studies provide a more complete chain: in MPTP mice, antibiotic treatment alters the improvement in intestinal NLRP3 and PD phenotype produced by electroacupuncture [69], and 16S rRNA sequencing, metabolomic analysis, and fecal microbiota transplantation (FMT) in 6-OHDA rats support a microbiota/LPS–microglial NLRP3–neuronal injury axis [70]. Electroacupuncture also reduces NLRP3-ASC indices in amygdala microglia and relieves PD-related pain [71], indicating that its effects are not confined to the classical nigrostriatal motor circuit. Evidence remains largely preclinical, and acupoint selection, stimulation parameters, and PD models differ substantially across studies; a role for acupuncture in modulating NLRP3-related inflammation and the gut–brain axis is plausible, but it cannot yet be concluded that clinical benefit is mediated by NLRP3 alone.

**Table 1:** Principal evidence for Chinese medicine interventions targeting the NLRP3 inflammasome in Parkinson's disease

| Intervention type  | Intervention                           | Experimental model                | Main pathway or target                  | Key findings                                                                                                                                                        | Ref. |
|--------------------|----------------------------------------|-----------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Herbal formula     | Qiji Shujiang formula                  | MPTP/probenecid PD model          | NLRP3/caspase-1/GSDMD                   | Improves motor function and dopaminergic neuronal injury; reduces NLRP3, caspase-1, GSDMD-N, and IL-1 $\beta$ ; mechanism verified with an NLRP3 overexpression arm | [53] |
| Herbal formula     | Bushen Yisui formula                   | PD model mice                     | NLRP3/ASC/caspase-1                     | Downregulates inflammasome-related proteins and inflammatory cytokines; increases TH expression                                                                     | [54] |
| Herbal formula     | Bushen Huoxue granules                 | PD model mice                     | Nrf2/NLRP3                              | Regulates the Nrf2/NLRP3 axis and reduces nigral inflammation                                                                                                       | [55] |
| Herbal formula     | Bushen Huoxue granule-containing serum | MPP+-treated PC12 cells           | Nrf2/NLRP3/caspase-1                    | Enhances Nrf2-mediated antioxidant responses and inhibits the NLRP3/caspase-1 pathway                                                                               | [56] |
| Bioactive compound | Dendrobium huoshanense polysaccharides | SH-SY5Y and BV2 cells; PD mice    | Oxidative stress/NLRP3                  | Reduces oxidative stress and NLRP3-related indices and alleviates neuroinflammatory injury                                                                          | [60] |
| Bioactive compound | Echinacoside                           | PD-related cell and animal models | $\alpha$ -Syn/TLR2/NF- $\kappa$ B/NLRP3 | Suppresses $\alpha$ -Syn-related inflammasome priming and NLRP3 activation                                                                                          | [61] |
| Bioactive compound | Baohuoside I                           | PD-related models                 | GPER/NF- $\kappa$ B/NLRP3               | Modulates NF- $\kappa$ B/NLRP3 signaling via GPER and reduces inflammation and neuronal injury                                                                      | [62] |
| Bioactive compound | Baicalin                               | Toxin-induced PD models           | Nrf2/NLRP3                              | Enhances Nrf2 antioxidant responses and inhibits NLRP3 activation                                                                                                   | [63] |
| Bioactive compound | Curcumin                               | Rotenone-induced PD mice          | Mitochondrial function/NLRP3            | Improves mitochondrial dysfunction and inhibits microglial NLRP3 activation                                                                                         | [64] |
| Acupuncture        | Electroacupuncture                     | PD model mice                     | Intestinal TXNIP/NLRP3                  | Modulates intestinal TXNIP/NLRP3 signaling and reduces intestinal inflammation                                                                                      | [66] |
| Acupuncture        | Electroacupuncture                     | PD model mice                     | Intestinal NEK7/NLRP3                   | Suppresses intestinal NEK7/NLRP3 signaling and improves related pathology                                                                                           | [67] |
| Acupuncture        | Electroacupuncture                     | Rotenone-induced PD mice          | Nrf2/NLRP3/caspase-1/GSDMD              | Increases Nrf2 and reduces NLRP3, caspase-1, and GSDMD levels, limiting inflammatory cell death                                                                     | [68] |
| Acupuncture        | Electroacupuncture                     | 6-OHDA-induced PD rats            | Gut microbiota/LPS/NLRP3                | 16S rRNA sequencing, metabolomic analysis, and FMT support a microbiota-LPS-NLRP3 axis                                                                              | [70] |

Abbreviations: GSDMD-N, GSDMD N-terminal fragment; MPP+, 1-methyl-4-phenylpyridinium; 6-OHDA, 6-hydroxydopamine; TXNIP, thioredoxin-interacting protein; NEK7, NIMA-related kinase 7; 16S rRNA, 16S ribosomal RNA; SH-SY5Y, human neuroblastoma cell line; BV2, mouse microglial cell line; PC12, rat pheochromocytoma cell line; FMT, fecal microbiota transplantation. Other abbreviations are defined at first mention in the text. The table lists representative studies; further studies cited in the text are not listed individually.

## 6. Discussion

The Fuxie–NLRP3 framework proposed here remains a working model derived from existing evidence; its value lies in organizing questions rather than in establishing a one-to-one correspondence between pathogenesis and pathway. Regulation of NLRP3 by  $\alpha$ -Syn is supported by microglial experiments [19]; the Parkin–NLRP3 relationship in neurons has evidence from disease models [27] and has been independently verified in microglia [28], with Parkin-mediated chaperone-mediated autophagy extending this degradative mechanism [29]; and ASC speck-mediated feedback between inflammation and abnormal protein has experimental support [39] as well as human-level corroboration from patient-derived material [40]. On the other hand, peripheral P2X7R/NLRP3 abnormalities [45], changes in ASC specks [46], and stage-dependent differences in inflammasome indices [47] indicate that NLRP3 activity is stage- and cell-type-specific, while peripheral measurements are not equivalent to central inflammasome status, and current toxin, PFF, and genetic models do not fully reproduce the natural history of sporadic PD. Although TCM studies have documented regulation of NLRP3-related steps by formulas, bioactive compounds, and acupuncture, most evidence comes from cell and animal experiments, and direct target engagement together with necessity and sufficiency remain inadequately established. Two questions merit priority. First, do cells relevant to prodromal or early PD show a measurable reduction in the NLRP3 activation threshold? Second, does restoring autophagy and mitochondrial quality control

simultaneously reduce DAMP accumulation and raise that threshold? Mechanistic studies of TCM interventions should incorporate gene knockout, overexpression, rescue experiments, and clinical sample validation, and should combine disease staging with cell-type analysis to determine whether an intervention acts on danger-signal generation, inflammasome assembly, or downstream injury.

## 7. Conclusions

Chronic progression in PD involves the sustained coupling of abnormal  $\alpha$ -Syn, declining mitochondrial quality control, and neuroinflammation. The Fuxie concepts of being concealed and unsensed, eruption on provocation, and a protracted and refractory course offer a disease-course framework for this temporal pattern. We have built a Fuxie–NLRP3 integrative framework in which declining quality control, accumulating danger signals, and sustained NLRP3 activation form a candidate mechanistic bridge. Available evidence suggests that Chinese medicine can act at multiple points, including abnormal protein handling, oxidative stress, mitochondrial homeostasis, the gut–brain axis, and the inflammasome, but stronger causal and clinical evidence is required.

## Declarations

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### Conflict of Interest

The authors declare that they have no competing interests.

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## Author Profile

**Xingkun Yang** (born 1998), male, from Xi'an, Shaanxi, China; Master of Medicine; research focus: integrated Chinese and Western medicine in the prevention and treatment of Parkinson's disease.

**Xiaoming Shen** (born 1978), male; Chief Physician, Professor, Doctoral Supervisor, and Postdoctoral Co-supervisor; Director of the Henan Provincial Key Laboratory of Traditional Chinese Medicine for the Prevention and Treatment of Parkinson's Disease and Deputy Director of the National Regional TCM Encephalopathy Diagnosis and Treatment Center; research focus: integrated Chinese and Western medicine in the prevention and treatment of Parkinson's disease.