Targeting the JAK/STAT signaling pathway by natural and synthetic agents: as a novel therapeutic approach against Parkinson's disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder in which inflammation plays a key etiopathological role. Clinical evidence suggests that stimulation of pro-inflammatory cytokines leads to neuroinflammation in the affected brain regions. Aberrant activation or phosphorylation of the components of Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway has been implicated in increased transcription of the inflammation-associated genes and many neurodegenerative disorders such as PD. Several cytokines, chemokines, growth factors, and hormones stimulate the JAK/STAT pathway, a critical signaling cascade for the development and function of the immune response, both innate and adaptive. Increasing evidence points to oxidative stress, chemokine-induced toxicity and inflammation as the critical factors with adverse effects on dopaminergic neurons, which might ultimately lead to PD. Dysregulation of the JAK/STAT in PD and its involvement in various inflammatory pathways make it a promising PD therapy approach. So far, a variety of synthetic or natural small-molecule JAK inhibitors (Jakinibs) have been found promising in managing a spectrum of ailments, many of which are in preclinical research or clinical trials. Herein, we provided a perspective on the function of the JAK/STAT signaling pathway in PD progression and gathered data that describe the rationale evidence on the potential application of Jakinibs to improve neuroinflammation in PD.

Keywords: Parkinson's disease; JAK/STAT; Jakinibs

1. Introduction

In the central nervous system (CNS), neuronal deterioration results from a series of dysfunctions that affect neuronal function, structure or survival. The most common neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal lobar dementia (FTLD), and amyotrophic lateral sclerosis (ALS) [1]. It is suspected that defects or mutations in specific genes and the consequent aberration in particular proteins are involved in the pathophysiology of neurodegenerative diseases including AD, PD and ALS.

PD is a chronic, widespread neurodegenerative disease that is manifested by a gradual loss of dopaminergic neurons in substantia nigra (SN) pars compacta (SNpc) throughout the midbrain [2]. Aggregation of protein α-synuclein (α-SYN) in the cytoplasmic region of dopaminergic neurons is the primary pathology of PD. Bradykinesia, muscular rigidity, resting tremor, sympathetic instability, and reduced dopamine levels are the main hallmarks of PD [3]. Mutations in Parkin, Protein deglycase DJ-1 (DJ-1), PINK1 (phosphatase and tensin homolog [PTEN]-induced putative kinase 1), α-SYN and leucine-rich repeat kinase 2 are additionally associated with PD (LRRK2). The microglial activation through the signal transducer and the transcription family activator (STATs) occurs in PD. This pathway contributes to intracellular signal transduction and many other biological events such as immunity, proliferation, differentiation, apoptosis, inflammatory responses, and oncogenesis [4]. In the CNS, the JAK/STAT pathway is majorly implicated in regulating genes during growth, releasing hormones, inflammation or tumorigenesis. Dysregulation in this pathway causes results in conditions such as cancer, inflammation, and neurodegenerative impairments. This will also lead to abnormal function of many downstream molecules. Members of STAT family such as STAT1 and STAT3 are shown to activate microglial cells responsible for the activity of various pro-inflammatory cytokines, chemokines, and complement proteins production. These cytokines can induce oxidase and inducible nitric oxide synthase of nicotinamide adenine dinucleotide phosphate (NADPH), which results in the formation of reactive oxygen species (ROS) and nitric oxide species (NO) [1]. Upon neuroinflammation, transcription factors such as nuclear factor κB (NF-κB), STAT1, STAT3, and SMADs are upregulated and induce the microglial activation, contributing to PD via dopaminergic neuron autophagy. Regulation of the JAK and STAT phosphorylation by phosphatases or modulation of the JAK kinase activity

by the suppressor of cytokine signaling (SOCS) have been proposed as the primary mechanisms by which mediates the JAK/STAT activity [1, 2]. The outcomes of several experimental and clinical trials have shown that targeting the JAK/STAT signaling with small-molecule JAK inhibitors (Jakinibs) downregulates the inflammatory responses in certain diseases such as the autoimmune and inflammatory diseases. Inhibition of the JAK/STAT activity may pave a way to manage PD and further produce novel small anti-inflammatory molecules [5]. Herein, we provide evidence that JAK/STAT signaling mediates neuroinflammation and discuss its relevance to PD initiation or progression. We also discuss synthetic- or natural-based Jakinibs that can control neuroinflammation in PD.

2. Methods

Electronic databases such as PubMed, Google Scholar, Scopus, and Cochrane library were searched and relevant clinical, *in vivo* and *in vitro* articles from 1993-2020 were selected. Search terms included "Parkinson's disease" OR "Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT)" OR "Neurodegeneration" OR "Inflammatory response" AND "Oxidative stress" OR "Natural JAK/STAT inhibitors" OR "Chemical JAK/STAT inhibitors" OR "Jakinibs" OR "Neuroprotective".

3. Neurodegenerative and Parkinson's disease

The complexity of the CNS is the crucial reason that makes the neurodegenerative diseases a challenge to treat. Degeneration of dopaminergic neurons in the extrapyramidal system of the midbrain results in an imbalance in excitatory (acetylcholine) and inhibitory (dopamine) neurotransmitters in this region, and also the accumulation of Lewy bodies; which altogether contributes to the development of PD. The extrapyramidal nerve tract mediates the body posture and movements, the coordination of gait, and regulates the autonomic and habitual activities [6]. Bradykinesia initiates gestures that usually along with stooped posture and a slow shuffling gait without arm swing, and can appear rigid without any facial expression in some instances. Dyskinesias describes involuntary dystonic and choreic movements [7]. Non-motor symptoms include olfactory dysfunction, gazing appearance, flat affect, cognitive impairment, psychotic symptoms, sleep disturbances, autonomic dysfunction, unexplained pain, depression, apathy, and tiredness [8]. PD affects 1% to 2% of adult males over the age of

65, and 4% of adults over 80. It is postulated that the prevalence of PD patients will rise by more than 50 percent by 2030 [9].

4. Current treatments for Parkinson's disease

Pharmacotherapy is usually started when symptoms of dopamine deficiency appear and cause disability. Increasing dopamine levels is considered a critical therapeutic strategy, via an agonist such as Levodopa, or by inhibiting dopamine breakdown [10]. Beta-blockers such as propranolol, anticholinergics such as benztropine or trihexyphenidyl, and antipsychotics like clozapine attenuate the early symptoms as tremor. When dopamine agonists lose their efficacy, several other strategies are used to improve their effectiveness including an increase of the dosage of dopamine agonists, combination therapy, more frequent divided doses, or addition of a catechol-O-methyltransferase inhibitor or a monoamine oxidase inhibitor to save Levodopa up to the CNS [11, 12]. Controlled release of Levodopa is suggested at bedtime since its efficacy reduces over the gastrointestinal absorption. Safinamide is an α-aminoamide, with an inhibitory effect on monoamine oxidase-B (MAO-B) and a modulatory effect on glutamate release is found to be beneficial for PD treatment. Combination of Safinamide with Levodopa and Amantadine has shown to improve dyskinesia. Zonisamide is a mixture of MAO-B inhibitor, sodium and calcium channel blockers, and a glutamate release inhibitor. Zonisamide can improve wearing-off symptoms. Subcutaneous injection of apomorphine and amantadine also reduces the experiencing troublesome off episodes [12-14]. Moderate side effects such as nausea, hypotension, leg edema, vivid dreams and constipation have been reported, although, there are categorized as non-serious effects (Table 1).

Table 1. Current treatments for Parkinson's disease

Chemical drug	Indications	Results	Possible side effects
Levodopa Levodopa-carbidopa Levodopa-benserazide	Controlling disability prolongs the ability to perform instrumental activities of daily living	Controlling disability to perform instrumental activities	Dyskinesia, agitation, ataxia, dystonia, malaise, nausea, diarrhea
Dopamine agonists Bromocriptine Pramipexole Ropinirole Rotigotine Apomorphine	Control motor symptoms	Development of dyskinesias, antidepressant benefits	Nausea, hypotension, leg edema, vivid dreams, impulse control disorder, hallucinations (especially in the elderly), somnolence, and sudden sleep attack
Monoamine oxidase B inhibitors Selegiline Rasagiline	Early mild symptoms, all motor symptoms, Commonly an adjunct medication	Rasagiline: minor effect on mild to moderate PD	Selegiline: stimulant effect, dizziness, headache, confusion, exacerbation of levodopa adverse effects Rasagiline: headache, arthralgia, dyspepsia, depression, flulike syndrome, exacerbation of levodopa adverse effects, constipation serotonin syndrome
Catechol-O-methyl transferase inhibitors (COMTIs) Entacapone Tolcapone	Early-mild symptoms, all motor symptoms, Commonly an adjunct medication	Reduces levodopa therapeutic dose due to blocking its decomposition	Dark-colored urine, exacerbation of levodopa adverse effects, diarrhea, hepatotoxicity
Anticholinergic **Benztropine** **Trihexyphenidyl**	Tremor	Used occasionally for control or rest or re-emergent tremor unresponsive to dopaminergic therapy at desired doses; does not treat akinesia; beware of anticholinergic side	Hallucinations, nausea, dry mouth, blurred vision, urinary retention, constipation

		effects. Concerns about long term risks of cognitive impairment.	
Beta-Blocker Propranolol	Tremor	Reduces tremor and anxiety	Fatigue, dizziness, depression
<u>**Antipsychotic**</u> Clozapine	Tremor, dyskinesia	Reduces Tremor, dyskinesia, anti-depressant	Agranulocytosis, myocarditis, seizures, sedation, orthostatic hypotension
<u>**Antiviral Amantadine**</u>	Gait dysfunction, dyskinesia	Most useful as add-on therapy for long term PD, reduces dyskinesia	Hallucinations, confusion, blurred vision, ankle edema, livedo reticularis, nausea, dry mouth, constipation

5. Interventions targetting neuroinflammation in Parkinson's disease

Aging, genetic predispositions, mutations in JAK and STAT genes, and glial activation may result in neuronal injury and inflammation. It is well established that mild chronic inflammation in SNpc results in the degeneration of dopaminergic neurons [15, 16]. Inflammation contributes to the initiation and progression of PD through the promotion of dopaminergic neurodegeneration. Microglial-mediated inflammation cascade is a primary sign of Parkinsonism. Lipopolysaccharide (LPS)-induced microglial activation of dopaminergic neurons in SN, leads to microglia degeneration and PD. Degeneration of dopaminergic neurons is accompanied by T-cells infiltration and microglia activation, mediated by inflammatory cytokines and chemokines production. Genetic mutations, such as a mutation in α-SYN or LRRK2 genes, directly participate in chronic PD progression by stimulating inflammatory responses by microglia and astrocyte activation. Several studies suggested that inflammation and immune responses are the main risk factors for the progression of PD [17, 18].

6. The JAK/STAT structure and signaling pathway

Given the significance of the JAK/STAT signaling pathway in induction and regulation of immune responses, up to date, several mediators have been identified to stimulate this pathway. The JAK/STAT facilitates the activation of cytokine-mediated pathways. Cytokine interactions with their unique cell membrane receptors contribute to the activation of JAKs [19]. Activated JAKs, phosphorylate a tyrosine residue in the cytokine receptor's cytoplasmic domain to prepare the docking sites for STATs. Accordingly, STATs interact with the cytokines receptors and are phosphorylated by JAKs on their tyrosine residues. This process leads to the formation of homo- or hetero-dimers via SH2-phosphate interactions. Such interactions result in

modulation of the expression of several cytokine-responsive genes JAK1, JAK2, JAK3, and TYK2 are the members of JAK family. So far seven STATs including STAT1, 2, 3,4, 5a, 5b, and 6 have been identified [4].

As mentioned, several mediators regulate the JAK/STAT signaling similar to SOCS proteins, which have an inhibitory effect on this pathway. Activated STATs induce SOCS proteins' expression, resulting in JAK/STAT signaling inhibition via interaction with the SH2 domain. An additional kinase-inhibiting region (KIR) also exists in other SOCS family members, such as SOCS1 and SOCS3, which may inhibit the catalytic action of JAKs. JAKs are part of the family of tyrosine kinases (TYKs), consisting of four structural domains from seven homologous regions [JH1-7]. JH1 and JH2 denote the domains of kinase and pseudokinase. JH1 domains have a high degree of homology with other TYKs, thereby are ideal candidates for the development of novel Jakinibs [20]. JH2 appears to have a modulatory effect on catalytic activity by interacting with JH1and can suppress the ligand-independent kinase activity. It is necessary for the activation of ligand-induced JAK. JH3 and JH4 contribute to stabilizing the enzyme's structural conformation, while Ezrin, Radixin and Moesin (FERM) bind JAKs to their cognate receptors with JH5, JH6 and JH7/Four-point-one proteins. Due to their structural differences, the FERM domain inhibits JAK1 and TYK2 selectively, allowing access to specific binding sites. The STAT transcription factors are downstream of the JAKs. STATs transmit type I/II cytokine signals. Amino-terminal, coiled-coil, DNA-binding domain (DBD), linker, Src-homology2 (SH2), and transcriptional activation domain are included in the STAT proteins (TAD) [19]. It was shown that the majority of the STAT inhibitors target the SH2 domain [21]. Currently, several JAK/STAT inhibitors are in Phase I, II and III clinical trials for the treatment of a variety of inflammatory and oxidative diseases such as rheumatoid arthritis (RA) and myeloproliferative diseases or various tumors. Thus, JAK/STAT inhibitors' therapeutic potential might be a promising approach for cancer, autoimmune inflammatory and oxidative diseases [5].

7. The JAK/STAT inflammatory signaling pathway in Parkinson's disease

Accumulated data confirmed the JAK/STAT pathway's involvement in the pathogenesis of PD (Figure 1). Interferon-gamma (IFN-γ) and interleukin (IL)-6 are among the most potent actuators of the JAK/STAT pathway, and it was shown that they are highly elevated in PD [19]. A higher IL-6 level is associated with a higher risk of PD. IFN-γ deficient mice are

shielded from neurotoxicity mediated by MPTP, indicating that IFN-y contributes to the degeneration of dopaminergic neurons via a microglia-facilitated process. The pro-inflammatory components in PD are increased by microglia. Activated microglia and infiltrating macrophages have been observed in the SN of human PD patients. Studies of genome-wide associations have shown a positive correlation between PD and haplotypes of class II genes of the main histocompatibility complex (MHC) [22]. MHC-II positive microglia are detected in the SN of PD patients. The degree of MHC Class II expression correlates with the level of, which is elevated with disease severity. In a mouse model of PD, α-SYN overexpression of α-SYN led to a noticeable upregulation of MHC Class II in microglia. In addition, microglial activation, CD4+ T cell proliferation, and dopaminergic neurodegeneration was prevented by MHC Class II deletion [19, 23]. *In vitro and in vivo* studies indicate that α-SYN drives the activation and penetration of microglia and macrophages, resulting in NO, TNF-αTNF-α, and IL-1β expression and development of MHC Class II. AZD1480, a JAK2 and STAT3 inhibitor, blocked these responses by suppressing the JAK/STAT pathway activation [22]. Chronic inflammation is caused by α-SYN and pro-inflammatory cytokines such as IL-1β, IFN-γ, and TNF-αTNF-α are increased, thereby inducing neuronal death and PD. Likewise, treatment with minocycline, a tetracycline which prevents microglial activation, inhibited nigrostriatal dopaminergic neuronal decline in the MPTP-induce PD model and improved the pathogenesis of PD s. It was reported that in IFN-γ deficient mice, dopaminergic neuron loss and PD symptoms were reduced, and was associated with increased polarization of pro-inflammatory macrophages via the activation of the JAK/STAT pathway [19]. The most frequently mutated gene in PD is LRRK2, and it has been shown to intensify neuroinflammation caused by α-SYN and dopaminergic neuronal degradation [3]. LRRK2 is an IFN-γ activator that increases the reactive oxygen species (ROS) and JAK/STAT overexpression. Studies also demonstrated that LRRK2 suppresses the microglial and JAK/STAT responses and improves PD. Together, the inhibition of microglia and the JAK/STAT signaling pathway may be a promising therapeutic target for PD management [19].
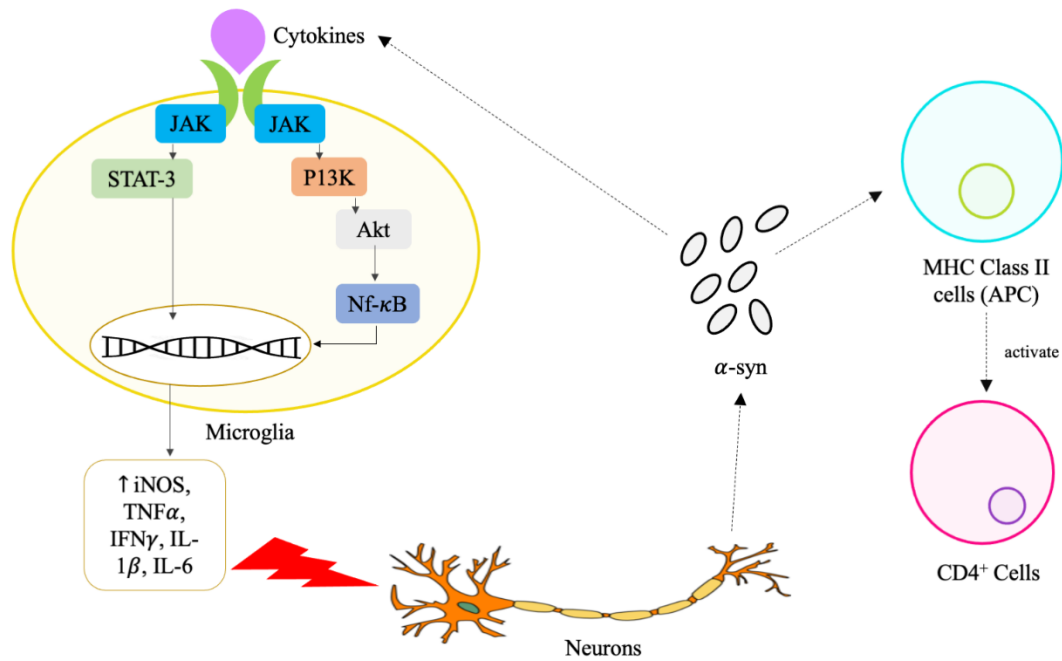
Figure 1. Parkinson pathogenesis mechanisms

Abbreviations: IL: Interleukin; IFN: Interferon; STAT3: signal transducer and activator of transcription 3; JAK: Janus kinase; iNOS: inducible nitrogen oxide synthase; TNF-α: tumor necrosis factor α; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; APC: antigen-presenting cell; MHC: major histocompatibility complex

8. Synthetic inhibitors of the JAK/STAT pathway as a novel treatment strategy for PD treatment

PD is a neuroinflammatory disorder, thereby to manage this condition; the use of immunomodulatory agents seems rational. For instance, Ruxolitinib [24, 25] has been developed to treat myeloproliferative disorders, Tofacitinib for RA treatment, and AZD1480 for PD treatment. AZD1480 reduces microgliosis and macrophage infiltration, suppresses pro-inflammatory cytokines, and the expression of MHC Class II. In addition, AZD1480 reduces CD4+ T cell infiltration into the CNS. It prevents the degeneration of dopaminergic neurons in the SN by blocking the JAK through the adenosine triphosphate-binding site in the JH1 domain [26-28].

The literature review showed that most clinical trials have focused on safety concerns about Jakinibs, for example, their impacts on hematopoiesis, and the host innate and adaptive defense

systems. Immunosuppression-induced infection is a significant problem in patients treated with Jakinibs. Common side effects include infections comprising nasopharyngitis or upper respiratory infections, bronchitis, and gastroenteritis [4, 29, 30]. As a result, low-dose and short-term treatment regimen with Jakinibs could be a therapeutic approach for PD. Overall, inhibition of JAK/STAT and its related inflammatory complications can be favorable for PD treatment, however, prolonged clinical trials are warranted (Table 2) [1, 31, 32].

Table 2. Chemical inhibitors of the JAK/STAT pathway

Ref.	Study Design	Disease Model	Intervention		Number of cases		Treatment Duration	Results
			Case	*Control*	*Case*	*Control*		
[33]	BEAS-2B human bronchial epithelial cell line	-	*L. pacari* extract (10, 50 or 250 mg/mL gallic acid, ferulic acid, ellagic acid, rosmarinic acid, apigenin, kaempferol, luteolin, rutin, quercetin)	DMSO 0.05%)	$1*10^5$ cells/mL	$1*10^5$ cells/mL	-	1. ↓ IL-6, IL-8 and CCL2 production 2. ↓ STAT3 expression 3. ↑IL-10
[34]	Male Sprague-Dawley rats	Renal ischemia/reperfusion injury (IRI)	Apigenin (4 mg/kg)	Normal saline	10	10	24 hours	1. ↓ JAK2/STAT3 expression 2. ↓ apoptosis 3. ↓ SOD, Caspase 3 expression
[35]	Male Sprague-Dawley rats	Myocardial reperfusion Injury	Apigenin (4 mg/kg)	normal saline (4 mg/kg)	-	-	72 hours	1. ↓ JAK2/STAT3 expression 2. ↓ apoptosis and ROS production
[36]	Male Wistar rats	Chronic restraint stress	*Spinacia* extract containing apigenin and luteolin	normal saline	5	5	21 days	1. ↓ IL-1β, IL-6, IL-8 and TNF-α 2. ↓ neuronal death in CA1 region of hippocampus 3. ↓ STAT1 expression
[37]	C57BL/6 mice	Ulcer colitis	Apigenin solution (200 mg/kg	-	-	-	21 days	↓ Levels of the inflammatory cytokines: TNF-α, IL-1β, IL-6, MCP-1, and CSF-1 and COX-2

Ref	Model	Disease	Treatment	Vehicle			Duration	Results
			(low dose) or 300 mg/kg (high dose)					
[37]	Balb/C mice	Colonic cancer	Apigenin (200 or 300 mg/kg/daily)	-	-	-	68	↓ TNF-α, IL-1β, IL-6, MCP-1, MPO and CSF-1 and of COX-2
[37]	HCT-116 human colon cancer cell line	Colonic cancer	Apigenin (200 or 300 mg/kg/daily)	-	$6.0×10^4$	$6.0×10^4$	24 hours	↓ STAT3 expression
[38]	RAW 264.7 macrophages	Double-stranded RNA (dsRNA)-induced macrophages	Quercetin (50 µg)	-	-	-	24 hours	1. ↓ NO, IL-6, MCP-1, IP-10, TNF-α 2. ↓ STAT3 and STAT1 expression
[39]	Male Sprague-Dawley rats	Parkinson disease	*Morinda citrifolia* fruits (150 mg/kg/body weight)	DMSO and PEG in the ratio of 1:1	10	10	30 days	↓ neuron loss
[40]	Male Sprague-Dawley rats	Cerebral ischemia-reperfusion injury	Curcumin (80 mg/kg)	-	10	10	24 hours	1. ↓ IL-1β and IL-8 2. ↓ JAK2/STAT3 expression
[41]	Male Wistar rats	T8 spinal cord injury	Curcumin (6 mg/kg)	olive oil	30	30	28 days	1. ↓ IL-4, IL-1, IL-2, IL-6, IL-12, TNF-α 2. ↓ STAT3 expression
[42]	Female C57BL/6J mice	Alzheimer's disease	Curcumin (150-300 mg/kg/day)	Normal saline	5	5	60 days	↓ STAT expression

Ref	Model	Condition	Treatment	Control	n (treat)	n (control)	Duration	Outcomes
[43]	Male Wistar rats	Lyolecithin-induced focal demyelination	Curcumin (12.5 mg/kg)	Normal saline	6	6	14 days	1. ↓ IL-1β, NO TGF-β, IL-6, IL-21, IL-12, IL-17 and TNF-α 2. ↓ STAT expression
[44]	Male C57BL/6 mice	Diabetes	Resveratrol) mixed with AIN93G diet (50 mg/kg/day)	-	-	-	6 weeks	1. ↓ Bodyweight 2. ↑ JAK1, Hdac4 expression 3. ↓ Hat1, ApoE, socs2, socs5, IL-15 and IL-22
[45]	Sprague-Dawley rats	Middle cerebral ischemia/reperfusion (I/R)	Trans-resveratrol (20 mg/kg)	-	-	-	7 days	1. Relieved anxiety-like behavior induced by I/R 2. protect rats from the cognitive impairment induced by I/R 3. ↓ neuronal loss in hippocampus 4. ↓MDA levels induced by I/R 5. ↓ SOD activity 6. ↓ IL-6, TNF-α, Bax (in hippocampus) 7. ↑ Bcl-2 (in hippocampus)
[46]	Male C57BL/6 mice	-	Resveratrol (50 mg/kg/day)		4	4	6 weeks	1. ↓IL-6, MAPKapk2 2. ↑P1KR2, Wnt7a
[47, 48]	RAW264.7 macrophages	Inflammatory responses	Luteolin (5 * 10³ μM)	-	2 *10⁵ cells/mL	-	24 hours	1. ↓ IL-1β, IFN-a NO, IL-6 and TNF-α 2. ↓ STAT3 expression
[49]	Male rats	Focal cerebral ischemia	Luteulin (20-80 mg/kg)	DMSO	-	-	48 hours	1. ↓ IL-1β, IFN-a NO, IL-6,COX2 and TNF-α 2. ↓ JAK/STAT expression
[50]	In vivo and in vitro study	Inflammation	Extra virgin olive oil polyphenol range 50-800	-	-	-	-	1. ↓ Inflammatory cytokines and JAK/STAT expression

	mg/kg as luteulin

Abbreviations: PD: Parkinson's disease ; DMSO: Dimethyl sulfoxide ; IL: Interleukin ; IFN: Interferon ; COX: Cyclooxigenase ; Bax: Bcl-2 associated X protein ; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetra- hydropyridine ; CSF-1: Colony stimulating factor 1 ; STAT3: signal transducer and activator of transcription 3 ; VM: ventral mesencephalic ; NO: Nitric Oxide ; MCP: Middle cerebellar peduncle ; ICP: Inferior cerebellar peduncle ; SD: Sprague-Dawley ; IL-10: interleukin-10 ; LPS: lipopolysaccharides ; TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling ; I/R: ischemia/reperfusion ; JAK: janus kinase ; DJ-1: CAP1/RS/PARK7 ; KO: knock out ; qPCR: quantitative real-time polymerase chain reaction ; BDNF: brain derived neurotrhophic factor ; PEG: Polyethylene glycol ; GDNF: glial cell line-derived neurotrophic factor ; iNOS: inducible nitrogen oxide synthase ; LC/NE: noradrenergic locus coeruleus ; RT-PCR: real-time PCR ; SOD: superoxide dismutase ; WST-1: water-soluble tetrazolium salt-1 ; P: paraquat ; M: Maneb ; QD: once daily ; BID: twice daily ; Tyk: Tyrosine kinase ; TNF-α: tumor necrosis factor α ; GLAST: glutamate/aspartate transporter ; LTP: long-term potentiation ; Nedd4-2: neuronal precursor cell expressed developmentally downregulated 4-2 ; TGF-β1: transforming growth factor-β1 ; GDNF: glial cell line-derived neurotrophic factor ; LUT-7G : luteolin-7-O-glucoside ; MPP$^+$: 1-methyl-4-phenylpyridinium

8.1. Tofacitinib

Tofacitinib was the first Jakinib that was licensed for use in autoimmune disorders. It is an inhibitor of JAK1/JAK3 with effective action against JAK2 [51]. Several experiments had found substantial progress in bone marrow edema and improved synovitis scoring when Tofacitinib was used alone. Besides its anti-inflammatory effects, Tofacitinib may relieve extreme RA symptoms, inflammatory bowel disease (IBD), and psoriasis. Studies have shown a decreased risk of infection in patients treated with Tofacitinib [52]. It was reported that adverse effects such as anemia, leukopenia, neutropenia, lymphopenia and thrombocytopenia less pronounced when lower doses of Tofacitinib was prescribed to patients. Long-term suppression of the JAK/STAT pathway is associated with a higher risk of developing malignancies such as lymphoma and non-melanomatous skin cancer due to decreased IFNs [28, 53]. There is evidence that use of Tofacitinib over a long period increased the risk of cardiovascular diseases due to a decrease in IL-6, which ultimately raises the levels of low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and

triglycerides. Clinically, no cases of hepatic or renal injury in patients treated with Tofacitinib have been published [54, 55].

8.2. Ruxolitinib

Ruxolitinib is a JAK1 and JAK2 inhibitor that developed for polycythemia vera, thrombocythemia, and myelofibrosis treatment. It was shown that Ruxolitinib inhibits the STAT3 phosphorylation and mediates autoimmune and inflammatory diseases. Ruxolitinib mediated anti-inflammatory effects, found beneficial for chilblain lupus erythematosus, dermatomyositis, alopecia, and plaque psoriasis treatment [56, 57].

8.3. Baricitinib

Baricitinib is also a selective JAK1/JAK2 inhibitor, able to inhibit the intracellular signaling of multiple pro-inflammatory cytokines, including IL-6, IL-12, IL-23, and IFNc. Baricitinib has been shown to improve RA, alopecia areata, as well as plaque psoriasis in clinical trials [58, 59].

8.4. Oclacitinib

Oclatinib is another JAK inhibitor that represents as a therapeutic strategy for allergic diseases, canine eczema, and atopic dermatitis [60, 61].

8.5. Decernotinib (VX-509)

Decernotinib is an anti-inflammatory agent against RA (in vitro) with improved selectivity to JAK3 relative to JAK1, JAK2, and TYK2. Adverse events included transaminitis and hyperlipidemia and are similar to first-generation medications. Current studies have indicated that synovitis and osteitis may improve in RA patients [62].

8.6. Filgotinib GLPG0634

Filgotinib inhibits both JAK1 and JAK2, with more specificity for JAK1 inhibition. Filgotinib also inhibits T-helper (Th)1 and Th2 cells dose-dependently. The therapeutic effect of Filgotinib in RA and IBD was reported in several studies. Filgotinib resulted in a rise of hemoglobin, and HDL with no change in LDL levels, leading to atherogenic profile [63-66].

8.7. ABT494

ABT-494 belongs to a recent (next) generation of Jakinibs with JAK1 over JAK2 selectivity and can bind to the JH1 adenosine triphosphate binding site. ABT-494 is more specific to JAK1, making it possible for mild patients with severe RA who have not responded to any anti-TNF therapy [67-69].

8.8. Peficitinib (ASP015K)

Peficitinib (ASP015K) is an enzyme inhibitor of JAK1, JAK2, JAK3 and TYK2, with mild JAK3 selectivity and an appropriate safety profile. Through its anti-inflammatory activity, Peficitinib has been shown to minimize paw swelling and ankle bone damage in patients with arthritis [70-72].

8.9. Solcitinib (GSK2586184)

Solcitinib is a selective JAK1 inhibitor with therapeutic efficacy in plaque psoriasis and systemic lupus erythematosus due to reduction of IFNs [73-76].

8.10. INCB039110

INCB039110 is a potent inhibitor of JAK1, but it is capable of blocking JAK2 and JAK3. It has also been shown that INCB039110 reduces inflammatory pathways that are involved in psoriasis and RA. Infectious nasopharyngitis, elevated transaminases, and hypertriglyceridemia were the typical adverse reactions similar to non-selective Jakinibs [77].

9. Natural inhibitors of the JAK/STAT pathway as a novel treatment strategy for the treatment of Parkinson disease

For managing various complex conditions, natural resources are used, which are readily accessible, easy to transport, low cost and have a relatively long shelf life. In vitro, animal and human studies have included studies on the toxicity of natural products, which have shown that the most important benefit of herbal medicine compared to conventional medicines is non-serious adverse effects and low toxicity. Natural products are better than chemical drugs and can be represented as a new alternative for treating various diseases [78-80]. Owing to their inhibitory effects against inflammation, oxidatiave stress, metal toxicity, AChE activity and protein aggregation, natural products and isolated phytochemicals have recently received

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increasing attention for their neuroprotective effects and potential therapeutic applications in neurodegenerative diseases. In terms of their anti-inflammatory and anti-oxidant effects, natural products or plant extracts (i.e. plants such as Spirulina platensis, Eisenia bicyclis, Uncaria rhynchophylla, Panax ginseng, Withania somnifera and extracts such as curcumin, resveratrol, quercetin, apigenin, luteolin) also fulfil the multi-target drug profile [81-83]. Here, we have compiled a list of natural products that can suppress inflammation and oxidative status by inhibiting the signaling pathway of JAK/STAT, thus has the potential to improve the pathophysiology of PD (Table 3) [81, 82].

Table 3. Natural inhibitors of the JAK/STAT pathway

Ref.	Study Design	Disease Model	Intervention		Number of cases		Treatment Duration	Results
			Case	*Control*	*Case*	*Control*		
[33]	BEAS-2B human bronchial epithelial cell line	-	*L. pacari* extract (10, 50 or 250 mg/mL gallic acid, ferulic acid, ellagic acid, rosmarinic acid, apigenin, kaempferol, luteolin, rutin, quercetin)	DMSO 0.05%)	$1*10^5$ cells/mL	$1*10^5$ cells/mL	-	1. ↓ IL-6, IL-8 and CCL2 production 2. ↓ STAT3 expression 3. ↑IL-10
[34]	Male Sprague-Dawley rats	Renal ischemia/reperfusion injury (IRI)	Apigenin (4 mg/kg)	Normal saline	10	10	24 hours	1. ↓ JAK2/STAT3 expression 2. ↓ apoptosis 3. ↓ SOD, Caspase 3 expression
[35]	Male Sprague-Dawley rats	Myocardial reperfusion Injury	Apigenin (4 mg/kg)	Normal saline (4 mg/kg)	-	-	72 hours	1. ↓ JAK2/STAT3 expression 2. ↓ apoptosis and ROS production
[36]	Male Wistar rats	Chronic restraint stress	*Spinacia* extract containing apigenin and luteolin	Normal saline	5	5	21 days	1. ↓ IL-1β, IL-6, IL-8 and TNF-α 2. ↓ neuronal death in the CA1 region of the hippocampus 3. ↓ STAT1 expression
[37]	C57BL/6 mice	Ulcer colitis	Apigenin solution (200 mg/kg (low dose)	-	-	-	21 days	↓ Levels of the inflammatory cytokines: TNF-α, IL-1β, IL-6, MCP-1, and CSF-1 and COX-2

Ref	Model	Disease	Compound	Vehicle			Duration	Outcome
			or 300 mg/kg (high dose)					
[37]	Balb/C mice	Colonic cancer	Apigenin (200 or 300 mg/kg/daily)	-	-	-	68	↓ TNF-α, IL-1β, IL-6, MCP-1,MPO and CSF-1 and of COX-2
[37]	HCT-116 human colon cancer cell line	Colonic cancer	Apigenin (200 or 300 mg/kg/daily)	-	6.0×10^4	6.0×10^4	24 hours	↓ STAT3 expression
[38]	RAW 264.7 macrophages	Double-stranded RNA (dsRNA)-induced macrophages	Quercetin (50 μg)	-	-	-	24 hours	1. ↓ NO, IL-6, MCP-1, IP-10, TNF-α 2. ↓ STAT3 and STAT1 expression
[39]	Male Sprague-Dawley rats	Parkinson disease	*Morinda citrifolia* fruits (150 mg/kg/body weight)	DMSO and PEG in the ratio of 1:1	10	10	30 days	↓ neuron loss
[40]	Male Sprague-Dawley rats	Cerebral ischemia-reperfusion injury	Curcumin (80 mg/kg)	-	10	10	24 hours	1. ↓ IL-1β and IL-8 2. ↓ JAK2/STAT3 expression
[41]	Male Wistar rats	T8 spinal cord injury	Curcumin (6 mg/kg)	olive oil	30	30	28 days	1. ↓ IL-4, IL-1, IL-2, IL-6, IL-12, TNF-α 2.↓ STAT3 expression
[42]	Female C57BL/6J mice	Alzheimer's disease	Curcumin (150-300 mg/kg/day)	Normal saline	5	5	60 days	↓ STAT expression
[43]					6	6	14 days	

Ref	Subject	Disease/Model	Treatment (dose)	Control			Duration	Results
	Male Wistar rats	Lyolecithin-induced focal demyelination	Curcumin (12.5 mg/kg)	Normal saline				1. ↓ IL-1β, NO TGF-β, IL-6, IL-21, IL-12, IL-17 and TNF-α 2. ↓ STAT expression
[44]	Male C57BL/6 mice	Diabetes	Resveratrol) mixed with AIN93G diet (50 mg/kg/day)	-	-	-	6 weeks	4. ↓ Bodyweight 5. ↑ JAK1, Hdac4 expression 6. ↓ Hat1, ApoE, socs2, socs5, IL-15 and IL-22
[45]	Sprague-Dawley rats	Middle cerebral ischemia/reperfusion (I/R)	Trans-resveratrol (20 mg/kg)	-	-	-	7 days	8. Relieved anxiety-like behavior induced by I/R 9. protect rats from the cognitive impairment induced by I/R 10. ↓ neuronal loss in hippocampus 11. ↓ MDA levels induced by I/R 12. ↓ SOD activity 13. ↓ IL-6, TNF-α, Bax (in hippocampus) 14. ↑ Bcl-2 (in hippocampus)
[46]	Male C57BL/6 mice	-	Resveratrol (50 mg/kg/day)		4	4	6 weeks	3. ↓ IL-6, MAPKapk2 4. ↑ P1KR2, Wnt7a
[47, 48]	RAW264.7 macrophages	Inflammatory responses	Luteolin (5 * 10³ μM)	-	2 *10⁵ cells/mL	-	24 hours	1. ↓ IL-1β, IFN-a NO, IL-6 and TNF-α 2. ↓ STAT3 expression
[49]	Male rats	Focal cerebral ischemia	Luteulin (20-80 mg/kg)	DMSO	-	-	48 hours	1. ↓ IL-1β, IFN-a NO, IL-6, COX2 and TNF-α 2. ↓ JAK/STAT expression
[50]	In vivo and in vitro study	Inflammation	Extra virgin olive oil polyphenol range 50-800 mg/kg as luteulin	-	-	-	-	1. ↓ Inflammatory cytokines and JAK/STAT expression

Abbreviations: PD: Parkinson's disease ; DMSO: Dimethyl sulfoxide ; IL: Interleukin ; IFN: Interferon ; COX: Cyclooxigenase ; Bax: Bcl-2 associated X protein ; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetra- hydropyridine ; CSF-1: Colony stimulating factor 1 ; STAT3: signal transducer and activator of transcription 3 ; VM: ventral mesencephalic ; NO: Nitric Oxide ; MCP: Middle cerebellar peduncle ; ICP: Inferior cerebellar peduncle ; SD: Sprague-Dawley ; IL-10: interleukin-10 ; LPS: lipopolysaccharides ; TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling ; I/R: ischemia/reperfusion ; JAK: janus kinase ; DJ-1: CAP1/RS/PARK7 ; KO: knock out ; qPCR: quantitative real-time polymerase chain reaction ; BDNF: brain derived neurotrhophic factor ; PEG: Polyethylene glycol ; GDNF: glial cell line-derived neurotrophic factor ; iNOS: inducible nitrogen oxide synthase ; LC/NE: noradrenergic locus coeruleus ; RT-PCR: real-time PCR ; SOD: superoxide dismutase ; WST-1: water-soluble tetrazolium salt-1 ; P: paraquat ; M: Maneb ; QD: once daily ; BID: twice daily ; Tyk: Tyrosine kinase ; TNF-α: tumor necrosis factor α ; GLAST: glutamate/aspartate transporter ; LTP: long-term potentiation ; Nedd4-2: neuronal precursor cell expressed developmentally downregulated 4-2 ; TGF-β1: transforming growth factor-β1 ; GDNF: glial cell line-derived neurotrophic factor ; LUT-7G : luteolin-7-O-glucoside ; MPP$^+$: 1-methyl-4-phenylpyridinium

9.1. Luteolin

Luteolin is a hydroxyflavone present in many dietary sources. Luteolin's anticancer property is implicated in apoptosis induction and inhibition of invasion, angiogenesis, and metastases of tumor cells. It also has antioxidant properties by the scavenging of free nitrite ions and oxides. Luteolin can cross the blood-brain barrier (BBB) and is a treatment choice for many neurodegenerative disorders, primarily based on its anti-inflammatory, anti-oxidant, and neuroprotective effects. In the AD mouse model of the brain, luteolin reduced the development of pro-inflammatory cytokines and blocked microglial activation [47-49]. Other studies have shown that luteolin lowers serum levels of pro-inflammatory cytokines such as TNF-αTNF-α and IL-6 by neuroinflammation mediated by microglia and by targeting the signaling pathways NF-arb, Jun N-terminal kinase (JNK), activator protein 1 (AP1), and STATs. Inhibiting the production of IL-1β, TNF-αTNF-α, cyclooxygenase-2 (COX-2), inducible nitrogen oxide synthase (iNOS) as well as NO production, Luteolin suppresses NF-1βB activation. To minimize IL-6, luteolin also inhibits JNK phosphorylation and subsequent binding of AP1, thus suppressing microglial activation. Besides, luteolin attenuates oxidative stress and in activated microglia blocks the pathways of mitogen-activated protein kinase (MAPK). Luteolin is also downregulated by STAT-mediated expression of the TNF-α and IL-6 pathways. Besides, luteolin attenuates oxidative stress and in activated microglia blocks the pathways of

mitogen-activated protein kinase (MAPK). Luteolin is also downregulated by STAT-mediated expression of the TNF-α and IL-6 pathways. In short, luteolin can ameliorate inflammatory and oxidative agents so that it may serve as a therapeutic agent in PD. [47-49].

9.2. Quercetin

Quercetin is a plant flavonol from the flavonoid group of polyphenols and is presented in many plants and food sources. Quercetin is a potent antioxidant and anti-inflammatory compound, with the ability to repair DNA dam. Thusthus it has therapeutic potential in cancer, neurodegenerative disorders, and heart disease. It has been demonstrated that quercetin could cross the BBB and reduce ROS in the CNS. Quercetin reverses behavioral alterations in olfactory bulbectomy-induced depression, and Huntington's disease via microglial inhibition. The neuroprotective effect of quercetin has been observed in many neurological impairments such as stroke, PD, and AD, which has been implicated in its anti-inflammatory, and antioxidant activities [38, 39]. Quercetin suppresses both NO production and MPP+ (an MPTP derivative that causes dopaminergic neuronal death) activity, thereby decreasing oxidative stress in activated microglia. Quercetin inhibits IL-12 expression and LPS-and IFNc-induced oxidative stress by inhibiting iNOS expression and NO secretion in activated microglia by blocking IKB kinase (IKK), NF-£B, AP-1, STAT-1, JAK-1, c-Jun N-terminal kinase, p38, and IFN regulatory factor-1 (IRF-1) signaling pathways. Quercetin also initiates the Ho-1 enzyme, which induces IL-10, and IL-1 antagonists as anti-inflammatory cytokines. These data demonstrate that quercetin is a potent anti-inflammatory and antioxidant therapeutic agent, particularly for treating neurodegenerative disorders such as PD [38, 39, 84].

9.3. Resveratrol

Resveratrol (3, 40, 5 trihydroxystilbene) is a well-known phenolic compound belonging to stilbenes. Medicinal application of resveratrol has been documented in various diseases, including neurodegenerative impairments, due to its antioxidant and anti-inflammatory potentials. Resveratrol reduces ROS production in the CNS, by mediating glutathione peroxidase and superoxide dismutase activities. Resveratrol also represses microglial activation and amyloid plaques formation. It was shown that administration of stilbene, a resveratrol analogue, significantly reduced the cognitive and behavioral deficits in animal models. Resveratrol significantly inhibited the inflammatory response and neuronal loss by

decreasing IL-6, IFN-γ, TNF-α, and COX-2 levels in PD. In another study, resveratrol mediated the inflammation state through prevention of NF-κB and the JAK/STAT signaling pathway phosphorylation, suppression of IL-6 and TNF-α expression, reduction of oxidative stress by downregulation of the NO production, and upregulation of suppressor of cytokine signaling-1 and IL-10 [44-46].

9.4. Curcumin

Curcumin (diferuloylmethane) is the main bioactive constituent of the rhizomes of *Curcuma longa* (turmeric), which is reputed for its safety as well as pharmacological effects such as anti-tumor, anti-inflammatory, antioxidant and as an anti-hyperglycemic activities [85-91]. Curcumin can cross the BBB and has medicinal potential against several neurodegenerative phenomena [40-43]. Curcumin has been shown to suppress apoptosis, oxidative stress, and pro-inflammatory mediators in neurons, thereby, contributing to synaptic plasticity recovery, a reduced period of brain injuries, and improved cognitive and motor capacity. Besides, curcumin decreases the inflammatory responses of the NF-nB-induced microglial and toll-like receptor-2 (TLR-2) and attenuates oxidative stress, ROS level, iNOS expression, NO development, and mitochondrial dysfunction. The expression levels of COX-2 and pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are downregulated by curcumin by inhibiting the nuclear translocation NF-p65 subunit. Curcumin also inhibits the JNK and p38 MAPK pathways and the NF-3B and AP1 transcription factors' DNA binding ability to control cytokine expression [40-43]. The microglial expression of intercellular adhesion molecule 1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1), a key microglial migration molecule, was mitigated by the compound. To block the JACK/STAT pathway and downregulate pro-inflammatory genes such as STAT-1, IL-6 and iNOS, curcumin was found. It has also triggered anti-inflammatory genes, i.e. IL-4, and a peroxisome proliferator-activated receptor alpha (PPARα) antioxidant genes [40-43]. Collectively, curcumin is an ideal candidate to regulate PD for potential drug design.

9.5. Apigenin

Apigenin is a plant-derived flavonoid with known antioxidant, anti-inflammatory, and anti-cancer activities. The neuroprotective effect of apigenin is correlated to its antioxidant activity. It was shown that apigenin increases the levels of superoxide dismutase, catalase, and

glutathione while reducing the activity of lipid peroxidation, caspase-3, and caspase-9 [33, 36]. PD-induced NF-βB activation is known to contribute to the elevation of many pro-inflammatory variables, including iNOS, IL-1β, IL-6, COX-2, and TNF-αTNF-α. By reducing IL-6 levels in vivo and suppressing CD40, TNF-αTNF-α and IL-6 development by inhibiting IFN-γ-induced phosphorylation of STAT1 in vitro, apigenin has been shown to reverse these effects significantly. By inhibiting iNOS and COX-2 in vivo and in vitro, Apigenin can suppress NO and prostaglandin levels, which may delay neuronal apoptosis and decrease the progression of PD. By inactivating the NF-diesB, STAT, MAPK/extracellular signal-regulated protein kinase (ERK), JNK and p38 pathways, apigenin attenuates the release of inflammatory cytokines [34, 35, 37].

10. Conclusion and future perspective

For the defense of the host and homeostasis of the immune system, the activation of immunity is vital; however, deregulation of the immune system results in deleterious consequences, such as neuroinflammatory diseases. Aberrant activity of innate immune cells leads to neuronal degeneration and demyelination. This process eventually stimulates the overproduction of inflammatory mediators (i.e., cytokines and chemokines), and oxidative factors such as ROS and NO, or activates the immune response (i.e., effector T cells). It is well evidenced that the JAK/STAT signal pathway is an active participant of these mechanisms. These data clarify that targeting the JAK/STAT pathway might be a prophylactic therapy for inflammation-induced neurodegenerative diseases. Up to date, more than 25 JAK/STAT inhibitors have been developed. They are in step I, II and III clinical trials for a variety of diseases such as psoriasis, transplant rejection, diabetic nephropathy, Crohn's disease, lupus, lymphoma and solid tumors [28, 51, 52, 58, 68]. Herein, we reported several synthetic or natural compounds (phytochemicals) that can control the inflammatory- and oxidative-related PD complications by mediating the JAK/STAT pathway. However, the number of these phytochemicals is minimal and concludes their efficiency, as jacknibs, difficult. Besides, blockade of LRRK2 is a way to suppress the microglial and JAK/STAT responses and is favorable for PD therapy. Our review suggests that JAK/STAT inhibitors may be a potential therapeutic option for PD patients by blocking neuroinflammatory, oxidative stress, and neurodegenerative processes, however, more clinical studies are warranted.

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