Review Paper
The Role of Dysregulated Neuroinflammatory Molecular Pathways in Parkinson Disease: A Systematic Review

Mohammadreza Kosari[1] , Afsaneh Asgari Taei[2] , Andis Klegeris[3] , Sevim Soleimani[4] , Arian Tavasol[4] , Kimia Jazi[5] , Kimia Eyvani[6] , Ashkan Bahrami[7] , Zahra Farrokhi[8] , Farnoosh Vosough[9] , Faraz Rahmani Khajeh[10] , Saleh Behzadi[11] , Zohreh Zamani[12*]

1. Tongji Medical College, Wuhan Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China.
2. Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3. Department of Biology, Faculty of Science, University of British Columbia Okanagan Campus, Kelowna, Canada.
4. School of Medicine, Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
5. Student Research Committee, School of Medicine, Qom University of Medical Sciences, Qom, Iran.
6. Student Research Committee, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
7. Student Research Committee, Faculty of Medicine, Kashan University of Medical Science, Kashan, Iran.
8. Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
9. Student Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
10. Student Research Committee, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
11. Student Research Committee, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.
12. Department of Neurology, Firoozabadi Clinical Research Development Unit (FACRDU), Iran University of Medical Sciences, Tehran, Iran.

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A B S T R A C T

Background: Parkinson disease (PD) is a prevalent neurodegenerative disorder affecting dopaminergic neurons in the substantia nigra (SN). Neuroinflammation has a vital role in PD pathophysiology.

Objectives: This study assesses whether the neuroinflammatory molecular and signaling pathways could be associated with PD's progression and clinical manifestations.

Materials & Methods: PubMed, Web of Science, Embase, and Scopus databases were investigated from 2006 until December 2023 to find relevant studies. All observational studies written in English and reporting qualitative or quantitative information on the relationship between neuroinflammation and PD were included in this review.

Results: Finally, 41 papers were involved in the systematic review. According to the involved studies, it is suggested that tumor necrosis factor-α, C-reactive protein, microsomal prostaglandin E synthase1, toll-like receptor-4 (TLR-4), CCL23, CCL25, TNF-receptor superfamily member 9,

* Corresponding Author:

Zohreh Zamani, MD.

Address: Department of Neurology, Firoozabadi Clinical Research Development Unit (FACRDU), Iran University of Medical Sciences, Tehran, Iran.

Tel: *+98 +98 (912) 8763524,* ***Fax:*** *+98 +98 (912) 8763524*

E-mail: *zamani.zhrh@gmail.com*

EV-derived cytokines, transforming growth factor alpha, vascular endothelial growth factor A, SH-SY5Y, TLR 2/4, miR-485-3p, leucine-rich repeat kinase 2, and α-synuclein may be upregulated in the PD patients. Also, the activity of astrocytes and microglial cells was reported to be increased in PD patients through different mechanisms.

Conclusion: This study demonstrated that the neurodegeneration in PD could be initiated by α-synuclein protein aggregation and the activation of astrocytes and microglial cells, which leads to neuroinflammation characterized by inflammatory responses in neurons. Finally, chronic neuroinflammation could be the cause of dopaminergic neuronal death in SN. The impact of both single and all factors involved in neuroinflammation was assessed to plan further studies in a particular pathway to intercept the onset of inflammatory pathways in favor of therapeutic purposes.

Keywords: C-reactive protein (CRP), Tumor necrosis factor (TNF)-α, α-Synuclein, Toll-like receptor (TLR)2, TLR9, Neuroinflammation, Parkinson disease (PD), Lipocalin-2 (LCN2)

Highlights

• The aggregation of alpha-synuclein protein can potentially trigger neurodegeneration in Parkinson disease (PD).

• Tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), microsomal prostaglandin E synthase1 (mPGES-1), toll-like receptor-4 (TLR-4), CCL23, CCL25, TNF-receptor superfamily member 9, EV-derived cytokines, transforming growth factor alpha (TGF-α), vascular endothelial growth factor A (VEGFA), SH-SY5Y, TLR 2/4, miR-485-3p, and leucine-rich repeat kinase 2 may be upregulated in Parkinson disease.

• The activity of astrocytes and microglial cells is increased in PD patients.

Introduction

Parkinson disease (PD) is a neurodegenerative disease characterized by the progressive degeneration of dopaminergic (DA) neurons in the substantia nigra (SN) and their projections to the striatum. Clinical hallmarks of PD consist of postural instability, bradykinesia, resting tremor, and rigidity. The major non-motor symptoms of PD are sensory deficits, sleep disorders, cognitive impairment, depression, anxiety, and autonomic dysfunctions [1-4].

Several pathological structures containing misfolded proteins are observed in PD brain tissue, including limbic and cortical Lewy bodies [5], senile plaques, and neurofibrillary tangles [6]. α-Synuclein (α-syn), the key factor of Lewy bodies, is the main protein involved in neurodegeneration and neuronal cell toxicity [7]. Monomeric α-syn and oligomeric aggregates of this protein are believed to be critical players in PD pathogenesis [8]. The deterioration of cognition in PD patients is caused by progressive neuronal dysfunction in various cortical regions affected by α-syn pathology [9], which is also associated with neuroinflammatory processes [10]. Neuroinflammation is crucial in different stages of PD progression, from early α-syn aggregation and degeneration of dopaminergic neurons to the onset of clinical symptoms [11-14]. Dysregulation of inflammatory pathways is one of the inflammatory components of PD, and it is likely caused by genetic predispositions, immunological changes brought on by aging, and the initial activation of glia as a result of neuronal injury [15, 16]. Also, the aggregation of misfolded proteins like α-syn and blood-brain barrier (BBB) disruption, are the initial changes in the pathogenesis of PD and can be induced by neuroinflammation [17, 18]. The selective injury of dopaminergic neurons in the nigrostriatal path can be due to the neurotoxic effects of inflammatory mediators mainly secreted by reactive microglia. The pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 have vital roles in the cellular death observed in PD and other chronic neuro-inflammatory conditions [19, 20]. Interferon-gamma (IFN-γ), which has an important role in autoimmune disease, also induces neurodegeneration in PD [21]. C-reactive protein (CRP) is another participant in neuro-inflammatory responses in PD. It is an acute-phase serum protein that becomes upregulated following an increase in IL-6 levels [22].
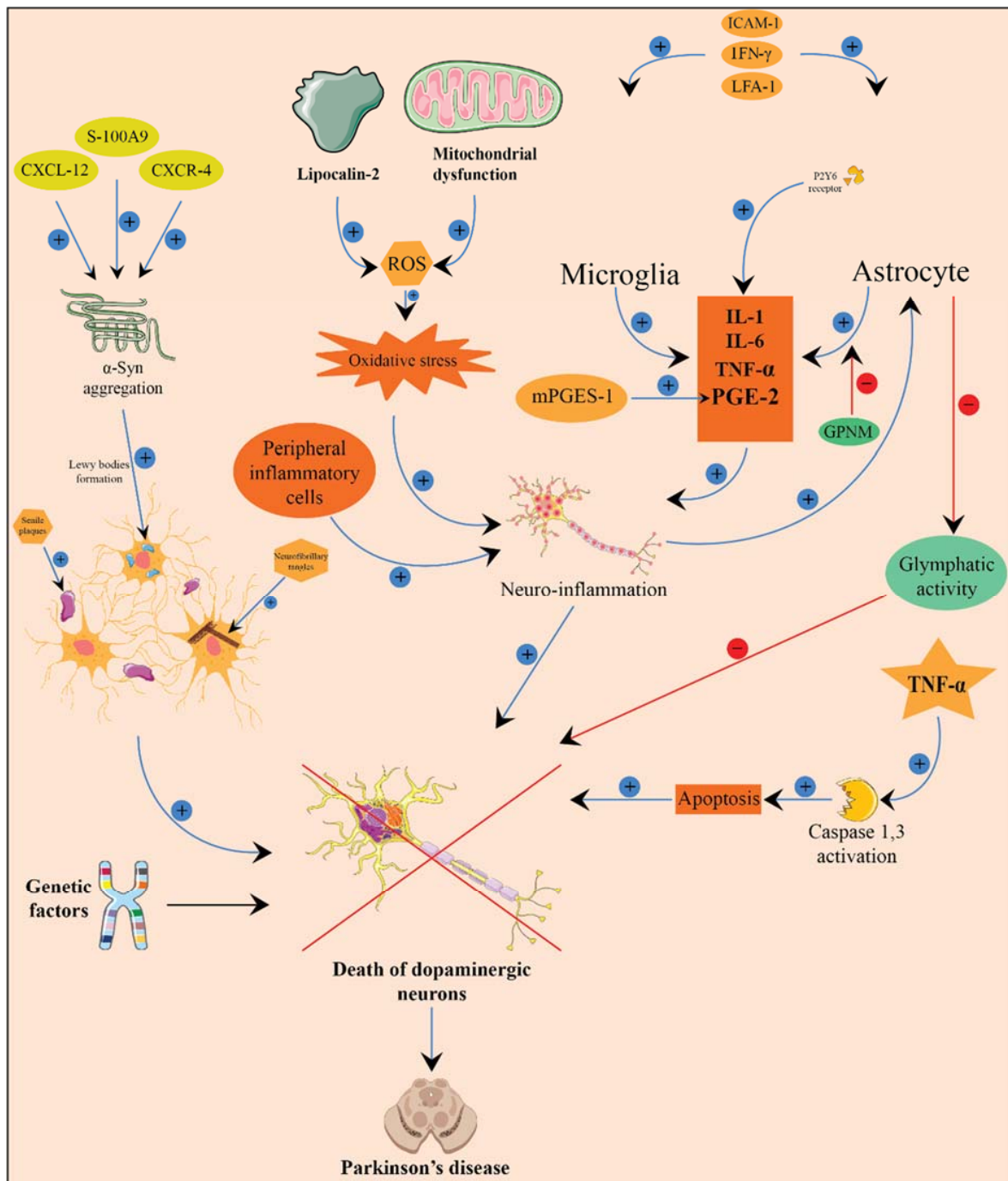
Figure 1. Schematic representation of the pathophysiology of PD

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Notes: Five main factors play a part in the pathophysiology of PD: 1) Neuroinflammation, 2) Apoptosis, 3) Protein aggregation, 4) Reduced glymphatic activity, and 5) Genetics.

In PD, systemic oxidative stress and neuroinflammation may lead to astrogliosis, which damages the glymphatic system [23]. Notably, reduced glymphatic activity is associated with aging, the primary risk factor for PD [23]. Even though the etiology of PD is not fully established, the importance of genetic factors has become evident [24]. Thus, genetic mutations in 18

chromosomal regions have been identified in familial PD. For example, heterozygous mutations involving the *GBA* gene encoding lysosomal enzyme glucocerebrosidase are one of the greatest common risk factors for PD, increasing its risk 5-6 times [25, 26]. In addition, different single nucleotide polymorphisms (SNPs) which increased PD risk have been detected in the promoter of

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the *TNF-α* gene; especially 238 G/A (rs361525) and 308 G/A (rs1800629) SNPs are demonstrated as important functional polymorphism [27-29].

The current systematic review aims to determine the effects of each neuroinflammatory molecular pathway involved in PD pathogenesis.

Materials and Methods

Search strategy

The literature search was done till December 2023 by two authors independently in PubMed, Web of Science, Scopus, and Embase databases. The following terms, their abbreviations, and MeSH terms were used without any restriction on publication date: "Inflammation," "neuroinflammation," "neurodegenerative disease," "Parkinson's disease," "brain," "inflammatory markers," "C-reactive protein," "C–C chemokine receptor type 3," and "prostaglandin." The reference lists of all identified publications were checked to prevent any duplicate.

Inclusion and exclusion criteria

All observational studies written in English reporting qualitative or quantitative data on the connection between neuroinflammation and PD were included in this review. We excluded animal studies, case reports, conference papers, review studies, studies without randomized sampling, and low-quality studies identified by the quality assessment using the Newcastle-Ottawa scale (NOS). Two authors independently conducted the initial screening based on "titles" and "abstracts" and then selected qualified papers after considering the full text of the nominated articles. A third author resolved differences in opinions.

Quality assessment

NOS was used to evaluate the quality of selected articles. Based on this scale, each study can obtain a maximum of 9 points from the following parameters: Selection of participants (4 points), comparability (2 points), and the valuation of outcomes (3 points). The studies with a score above 6 were considered high-quality studies. Studies with modest quality had points of 4-6, and the quality of studies scored under 4 was low (Table 1).

Data extraction

The following information was extracted from all qualified articles: The first author's name, country of study, date of publication, sample size, and all characteristics of the patient and control groups, including studied inflammatory markers, factors, genes, and the clinical stage of the disease. Data extraction was conducted independently by two authors, and afterward, their results were compared to eliminate discrepancies.

Results

Study selection

We used the PRISMA (preferred reporting items for systematic reviews and meta-analyses) checklist to conduct the present review [18]. A total of 2499 studies were extracted through the search on PubMed, and 7560 by searching other databases (Google Scholar, Scopus, Web of Science, and Embase). Next, 4823 papers were excluded because of repetition in various databases. After reviewing the "titles" and "abstracts" of these chosen articles, 2121 more studies were excluded because of the absence of validation in abstracts, being review studies or non-English. Furthermore, 3003 more papers were excluded because they were unrelated to the key subject or animal articles.

At last, from the 112 remaining studies, 29 records were excluded due to being irrelevant to the subject and the primary effect size of the study. The complete manuscripts of the 83 studies were utterly evaluated, and 42 papers were excluded because of unclear or insufficient data (n=31) and low quality (n=11). Lastly, 41 papers published before December 2023 were selected (Figure 2).

C-reactive protein (CRP)

Seven studies, including 1055 PD patients and 698 healthy controls, reported the participants' CRP levels in the serum [30-34] and plasma [35, 36]. Among studies assessing the CRP in the serum samples of PD patients and their controls, there are four studies by Song et al. [31-34] stating significantly higher stages of high-sensitivity (hs)-CRP in the serum of early PD patients, PD patients with or without dementia, and a whole sample of PD patients in comparison with the control groups. However, Yazar et al. [30] reported that the difference between CRP stages in the serum sample of PD individuals and the control group was not significant (P=0.854).

C–C chemokine receptor type 3

The innate immune system mainly expresses c chemokine receptor type 3 (CCR3) and can bind with several chemokines to activate some inflammatory cells' responses. CCR3 was extracted from isolated granulocytes of the cases, and no significant difference was detected in the CCR3 levels
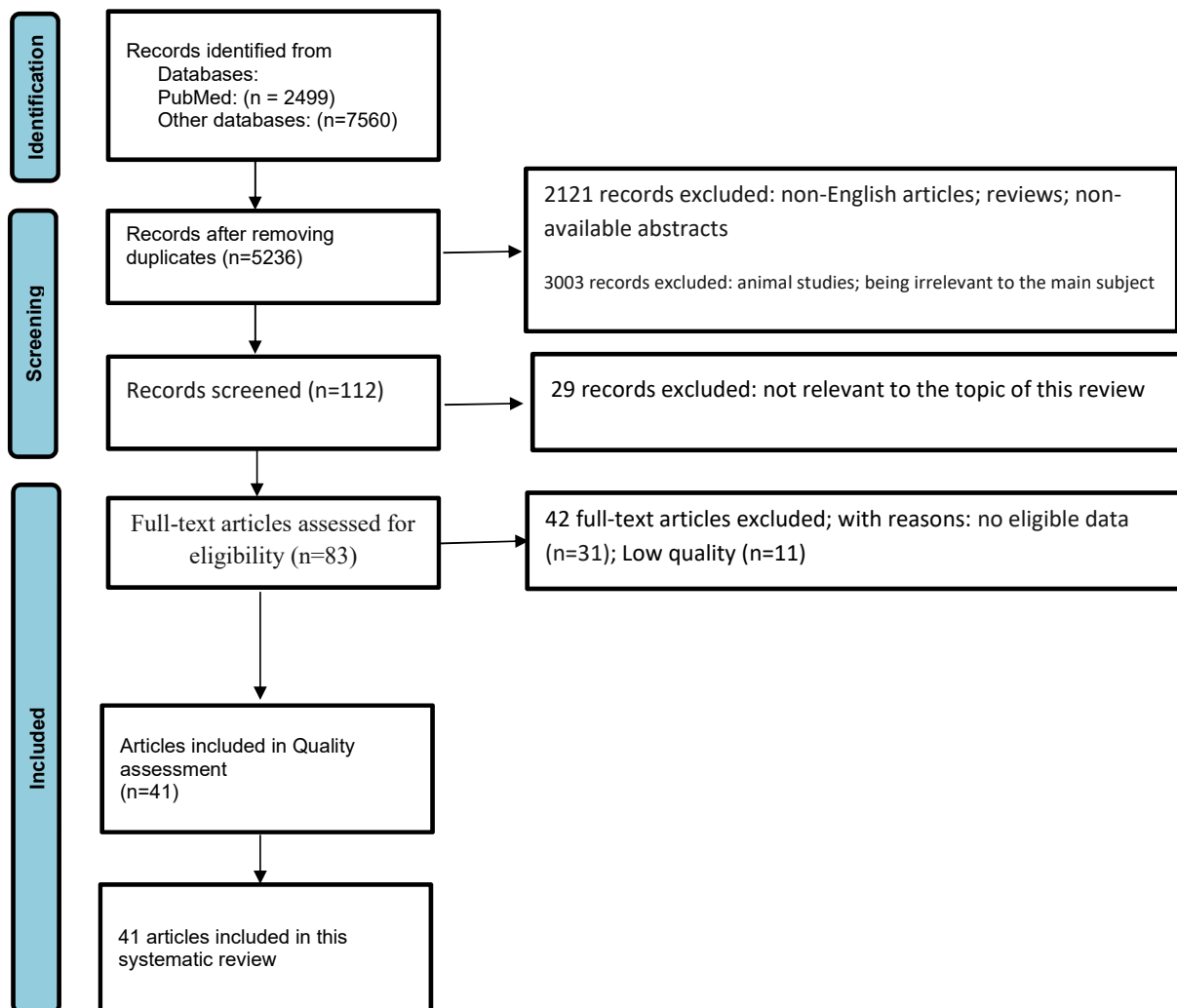
Figure 2. Flow diagram for the search and selection process of included studies according to PRISMA 2020

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among the PD and health control (HC). Therefore, it is not eligible for diagnosing the disease [37].

Some microRNA subtypes role in the inflammatory pathogenesis of PD

MicroRNAs (miRNAs) are small single-stranded classes of RNAs that contribute to regulating gene expression. MiRNA-29a potentially regulates angiogenesis in endothelial cells, leading to BBB dysfunction and neuroinflammation. MiRNA-22 is also associated with angiogenesis-related alterations alongside miRNA-29a. Evaluation of the blood samples obtained from the subjects demonstrates that miRNA-29a and miRNA-22 are remarkably upregulated in the PD individuals compared to the HC group [38]. Quantitative real-time PCR has shown that the expression levels of microRNA-150 are reduced in the serum of PD patients. Thus, it can be considered a diagnostic biomarker for evalu-

ating the disease. There was also a negative association between the pro-cytokines and miR-150 in PD patients [39].

Gut microbiota and inflammatory cytokines responses

Examination of the stool and blood samples collected from PD and control subjects demonstrated an alteration in the fecal gut microbiota in the PD group. The alteration included an increment of *Verrucomicrobia*, *Lactobacillus*, *Porphyromonas*, *Mucispirillum*, and *Parabacteroides* in the PD samples. However, *Prevotella* was more abundant in HC. These alterations were also associated with the severity of some symptoms, such as tremors, in PD patients. The plasma levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin(IL)-1β, IL-4, IL-2, IL-18, IL-6, IL-13, TNFα, and IFNγ were analyzed. An increase in IFNγ, TNFα, and IL-13 was seen in the PD samples compared with the control group [40].

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Table 1. Baseline characteristics of the included human studies

Authors, year	Types of Human Samples or Tissues/Methods	Sample Size (PD)	Sample Size (HC)	Inflammatory Markers/Genes	Outcome	Quality Assessment
Chan et al. 2023 [105]	Plasma	101	45	Interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL6	EV-derived cytokine profiles significantly influenced the severity of postural instability and gait disturbance (PIGD) and cognitive symptoms in patients with PIGD.	7
Hepp et al. 2023 [59]	Plasma	66	52	TGF-alpha, TNFRSF9, CCL23, CCL25, and VEGFA	Patients diagnosed with PD displayed elevated levels of five inflammation-related proteins (TNFRSF9, TGF-alpha, CCL23, CCL25, and VEGFA).	7
Chung et al. 2022 [58]	Transwell coculture system, lipopolysaccharide-activated microglia on the upper point, and retinoic acid-differentiated SH-SY5Y cells	516	513	The multiplex cytokines, sRAGE, and HMGB1, TLR2/4	SH-SY5Y cells cocultured with microglia in an activated state showed increased proinflammatory cytokines, phosphorylation, aggregation, and upregulation of TLR2/4 expression.	7
Lerche et al. 2022 [106]	Cerebrospinal fluid (CSF) and serum	453	-	IL-8, FABP, ICAM-1, MIP-1-beta, MCP-1, and SCF	CSF and serum correlations were weak, with pro-inflammatory mediators like IL-8, FABP, MIP-1-beta, ICAM-1, MCP-1, and SCF	7
Lin et al. 2022 [107]	Serum	92	64	MiR-485-3p	In the serum of PD patients, there was a significant increase in the expression of miR-485-3p compared to healthy individuals. LPS-induced microglia BV2 cells showed elevated miR-485-3p levels, inhibiting pro-inflammatory cytokine release. Knockdown of miR-485-3p targeted FBXO protein 45	6
Diaz et al. 2022 [71]	Blood	26	14	IL-1β, IL-8, IL-2, IL-5, IL-6, IL-7, IL-13, IL 4, IL-10, IL12p70, IFN-γ, GM-CSF, and TNF-α	Parkinson disease has elevated levels of IL-6, IL-4, and minor levels of IFNγ	7
Liao et al. 2022 [60]	Colonic biopsied samples	51	40	Colonic LRRK2	PD patients had a higher fraction of LRRK2-positive cells in their colonic tissues. Individuals with genetic variants also exhibited an elevated expression of LRRK2.	5
Miliukhina et al. 2020 [21]	Plasma	36	28	IFN-γ, IL-6	IFNγ plasma level elevated in PD compared to HC (P<0.001). IL-6 decreased in PD in comparison with HC.	7
Miliukhina et al. 2020 [21]	Serum	31	c29	IFN-γ, TNF-α, IL-6	Decreased IL-6 serum levels in PD patients in comparison with control (P<0.01) TNF-α levels were higher in PD than in the control group (P<0.0001). IFNγ differed from PD but did not have a significant correlation.	7
Iwaoka et al. 2020 [48]	CSF	20	13	IFN-γ, TNF-α, IL-6, IL-1β	TNF-α and IL-1β were highly elevated in PD patients compared to the control group (P = 0.020 and 0.015) No significant differences between the groups IL-6 or IFN-γ.	7

Authors, year	Types of Human Samples or Tissues/Methods	Sample Size (PD)	Sample Size (HC)	Inflammatory Markers/Genes	Outcome	Quality Assessment
Wang et al. 2020 [42]	Peripheral blood samples of individuals	380	380	TLR3 (Rs377529)	*T* allele of rs3775290 decreased susceptibility to PD	7
Moghadam-Ahmadi et al. 2020 [37]	Messenger RNA (mRNA) extracted from isolated granulocytes	30	30	CCR3	Insignificant change in CCR3 expression in patients with Parkinson's disease than the healthy controls.	7
Li et al. 2020 [39]	Quantitative real-time polymerase chain reaction (PCR)	80	60	MicroRNA-150	Downregulated in PD patients in comparison with HC	7
Yu et al. 2020 [38]	Blood samples	33	27	Vascular cell adhesion molecule-1 (VCAM-1)	VCAM-1 expression was higher in PD patients in comparison to HC	5
				Intercellular adhesion molecule-1 (ICAM-1)	ICAM-1 expression was not significantly different in PD compared to HC	
				MicroRNAs (miR-22 and miR-29a)	Significantly upregulated in PD in comparison to HC	
Lin et al. 2019 [40]	DNA extracted from stool samples and blood samples	77	80	Tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ)	Increased in the PD group compared to the HC	9
		120	120	TNF-α, IFN-γ, IL-13	Increased significantly in PD compared to HC	
Wilson et al. 2019 [108]	Imidazoline-2 binding sites (I2BS)	22	14	Astroglia cells	There was an upregulation of I2BS, indicative of reactive astrogliosis, in early-stage PD patients' cortical regions and brainstem. In patients with moderate to advanced PD, there was a noted decrease in I2BS expression in both cortical and subcortical regions.	7
Perez-Pardo, et al. 2019 [41]	Colon biopsies, fecal and blood samples	6	6	TLR-4	Increased TLR4 and pro-inflammatory gene expression in PD patients' colon compared to healthy controls.	6
Ikeda-Matsuo, et al. 2019 [44]	PD postmortem brain specimens	7	4	Microsomal prostaglandin-E synthase 1	Upregulated in dopaminergic neurons in the SN pars compacta of postmortem PD brains	5
Yazar, 2019 [30]	Serum	63	48	CRP	No significant difference in CRP levels (P=0.854)	
Neal et al. 2018 [45]	SN (human gene expression data)	31	17	Glycoprotein non-metastatic melanoma protein B (GPNMB)	GPNMB had higher expression in PD patients compared to HC	6
				CD44	CD44 expression in SN of PD patients increased compared to HC	
Bagheri et al. 2018 [46]	Peripheral blood mononuclear cells (PBMC)	30	40	CXCR4	Expression of CXCR4 elevated in PBMC from PD patients in comparison with controls	6
	Serum levels	30	40	CXCL12	Elevated serum levels in PD patients in comparison with the healthy controls.	
Horvath et al. 2018 [47]	*Escherichia coli*	5	4	S100A9	S100A9 and α-syn were co-localized and co-aggregated in 20% of Lewy bodies and 77% of neuronal cells in the SN.	6
		5	4	α-Synuclein (α-syn)		

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Authors, year	Types of Human Samples or Tissues/Methods	Sample Size (PD)	Sample Size (HC)	Inflammatory Markers/Genes	Outcome	Quality Assessment
Agliardi et al. 2018 [52]	Genomic DNA extracted from PBMC	354	443	rs361525 tumor necrosis factor- single nucleotide polymorphism (TNF-α SNPs)	There is no consequential distinction in distributions of TNF-α polymorphisms genotypes and alleles between PD patients and healthy controls (HC)	7
		354	443	rs1800629 (TNF-α SNPs)		
Wood et al. 2018 [109]	Frontal cortex tissue from postmortem samples	15	43	Diacylglycerols (DAG)	DAG levels increased in the frontal cortex of PD patients compared to controls/HC	6
Yang et al. 2017 [110]	Blood samples	80	80	T-helper 17(Th 17)	Highly elevated serum levels in PD in comparison with HC.	7
				Myeloid-derived suppressor cells (MDSCs)		
Yang et al. 2017 [53]	Peripheral blood mononuclear cells	145	170	P2Y6 receptor (P2Y6R)	P2Y6R expression level increased in PD patients compared to healthy controls	8
Kim et al. 2016 [54]	SN samples obtained from postmortem PD	7	7	Lipocalin-2 (LCN2)	LCN2 expression increased in the SN of PD compared to controls	7
		7	7	Tyrosine hydroxylase (TH)	TH expression decreased in the SN of patients with PD compared to controls	
Zhou et al. 2016 [111]	Blood samples	12	12	IL-1β	PD patients exhibited elevated IL-1β serum levels and enhanced caspase-1 activity compared to controls	6
				Caspase-1		
Shin et al. 2015 [55]	Postmortem SN	4	4	TLR4	TLR4 expression increased in the SN of PD patients compared to controls	6
				Prothrombin kringle-2(pKr-2)	Increase in pKr-2 expression in the SN of PD patients compared to controls	
				TH	TH expression decreased in the SN of PD patients compared to controls	
Hurley et al. 2015 [56]	Postmortem human brain	29	14	Proteinase-activated receptor-2 trypsin-2 serpin-A5 serpin-A13	Neurons and microglia expressed these proteins, and there were alterations in their immunoreactivity in some brain regions	7
Garcia-Esparcia, 2014 [50]	SN	56	43	TNF-α, IL-6	Increased TNF-α levels in neurons and microglia. Increased IL-6 levels in the frontal cortex of PD patients compared to HC.	6
Song, 2014 [31]	Serum	435	221	CRP	hs-CRP[3] level significantly increased in PD patients compared to HC (P<0.001)	8
Çomoğlu, 2013 [49]	Tear	18	17	TNF-α	Tear TNF-α levels are significantly higher in PD compared to HC (P=0.02)	6
Lindqvist, 2013 [51]	CSF	71	33	TNF-α, IL-6	The two groups have no statistically significant difference in inflammatory marker levels.	8
Kalinderi et al. 2013 [43]	DNA isolated from whole blood	215	118	TLR9 -1237 T/C	No significant change in the genotypes or alleles of PD compared to control	7
				TLR2 -196 to -174 deletion		

Authors, year	Types of Human Samples or Tissues/Methods	Sample Size (PD)	Sample Size (HC)	Inflammatory Markers/Genes	Outcome	Quality Assessment
Song, 2013 [32]	Serum	72	84	CRP	Higher hs-CRP in PD patients with and without dementia than HC (P<0.001).	8
Andican, 2012 [35]	Plasma	45	25	CRP	A significant increase in the hs-CRP levels of the stage 2 PD patients compared with normal controls (P<0.01). There is no statistically significant difference in plasma levels of hs-CRP level between other stages of PD patients and controls.	8
Song, 2011 [33]	Serum	63	117	CRP	hs-CRP levels were higher in the early PD group than HCs (P=0.002).	9
Song, 2009 [34]	Serum	212	119	CRP	hs-CRP levels were higher in the PD patients than in the HCs (P=0.002).	8
Chen, 2008 [36]	Plasma	165	84	CRP	Higher plasma levels of IL-6 in PD patients compared to HC—no significant difference in CRP between the two groups.	10
Mihara et al. 2008 [113]	Heparinized peripheral venous blood samples	20	20	T helper-1(Th1) cytokines (IFN-γ, IL-2) Th2 cytokines (IL-4, IL10)	Serum levels are similar in PD and controls	6
	Blood samples PBMC	20	20	Natural killer (NK) cells	The NK cell-to-lymphocyte ratio was higher in the PD group than in the controls.	
Miklossy et al. 2006 [57]	SN	14	11	Intercellular adhesion molecule-1(ICAM-1)	Increased ICAM-1-positive reactive astrocytes in the SN of PD cases compared to controls	6
				Lymphocyte function-associated antigen 1 (LFA-1)	Increased reactive microglia expression of LFA-1 in SN of the PD group	

Abbreviations: HC: Healthy controls; PD: Parkinson disease; hsCRP: High-sensitivity C-reactive protein.

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Toll-like receptors (TLRs) and their polymorphisms

Toll-like receptor-4 (TLR-4) is a member of the toll-like receptor family and produces an inflammatory response to lipopolysaccharide (LPS) of the gram-negative bacteria. Examining colon biopsies and fecal and blood samples from PD patients reveals that these patients are more susceptible to intestinal barrier rupture and display increased expression of TLR-4 and pro-inflammatory genes in colonic biopsy samples, including CD3+ T cells and cytokines. Also, examination of SN of the postmortem brain showed an increased level of TLR-4 in PD cases compared to controls [41]. TLR-3 is a pattern recognition receptor that is involved in innate immune responses. The *T* allele of *TLR-3* gene SNP (rs3775290) was revealed to decrease the risk of developing PD [42].

Also, the evaluation of TLR-9 and TLR-2 polymorphisms showed no statistical difference in TLR-9 -1237 T/C nor TLR-2 -196 to -174 del polymorphism between PD and control cases [43].

Microsomal prostaglandin E synthase1

Microsomal prostaglandin E synthase1 (mPGES-1) is an inducible enzyme that, under inflammatory conditions, increases prostaglandin E_2 production. Compared to control brains, assessing mPGES-1 protein levels demonstrated its up-regulation in dopaminergic SN pars compacta neurons from PD postmortem brain specimens [44].

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Glycoprotein non-metastatic melanoma protein B (GPNMB) inflammatory response in interaction with CD44

CD44 is an astrocyte-expressed receptor that binds GPNMB, an endogenous glycoprotein. The binding of GPNMB to CD44 reduces nuclear factor kappa light chain enhancer of activated B cells (NFκB) activation and inflammatory responses in macrophages. Evaluation of *GPNMB* and *CD44* gene expression showed their increased levels in the SN of PD patients compared to controls [45].

CXCL12/CXCR4 as potential biomarkers of inflammation in PD

CXCL12 is a chemokine responsible for physiological functions such as CNS development by cell migration, proliferation, and neuronal circuit formation. CXCL12/CXCR4 is expressed in astrocytes, microglia, and neuronal areas such as SN. The expression of CXCR4 was shown to be expressively increased in the peripheral blood mononuclear cells of PD patients. In addition, CXCL12 serum levels measured using enzyme-linked immunosorbent assay (ELISA) were significantly developed in PD patients [46].

Accumulation of S100A9 and α-synuclein in PD

S100A9, as a pro-inflammatory mediator, participates in neuro-inflammatory pathways in Alzheimer disease and is expressed by both intracellular and Lewy body amyloid deposits and a calcium-binding protein, which participates in a broad range of inflammatory and neurodegenerative diseases. Ex-vivo measurements of S100A9 and α-syn (a presynaptic neuronal protein) protein levels showed that they both were elevated in the same brain areas and structures, including the SN neurons, Lewy bodies of SN, and also the Lewy bodies of the frontal lobe [47].

TNF-α and its polymorphisms

TNF-α is an inflammatory cytokine that regulates neuroinflammation activates microglia, and astrocytes can produce it. In four studies, TNF-α was higher among PD patients than controls in plasma, SN, tear, and cerebrospinal fluid (CSF) samples [21, 48-50]. However, in one study on the CSF sample, there was no notable change in the TNF-α level between the two study groups [51]. Two of the TNF-α single-nucleotide polymorphisms (SNP), rs361525 and rs1800629, were identified in the *TNF-α* gene promoter extracted from peripheral blood mono-nuclear cells, and the evaluation of the genomic DNA demonstrated no significant difference in the TNF-α SNPs between PD and control cases [52].

Microglia P2Y6 receptor participation in PD neuroinflammatory processes

The purinoceptor P2Y6 receptor (P2Y6R) is mostly responsible for microglia activation and some inflammatory pathways like triggering pro-inflammatory responses in macrophages in the central nervous system. The evaluation of P2Y6R expression in the peripheral blood mononuclear cells demonstrated that its levels in PD were increased compared to healthy controls. P2Y6R is also activated in LPS-treated BV2 cells and is involved in releasing pro-inflammatory cytokines through an autocrine feedback loop based on LPS-triggered uridine diphosphate (UDP) secretion; therefore, blocking UDP/P2Y6R signaling can opposite pathological procedures [53].

Upregulation of lipocalin-2 expression in the SN of PD patients

Lipocalin-2 (LCN2) is a glycoprotein involved in innate immune system functions due to its antimicrobial activity. Meanwhile, tyrosine hydroxylase (TH) is the enzyme that changes tyrosine to dopamine. Evaluation of LCN2 and TH protein levels by western blotting of SN samples obtained from postmortem brains presented that LCN2 expression was increased significantly in the SN of PD patients compared with age-matched healthy controls. In contrast, TH expression was lower in PD's SN than in healthy patients [54].

Microglia-mediated neuro-inflammation in the pathogenesis of PD

Evaluation of SN of the postmortem PD patients' brains demonstrated a reduction in neuromelanin-positive neurons (DA neurons). There was also a decrease in tyrosine hydroxylase (TH) expression, which is a marker for DA neurons. Activation of TLR-4, a receptor in the neuroinflammation pathway of microglial cells, generates inflammatory cytokines that lead to neurodegeneration of the brain, and the expression levels of TLR-4 increase in the SN of PD brains. Prothrombin kringle-2 (pKr-2) is produced from prothrombin through the activation of thrombin, and pKr-2 is related to inducing the death of DA neurons. The levels of pKr-2 increased significantly in SN of PD individuals compared to healthy patients [55].

Altered expression of proteinase-activated receptor-2 (PAR2) and associated proteins

PAR2 are G-protein-coupled receptors activated by proteases, which play a role in inflammation and pain pathways. PAR2 expression is increased in neurologic disorders, such as Alzheimer disease and multiple sclerosis. Levels of PAR2 activator trypsin-2 and its inhibitors, serpin-A5 and serpin-A13, are altered in different PD brain areas. With higher stages of the disease, a decrease in the number of neurons expressing the proteinase inhibitors was seen in brain regions, including the dorsal motor nucleus, locus coeruleus, SN, and primary motor cortex. Also, an increase in the expression of serpins in the microglia of the dorsal motor nucleus of the vagus and the SN, an increase of trypsin-2 expression in the microglia of the dorsal motor nucleus of the vagus and primary motor cortex, and PAR-2 expression increase in the locus coeruleus and cingulate cortex were seen. However, in the early stages of PD, there was an increase in serpin-A13 [56].

Roles of intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and lymphocyte function-associated antigen-1 in neuroinflammation

Intracellular adhesion molecule-1 (ICAM-1), a transmembrane glycoprotein expressed chiefly on endothelial cells and some immune system cells, along with its counter receptor, lymphocyte function-associated antigen-1 (LFA-1), plays a crucial part in the inflammatory procedure and T-cell mediated defense. Increased ICAM-1-positive reactive astrocytes were detected in the SN of PD cases. ICAM-1-positive astrocytes are focused around residual neurons and areas containing extracellular melanin aggregates. LFA-1, expressed by activated microglia and activated T cells, is upregulated in reactive microglia from within the SN of the PD brain. Also, weak reactivity of LFA-1 in resting microglia is detected in the SN of control brains [57]. It is indicated that neurovascular changes can lead to BBB dysfunction through neo-angiogenesis; BBB dysfunction can cause neuro-inflammation in the CNS, and neutrophil infiltration can lead to neuronal injury in the SN. The presence of pro-inflammatory cytokines such as TNF-α and IL-1β in the CNS can cause BBB cells to upregulate ICAM-1 and VCAM-1. These factors can transfer leukocytes into the CNS and eventually cause neuro-inflammation. Blood samples from the cases demonstrated a higher vascular cell adhesion molecule-1 (VCAM-1) expression in PD subjects compared to HC. However, ICAM-1 expression wasn't significantly different among the two groups [38].

Multiplex cytokines, soluble (s)RAGE, and high mobility group box-1 (HMGB1), TLR2/4 in PD neuroinflammation

Chung and colleagues' study sheds light on how inflammation in the brain can trigger a cascade of events leading to the worsening of α-synuclein pathology and nerve cell degeneration. They found that certain receptors, TLR-2 and TLR-4, become more active in response to this inflammation, setting off a chain reaction involving a signaling pathway called p38/JNK. This pathway, in turn, affects the process of autophagy, which is like a cellular cleaning system. When this system gets disrupted, it cannot properly clear out harmful proteins like α-synuclein, leading to their buildup and damage to nerve cells. Their research also revealed that during inflammation, there is an increase in markers associated with autophagy, suggesting that the cell is trying to ramp up its cleaning efforts. However, they noticed a hitch in the process: The fusion of certain cellular compartments essential for proper cleaning seems to be impaired. This condition leads to a backlog of protein waste and further damage. Interestingly, when they blocked TLR-2 and TLR-4, they saw a reduction in one marker of protein buildup but not in others related to the cleanup process. This outcome suggests that while blocking these receptors might alleviate some aspects of the problem, it does not fully restore the cell's ability to clean up. Their findings provide valuable insights into the complex interplay between inflammation, protein buildup, and cellular cleanup mechanisms in neurodegenerative diseases like PD [58].

TNFRSF9, CCL23, CCL25, VEGFA, and TGF-α neuroinflammatory role in PD

According to a panel of four proteins, in the research headed by Hepp et al., PD patients displayed a different immune response from controls (CXCL11, OPG, IL-12B, and CSF-1). Five inflammation-associated proteins (TNFRSF9, CCL23, CCL25, TGF-α, and VEGFA) had higher PD expression levels and were partially related to more severe motor and cognitive symptoms during follow-up. Decreased cognitive function and the APOE4 genotype were linked to elevated CCL23 levels [59].

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Colonic LRRK2 neuroinflammatory role in PD

According to a study by Liao et al., colonic biopsied specimens from PD patients had higher levels of *LRRK2* expression than did age- and gender-matched controls. Colonic *LRRK2* levels in PD patients were found to be connected with disease severity in cognitive function and motor, and those with pathogenic mutations or those bearing *LRRK2* risk had higher expression levels than the wild-type *LRRK2*. Furthermore, individuals with PD in the prodromal phase showed elevated levels of *LRRK2* expression in the colon compared to those without the condition, and this expression increased further as the disease progressed. These results suggest that heightened expression of *LRRK2* in the colon could serve as an indicative marker for PD with gut involvement [60].

Discussion

In addition to the hallmark degeneration of dopaminergic neurons in SN and accumulation of α-syn in neural cell bodies in PD [61, 62], several other biochemical and functional changes have been associated with this disease. They include mitochondrial dysfunction, oxidative stress, protein aggregation, impaired autophagy, and immune system overreaction, followed by neuroinflammation [63-65]. This systematic review studied 34 original studies involving PD patients to identify evidence supporting the contribution of neuro-inflammatory mechanisms to the pathogenesis of this disease.

The Mean±SD functional disability of included patients was 2.13±1.22 (Table 1). Hoehn and Yahr's scale representing the disease severity has been significantly correlated with a cytokine blood level called RANTES. This finding highlights the importance of further investigations on cytokines as potential biomarkers for disease advancement [67].

IFN-γ has been proven to be associated with typical brain pathogenesis [68]. Studies on animal subjects have illustrated that a high serum level of INF-γ is responsible for microglia and astroglia activation, leading to dopaminergic neural death [69, 70]. Recent studies have consistently approved a correlation between IFN-γ expression network signatures and its part in the selective susceptibility of dopaminergic neurons in PD patients [71]. Comparing 26 PD patients with 14 healthy controls, Diaz and colleagues showed insignificantly higher levels of peripheral IFN-γ in PD patients [71]. However, although IFN-γ has been associated with microglia, astroglia activation, and dopaminergic neural degeneration [72], it has been reported that the lower levels of IFN-γ, the more severe the tremors [71, 73]. The involvement of cytokines in motor symptoms of PD and their independent, non-responsive innate to dopaminergic treatment [74, 75] suggests the importance of cytokine-mediated symptomatic therapies in PD along with dopaminergic interventions. A study on postpartum brain samples has also demonstrated the role of TNF-α in the apoptosis of neuronal and glial cells due to its interaction with TNF receptor (TNFR) 1 by activating caspase 1 and 3 in SN. In another study conducted in vitro, lipopolysaccharide (LPS) targeted glial cells containing IL1β and TNF-α caused the death of dopaminergic rat neurons [76, 77]. A recent study based on GWAS statistics implied that TNF-TNFR1 signaling inhibition could not be used to delay or prevent PD onset [78]. The multifactorial nature of PD pathogenesis could explain this phenomenon.

Similarly, according to our results of systematic review, IFN-γ, TNF-α, CRP, and IL-6 are the most important neuroinflammatory markers associated with PD pathogenesis (Table 1). Confirming our data, a recent meta-analysis on higher CRP levels in serum, plasma, and cerebrospinal fluid concluded that it could be a risk factor for PD, leading to inflammatory responses [79]. Interestingly, an ultrasensitive assay demonstrates that high serum CRP is highly associated with freezing of gait in PD patients [80]. IL-6 levels are higher in cerebrospinal fluid and nigrostriatal region of PD patients, and they positively correlated with disease severity and motor symptoms, similar to our results [81, 82]. A meta-analysis has also approved higher CSF levels of IL-6 (Hedges'g, 0.468; 95% CI, 0.049, 0.887; P=0.026) than controls [83].

Our results determined that LCN2 and mPGES-1 expression was upregulated in SN samples of postmortem PD patients, while TH expression showed a significant decrease. Upregulation of LCN2 and mPGES-1 indicates that they could be used as novel biomarkers of PD. In a study on both SN of postmortem brain tissue from neurotoxin 6-hydroxydopamine (6-OHDA)-induced PD mice and PD patients, it has been demonstrated that mPGES-1 contributes to the inflammatory process and PD pathogenesis, by increasing PGE2, which triggers dopaminergic neuronal loss. Ikeda-Matsuo et al. [44] showed elevated levels of mPGES-1 in the PD patients' SN dopaminergic neurons of postmortem brain tissue. They suggested it could be a therapeutic target [84]. LCN2 is an iron-trafficking protein that upregulates oxidative stress and inflammation [84].

In contrast to the high LCN2 level in the SN samples of postpartum PD patients, Xiong et al. reported that the serum level of this protein is not considerably higher in PD patients than in healthy controls [85]. Thus, LCN2 may not be a biomarker for PD, but its suitability as a therapeutic target requires further investigation. TH, an iron-containing monooxygenase, plays a significant catalytic role in L-tyrosine to L-DOPA conversion [86]. It is considered a fundamental rate-limiting step in the biosynthesis of catecholamines [87]. Importantly, PD mainly affects TH-containing neurons. TH deficiency could be compensated by levodopa, DA agonists, inhibitors of DA metabolism, or grafts of brain cells expressing TH [88]. Our result showed an increase of CXCL12 and CXCR4, respectively, in peripheral blood mononuclear cells and serum of PD patients, revealing two new potential markers [46] (Table 1). A recent study also showed a positive correlation between CXCL12 and α-synuclein in the postmortem brain tissue of PD patients. In addition, they found upregulated levels of CXCR4 in SN microglia of transgenic expressing human A53T mutant α-synuclein (A53T) mice. The authors suggested that inhibition of CXCL12/CXCR4 is a potential preventive approach for α-synuclein-triggered microglial responses and, consequently, PD treatment [89].

As reported in the results, we have noticed that S100A9 and α-syn concentrations were elevated in the SN of PD patients [47] (Table 1). Recently, Toleikis et al. demonstrated the aggregation of α-syn depends on the presence of S100A9, which could promote an earlier onset or a novel pattern of α-syn aggregates, increasing their toxicity and the accompanying neurodegeneration [90]. Therefore, we suggest that by focusing on S100A9 and its effect on α-synuclein aggregation, further studies could create more effective therapeutic and preventive programs for diverse synucleinopathies like PD.

P2Y6R is expressed by immune cells, such as the microglia. It modulates the phagocytic activity of microglia and upregulates their inflammatory cytokine secretion, thus stimulating microglial-related inflammation in neurological disorders [91, 53] (Table 1).

MicroRNA-150 downregulation is a potential diagnostic biomarker in PD inflammation [92] (Table 1). The authors claimed that miR-150 is decreased in microglia by LPS treatment. A study by Yang et al. showed that micoRNA-105-5p was significantly overexpressed in PD patients compared with healthy control [93]. In addition, according to Caggiu et al., a considerable increase in miRNA-155-5p expression in PD patients showed its potential as a novel diagnostic biomarker by assessing peripheral blood samples [94]. Besides, the considerable decrease in microRNA-155-5p after levodopa treatment revealed its potential as a promising therapeutic target [94]. The authors also investigated the expression patterns of miR-26a-5p and miR132-5p, which did not show any difference between healthy controls and PD patients, while miRNA-146a-5p expression was decreased. We also found that blood levels of miRNA-29a and miRNA-22 were considerably upregulated in PD patients. Associated with apoptosis, neural survival, angiogenesis, and immune regulation, miRNA-29 has four different sequences called miRNA-29a, miRNA-29b-1, miRNA-29b-2, and miRNA-29c [95-98].

During PD progression, astrocytes produce TNF-α, IL-1β, NO, prostaglandin-E2, and other inflammatory mediators, which activate signal transduction pathways in dopaminergic neurons, leading to their degeneration [99]. Interestingly, GPNM prevents such inflammatory cytokine release by binding to CD44 receptors on astrocytes. Notably, the neuroprotective effects of GPNMB have already been reported in amyotrophic lateral sclerosis and ischemia [45]. CD44-dependent reduction of inflammatory mediators and oxidative stress by GPNMB has been reported in an astrocyte cell line and primary mouse astrocytes [45]. Recently demonstrated in the Chinese population that rs156429 single nucleotide polymorphism in the *GPNMB* gene could be related to pain symptoms and cognitive dysfunction in female PD patients [100].

PD patients had significantly higher levels of both CCL25 (C-C motif chemokine ligand 25, which has chemotactic action to inflammatory cells) and TNFRSF9 (a protein that induces T cell death) at follow-up, which is reliable with a prior finding for CCL25 [101]. At follow-up, a higher TNFRSF9 level was associated with worse cognitive function. TNFRSF9 may contribute to cell death in multiple sclerosis by inducing microglia activation [102]. Recently, modifications in the *TNFRSF9* gene have been linked to PD; in individuals with a known DJ-1 mutation, the TNFRSF9 genotype may act as a disease modifier [103].

Upregulated production of miR-205 could offer a viable healing approach for PD patients since Goh et al. discovered that downregulated expression of miR-205 can cause the sporadic PD patients' brains to show a pathogenic elevation of LRRK2 protein [95]. Additionally, some research has demonstrated that miR-19b, miR-24, and miR-195 serum levels may be highly accurately utilized to diagnose PD [104]. However, no research has been done on miR485-function 3p's in PD diagnosis or treatment.

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Conclusion

The current review aimed to summarize the outcomes of previous studies focused on mechanisms of neuro-inflammation involved in PD. We found that inflammatory pathways play key roles in the neuroinflammation and, subsequently, initiation and progression of PD. This study demonstrated that the neurodegeneration in PD could be initiated by neuron-derived α-syn protein, which leads to neuro-inflammation characterized by inflammatory responses in neurons. Also, inflammatory markers, astrocytes, and microglial cells can be involved in the progression of PD. Finally, chronic neuroinflammation could cause dopaminergic neuronal death in SN. By collecting and analyzing the latest outcomes and information, the impact of both single and all factors was assessed for planning possible further studies in a particular pathway to intercept the onset of inflammatory paths in favor of therapeutic purposes. Estimating the influence of each factor that has a part in the pathogenesis of PD gives us this opportunity to define new subsequent studies to dream up for solving the mystery of PD.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

Conceptualization: Mohammadreza Kosari, Supervision: Zohreh Zamani, Data collection: Sevim Soleimani; Writing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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