Supplementary file 2 Potential mechanisms of frequent herbs for Parkinson's disease and associated non-motor symptoms

Herb	Scientific names	Preparation	Chemical constituents	Subject	Administration	Bioactivity	Mechanism of action
Gan cao	1. *Glycyrrhiza uralensis* Fisch. 2. *Glycyrrhiza inflata* Batalin 3. *Glycyrrhiza glabra* L.	Extracts (water)	Glabridin (specific for G. Glabra), glycyrrhizic acid, liquiritin, liquitinapioside, and licoricesaponin-G2	IMR32 cell	In-vitro	Neuroprotective effect	Preventing rotenone-induced toxicity via regulating ERK-1/2 pathways (1).
		Extracts (water)	Glabridin (specific for G. Glabra), glycyrrhizic acid, liquiritin, liquitinapioside, and licoricesaponin-G2	IMR32 cell	In-vitro	Neuroprotective effect	Preventing the dysregulation of the citric acid cycle by rotenone-induced energetic stress via regulating the mtorc1-AMPK1 axis (2).
		Extracts (water)	Phenolic acids and their derivatives (vanillic acid, 5-caffeoylquinic acid, syringic acid, and p-coumaric acid)	Cell	In-vitro	Inhibiting MAO-B	Excreting the most potent MAO-B inhibitory action (3).
		Compounds	Licopyranocoumarin and glycyrurol	PC12D cell	In vitro	Neuroprotective effect	Suppressing reactive oxygen species generation, thereby inhibiting MPP+-induced neuronal PC12D cell death (4).
		Compound	Isoliquiritigenin	Dopaminergic cell line	In vitro	Neuroprotective effect	Protecting dopaminergic cell under oxidative stress conditions by regulating the apoptotic process (5).
		Extracts (water, in combination with *Vicia faba* and *Uncaria rhyncophylla*)	Phenolic compounds, namely, gallic acid, catechin, epicatechin, and resveratrol	Hypoe22 cell, Striatum specimens from SD rats	In-vitro, Ex vivo	Antioxidant effects and neuroprotective effects	Contrasting the upregulated lactate dehydrogenase and nitrite levels and in reducing striatal dopamine turnover (6)
Huang qi	*Astragalus mongholicus*	Compound	Astragaloside IV	Long culture-induced	In vivo and in vitro,	Preventing dopaminergic	Inhibiting of astrocyte senescence through promoting mitophagy (7).

Bunge			replicative senescence model and LPS/MPP+-induced premature senescence model and MPTP-induced PD mouse model	intraperitoneal injection	neurodegeneration in PD	
	Compound	Astragaloside IV	MPTP-induced PD mouse model, LPS-induced BV2 microglia cell	In vivo and in vitro, oral gavage	Anti-inflammatory, antioxidant, and neuroprotective effects	Protecting dopaminergic neuron from neuroinflammation and oxidative stress via activating the Nrf2 pathways and suppressing nfκb/NLRP3 inflammasome signalling pathway (8).
	Compound	Astragaloside IV	6-OHDA-treated SH-SY5Y cell	In vitro	Anti-inflammatory, antioxidant, and neuroprotective effects	Enhancing the cell viability, and inhibiting apoptosis, inflammation and oxidative stress of 6-OHDA-treated SH-SY5Y cell via activating the JAK2/STAT3 signalling pathway (9).
	Compound	Astragaloside IV	6-OHDA treated nigral cell cultures	In vitro	Neuroprotective and neurosprouting effects	Protecting dopaminergic neurons against 6-OHDA-induced degeneration, promoting neurite outgrowth and increased TH and NOS immunoreactive of dopaminergic neurons (10).
	Compound	Astragaloside IV	H_2O_2-exposed SH-SY5Y cell	In vitro	Neuroprotective effect	Inhibiting the expression of the α-synuclein via the p38 MAPK signalling pathway (11).
	Compound	Astragalus polysaccharide	6-OHDA-treated PC12 cell	In vitro	Anti-Parkinson effect	Increasing autophagy via inhibiting PI3K protein to activate PI3K/AKT/mtor pathway (12)
	Compound	Calycosin	MPTP-induced PD mouse model,	Intracerebrovent ricularly injection	Anti-parkinsonism and anti-	Mitigating PD symptoms through TLR/NF-κb and MAPK pathways in mice and cell lines (13)

				LPS-induced BV2 microglia cell		neuroinflammatory effects	
Bai zhu	*Atractylodes macrocephala* Koidz.	Compound	Atractylenolide-I	LPS-stimulated BV-2 cell, MPTP-intoxicated C57BL6/J mouse model	In vivo and in vitro, Intraperitoneal administration	Anti-neuroinflammatory	Abating the nuclear translocation of NF-κb and by inducing HO-1 (in vitro). Reversing MPTP-induced behavioural deficits, decreasing microglial activation, and conferring protection to dopaminergic neurons (in vivo) (14).
		Compound	Atractylenolide-I	MPP^+-induced cytotoxicity in SH-SY5Y cell	In vitro	Anti-apoptosis and antioxidant effects	Reducing pro-apoptotic signals and also by induction of antioxidant protein (15).
		Compound	Atractylon	MPTP-induced PD mouse model, SY-SY5Y cell	In vivo and in vitro, oral administration	Anti-Parkinson effect	Activating DRD2, attenuating motor deficits and gait disorders, and protecting dopaminergic neurons in MPTP-induced PD mice (16).
		Extracts (ethanol)	Atractylenolide I, atractylenolide III, and atractylodin	LPS-stimulated microglial BV2 cell	In vitro	Anti-neuroinflammatory	Attenuating the production of NO and inflammatory cytokines induced by LPS, also inhibiting the expression of inos and COX-2 without causing cytotoxicity, attenuating the transcriptional activities of NF-κb and MAPK phosphorylation, and induced HO-1 expression (17).
Dang gui	*Angelica sinensis* (Oliv.) Diels	Compound	*N*-Butylidenephthalide	MPTP-induced PD mouse model, adipose-derived stem cell	In vitro	Anti-inflammatory and neuroprotective effects	Stimulating adipose-derived stem cell with n-Butylidenephthalide improved PD recovery efficiency (18).
		Compound	*N*-Butylidenephthalide	*Caenorhabditis elegans* PD model	Mixed with the OP50/NGM plates for animal incubation	Antiparkinsonian activities	Blocking egl-1 expression to inhibit apoptosis pathways and by raising rpn-6 expression to enhance the activity of proteasomes (19).
Di huang	*Rehmannia glutinosa*	Compound	Catalpol	H_2O_2-injured astrocytes	In vitro	Antioxidant and neuroprotective	Increasing the cell viability and reducing the intracellular ROS

	(Gaertn.) DC.					effects	formation; attenuating H_2O_2-induced oxidative stress via preventing the decrease in the activities of antioxidant enzymes in glutathione redox cycling such as glutathione peroxidase, glutathione reductase and glutathione content (20).
		Compound	Catalpol	LPS-induced microglia	In vitro	Antioxidant, anti-inflammatory and neuroprotective effects	Inhibiting microglial activation and reducing the production of proinflammatory factors (21).
		Compound	Catalpol	MPTP-induced astrocytes	In vitro	Neuroprotective effect	Attenuating mitochondrial dysfunction and MAO-B activity (22).
		Compound (*Dihuang* Granule)	*Quercetin*, *kaempferol*, *luteolin*, *tanshinone IIA*, *yohimbine*, *salviolone*, *beta-sitosterol*, *4-methylenemiltirone*, *dihydrotanshinlactone*, and *2-isopropyl-8-methylphenanthrene-3,4-dione*, etc.	6-OHDA-induced PD rat model	Intragastric administration	Anti-Parkinson therapeutic effect	Modulating apoptosis through MAPK signalling (23).
		Compound (*Dihuang* Granule)	N/A	MPTP-induced PD mouse model	Oral administration	Improving gut microbial in PD	Blocking the pathway of TLR4/NF-κb (24).
		Extract (water, in formula *Liuwei dihuang*)	5-hydroxymethyl-2-furaldehyde, morroniside, loganin, paeoniflorin, verbascoside and paeonol	MPTP-induced PD mouse model, MPP^+-treated primary mesencephalic neurons	In vitro, Intraperitoneal administration	Dopaminergic neurons protection effects	Protecting dopaminergic neurons through enhancing antioxidant defense and decreasing apoptotic death (25).
Bai shao	*Paeonia lactiflora* Pall.	Compounds	Total Glucosides	MPTP-induced mouse model	Intragastric administration	Neuroprotective effect	Regulating LRRK2/alpha-synuclein signalling
		Compound	Paeoniflorin	MPTP-induced	Intragastric	Neuroprotective	Regulating the α-synuclein/PKC-δ

				PD mouse model	administration	effect	signalling pathway to reduce neuronal apoptosis (26).
		Compound	Paeoniflorin	MPP^+-induced PC12 cell	In vitro	Neuroprotective effect	Regulating mitochondrial membrane potential and Bcl-2/Bax/caspase-3 signalling pathways (27).
		Compound	Paeoniflorin	MPP^+-induced dopaminergic neurons	In vitro	Neuroprotective and anti-ferroptosis effects	Preventing ferroptosis via activation of the Akt/Nrf2/Gpx4 pathway in vitro (28).
		Compound	Paeoniflorin	MPTP-induced PD mouse model	Subcutaneous administration	Anti-neuroinflammatory effect	Inhibiting neuroinflammation by activation of the adenosine A1 receptor (29).
		Compound	Paeoniflorin	6-OHDA-induced PC12 cell	In vitro	Antioxidant and anti-apoptosis effects	Inhibiting reactive oxygen species (ROS)/pkcδ/NF-κb signalling pathway (30).
		Compound	Paeoniflorin	Glutamate induced PC12 cell	In vitro	Neuroprotective effect	Mitochondrial membrane potential and Bcl-2/ Bax signal pathway (31).
		Extract (aqueous ethanol fraction)	Total glucosides of paeony, including paeoniflorin and albiflorin	MPTP-induced PD mouse model	Intragastric administration	Neuroprotective effect	Regulating the camp/PKA/CREB signalling pathway (32)
Chai hu	1. *Bupleurum chinense* DC. 2. *Bupleurum scorzonerifolium* Willd.	Extracts (ethanol, with *Moutan* cortex, *Angelica Dahurica* root)	N/A	MPP^+-treated SH-SY5Y cell, MPTP-induced PD mouse model	Oral administration, In vitro	Neuroprotective effect	Alleviating mitochondria damage in experimental models of PD (33). Regulating nuclear receptor-related 1 protein (34).
		Extracts (ethanol)	Saikosaponin (C, A B3 and B4)	LPS-stimulated microglial cell and LPS-intraperitoneal injected C57BL/6 mouse model	In vitro, oral administration	Anti-inflammatory effect	Suppressing NF-κb-mediated inflammatory pathways (35).
Zhi	*Citrus aurantium*	Extracts	Naringin, hesperidin,	Multistress-	Oral	Prokinetic effect	Reducing gastric residual rate and

qiao/*Zhi shi*/*Chen pi*	L.	(water, in combination with *Citrus reticulata* Blanco and *Bupleurum chinense* DC.)	neohesperidin, saikosaponin a, and saikosaponin b2	induced delayed gastric emptying mouse model	administration, in vitro		increasing serum levels of 5-HT, MTL and SP (36).
		Extracts (water, in combination with *Rhizoma Atractylodis*)	N/A	Loperamide-induced constipated rats	Oral administration	Anti slow transit constipation	Regulation the metabolism of caffeine and vitamin B6 (37).
Ren shen	*Panax ginseng* C. A. Mey.	Compound	Ginsenoside Re	Rotenone-induced SH-SY5Y cell and *Drosophila* model	In vitro, flies administered	Neuroprotective effect	Inducing Nrf2/heme oxygenase-1 expression and activation of the dual PI3K/AKT and ERK pathways (38).
		Compounds	Ginsenosides	MPTP-induced PD mouse model	Oral administration	Neuroprotective effect	Anti-apoptosis, antiinflammation, antioxidant, and maintenance of blood-brain barrier integrity (39).
		Compounds	Ginsenosides Rd and Re	Ccl4-induced primary dopaminergic cell	In vitro	Neuroprotective effect	Lowering oxidative stress and anti-inflammation (40).
		Compound	Ginsenoside Rb1	MPTP-induced PD mouse model	Administered intraperitoneally	Neuroprotective effect	Regulating prefrontal cortical gabaergic transmission (41).
		Compound	Ginsenoside Rg1	MPTP-induced PD mouse model	In vivo and in vitro, Intraperitoneal administration	Neuroprotective effect	Regulating the Wnt/β-catenin signalling pathway (42).
		Compound	Ginsenoside Rg1	MPTP-induced PD mouse model	Intraperitoneal administration	Immunomodulatory and neuroprotective effects	Regulating the peripheral and central inflammation (43).
		Compound	Ginsenoside Rg1	MPTP-induced PD mouse model	Intraperitoneal administration	Anti-Parkinson effect	Restoring motor functions to physiological level in MPTP-treated PD mice, and attenuating the

					MPTP-induced loss of dopaminergic neurons in the substantia nigra and striatum (44).
Compound	Ginsenoside Rg1	MPTP-induced PD mouse model	Oral administration	Neuroprotective and anti-inflammatory effects	Reducing aberrant α-synuclein-mediated neuroinflammation (45).
Compound	Ginsenoside Rg1	MPTP-induced PD mouse model	Intraperitoneal injection	Neuroprotective effect	Remitting the iron-regulated protein dyshomeostasis by ferritin and against lipid peroxidation stress in oligodendrocytes (46).
Compound	Ginsenoside Rg3	Rotenone-induced PD mouse model	Intragastric administration	Neuroprotective and antioxidant effects	Regulating glutathione cysteine ligase modulatory subunit and glutathione cysteine ligase regulatory subunit expression (47).
Extract	Ginsenosides	BSSG-induced PD mouse model	Oral administration	Neuroprotective, anti-inflammatory, anti-apoptosis and antioxidant effects	Protecting against dopaminergic neurons in the substantia nigra. Reducing indices of inflammation, apoptosis and cell stress, preventing the accumulation of insoluble α-synuclein aggregates (48).
Extract (water)	Ginsenosides Rg1, Re and Rb1	SH-SY5Y human neuroblastoma cell	In vitro	Neuroprotective and anti-cytotoxicity effects	Suppressing ROS generation and inhibiting mitochondria-dependent apoptotic pathway (49).
Extract (water)	Ginsenosides	MPTP-induced PD mouse model	Oral administration	Neuroprotective effect	Inhibiting MPTP-induced dopaminergic neuronal death and suppressing the cleavage of p35 to p25 in the substantia nigra and striatum (50).
Extract (ethanol)	Gintonin	MPTP-induced PD mouse model	Oral administration	Anti-apoptosis, anti-inflammatory and antioxidant agent effects	Activation of the nuclear factor erythroid 2-related factor 2 pathways and the inhibition of phosphorylation of the mitogen-activated protein kinases and nuclear factor-kappa B signalling pathways (51).
Extracts	Ginseng total protein	Dm $PINK_1$	Oral	Neuroprotective	Protecting against mitochondrial

				model of PD	administration	effect	dysfunction and neurodegeneration by inducing uprmt in the Dm PINK1B9 model of PD (52).
		Extract (water)	N/A	MPTP-induced PD mouse model	Oral administration	Anti-Parkinson effect	Preventing MPTP-induced leaky gut barrier, inflammation, and accumulation of asyn (53).
		Extract (water)	N/A	MPTP-induced PD mouse model	Oral administration	Anti-Parkinson effect	Regulating neuronal formation and energy metabolism for survival (54).
		Extract (water)	N/A	MPP+-induced SH-SY5Y cell	In vitro	Anti- apoptosis and anti-mitophagy effect	Regulating cytochrome c release from mitochondria and PINK1/parkin-mediated mitophagy, through regulation of the Bcl-2 family (55).
		Extract (water)	N/A	MPTP-induced mouse model	Oral administration	Anti-Parkinson effect	Suppressing dopaminergic neuronal death, augmenting the number of brdu- and brdu/double cortin (Dcx) and enhancing the expression of proliferation cell nuclear antigen, BDNF, GDNF, CDNF, CNTF, DRD3 and D5 mrnas (56).
		Extract	Pseudoginsenoside-f11	6-OHDA-induced PD rat model	Oral administration	Anti-Parkinson effect	Inhibiting free radical formation and stimulating endogenous antioxidant release (57).
Fu ling	*Poria cocos* (Schw.) Wolf	Compound	Acidic polysaccharides	CUMS rat model	Intragastric administration	Antidepressant effect	Regulating neurotransmitters and NLRP3 inflammasome signalling pathway (58).
		Compound	Pachymic Acid	Pentobarbital-induced sleep mouse model	Intragastric administration	Sedative-hypnotic effect	Enhancing pentobarbital-induced sleeping behaviours via GABAA-ergic mechanisms in rodents (59).
		Compound	Pachymic acid	Cerebral ischemia/reperfusion injury rat model	Intragastric administration	Neuroprotective effect	Activating PI3K / Akt signalling pathway(60).
		Extract (ethanol)	N/A	ACTH-induced sleep disturbed mouse model	Intragastric administration	Sedative-hypnotic effect	Improving sleep quality under a normal sleep state through the $GABA_A$ receptor; promoting and improving sleep quality and sleep

							structure in both the arousal activation state and stress- based sleep disturbance (61).
		Extract (water)	Polysaccharides	CUMS rat model	Intragastric administration	Antidepressant-like effect	Regulating monoaminergic neurotransmission (DA, 5-HT) and inactivation of inflammation (p38, NF-κb and TNF-α) (62).
Dang shen	1. *Codonopsis pilosula* Nannf. 2. *Codonopsis pilosula var.* Pilosula 3. *Campanumoea pilosula* Franch.	Compound	Isorhapontigenin	PC12 cell	In vitro	Antioxidant effect	Enhanced the antioxidant effect induced by 1-Methyl-4-phenylpyridine in PC12 cell by suppressing the activation of the PI3K/Akt signaling pathway (63).
Bu zhong yi qi tang		Extracts (water)	ferulicacid, isoferulicacid, hesperidin, calycosin, glycyrrhizicacid, aposaponind, etc.	Cerebral ischemia mouse model	Intragastric administration	Neuroprotective effect	Regulating intestinal microbiota and increasing the abundance of butyrate-producing Prevotellaceae_NK3B31_group and probiotic *Akkermansia* in mice 72h after surgery (64).
		Extracts (water)	Liquiritin apioside, Liquiritin, Nodakenin, Hesperidin, Glycyrrhizin, Decursin, Decursinol angelate	Aβ-injected mouse model	In vitro, intragastric administration	anti-dementia and neuroprotective effects	Enhancing inhibition of Aβ aggregation and BACE activity in vivo, as well as antioxidant activity in vitro, suppressing Aβ aggregation and expression, as well as expression of Aβ, NeuN, and BDNF in the hippocampi of Aβ-injected mice (65).

Note: Aβ: amyloid-β; ACTH: adrenocorticotropic hormone; aSyn: alpha-synuclein; BDNF: brain derived neurotrophic factor; BSSG: β-sitosterol β-d-glucoside; CCl4: Carbon tetrachloride; CDNF: cerebral dopamine neurotrophic factor; CNTF: ciliary neurotrophic factor; COX-2: cyclooxygenase; CUMS: chronic unpredictable mild stress; Dm: Drosophila melanogaster; GDNF: glial cell derived neurotrophic factor; DRD3: dopamine receptor D3; N/A: not available. H_2O_2: hydrogen peroxide; HO-1: heme oxygenase-1; iNOS: inducible nitric oxide synthase; SD: Sprague-Dawley; LPS/MPP+: lipopolysaccharide/1-methyl-4-phenylpyridinium; MAPK: mitogen-activated protein kinase; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-κB: nuclear factor-κB; NO: nitric oxide; NOS: nitrite oxide synthase; PC12: pheochromocytoma cell; PD: Parkinson's disease; $PINK_1$: PTEN-induced putative kinase 1; ROS: reactive oxygen specie; SH-SY5Y cell: SK-N-SH neuroblastoma cell line; TH: tyrosine hydrolase;

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