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REVIEW

Neuroprotective Attributes of Gut-derived Urolithins in Parkinson's Disease

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Abstract

Urolithins, a class of gut microbiota-derived metabolites, are produced from dietary ellagitannins and ellagic acid. Their pleiotropic activities, including antioxidant, anti-inflammatory, and mitophagy-enhancing effects, position them as promising candidates for Parkinson's disease (PD), a disorder increasingly understood through the lens of gut–brain axis dysfunction. Mounting evidence implicates gastrointestinal disturbances, including dysbiosis, increased intestinal permeability, and aberrant microbial signaling, as early events that may initiate or exacerbate neuropathological cascades in PD. In this context, urolithins represent a unique class of neuromodulatory agents operating at the intersection of host–microbiota co-metabolism and neuroprotection. This review synthesizes mechanistic insights into urolithin biosynthesis and interindividual variability in bioavailability, followed by a critical appraisal of their efficacy in preclinical PD models. We outline their relevance across key pathogenic dimensions, including preservation of dopaminergic neurons, inhibition of pathological α-synuclein aggregation and propagation, suppression of oxidative stress via nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway activation and enhancement of endogenous antioxidant defenses, attenuation of neuroinflammation through downregulation of pro-inflammatory cytokines and glial reactivity, rescue of mitochondrial dysfunction, and promotion of autophagy-lysosomal pathways to mitigate proteostatic failure. By translating mechanistic insights into a coherent therapeutic framework, this review highlights the promise of urolithins as microbiota-derived interventions capable of modifying the course of PD.

Keywords Urolithin A · Gut · Dopamine · α-Synuclein · Oxidative stress · Inflammation

Introduction

Parkinson's disease (PD) is a progressive, age-associated neurodegenerative disorder characterized by cardinal motor symptoms, including bradykinesia, rigidity, and postural instability [1, 2]. Affecting millions worldwide, the incidence of PD is expected to rise sharply with the aging global population [2]. Despite extensive research, the precise pathobiology of PD remains incompletely understood. Converging evidence implicates multiple interrelated mechanisms, such as pathological aggregation of α-synuclein (α-syn) [3–5], oxidative stress [6], inflammation [7], mitochondrial impairment [6], and autophagy dysfunction [8, 9], which are considered to be drivers behind disease progression. These pathological processes are further modulated by genetic predispositions and environmental factors [10, 11]. More recently, dysregulation of the gut-brain axis has emerged as a potential upstream contributor to PD pathogenesis [12–14]. This imbalance in intestinal microbiota elevates intestinal permeability, inflammation, oxidative stress, and α-syn accumulation that trigger PD onset and progression [14–20]. Conversely, certain microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), tauroursodeoxycholic acid (TUDCA), and urolithins, exhibit neuroprotective properties with potential to mitigate disease progression [16, 21, 22].

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Among them, urolithins have gained significant attention for their anti-aging properties, and emerging evidence has highlighted their therapeutic effects in PD [22, 23].

Urolithins are a group of metabolites containing a benzocoumarin scaffold obtained from the metabolism of polyphenol, ellagitannin, and ellagic acid, which are present in fruits and nuts [24–28]. This process yields several structurally related urolithins, among which urolithin A (UA), urolithin B (UB), urolithin C (UC), and urolithin D (UD) are the most studied [25]. However, their production varies widely depending on inter-individual differences in gut microbiota composition [29–31], concentration of the polyphenol consumed [32], genetic factors [32], intestinal permeability [25], and age [32]. Urolithins have demonstrated a broad spectrum of therapeutic properties across diverse pathological contexts. UA and UB exhibit anti-inflammatory, antioxidant, and cytoprotective effects in preclinical models of cancer [33, 34], cardiovascular disease [35, 36], and obesity [35]. Meanwhile, UC and UD are explored for their anti-diabetes [37, 38] and anti-cancer [39] properties, respectively. Despite this broad pharmacological relevance, the potential of urolithins in PD remains underexplored. Therefore, this review aims to systematically evaluate the emerging evidence on urolithins in PD, with particular emphasis on their modulatory effects on key pathogenic pathways, including dopamine (DA) metabolism, tyrosinase activity, α-syn aggregation, oxidative stress, neuroinflammation, mitochondrial dysfunction, and impaired autophagy. Additionally, we outline the microbiota-dependent biosynthetic pathways of urolithin formation.

Critical Events Associated with Parkinson's disease: From Peripheral Triggers to Central Manifestation

A defining pathological hallmark of PD is the selective degeneration of DA neurons within the substantia nigra pars compacta (SNpc) of the midbrain [3, 40, 41]. The resultant depletion of striatal DA disrupts basal ganglia circuitry, culminating in the cardinal motor symptoms of PD, including bradykinesia, muscular rigidity, resting tremor, and postural instability [40, 42–45]. In addition to motor deficits, patients frequently exhibit a constellation of non-motor symptoms, including cognitive dysfunction, effective disturbances, and sleep abnormalities that further contribute to disease burden and reduce quality of life [43, 45].

Biochemically, the loss of synaptic DA in PD is accompanied by elevated activity of DA-catabolizing enzymes, suggesting either a compensatory or maladaptive response to neurodegeneration [46, 47]. Despite substantial therapeutic advances, current clinical management remains largely palliative, focusing on symptomatic relief rather than modifying disease progression [48, 49]. The etiopathogenesis of PD remains incompletely understood. However, converging evidence points to a multifactorial interplay of pathogenic processes, including oxidative stress [6], inflammation [7], impairment in mitochondria [6], and autophagy dysfunction [8, 9]. These cellular disturbances are triggered by a variety of intrinsic and extrinsic risk factors, such as genetic susceptibility, environmental neurotoxins, and aging [10, 11]. Recently, the gut-brain axis has gained attention as a potential initiator of PD pathology. Compelling data suggest that gut dysbiosis, defined as alterations in the composition and function of the intestinal microbiota, may act as a peripheral trigger, contributing to systemic and central pathophysiological cascades [12–14]. Notably, gastrointestinal symptoms, particularly chronic constipation, often precede motor manifestations by several years, suggesting a prodromal phase of PD localized within the enteric nervous system [16, 50]. Microbial imbalance disrupts mucin production, an essential component for maintaining intestinal barrier integrity, leading to increased permeability to toxic metabolites and contributing to the progression of PD [14, 15]. As gut dysbiosis worsens in affected individuals, it results in elevated levels of metabolites like trimethylamine-N-oxide (TMAO) and lipopolysaccharides (LPS), which can readily pass through the compromised gut barrier [16]. These metabolites trigger the systemic release of pro-inflammatory cytokines, which in turn disrupt the blood–brain barrier (BBB), a phenomenon linked to the degeneration of dopaminergic neurons in the SNpc of the midbrain [16]. Other than this, these metabolites are also involved in the activation of microglial cells and further exacerbate PD progression [17, 18]. Additionally, fecal samples from PD patients have shown increased levels of calprotectin, a marker of intestinal inflammation, along with a reduction in anti-inflammatory bacterial species, further supporting the link between gut dysbiosis and PD occurrence [14, 51]. Moreover, a study has further demonstrated that microbial imbalance can activate the Toll-like receptor 4/Nuclear factor kappa-light-chain-enhancer of activated B cells (TLR4/NF-κB) signaling pathway, thereby enhancing inflammation through glial cell activation in the substantia nigra [14, 52]. Beyond promoting inflammation, dysbiosis exacerbates oxidative stress by impairing antioxidant defenses. For example, it downregulates nicotinamide mononucleotide adenylyl transferase, a key gene in NAD^+ biosynthesis in PD mice [19]. Additionally, gut microbial imbalance also increases adenosine levels, which inhibits NRF2 and Nicotinamide adenine dinucleotide phosphate (NADPH), thereby amplifying oxidative damage in dopaminergic neurons [53]. Furthermore, microbial imbalance facilitates the misfolding of α-syn within the enteric nervous system (ENS)

and gastrointestinal epithelium, promoting proinflammatory immune responses and facilitating its propagation to the central nervous system (CNS) [14]. Notably, *Proteus mirabilis* secretes hemolysin A, which has been shown to trigger α-syn oligomerization, leading to motor dysfunction and neurodegeneration[14, 20]. Similarly, oral administration of *E. coli* in mice has led to α-syn accumulation in the colon, followed by its transmission to the CNS [14, 54]. Collectively, these findings suggest that targeted modulation of gut microbiota holds therapeutic potential in mitigating the pathophysiology of PD.

Imbalances in the gut also alter the production of other metabolites, which are known to alleviate PD; for instance, SCFAs and TUDAC [21, 55]. Dietary interventions that enhance SCFA production, such as increased fiber and prebiotic intake, have shown potential to improve both motor and non-motor symptoms in PD patients [50]. SCFA supplementation is further linked to modulation of microglial activation states, attenuation of neuroinflammation, and restoration of synaptic DA homeostasis [56]. Additionally, SCFAs may influence serotonergic pathways, which are often disrupted in PD. Tryptophan metabolism, a precursor for serotonin (5-HT) biosynthesis, is regulated by gut microbiota activity; thus, dysbiosis in the gut can impair 5-HT production, potentially worsening neuropsychiatric and cognitive symptoms in PD [57–59]. TUDCA, a bile acid derivative produced by colonic microbial metabolism, has also emerged as a promising neuroprotective agent. Experimental PD models have demonstrated that TUDCA ameliorates mitochondrial dysfunction, reduces neuroinflammation, promotes autophagic clearance of aggregated proteins, and prevents DA neurodegeneration in the striatum [60]. The importance of microbial metabolite production was observed when the administration of probiotics improved serum metabolite levels in PD patients. Additionally, they show improvement in gut environment and motor function [61]. Therefore, these findings suggest that the development of PD may be linked to a reduction in metabolites due to gut imbalance, and maintaining a balanced gut microbiota could be crucial in preventing the onset and progression of PD. Furthermore, urolithins have recently been identified as potent modulators of mitochondrial health and oxidative stress. Their documented anti-aging [22] and antioxidant properties [62] position urolithins as promising candidates for therapeutic intervention in PD. Collectively, these findings represent a paradigm shift in PD pathogenesis, highlighting the pivotal role of peripheral events (especially gut microbial alterations) as potential upstream drivers of central neurodegeneration. Ongoing research into the gut-brain axis is poised to reveal novel biomarkers and therapeutic targets aimed at disease modification rather than solely symptomatic management.

The Molecular Landscape of Urolithins: Enzymatic Biosynthesis, Sources, and Multifaceted Bioactivities

Urolithins are bioactive microbial metabolites produced through the biotransformation of the polyphenolic compounds ellagitannins and ellagic acid, predominantly within the colon [28, 63]. Dietary sources rich in ellagitannins and ellagic acid include various fruits such as strawberries, raspberries, blackberries, pomegranates, muscadine grapes, and rambutans, as well as nuts like walnuts and chestnuts, and beverages including teas [25–28]. Upon ingestion, ellagitannins undergo hydrolysis into ellagic acid, which is subsequently metabolized by gut microbiota into various urolithins. To date, approximately 25 urolithin derivatives have been identified, with UA, UB, UC, and UD representing the most extensively characterized forms [25]. These compounds exhibit oral bioavailability and varying degrees of BBB permeability, with UA, UB, and UC demonstrating superior brain bioavailability [64].

Ellagitannin (ET) undergoes hydrolysis and lactonization forming hexahydroxydiphenic acid (HHDP) and ellagic acid (EA) respectively [65, 66]. Then, the conversion of ellagic acid to urolithins is mediated by a series of enzymatic reactions orchestrated by gut microbes (Fig. 1). Despite growing understanding of urolithin biosynthesis, the precise microbial taxa responsible remain incompletely characterized. Several bacterial species implicated in urolithin production are predominantly gram-positive anaerobes; although, the microbes responsible for UD formation have yet to be identified (Table 1). Recently, a novel urolithin, urolithin G (UG), was discovered; it is synthesized from UD via 9-dehydroxylation catalyzed by the enzyme 9-dehydroxylase [76]. The biological role of UG remains unexplored. Bacterial strains linked to UG production include *Enterocloster bolteae* (DSM 34392, DSM 29485), *Enterocloster asparagiformis* (DSM 15981^T), *Enterocloster citroniae* (DSM 19261^T), and *Ellagibacter isourolithinifaciens* (DSM 104140^T) [76]. Structurally, urolithins contain a benzo-coumarin scaffold where UA is chemically named by IUPAC (International Union of Pure and Applied Chemistry) as 3,8-dihydroxybenzo(c) chromen-6-one. Preclinical studies have reported UA to suppress the progression of cancer [77, 78] and protect beta cell apoptosis, which improves insulin secretion in diabetes [79]. UA has also improved the normal activity of mobility and pharyngeal pumping in *C. elegans* and other age-related muscle impairments in rodents [22]. Along with this, UA mitigates dysfunctional mitochondria and extends the life span of *C. elegans* [22], while UB (3-hydroxybenzo(c)chromen-6-one) [34], UC [80],

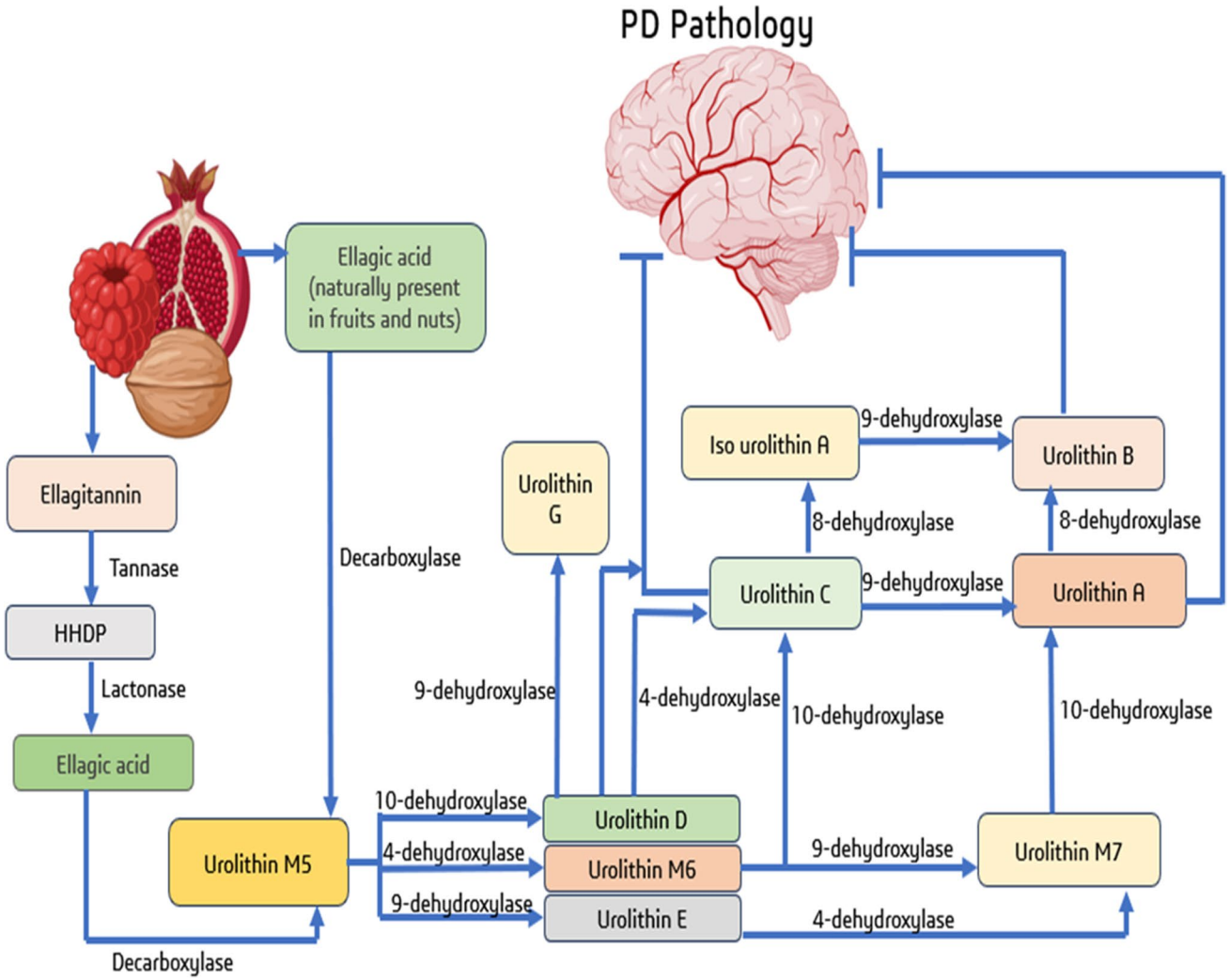

Fig. 1 Biosynthetic pathway of urolithins and the enzymatic processes involved in their anabolism. Ellagitannin undergoes hydrolysis and lactonization forming hexahydroxydiphenic acid (HHDP) and ellagic acid respectively. Following this, EA is metabolized in the later part of the gut for urolithin production. Initially, urolithin M5 formation occurs, which forms a key intermediate for different urolithins. Further, the downstream process undergoes dihydroxylation, as seen in the figure and leads to the formation of UA, UB, UC, and UD that have the potential to mitigate the pathophysiology of Parkinson's disease

Table 1 Bacterial species involved in the formation of urolithins and their precursors in the gut

SL no	Bacterial species and strain	Urolithins and their precursor	References
1	*Lactobacillus plantarum, Lactobacillus paraplantarum, and Lactobacillus pentosus*	Ellagic acid	[67]
2	*Enterococcus faecium* FUA027, *Streptococcus thermophilus* FUA329, *Enterocloster bolteae* DSM 15670 T, *Lactococcus garvieae* FUA009, *Lactobacillus plantarum* CCFM1286, *Lactobacillus plantarum* CCFM1290, *Lactobacillus plantarum* CCFM1291, *Bifidobacterium pseudocatenulatuma* INIA P815, *Enterocloster bolteae* DSM29485, *Enterocloster bolteae* CEBAS S4A9, *Enterocloster asparagiformis* DSM15981T, *Enterocloster citroniae* DSM 19261 T	UA	[63, 68–72]
3	*Bifidobacterium pseudocatenulatuma* INIA P815, *Enterocloster bolteae* DSM29485, *Enterocloster bolteae* CEBAS S4A9, *Enterocloster asparagiformis* DSM15981T, *Enterocloster citroniae* DSM 19261 T	UB	[63, 69, 72]
4	*Gordonibacter pamelaeae* DSM 19378 T, *Gordonibacter faecis* KGMB12511T, *Gordonibacter urolithinfaciens* DSM27213T	UC	[63, 73–75]

and UD (3,4,8,9-tetrahydroxybenzo(c)chromen-6-one) [39] are explored for their effective therapeutic potential in inhibiting cancer. Moreover, UC exerts biological activities, such as stimulating insulin secretion by facilitating calcium channel opening to enhance calcium influx in beta cells [37] and alleviates liver disease [81]. Furthermore, all these major urolithins are considered to show effectiveness against various cardiovascular diseases like atherosclerosis, hypertension, myocardial infarction, cardiac fibrosis, cardiomyopathy, cardiac arrhythmias, and cardiotoxicities [82]. The concentration of these urolithins in the bloodstream is influenced by their lipophilicity and intestinal absorption [25]. UA and UB are the predominant urolithins detected in the urine samples of animals, suggesting their higher absorption into the bloodstream compared to other urolithins [25]. Furthermore, the presence of UA in feces has also been observed, unlike others. But urolithins' level are affected by production variations, which can depend on factors such as microbial composition [83]. In germ-free rats lacking gut microbiota, a diet rich in ET and EA demonstrates that, although the rats were fed with an ET and EA rich diet, the model does not produce urolithins. Hence, the conversion of ET and EA to urolithins is highly dependent on the individual's gut microbiota composition [29–31]. This is supported by findings showing that the abundance of *Gordonibacter urolithinfaciens* increased in mice fed EA, leading to elevated levels of UA [84]. This suggests that greater microbial diversity in the human gut may enhance the production of different urolithins following consumption of ET and EA. In line with this, emerging studies have shown promising results on fecal microbial transplantation (FMT) in PD treatment. FMT treatment was found to significantly improve motor function, increase striatal neurotransmitters, increase dopaminergic neurons, and reduce glial-based neuroinflammation in the MPTP induced PD model [85]. In another study, FMT treatment showed significant alterations in the gut microbiome; particularly, an increase in the *Akkermansia* genus, which is known to degrade the intestinal mucosal barrier, and a decrease in the *Bacteroidetes* phylum and *Helicobacter pylori* in rotenone-induced PD mice, following which the gut microbial composition of the PD mice closely resembled that of the healthy group [86]. Also, in PD patients, FMT treatment significantly improved crucial symptoms, particularly constipation [87]. In a case study, a single patient who received FMT experienced short-term improvements in tremor and constipation [88]. Similarly, another study involving 12 PD patients found that FMT led to improvements in both motor and non-motor symptoms [89]. These reports cumulatively suggest that FMT may prove to be a promising therapeutic strategy for PD. Interestingly, FMT treatment is also reported to increase urolithin production in ellagic acid-fed pseudo-germ-free mice. Although no such observation has yet been reported in PD models, the abovementioned reports point towards the therapeutic efficacy of FMT in PD through the production of beneficial microbial metabolites including urolithins [90]. Moreover, genetic factors, dietary habits, metabolic capacity, intestinal permeability, renal function, and age also contribute to interindividual variability in urolithin production [32]. However, to achieve consistent and health-relevant levels of urolithins, supplementation with these metabolites may offer a more reliable alternative [23].

Senolytic Effects of Urolithins

Ageing is a physical deterioration whose occurrence elevates the risk of diseases, including PD [91]. Potential biomarkers of ageing include mitochondrial impairment, autophagy dysfunction, inflammation, and oxidative stress that share common underlying factors with PD [92]. Therefore, strategies aimed at delaying the aging process may hold significant potential in mitigating PD. Evidence has shown that urolithins play an important role for their anti-aging properties. As studied among all the urolithins, UA has been explored robustly in its anti-aging properties. UA treatment was found to increase mobility and life span of the nematode *C. elegans* by inducing mitophagy and preventing the buildup of dysfunctional mitochondria [22]. A similar outcome was observed in both the young and the age-related muscle decline model of rodents in the same study [22]. In aging mice, UA mitigated muscle atrophy, decreased neuronal apoptosis, oxidative stress, and inflammation, plausibly by inhibiting the mammalian target of rapamycin (mTOR) pathway and activating the sirtuin 1 (SIRT1) pathway [93]. The other metabolite UB is found to improve learning and memory, attenuate oxidative stress and neuronal apoptosis in aging mice plausibly by downregulating c-Jun N-terminal kinase (JNK) signaling and activating mitogen-activated protein kinase (MAPK) [94]. A study also demonstrated the anti-aging role of the metabolite UC as evidenced by improved cognition and synaptic functioning, decreased amyloid beta aggregation, downregulated MAPK and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, and decreased inflammation in the brain of aging mice [95]. However, to our knowledge, UD has not yet been explored for its effects against aging.

Urolithins as Emerging Modulators of Parkinsonian Mechanisms: Therapeutic Implications

Translational evidence has suggested several drugs for the therapeutic intervention of various hallmarks of PD, while clinical outcomes are still being evaluated to establish

their safety profiles. Currently, levodopa (L-DOPA), often administered in combination with dopamine receptor agonists, monoamine oxidase B (MAO-B) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors, constitutes the mainstay of treatment [96–99]. However, the efficacy of these anti-PD drugs is largely restricted to symptomatic relief. Furthermore, long-term use of these medications is frequently associated with adverse effects, including vomiting, nausea, insomnia, and hallucinations [100]. Given these limitations, there remains a critical need for effective disease-modifying therapies. In response to this unmet demand, extensive research has been directed toward exploring the neuroprotective potential of various compounds, including the metabolites obtained in the gut [50, 57, 59, 60, 101]. One such group of metabolites includes urolithins, which have garnered immense attention due to their colossal therapeutic abilities, for instance dopamine degrading enzymes, overactivation of tyrosinase, synucleinopathy, oxidative stress, inflammation, mitochondrial impairment, and autophagy dysfunction. However, comprehensive evaluation of their potential anti-PD reports supporting prognostic therapeutic approaches in mitigating this devastating disorder is yet to be understood. Therefore, in this section, we delve deep into various mechanistic roles of urolithins in the pathobiology of PD.

Urolithins as Modulators of Dopaminergic Neuronal Survival and Dopamine Metabolism in Parkinson's Disease Pathology

Degeneration of DA neurons within the nigrostriatal pathway constitutes a cardinal pathological hallmark of PD, culminating in profound striatal DA depletion and resultant motor impairments [102, 103]. Emerging evidence highlights the neuroprotective capacity of urolithins, particularly UA, in mitigating DA neuronal loss and restoring DA homeostasis. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced murine model of PD, intraperitoneal administration of UA at 20 mg/kg daily for 7 days significantly attenuated neuronal loss within the SNpc and preserved DA terminals in the striatum. These neuroprotective effects were concomitant with marked improvements in motor coordination and balance [102]. Similar findings were reported in the 6-hydroxydopamine (6-OHDA) lesion model of Parkinson's disease, where treatment with UA (10 mg/kg, i.p. for 7 days) was observed to safeguard dopaminergic neurons and ameliorate motor deficits [103]. In vitro analyses further substantiated UA's neuroprotective efficacy, demonstrating a significant reduction in DA cell death following 24-h treatment with 10 µM UA [103]. Collectively, these data emphasize UA's potential as a therapeutic agent in PD. Nonetheless, the neuroprotective roles of other urolithins within the nigrostriatal axis remain inadequately characterized, warranting comprehensive investigations. DA depletion in PD is exacerbated by the hyperactivity of DA-catabolizing enzymes, notably MAO-B and COMT. These enzymes accelerate DA catabolism and generate neurotoxic by-products like DOPAL (3,4-dihydroxyphenylacetaldehyde), 3-MT(3-methoxytyramine), 3-O-methyldopa, and H2O2 (hydrogen peroxide), which potentiate neuronal injury and disease progression [46–49, 104]. Recent in vitro and in silico studies have implicated urolithins as potential inhibitors of these enzymatic pathways. Among the major urolithins, UA exhibits the most potent MAO-B inhibitory activity in vitro [105]. Molecular docking analyses further predict that UD possesses superior binding affinity for MAO-B relative to UA, UC, and UB [64], identifying UD as a promising candidate for MAO-B inhibition pending empirical validation. Similarly, computational studies designate UD as the most efficacious COMT inhibitor among the urolithins tested, followed sequentially by UA, UC, and UB [64], though further experimental corroboration remains necessary. Additionally, MAO-A, albeit less studied in PD, contributes to DA metabolism [106, 107]. Interestingly, UB demonstrates the strongest inhibitory effect against monoamine oxidase A (MAO-A), with UC and UA exhibiting lesser potency [105]. This study also suggests that urolithins may exert a more robust inhibitory effect on MAO-A than MAO-B. Independent evidence confirms UA's capacity to inhibit MAO-A activity and mitigate DA neurotoxicity [108], but rigorous in vitro and in vivo studies are imperative to validate and elaborate these effects across urolithin analogs. Beyond classical DA-metabolizing enzymes, tyrosinase overexpression is increasingly recognized as a contributor to PD pathogenesis. Enhanced tyrosinase activity promotes the formation of neurotoxic dopaquinone and neuromelanin species implicated in Lewy body formation and lysosomal dysfunction [109, 110]. Notably, UA attenuates tyrosinase overactivity in hydrogen peroxide–challenged Neuro-2a cells [108]. Given that excessive neuromelanin accumulation correlates with lysosomal impairment and α-syn misfolding, UA-mediated modulation of tyrosinase may represent a novel neuroprotective mechanism [109]. Nonetheless, further studies are required to validate this regulatory role of UA and other urolithins in neuromelanin-associated neurodegeneration. In summary, these converging lines of evidence underscore the multifactorial neuroprotective actions of UA, encompassing prevention of DA neuronal loss, modulation of DA metabolism, and attenuation of enzyme-mediated neurotoxicity. However, expanded characterization of other urolithins such as UD and UB is imperative to fully elucidate their therapeutic potential within the PD context (Table 2).

Table 2 Evidences supporting the mechanism of action behind the neuroprotective effects of Urolithins in PD

Effects of urolithins	Experimental model/dose of urolithins	Outcomes	References
Dopaminergic system	MPTP induced PD mice model: UA-20 mg/kg b.w., daily for 7 days 6 OHDA induced PD model: UA- 10 mg/kg b.w., for 7 days	• Mitigated dopaminergic neuronal degeneration in the substantia nigra region • Preserved dopaminergic neuron terminal in the striatum • Improved motor function • Dopaminergic neuronal protection in substantia nigra • Reduced motor deficits	[102] [103]
	In vitro MAO-A and MAO-B enzyme assay: UA (3 µM, 12 µM), UB (0.4 µM, 2 µM) and UC (15 µM, 60 µM) H2O2 induced neuro2a cells: UA- 0.5 µM-4 µM	• Reduced activity of MAO-B and MAO-A • Decreased MAO-A and tyrosinase activity	[105] [108]
	In silico UA, UB, UC, UD	• Inhibit MAO-B and COMT	[64]
Alpha-synucleinopathy	Rotenone induced N2A cells: UA-31.25 µM	• Decreased the alpha synuclein aggregation	[64]
	In silico UA, UB, UC, UD	• Holds the potential to inhibits alpha-synuclein	[64]
Oxidative stress	LPS induces BV2 microglial cells: UA, UB- 10 µM,5 µM,1 µM,0.5 µM H2O2 induced SK-N-MC cells: UA- 1.25 µM,2.5 µM,5 µM LPS induced BV2 microglial cells: UA, UB, UC-3 µM,10 µM,30 µM H2O2 induced neuro2a cells: UA- 0.5 µM-4 µM LPS induced BV2 microglial cells: UB- 30 µM,50 µM,100 µM 6-OHDA induced PC12 cell: UA-2.5 µM,5 µM,10 µM	• Reduced NO levels • Suppressed phosphorylation of P38 MAPK pathway • Decreased ROS generation • Reduced NO levels • Reduced ROS production, • Decreased Lipid peroxidation, • Increased the level of anti-oxidant enzymes (CAT, SOD, GR, GPx) • Inhibit NADPH • Upregulates H0-1 expression • Reduced ROS levels	[111] [112] [113] [108] [114] [103]
Inflammation	MPTP induced PD mice model: UA-20 mg/kg b.w., daily for 7 days LPS induced inflammation in mice model: UB-50 mg/kg b.w. for 4 days	• Reduced NLRP3 inflammasome in the SN • Decreased microglial activation in substantia nigra region	[102] [114]
	H2O2 induced BV2 microglial cells: UA, UB- 10 µM BV2 microglial cells: UB- 30 µM,50 µM,100 µM LPS induced BV2 microglial cells: UA, UB- 3 µM,10 µM,30 µM	• Decreased proinflammatory cytokines TNF-alpha and IL-6 • Suppressed the expression of IL-1 beta, COX2, and iNOS • Suppressed NF-KB • Reduced the phosphorylation of AKT, ERK and JNK • Increased AMPK phosphorylation • Suppressed AP-1 signaling pathway • Decreased proinflammatory cytokines TNF-alpha, IL-6, IL-1 beta, iNOS, COX2 • NF-KB signaling pathway, • reduced phosphorylation of ERK1/2, p38MAPK and AKT	[111] [114] [113]
	In silico*:* UA	• Inhibits COX2	[115]

Table 2 (continued)

Effects of urolithins	Experimental model/dose of urolithins	Outcomes	References
Mitochondrial impairment	6 OHDA induced mice model of PD: UA-10 mg/kg b.w., for 7 days	• Increased mitochondrial activity and expression of SIRT1	[103]
	rotenone induced N2A cells: UA- 31.25 µM H2O2 induced SK-N-MC cells: UA- 1.25 µM,2.5 µM,5 µM H2O2 induced neuro2a cells: UA- 0.5 µM–20 µM 6-OHDA induced PC12 cell: UA- 2.5 µM,5 µM,10 µM	• Improved mitochondrial membrane potential (MMP) • Suppressed mitochondrial apoptotic proteins (Cyt c, cleaved Caspase 9, cleaved caspase, cleaved PARP) • Improved mitochondrial activity • Improved TIM23, TOM20, PGC1alpha, TFAM, SIRT1 expression	[64] [112] [108] [103]
Autophagy dysfunction	MPTP induced PD model: UA-20 mg/kg b.w., daily for 7 days	• Increased LC3-II levels in the SN	[102]
	LPS induced BV2 microglial cells: UA-2.5 µM, 5 µM,10 µM	• Increased mitophagy	[102]

In silico Insights and Translational Perspectives on Urolithins as Inhibitors of α-Synuclein Aggregation

The aberrant aggregation of α-syn, a 14-kDa presynaptic protein, constitutes a central pathological feature of PD, culminating in the formation of Lewy bodies, which are intracellular inclusions predominantly observed in affected brain regions [116]. This pathogenic process has been recapitulated both in vitro and in vivo through the administration of preformed fibrils (PFFs) derived from recombinant α-syn monomers, which serve as seeds to induce the misfolding and propagation of endogenous α-syn species [117–120]. Structurally, α-syn comprises discrete domains with distinct functional attributes. The non-amyloid-β component (NAC) region, comprising residues 61–95, has been identified as the principal aggregation-prone segment of α-syn, playing a critical role in fibrillogenesis and associated neurotoxicity [121, 122]. Recent computational analyses have proposed that urolithins may act as modulators of α-syn aggregation by interacting with its fibrillogenic domains. Among these, UA demonstrated the highest predicted binding affinity to the NAC region, followed in rank order by UC, UD, and UB [64]. These in silico findings suggest a potential therapeutic role for urolithins as inhibitors of α-syn misfolding and assembly, thereby offering a novel approach to counteract synucleinopathy in PD. Despite these promising predictions, experimental validation remains sparse. Robust in vitro investigations are warranted to systematically assess the efficacy of urolithins in preventing α-syn fibril formation, seeding capacity, and associated cytotoxicity under physiologically relevant conditions. Furthermore, in vivo studies employing established PD models are essential to determine the bioavailability, pharmacodynamics, and neuroprotective potential of urolithins in mitigating α-syn pathology and neurodegeneration. Elucidating the molecular mechanisms underlying urolithin-mediated modulation of α-syn aggregation will be critical for advancing these compounds as candidate disease-modifying agents in the treatment of PD. Additionally, α-syn aggregation and accumulation have been linked with the activation of the unfolded protein response (UPR), that initiates pancreatic endoplasmic reticulum kinase (PERK) activation, which phosphorylates eukaryotic initiation factor 2 alpha (eIF2α), and blocks protein synthesis [123]. Moreover, long-term ER stress may lead to a shift in UPR towards the cell death pathway, which is considered to be a possible cause of neurodegeneration. Further, small-molecule inhibitors of the PERK-mediated signaling have shown promising therapeutics in neurodegeneration [124]. However, urolithin studies related to this pathway in the PD model are yet to be explored (Table 2). Moreover, the therapeutic effects of urolithins on interlinked pathways of PD pathogenesis, as discussed above, are depicted in Fig. 2.

Urolithins as Regulators of the SIRT1–NRF2/ARE Axis: Therapeutic Potential in Oxidative Stress-driven Parkinson's Disease

Oxidative stress is a central driver of PD pathogenesis, critically contributing to the selective degeneration of DA neurons. Reactive oxygen species (ROS), produced through both direct mechanisms (such as the Fenton and Haber–Weiss reactions) and indirect metabolic pathways, are key mediators of neuronal injury in PD [125–127]. Increasing evidence implicates urolithins (particularly UA and UB) as potent antioxidants capable of attenuating oxidative stress and promoting neuroprotection. Preclinical studies have demonstrated that UA treatment enhances neuronal viability and significantly reduces intracellular ROS levels, underscoring its strong antioxidative potential [111]. These results are corroborated by other studies showing that UA upregulates the activity of key antioxidant enzymes, including catalase

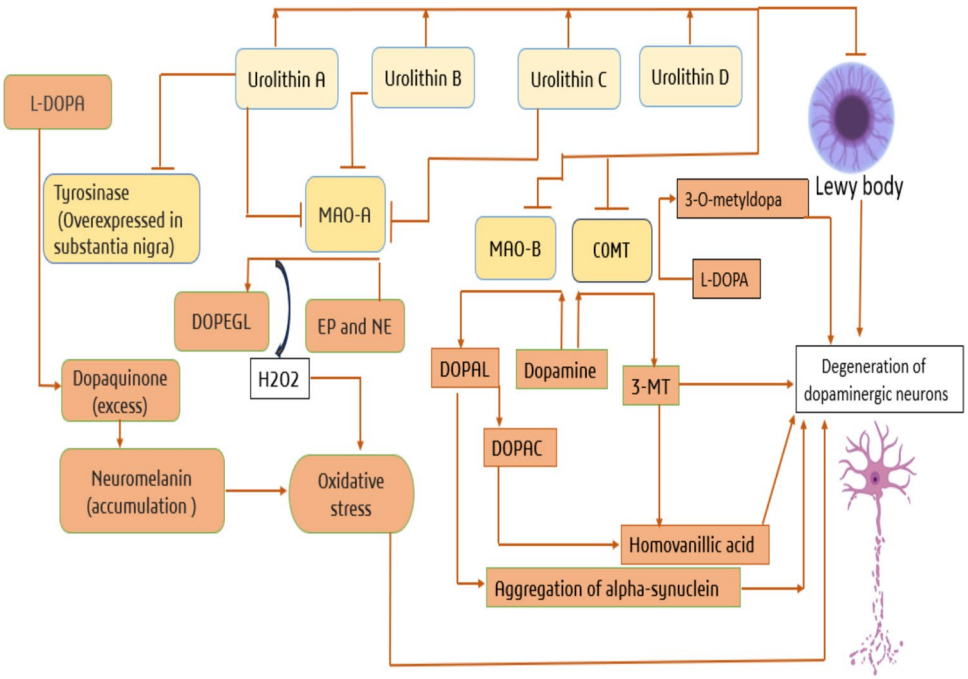

Fig. 2 Urolithins A, B, C, and D exert neuroprotective effects by targeting multiple pathological features of PD. Urolithins inhibit the activity of DA-degrading enzymes, MAO-B, and COMT, which are responsible for DA depletion and the production of neurotoxic metabolites and ROS. MAO-A contributes to the breakdown of norepinephrine and epinephrine releasing a precursor of free radicals, H2O2. Urolithins further reduce the pathological aggregation of α-syn, thereby limiting Lewy body formation and preserving DA neuronal integrity. Additionally, by modulating tyrosinase activity, urolithins help prevent excessive neuromelanin accumulation, which is associated with oxidative stress leading to dopaminergic neural degeneration in PD

(CAT), superoxide dismutase (SOD), glutathione reductase (GR), and glutathione peroxidase (GPx), thereby reinforcing endogenous antioxidant defenses [108]. UB similarly reduces ROS levels and supports neuronal survival, primarily via inhibition of NADPH oxidase, a major enzymatic source of ROS in neurons [111, 114]. While both UA and UB exhibit neuroprotective effects against oxidative insults, UA consistently demonstrates greater efficacy in enhancing antioxidant capacity and preserving cellular homeostasis [111]. Beyond its direct antioxidant activity, UA modulates several redox-sensitive signaling pathways. Notably, it inhibits the p38 mitogen-activated protein kinase (MAPK) pathway, which is associated with oxidative stress-induced neuronal damage in PD [112, 113]. In addition, UA attenuates mitochondrial-mediated apoptosis by reducing cytochrome c release, thereby mitigating ROS amplification and apoptotic signaling [112]. Emerging evidence suggests that UA's antioxidative effects are partially mediated through the SIRT1 signaling axis, which intersects with the nuclear factor erythroid 2–related factor 2/antioxidant response element (NRF2/ARE) pathway [103]. NRF2 activation promotes nuclear translocation and binding to ARE sequences, leading to transcriptional induction of cytoprotective genes, including heme oxygenase-1 (HO-1), a key regulator of oxidative balance. Although this mechanism is mechanistically plausible, further studies are needed to validate its role in PD-specific contexts. UB has also been shown to activate the NRF2/ARE pathway and upregulate HO-1 expression, reinforcing its contribution to antioxidative defense and neuroprotection [114]. In contrast, the antioxidant potential and underlying molecular mechanisms of UC and UD remain largely unexplored in the context of PD. Comprehensive in vitro and in vivo studies are warranted to assess whether these lesser studied urolithins confer similar neuroprotective benefits. In summary, the ability of UA and UB to mitigate oxidative stress through both enzymatic and signaling mechanisms underscores their promise as disease-modifying candidates in PD (Fig. 3). Targeting oxidative injury with urolithins offers a compelling strategy for preserving DA neuron integrity and slowing disease progression (Table 2).

Anti-inflammatory Potential of Urolithins in Parkinson's Disease: Molecular Insights Into Microglial Modulation

Chronic neuroinflammation is increasingly recognized as a critical driver of PD progression, contributing to the selective degeneration of DA neurons [125, 126]. Postmortem analyses of PD brains consistently reveal sustained microglial activation and elevated levels of proinflammatory cytokines, underscoring the centrality of inflammatory cascades in disease pathogenesis [128–130]. Among emerging neuroprotective agents, UA has demonstrated compelling anti-inflammatory properties. UA significantly reduces the production of major proinflammatory mediators, such as nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), and is associated with decreased microglial activation both in vitro and in vivo [111, 113]. In LPS-stimulated BV2 microglial cells, UA further suppresses the expression of interleukin-1β (IL-1β), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS), all of which play pivotal roles in the neuroinflammatory milieu

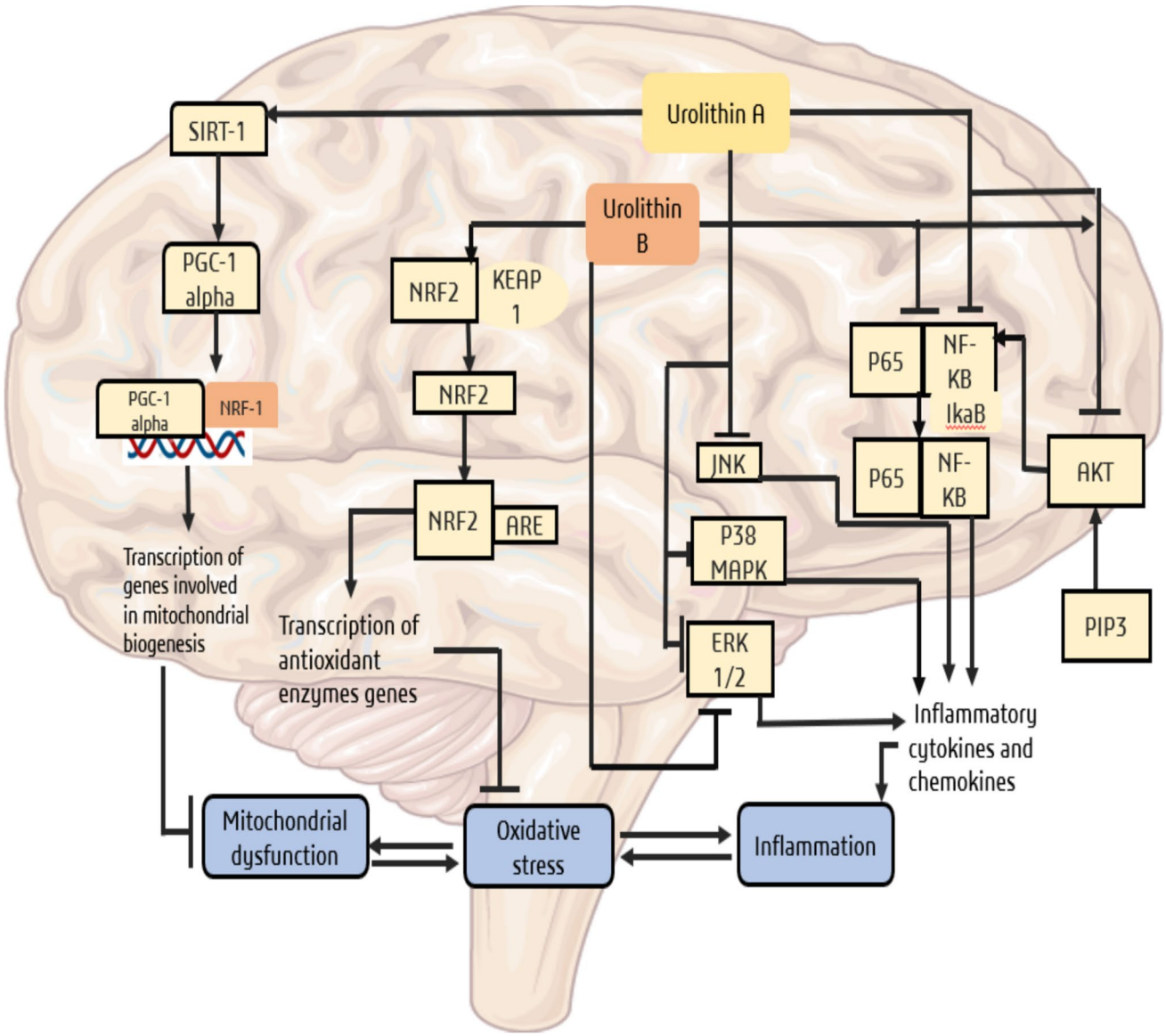

Fig. 3 Schematic representation of the molecular mechanisms by which UA and UB mitigate oxidative stress, inflammation, and mitochondrial dysfunction. UA enhances mitochondrial biogenesis by upregulating SIRT1 expression, which activates downstream signaling leading to the stimulation of PGC-1α and improved mitochondrial function. Additionally, UA exerts anti-inflammatory effects by inhibiting key signaling pathways, including AKT/PKB, NF-κB, JNK, p38 MAPK, and ERK1/2. In parallel, UB reduces oxidative stress by activating the NRF2–ARE signaling pathway, which promotes the expression of antioxidant genes. UB also attenuates inflammation through inhibition of ERK1/2, AKT/PKB, and NF-κB pathways

[113]. Complementary in vivo findings demonstrate that UA downregulates components of the Nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome in the SN of MPTP-induced PD models and corresponding cellular systems, highlighting its potential to modulate innate immune responses at the site of neurodegeneration [131]. Supporting these biological effects, in silico molecular docking analyses reveal that UA binds with higher affinity to COX-2 than several commonly used non-steroidal anti-inflammatory drugs, including acetylsalicylic acid, ibuprofen, naproxen, ketorolac, and indomethacin [115], further underscoring its therapeutic promise as an anti-inflammatory compound in PD. UB similarly demonstrates anti-inflammatory efficacy, attenuating LPS-induced upregulation of proinflammatory markers in microglial cells and offering neuroprotection in preclinical PD models [111, 113, 114].While UC exhibits limited anti-inflammatory activity in vitro [113], the potential of both UC and UD remains poorly defined, warranting further mechanistic and pharmacological exploration. At the molecular level, UA and

UB exert their anti-inflammatory effects, at least in part, via inhibition of the NF-κB signaling pathway. Under resting conditions, NF-κB is sequestered in the cytoplasm by inhibitor IκB-α. Upon stimulation, IκB-α undergoes phosphorylation and degradation, allowing NF-κB to translocate to the nucleus and initiate transcription of proinflammatory genes [132]. Both UA and UB inhibit NF-κB nuclear translocation in activated BV2 cells, thereby suppressing inflammatory gene expression at the transcriptional level [113]. Moreover, the PI3K/AKT signaling axis, which can activate NF-κB, is also downregulated by UA and UB, providing an additional anti-inflammatory mechanism [113]. These urolithins further modulate MAPK pathways, including extracellular signal-regulated kinase (ERK) 1/2 and p38 MAPK, to dampen inflammatory signaling. Interestingly, UB appears less effective in inhibiting p38 MAPK compared to UA, suggesting divergent molecular profiles and potential for synergistic or complementary therapeutic use. UA also suppresses JNK phosphorylation, adding to its broad anti-inflammatory spectrum [133]. Despite the accumulating evidence supporting the anti-inflammatory actions of UA and UB, the roles of UC and UD remain inadequately characterized. Comprehensive in vitro and in vivo studies are essential to delineate their anti-inflammatory efficacy, molecular targets, and relevance to PD pathology. In summary, UA and UB exert multifaceted anti-inflammatory effects by modulating both cytokine expression and intracellular signaling pathways (Fig. 3). Their capacity to suppress microglial activation and dampen neuroinflammatory cascades positions them as promising therapeutic candidates for halting or slowing inflammation-mediated neurodegeneration in PD (Table 2).

Mitochondrial Restoration in Parkinson's Disease: Emerging Roles of Urolithin A and Related Metabolites

Mitochondrial dysfunction represents a fundamental pathological feature of PD and plays a pivotal role in the selective degeneration of DA neurons [108, 112, 134]. Disruptions in mitochondrial bioenergetics and dynamics contribute to a cascade of deleterious processes, including impaired calcium homeostasis, excessive production of ROS, and activation of the intrinsic apoptotic pathway [135]. These perturbations ultimately lead to mitochondrial-mediated neuronal death, thereby accelerating disease progression. Among emerging therapeutic compounds, UA has demonstrated promising neuroprotective effects through its ability to ameliorate mitochondrial impairment. Preclinical reports reveal that UA treatment enhances mitochondrial function, improves membrane potential, and significantly reduces ROS-induced cytotoxicity in neuronal cells [108]. Improvement in mitochondrial membrane potential by UA has also been supported by another study [64]. Notably, UA lowers the release of cytochrome c, a key pro-apoptotic factor released during mitochondrial outer membrane permeabilization, indicating suppression of mitochondrial-mediated apoptosis and enhanced neuronal survival [112]. Additional in vitro and in vivo investigations further support UA's ability to preserve mitochondrial ultrastructure and restore bioenergetic integrity, evidenced by improved mitochondrial morphology and function [102, 103]. Mechanistically, these protective effects are mediated, at least in part, through the sirtuin 1−peroxisome proliferator-activated receptor gamma coactivator-1 alpha (SIRT1–PGC-1α) signaling axis, a critical regulator of mitochondrial biogenesis, oxidative metabolism, and antioxidant defenses [103]. Activation of this pathway by UA enhances mitochondrial resilience and may counteract the degenerative cascade characteristic of PD (Fig. 3). Despite the compelling evidence supporting UA's role in mitochondrial restoration, the effects of other urolithin metabolites (UB, UC, and UD) remain largely unexplored. To date, no comprehensive studies have elucidated their potential impact on mitochondrial function or their molecular targets within relevant signaling networks. As such, systematic investigations employing validated PD models are critically needed to determine whether these compounds exhibit similar or complementary neuroprotective mechanisms. In summary, UA demonstrates strong potential as a disease-modifying agent in PD due to its ability to restore mitochondrial function and suppress apoptotic signaling. Further exploration of other urolithins may uncover additional mitochondrial-targeted strategies for the treatment of PD and other neurodegenerative disorders (Table 2).

Modulation of Autophagy by Urolithins to Preserve Neuronal Proteostasis in Parkinson's Disease

Autophagy is a critical catabolic pathway responsible for the clearance of misfolded proteins and damaged organelles, thereby maintaining proteostasis and neuronal survival. Impaired autophagy is a well-established contributor to PD pathogenesis, particularly through the accumulation of toxic protein aggregates such as α-syn, which disrupt cellular homeostasis and promote neurodegeneration [136, 137]. Autophagy involves the sequestration of cytosolic debris into double-membraned autophagosomes, which subsequently fuse with lysosomes to form autolysosomes where enzymatic degradation occurs [137, 138]. This process yields reusable macromolecules essential for cellular function. Key molecular markers include the conversion of LC3-I to LC3-II (indicative of autophagosome formation) and the degradation of p62, a selective autophagy receptor that targets ubiquitinated cargo for lysosomal clearance [139, 140]. Autophagic impairment in PD models is typically characterized by reduced LC3-II levels and accumulation of p62, both of which correlate with disease severity. Disruption of

autophagy also impairs the regulation of genes central to PD pathology, such as SNCA and PINK1, exacerbating mitochondrial dysfunction and neuronal loss [141]. Notably, UA has been shown to restore autophagic function. In MPTP-induced PD mouse models, UA treatment increased LC3-II levels in the SN, suggesting enhanced autophagosome formation [131]. Moreover, UA improved mitophagy in LPS-stimulated BV2 microglial cells, further supporting its role in mitochondrial and cellular quality control [131]. Although these findings suggest that UA promotes autophagy and neuronal survival, further validation is needed through dynamic assays such as p62 turnover and autophagic flux analysis. The precise mechanisms by which UA modulates autophagy remain under investigation. One proposed pathway involves the suppression of the AKT/mTORC1 axis, a well-characterized negative regulator of autophagy. mTORC1 inhibits autophagy initiation under nutrient-rich conditions and is activated by upstream AKT signaling [142]. Given that UA has been reported to downregulate AKT expression [113], it may exert indirect inhibition on mTORC1, thereby facilitating autophagy. However, direct mechanistic evidence for this interaction in PD models is currently lacking. Furthermore, upregulation of autophagy has also been facilitated with autophagy-related genes (ATGs), which constitute the core machinery responsible for autophagosome formation [8]. This suggests that elevation of ATGs plays a crucial role in mitigating autophagy dysfunction; however, to our knowledge, the specific influence of urolithins on the modulation of these ATGs in the PD model is yet to be explored. In contrast, the effects of other urolithin metabolites on autophagic regulation remain largely unexplored. No studies to date have comprehensively assessed their impact on autophagy in PD-relevant systems. Rigorous in vitro and in vivo investigations are required to determine whether these compounds similarly promote proteostatic resilience and contribute to neuroprotection. Also, evidence concerning the impact of urolithins on genes like PINK1/Parkin mutations related to mitophagy in PD models is still to be investigated. In summary, UA's ability to modulate autophagy and mitophagy positions it as a promising therapeutic agent for mitigating proteostatic failure in PD. Elucidating the autophagy-related mechanisms of other urolithins may uncover additional strategies for targeting protein aggregation and neuronal dysfunction in neurodegenerative diseases (Table 2).

Conclusion and Future Perspective

The multifactorial nature of PD poses a significant challenge to the development of effective, comprehensive therapies. Recent advances have spotlighted the gut microbiota and its ability to generate bioactive metabolites such as urolithins as promising modulators of PD's complex pathogenesis through multitargeted mechanisms. This review highlighted the emerging roles of urolithins in counteracting key pathological features of PD, including dysregulated DA metabolism, neuromelanin-induced toxicity, α-syn aggregation, oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, and impaired autophagy. Among these metabolites, UA stands out as the most thoroughly characterized, exhibiting strong neuroprotective effects across multiple experimental models of PD. UB also demonstrates notable antioxidant and anti-apoptotic properties, though it has been studied less extensively. In contrast, UC and UD remain relatively unexplored, with preliminary evidence suggesting potential roles in supporting DA neuron survival and function. Taken together, these findings underscore the therapeutic potential of urolithins as multitarget agents capable of modulating the intersecting pathological pathways of PD. However, further mechanistic studies and translational research are needed to better understand their bioavailability, pharmacokinetics, safety, and efficacy in both preclinical and clinical contexts. Additionally, investigating combinatorial therapies that pair urolithins with other natural compounds may reveal synergistic neuroprotective effects. A particularly exciting avenue for future research is the recently identified UG, whose biological activities remain unknown. Exploring UG's effects in PD-relevant in vitro and in vivo models may uncover novel neuroprotective mechanisms and broaden the therapeutic possibilities of microbiota-derived metabolites. In summary, advancing our knowledge of urolithins and their interactions within the gut-brain axis offers promising prospects for developing innovative metabolite-based interventions aimed at combating PD.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Informed Consent Not applicable.

Competing interests The authors declare no competing interests.

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