Movement of Prion-Like α-Synuclein along the Gut-Brain Axis in Parkinson's Disease: A Potential Target of Curcumin Treatment

Devina Chetty[1*], Shameemah Abrahams[1], Riaan van Coller[2], Jonathan Carr[3], Colin Kenyon[1,4,5], Soraya Bardien[1*]

[1] Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

[2] Faculty of Health Sciences, School of Medicine, Department of Neurology, University of Pretoria, South Africa.

[3] Division of Neurology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

[4] DST-NRF Centre of Excellence for Biomedical Tuberculosis Research, South African Medical Research Council Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

[5] South African Medical Research Council Centre for Tuberculosis Research, Stellenbosch University, Cape Town, South Africa.

* Correspondence to: Devina Chetty (DC) and Soraya Bardien (SB), Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; devinachetty@sun.ac.za ; sbardien@sun.ac.za

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Abstract

A pathological hallmark of the neurodegenerative disorder, Parkinson's disease (PD), is aggregation of toxic forms of the pre-synaptic protein, alpha-synuclein (α-synuclein) in structures known as Lewy bodies. Alpha-synuclein pathology is found in both the brain and gastrointestinal tracts of affected individuals, possibly due to the movement of this protein along the vagus nerve which connects the brain to the gut. In this review, we discuss current insights into the spread of α-synuclein pathology along the gut-brain axis which could be targeted for therapeutic interventions. The prion-like propagation of α-synuclein, and the clinical manifestations of gastrointestinal dysfunction in individuals living with PD, are discussed. There is currently insufficient evidence that surgical alteration of the vagus nerve, or removal of gut-associated lymphoid tissues, such as the appendix and tonsils, are protective against PD. Furthermore, we propose curcumin as a potential candidate to prevent the spread of α-synuclein pathology in the body by curcumin binding to α-synuclein's non-amyloid β-component (NAC) domain. Curcumin is an active component of the food spice turmeric and is known for its antioxidant, anti-inflammatory, and potentially neuroprotective properties. We hypothesize that once α-synuclein is bound to curcumin, both molecules are subsequently excreted from the body. Therefore, dietary supplementation with curcumin over one's lifetime has potential as a novel approach to complement existing PD treatment and/or prevention strategies. Future studies are required to validate this hypothesis, but if successful, this could represent a significant step towards improved nutrient-based therapeutic interventions and preventative strategies for this debilitating and currently incurable disorder.

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1. Introduction

Parkinson's disease (PD) is an age-related neurological disorder characterized by loss of dopaminergic neurons, predominantly in the substantia nigra, leading to dopamine deficiency in the brain (Miyasaki *et al.*, 2002). In 2016, 6.1 million individuals were living with PD, which is more than double the 1990 statistic of 2.5 million individuals (Dorsey *et al.*, 2018), and this trend is set to continue. PD may not be caused by only one mechanism, but rather several interdependent molecular events that result in the manifestation of the disease (Brundin & Melki, 2017). Neuronal degeneration in PD has been associated with various processes including oxidative stress, mitochondrial dysfunction, protein aggregation, proteasomal inhibition, and neuroinflammation (Mythri & Srinivas Bharath, 2012). A pathological hallmark of PD brains is the aggregation of misfolded α-synuclein protein in Lewy bodies (LBs). Notably, the presence of misfolded α-synuclein along the axis joining the gut and the brain, suggests that the gut may play an important role in PD pathogenesis and progression.

In this review, we examine the evidence supporting the prion-like behavior of α-synuclein along the gut-brain axis which may contribute to PD pathogenesis. Also described are the various clinical manifestations of gastrointestinal (GI) dysfunction experienced by individuals with PD. In addition, controversial evidence for the effect of various GI tract-associated surgeries and their effect on PD development are discussed. Furthermore, in this review, we explore the role of curcumin as a potential nutraceutical for the treatment of PD. Nutraceuticals are bioactive compounds in plant- or animal-based food that have beneficial pharmaceutical properties beyond their nutritional value (Biesalski *et al.*, 2009). This therapeutic approach addresses possible long-term treatment options for PD based on the involvement of the gut and pathogenic α-synuclein in disease progression.
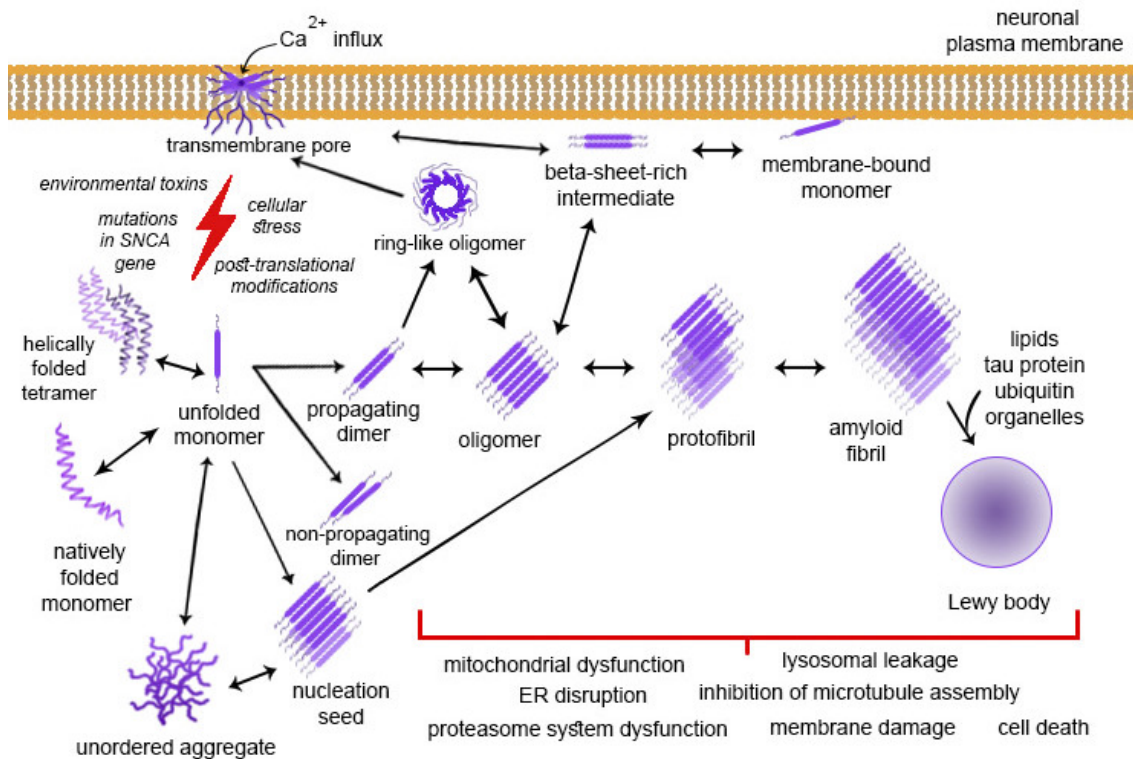
2. Alpha-synuclein

Approximately, 5-10% of PD cases have been linked to mutations in different genes. Genes that have been linked to PD pathogenesis include *SNCA* and *LRRK2,* responsible for autosomal dominant forms of PD, as well as *PINK1*, *PRKN, FBXO7,* and *DJ-1* which cause autosomal recessive PD (Cherian & Divya, 2020). Juvenile onset parkinsonism has been linked to *ATP13A2, SVE, DNAJC6,* and *SYNJ1* (Minakaki *et al.*, 2020). Notably, the *SNCA* gene, which encodes α-synuclein, has point mutations as well as duplications and triplications that increase the production of this protein, resulting in toxic α-synuclein accumulation in the body which correlates with disease severity (Chartier-Harlin *et al.*, 2004; Ibanez *et al.*, 2004).

Although α-synuclein's precise role in the body remains unknown, it is a presynaptic nerve terminal protein believed to be involved in the release of dopamine, vesicle recycling, and membrane remodeling (Bourdenx *et al.*, 2017). Native, or properly folded, forms of α-synuclein are thought to regulate the presynaptic vesicular pool and protect neuron terminals against injury (Uversky & Eliezer, 2009). As illustrated in Figure 1, the α-synuclein protein comprises an amphipathic amino terminal domain (amino acids 1 – 60) which contains PD-causing point mutations, a central non-amyloid β-component (NAC) domain (amino acids 61 – 95), and an acidic carboxyl terminal domain (amino acids 96 – 140) (Giasson *et al.*, 2001).

Discovery of the causal link between α-synuclein assembly and synucleinopathies has led to several comparative studies on amyloid fiber aggregation (Boyer *et al.*, 2019; Schweighauser *et al.*, 2020). Structural analysis has revealed that variable fold forms of these fibers are possible, and are affected by gene mutations, post-translational modifications, and non-proteinaceous molecules. Mutations may affect the hydrogen-bonding network within the filament rearrangements, as well as the kinetics of α-synuclein aggregation. This has been found in the α-synuclein associated with multiple system atrophy as well as the tauopathies of chronic traumatic encephalopathy and corticobasal degeneration (Falcon *et al.*, 2019;

Schweighauser *et al.*, 2020; Zhang *et al.*, 2020). Understanding the structural specificity of α-synuclein assembly in PD will facilitate defining the respective roles of mutations, aberrant α-synuclein expression regulation, and lifestyle on PD progression.

Figure 1. Protein domains of human α-synuclein. Schematic α-synuclein protein structure that is composed of the amphipathic amino terminal domain (orange), non-amyloid β-component (NAC) domain (yellow), and the acidic carboxyl terminal domain (green) (Flavin et al., 2017). The amphipathic amino terminal domain is lysine rich and is important for membrane interactions. The central NAC domain has hydrophobic and lipid sensing properties, modulates membrane binding affinity, and promotes protein aggregation (Giasson et al., 2001). The carboxyl terminal domain contains phosphorylation sites and plays a role in protein–protein interactions (Uversky & Eliezer, 2009). The numbers refer to amino acid positions, the solid lines refer to Parkinson's disease-causing point mutations, and the dashed lines refer to phosphorylation sites

Figure 2. Process of α-synuclein misfolding and aggregation into pathogenic intermediates and, finally, Lewy bodies that are characteristic of Parkinson's disease. Native α-synuclein exists in the cytosol as an unordered monomer, a folded monomer, an unordered aggregate (Swart et al., 2014), or as a degradation-resistant, helically folded tetramer (Bartels et al., 2011). A pre-formed fibril or fibril fragment, known as a seed, accelerates fibril formation by the dominant process of secondary nucleation. Secondary nucleation involves aggregate formation from surface monomers (Gaspar et al., 2017). The toxic species produced during polymerization may damage mitochondria and lysosomes (Hashimoto et al., 2004; Hsu et al., 2000), disrupt microtubules (Alim et al., 2004), promote aggregate formation (Bousset et al., 2013; Brehme et al., 2014), cause organelle dysfunction (Flavin et al., 2017), and trigger inflammation and eventual cell death (Gustot et al., 2015). Ca^{2+}, calcium; ER, endoplasmic reticulum; SNCA, α-synuclein

New data regarding the precise process of misfolding and aggregation of this protein into toxic β-rich intermediates and LBs are continually being elucidated. As seen in Figure 2, α-synuclein monomers can progressively be misfolded into toxic species due to many triggers, including neurotoxin exposure (e.g. paraquat, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

(MPTP), and rotenone), and mutations in the gene encoding α-synuclein, *SNCA* (Ingelsson, 2016). The NAC domain of α-synuclein is responsible for the conformational change of the protein from the random coil structure of monomers and dimers to the β-sheet conformation of oligomers (Fusco *et al.*, 2014). β-sheet-rich oligomers grow into protofibrils and continue to polymerize to form LBs (Lashuel *et al.*, 2013). LBs (proteinaceous structures with radiating filaments) and Lewy neurites (less structured fibrillary inclusions) are predominantly composed of insoluble α-synuclein, ubiquitin, tau protein, and phosphorylated neurofilaments (del Tredici *et al.*, 2002; Alafuzoff & Hartikainen, 2018). The toxic species of α-synuclein produced during misfolding and polymerization lead to cellular dysfunction and eventually, cell death (Gustot *et al.*, 2015).

Neuronal loss and Lewy pathology in the brainstem and cerebral cortex are pathognomonic for PD (Ruffmann & Parkkinen, 2016). However, alternative, less invasive methods are being explored to identify LBs and α-synuclein outside the central nervous system (CNS). Extensive research has been undertaken to investigate the possibility that α-synuclein pathology in PD may even begin in the gut (Holmqvist *et al.*, 2014; Chandra *et al.*, 2017; Lionnet *et al.*, 2018). Notably, dysfunction of the GI system gives rise to symptoms that may precede the motor features of the disease by decades (Houser & Tansey, 2017). The GI tract represents a more accessible region than the CNS, which would be valuable for early detection of PD (Mukherjee *et al.*, 2016). Therefore, elucidation of the involvement and role of the GI tract in PD pathology could provide a major stepping stone towards the goal of developing more effective methods of detecting, treating, and even preventing the disease.

3. Alpha-synuclein found in the gut of PD patients

Support for the gut's involvement in PD is derived, in part, from studies in which pathogenic α-synuclein has been found in the GI tracts of PD patients. Stockholm and colleagues studied this protein in a total of 57 PD patients and 90 controls from the Danish National Pathology Registry (DNPR) (Stokholm *et al.*, 2016). Pathogenic phosphorylated α-synuclein was found in 22 of 39 (56%) PD patients who had tissue removed during the prodromal phase (early stage of the disease prior to disease diagnosis) compared to only 23 of 90 (26%) age- and sex-matched controls. The tissue samples were taken from a variety of anatomical regions including the nose and mouth regions, salivary glands, esophagus, stomach, small intestine, colon, and appendix. Importantly, this study identified Lewy pathology in the GI tract up to 20 years before patients were diagnosed with PD (Stokholm *et al.*, 2016). This correlates with the reported prodromal period for PD of over 20 years, in which early signs and symptoms are present but a classical diagnosis based on fully developed motor impairment is not yet possible (Schenck *et al.*, 2013; Berg *et al.*, 2015). Hilton and colleagues reported α-synuclein accumulation in the bowel of PD patients and suggested this as an accessible biomarker for studying early stages of PD (Hilton *et al.*, 2014). Further reports identified pathogenic phosphorylated α-synuclein deposits in the submandibular gland (Adler & Beach, 2016), as well as the myenteric plexus, submucosal layer, and mucosal nerve fibers of the intestine in individuals living with early untreated PD (Shannon *et al.*, 2012).

In a large study measuring the PD diagnostic sensitivity and predictive ability of α-synuclein in different tissue biopsies, the sensitivity of colon biopsies (24%) was lower than skin and submandibular gland biopsies, with a negative predictive value of 67% (Chahine *et al.*, 2020). A meta-analysis reported that only nine of sixteen studies showed a positive association between the presence of gut α-synuclein and PD diagnosis (Bu *et al.*, 2019). Specifically, colon α-synuclein had the highest degree of discrimination between PD and

controls, with a specificity of 81.9% but a low sensitivity of only 56.8%. Biopsy site and histochemical technique can be confounders. Taken together, these findings show that the variable sensitivity and specificity reported for α-synuclein-positive colon biopsies raises questions for this technique as an early diagnostic or biomarker for PD (Visanji *et al.*, 2015; Chung *et al.*, 2016; Lee *et al.*, 2017).

Moreover, although α-synuclein occurs at a statistically higher level in the ENS of PD patients compared to control individuals (Aldecoa *et al.*, 2015), the presence of α-synuclein aggregates throughout the body in healthy individuals raises further concerns about its use as a biomarker for PD. Even though α-synuclein's expression is highest in the brain, it is known to be expressed throughout the body in non-diseased individuals (https://www.proteinatlas.org/ENSG00000145335-SNCA/tissue). Consequently, improved methods for a detailed structural analysis to discriminate between pathogenic and non-pathogenic forms of this protein on the cellular and biochemical levels are necessary before interpreting the role of α-synuclein in PD diagnosis (Schaeffer *et al.*, 2020).

3.1. Alpha-synuclein distribution in the brain and gut

The distribution of α-synuclein in the gut generally follows a rostrocaudal (top to bottom) gradient, with more misfolded protein found in the upper than the lower GI tract (Cersosimo, 2015). Studies have reported that the greatest levels of pathogenic α-synuclein are in the submandibular gland and lower esophagus of PD patients, followed by the stomach, small intestine, colon, and rectum (Beach *et al.*, 2010).

In monogenic PD, neuropathological findings of synuclein deposition range from being characteristic of *SNCA* mutations (Duda *et al.*, 2002) to relatively uncommon in cases with *PRKN* mutations (Seike *et al.*, 2021), and are frequently variable in *LRRK2* mutations (Wszolek

et al., 2004). LBs are not restricted to cases of PD, as Lewy-type pathology is well described in Alzheimer's disease, both sporadic and genetic forms (Compta & Revesz, 2021). Many cases of sporadic PD likely arise in patients with an incidental 'Lewy Body State' (de la Fuente-Fernandez *et al.*, 1998). In sporadic PD, LBs are distributed throughout the brainstem (substantia nigra, raphe nuclei, mesopontine tegmentum, locus coeruleus, and dorsal motor nucleus of the vagus (DMNV)) and basal forebrain (N basalis Meynert) (Dickson, 2018); additional cortical LBs are found in the amygdala and neocortex. Lewy neurites, largely representing disrupted axonal processes, are an important source of synuclein pathology and are commonly identified in the anterior olfactory nucleus and other sites (Braak, del Tredici, *et al.*, 2003). Synuclein pathology is largely found in neurons and not glia, and the presence of cytoplasmic inclusions reflects displacement of synuclein from its location in the presynaptic terminals (Dickson, 2018).

In addition to the brain and the gut, α-synuclein pathology is also distributed throughout the body, particularly in the spinal cord, the sympathetic ganglia, skin, the vagus nerve, and endocrine organs (Beach *et al.*, 2010). Similar changes are also frequently found in the spinal cord and sympathetic ganglia in incidental LB disease (Beach *et al.*, 2010). These pathological findings, together with clinical evidence of prodromal autonomic dysfunction and abnormal metaiodobenzylguanidine (MIBG) cardiac imaging showing postganglionic sympathetic cardiac denervation (Yoshita, 1998), point to early involvement of the autonomic nervous system (ANS) by α-synuclein pathology.

Lewy pathology is usually restricted to certain cell types, for example within the DMNV only the cholinergic and catecholaminergic neurons are affected, whereas neurons producing γ-aminobutyric acid are not (Kingsbury *et al.*, 2010). The selective vulnerability of cells in individuals living with PD may be explained in part by the proposal made by Braak and colleagues that a relationship exists between axonal characteristics of neurons and

susceptibility to pathogenic α-synuclein (Braak, Rüb, *et al.*, 2003). The vagus nerve contains long, thin, poorly myelinated fibers of the visceromotor system. These fibers appear to be more susceptible to LB pathology than the myelinated fibers that relay viscerosensory inputs or fibers derived from the nucleus ambiguus. It is speculated that this phenomenon may be related to the bioenergetic demands of sustaining electrical excitability along these axons or the physiological traits of neurons, such as slow calcium oscillations, leading to mitochondrial oxidative stress (Breen *et al.*, 2019). However, at this stage, it remains unclear why only certain cells are affected by α-synuclein pathology.

4. Prion-like movement of alpha-synuclein in PD

In 1976, it was established that diseases such as Creutzfeldt–Jakob disease (CJD) could be transmitted through direct intracerebral injection of brain tissue from affected patients (Gibbs *et al.*, 1968; Masters *et al.*, 1981). Stanley B. Prusiner discovered a transmissible agent unlike bacteria or viruses that consists of protein, which he named a "prion" – an amalgamation of the words "protein" and "infectious" (Prusiner, 1982). Prions are known to be proteinaceous infectious agents which are responsible for several fatal neurological diseases in humans. Prions lack nucleic acids and are instead solely composed of misfolded, host-encoded prion protein, which is a glycoprotein expressed in all vertebrates (Wickner *et al.*, 2011). Interestingly, a recent study reported a case of variant CJD that was diagnosed 7.5 years after accidental occupational exposure to bovine spongiform encephalopathy prions from infected mice brain tissue, which emphasizes the need to improve identification and prevention strategies for prion disease transmission to humans (Brandel *et al.*, 2020). The understanding of prion diseases is still incomplete and the existence of prion-like mechanisms in PD pathology remains unknown (Jucker & Walker, 2013; Collinge, 2016).

4.1. PD and the prion hypothesis

Several features are shared between PD and prion diseases, and these similarities have been reviewed previously (Prusiner, 2001; Olanow & Brundin, 2013; Brundin & Melki, 2017). Human prion disease and PD are neurodegenerative disorders in which the affected neurons display selective vulnerability. Both pathologies are characterized by propagating protein deposits which can be taken up by neurons and transferred to unaffected cells nearby. Misfolded prions may migrate along the peripheral nerves and up the spinal cord in prion diseases (Olanow & Brundin, 2013). At the cellular level, this migration and transmission of the prion protein can occur horizontally from one cell to its neighbors as well as vertically when a single cell divides into identical daughter cells, although the exact mechanisms underlying these processes remain unclear. It is hypothesized that pathogenic α-synuclein spreads from the gut and olfactory bulb to the CNS in PD (Niu *et al.*, 2018).

Animal studies have demonstrated cell-to-cell transmission and centripetal spread of α-synuclein in a prion-like fashion (Breid *et al.*, 2016; Ayers *et al.*, 2017). Human studies have also provided evidence for a possible prion-like spread of α-synuclein through observations of neural grafts in PD patients. Specifically, α-synuclein-positive LBs and Lewy neurites were identified in fetal neuronal grafts in three PD patients 11-16 years after transplantation (Kordower *et al.*, 2008; Li *et al.*, 2008).

PD pathology and symptoms are known to worsen as the disease progresses. The healthy donor-grafted neurons may undergo a similar neurodegenerative process to that present in PD with synuclein pathology becoming evident following the graft. Although insufficient epidemiological evidence currently exists on the infectious transmission of synucleinopathies between humans (Irwin *et al.*, 2013; Beekes *et al.*, 2014), the evidence from human neural grafts and animal models provides support that there is similarity in the mechanism of spread of α-synuclein pathology in PD and prion pathology in prion diseases. From the above, it

appears that while there is much evidence for the prion hypothesis in PD (Brundin & Melki, 2017), the alternative argument that PD is not simply a prion disorder and could be due to regional or cell-autonomous factors such as specific vulnerability of neurons (Surmeier *et al.*, 2017) should also be considered.

The similarities between prion disease and PD suggest that the prion-like movement of α-synuclein partly contributes to PD pathogenesis and spread of pathology. However, α-synuclein will as yet only be referred to as a "prion-like", or "prionoid", protein (Ma *et al.*, 2019).

5. Movement of α-synuclein along the gut-brain axis

As noted previously, α-synuclein is found in the GI tracts of many PD patients, and it is believed that the physical connection between the brain and the gut may shed light onto the pathophysiological mechanisms that allow gut involvement in this neurodegenerative disease. The gut-brain axis (Figure 3) refers to a complex, bidirectional line of communication between the CNS, ANS, and GI tract (Carabotti *et al.*, 2015). Gut-brain crosstalk regulates GI homeostasis by monitoring intestinal permeability, immune activation, entero-endocrine signaling, and enteric reflex. The vagus nerve is composed of 80% afferent and 20% efferent fibers and plays an important role in the regulation of parasympathetic activity such as digestion and heart rate (Babic & Browning, 2014; Bonaz *et al.*, 2018).
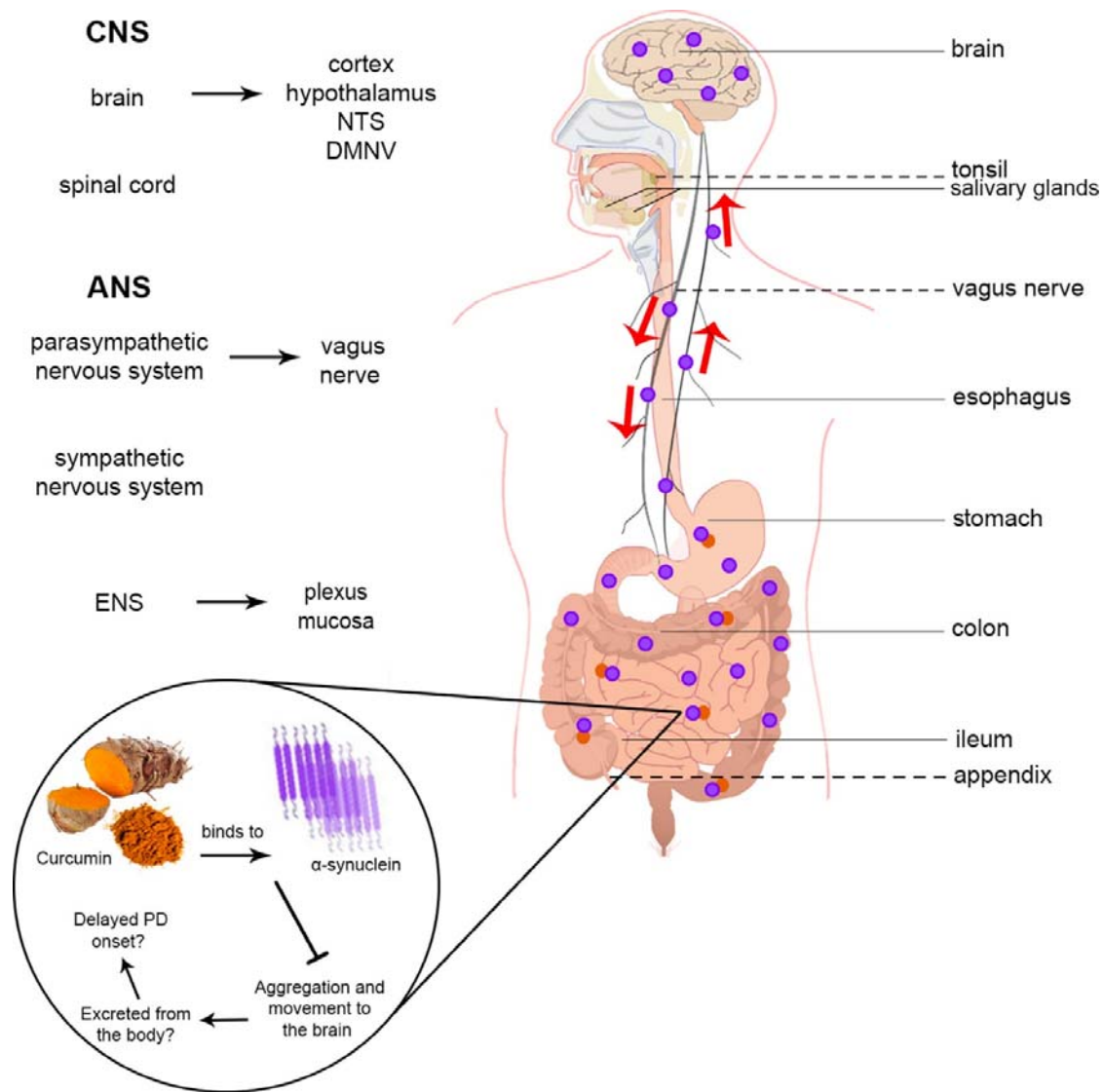
Figure 3. Bidirectional movement of α-synuclein along the gut–brain axis via the vagus nerve, and potential intervention with curcumin. Following oral consumption, curcumin (orange dots) binds to α-synuclein (purple dots), thereby preventing aggregation and movement to the brain. Thereafter, it is hypothesized that the curcumin–α-synuclein complex is excreted from the body due to the rapid metabolism of curcumin in the body. Red arrows along the vagus nerve indicate the direction of α-synuclein movement: gut-to-brain or vice versa. Gut components that may be linked to Parkinson's disease risk following surgical alteration or removal are indicated (dashed line). ANS, autonomic nervous system; CNS, central nervous system; DMNV, dorsal motor nucleus of the vagus nerve; ENS, enteric nervous system; NTS, nucleus tractus solitarius

α-Synuclein inclusions are proposed to form initially in nerve terminals of the enteric nervous system (ENS) and then spread via autonomic connections to the medulla and spinal cord (Borghammer, 2018). However, staging is made complex by the range of patterns of synuclein deposition, which may be limbic or neocortical predominant (Beach *et al.*, 2009). A major distinction may lie between two subtypes in which dysfunction originates either in the peripheral ANS, and subsequently ascends via autonomic afferents to the brain, and one in which the pathology arises in the brain itself (Horsager *et al.*, 2020). This may be illustrated by premotor rapid eye movement (REM) sleep behavior disorder, which is postulated to be a prominent premotor marker of onset in the peripheral ANS and gut, spreading to the brainstem (Horsager *et al.*, 2020).

Perturbation of the gut-brain axis has been implicated in the pathophysiology of GI disorders such as inflammatory bowel disease (Bonaz *et al.*, 2017) and several neurological diseases, including PD (Cenit *et al.*, 2017; Kobayashi *et al.*, 2017; Quigley, 2017). Evidence of the involvement of the gut in PD pathophysiology is mounting, particularly placing the gut or ENS as the possible starting point of PD pathology. This stems from the finding of misfolded α-synuclein in nerves of the enteric system before it appears in the brain (Chandra *et al.*, 2017). The vagus nerve may act as a path whereby PD pathology can spread from the GI tract to the CNS (Mukherjee *et al.*, 2016). However, a recent primate study investigated the injection of α-synuclein-containing LB extracts from patients with PD and found no α-synuclein pathological lesions in the primate vagus nerve (Arotcarena *et al.*, 2020). Furthermore, there is some *debate regarding the direction of α-synuclein movement along the gut-brain axis*.

Inoculation of duodenal walls with α-synuclein fibrils has been shown to lead to increased progression of α-synuclein histopathology in the midbrains of aged mice, indicating caudorostral, or gut to brain, movement of α-synuclein pathology (Challis *et al.*, 2020). This is one of the many studies that support this direction of α-synuclein spread along the gut-brain

axis (Ulusoy *et al.*, 2013; Holmqvist *et al.*, 2014; Chandra *et al.*, 2017). Conversely, a small number of studies have demonstrated the movement of α-synuclein pathology from the brain to the gut along the course of the vagus nerve. One such study used rat models to show that the DMNV may be a relay center for α-synuclein transmission from central to peripheral tissues (Ulusoy *et al.*, 2017). Despite these conflicting reports, it remains probable that the vagus nerve and LB movement along this track are implicated in PD pathology.

In 2003, Braak and colleagues published their hypothesis regarding the staged manner in which PD pathology may spread in the brain (Braak, del Tredici, *et al.*, 2003). They noted the pathological findings of α-synuclein-immunopositive LBs and Lewy neurites initially appearing in the DMNV, the glossopharyngeal nerve, and the olfactory bulb. Thereafter, rostral regions of the brainstem and cortical and prefrontal regions sequentially became affected. However, it was unclear as to the origin of abnormal α-synuclein deposition in the caudal brainstem and olfactory bulb, and subsequently, Braak, Rüb *et al*. (2003) proposed that LB formation might begin in the ENS and then spreads to the brain. They speculated that this could arise following the ingestion of an exogenous pathogen that triggered abnormal α-synuclein accumulation (Braak, Rüb, *et al.*, 2003). Such a pathogen would potentially have prion-like properties and would consist of α-synuclein fragments (Liautard, 1991). With some modifications, the proposal was that α-synuclein might cross the mucosal barrier of the gut, and then travel along enteric neurons and preganglionic fibers of the vagus nerve to the CNS in a prion-like manner (Braak, Rüb, *et al.*, 2003; Braak *et al.*, 2006). This retrograde axonal and transneuronal movement resulted in the deposition of α-synuclein in the vulnerable subcortical nuclei of the brainstem, triggering disease onset and furthering disease progression. *In vitro* and *in vivo* clinical evidence has accumulated to support this hypothesis (Rietdijk *et al.*, 2017).

However, some skepticism remains regarding the validity of the prion-like, gut-to-brain hypothesis of α-synuclein movement and therefore, further experimental evidence is required for its wider acceptance. Another possibility is that the gut-brain axis may provide a pathway by which α-synuclein travels bidirectionally from either the brain or the gut to trigger PD (Arotcarena *et al.*, 2020). In support of this view, Borghammer and van den Berge describe a theory wherein PD is separated into two subtypes based on the region in which α-synuclein initially appears in the patient: CNS-first and peripheral nervous system (PNS)-first (Borghammer & van den Berge, 2019). Additionally, there is the threshold theory, whereby both the CNS and PNS degenerate simultaneously, albeit with different thresholds for emergence of symptoms related to dopamine reserves (Engelender & Isacson, 2017). These thresholds are based on compensatory mechanisms which tolerate a certain level of neuronal damage before symptoms manifest. The PNS appears to have a lower threshold since less neuronal damage (20% reduction) is required to elicit prodromal non-motor symptoms. By contrast, the CNS has a higher threshold requiring over 50% loss in dopaminergic neurons to elicit the classical motor symptoms of PD. Furthermore, the role of the brain-gut-microbiota axis in PD (Mulak & Bonaz, 2015) has gained traction from a study that found changes in the microbiome following nigral injection of α-synuclein in rat brains (O'Donovan *et al.*, 2020). Such a study suggests a potential role of the microbiome in PD, but factors such as dopaminergic medication, GI motility, and the translatability of animal model findings to human diseases make interpretation difficult. Therefore, longitudinal studies in large cohorts (Wallen *et al.*, 2020) including prodromal subjects are recommended to clarify the relationship between the microbiome and α-synuclein, and ultimately its role in PD pathogenesis and progression (Keshavarzian *et al.*, 2015).

6. Clinical manifestations of GI and motor dysfunction in PD

Cardinal motor symptoms such as tremor and bradykinesia are frequently observed at clinical diagnosis (Darweesh *et al.*, 2016). However, many non-motor symptoms manifest in the prodromal phase before PD diagnosis. One such symptom is GI dysfunction which affects 80% of PD patients over the course of the disease (Cersosimo *et al.*, 2013). Defecatory dysfunction (Savica *et al.*, 2009) and gastric dysfunction are common in both early and late stages of the disease (Tanaka *et al.*, 2011; Heetun & Quigley, 2012; Marrinan *et al.*, 2014). This leads to early satiety and dysphagia which contribute to reduced appetite and malnutrition (Sheard *et al.*, 2013). Malnutrition, as well as immobility and lack of sunlight, are also correlated with vitamin D deficiencies which are common among PD patients (Lv *et al.*, 2014).

Furthermore, delayed gastric emptying (Pasricha & Parkman, 2015) impairs levodopa absorption, contributing to symptom fluctuations (Doi *et al.*, 2012). Constipation has been found to occur as early as 20 years prior to motor symptoms, making it one of the earliest non-motor symptoms in PD (Savica *et al.*, 2009). It is evident that many components of the GI system are affected in PD, from the salivary glands and stomach (dysphagia and gastroparesis) to the colon and rectum (constipation and defecatory dysfunction) (Pfeiffer, 2003). This suggests that the GI tract may play a role in the pathogenic mechanisms underlying PD (Schaeffer *et al.*, 2020).

7. Effects of GI tract surgeries on PD risk

Several medical procedures including vagotomy, appendectomy, and tonsillectomy have been investigated for their effect on an individual's risk of subsequently developing PD (Breen *et al.*, 2019). It should be noted that, due to inconsistent findings, it remains controversial as to whether these surgeries are truly beneficial in delaying or preventing PD onset. Furthermore, epidemiological studies only infer associations, which makes it challenging to deduce causality

from this type of study (Grimes & Schulz, 2012). Therefore, unless conclusive evidence is produced through large, matched-cohort studies that accurately account for all potential confounders, these surgeries should not be promoted as prevention or treatment strategies against this disease.

7.1. Appendectomy

The appendix was identified as having particularly enriched α-synuclein staining with immunohistochemistry in its mucosal plexus, suggesting that it might be involved in enteric α-synuclein aggregation (Gray *et al.*, 2014).

Subsequently, it was reported that appendectomy might delay the onset of PD (Mendes *et al.*, 2015). In a group of 295 PD patients, appendectomy in those with PD onset after the age of 55 had a delayed onset of PD with a hazard ratio of 0.63 (95% CI 0.41–0.98). Appendectomy appeared to be associated specifically with delayed onset of motor symptoms in patients with late onset of PD. The authors recognized the possibility that α-synuclein spread may have occurred prior to the surgical procedure. In a subsequent population-based study from Ontario, no differences were found in the risk of PD when comparing those who had undergone appendectomy with those who had undergone cholecystectomy. The authors did find a higher risk of PD shortly after appendectomy, but noted that it was probable that PD was already present at the time of surgery in those developing the disease within 5 years after appendectomy.

As with the Canadian study, when the issue was examined over a 30 year period reviewing data from the DNPR, the results were in the opposing direction to the initial findings of Mendes *et al*. (2015), in that appendectomy was associated with a slightly *increased* risk of PD (adjusted hazard ratio 1.14; 95% CI 1.03-1.27). Nearly 266 000 individuals underwent appendectomy, of whom 786 had a diagnosis of PD, resulting in a PD incidence rate of 0.16

per 1000 person years, versus a lower PD incidence of 0.15 for the general population (Svensson *et al.*, 2016).

In a further report derived from participants in the Nurses' Health Study and the Health Professionals Follow-up Study (Palacios *et al.*, 2018), appendectomy in women related to actual appendicitis was associated with a modestly elevated risk of PD (HR 1.23, 95% CI 1.00-1.50). However, a subsequent study (Killinger *et al.*, 2018) reviewed data from the Swedish National Patient Registry (SNPR) and the Parkinson's Progression Markers Initiative (PPMI). From the SNPR cohort, the cumulative prevalence of PD was reduced by 16.9% compared with the general population, and age at PD diagnosis was 1.6 years later in those who had undergone surgery 20 years or more prior as compared to those without appendectomy. This finding of delayed onset of PD was replicated in the PPMI cohort, including confirmation of nigral cell loss by nuclear imaging. In a further study using data from 78 650 PD patients in the SNPR, there was a 16% lower risk of PD linked to previous appendectomy (OR=0.84, 95% CI: 0.80-0.88), and temporal analyses confirmed the finding at 5, 10, and 20 years following surgery (Liu *et al.*, 2020).

7.2. Vagotomy

The vagus nerve controls acid secretion and gastric motility. Truncal vagotomy refers to resection of the trunks of the anterior and posterior nerves, and therefore, removes all vagal and parasympathetic supply to the abdominal contents except for the gut distal to the transverse colon, which receives parasympathetic outflow from the sacral segments of the spinal cord. Selective vagotomy refers to resection of the fibers supplying only the stomach, and in highly selective or superselective vagotomy only nerve branches to the esophagus, fundus, and body are divided, sparing the antrum and pylorus (Seeras & Prakash, 2019).

The effect of these procedures on the risk of PD has been studied in large national registries available in Nordic countries which have allowed for the examination of the uncommon association of vagotomy with PD (Svensson *et al.*, 2015; Liu *et al.*, 2017). The initial analysis was performed using the DNPR and analyzed a cohort of patients who underwent vagotomy between 1977 and 1995. This analysis showed that if a diagnosis of PD was made 5 years or more after a vagal resection, those with a truncal vagotomy compared to superselective vagotomy had a lower risk of being diagnosed with PD (hazard ratio 0.85, although this did not reach significance in both groups). At the 20 year follow-up after surgery, the cumulative incidence of PD in individuals who had the superselective vagotomy (0.96 per 1000 person years) was similar to that of the general population (0.87 per 1000 person years), versus an incidence of 0.65 per 1000 person years for those with truncal vagotomy (Svensson *et al.*, 2015). However, in a further analysis of the same Danish registry, but which assembled a cohort of patients over an extended period (1977-2011), no significant finding was found in any group, including those with a 20 year follow-up after surgery (Tysnes *et al.*, 2015).

When a similar analysis was carried out using the Swedish SNPR, almost 5000 cases of PD were identified, of whom only 101 also had a vagotomy (Liu *et al.*, 2017). The crude incidences for PD were 80.4 (per 100 000 person years) for truncal vagotomy, 55.1 for selective vagotomy, with an intermediate value (67.5) for matched cases from the general population without vagotomy. Cumulative incidences were similar to the Danish study for the different types of vagal surgery, with selective vagotomy again resembling the general population, and with a lower risk of PD >5 years after truncal vagotomy (HR 0.59, 95% CI 0.37–0.93).

7.3. Tonsillectomy

Like the appendix, tonsils are also part of the gut-associated lymphoid tissues but are not directly innervated by the vagus nerve (Breen *et al.*, 2019). However, prion infection in variant CJD is identified in the tonsils, and may spread rostrally to the brain through autonomic fibers and the spinal cord. Using the DNPR, approximately 195 000 patients who had undergone tonsillectomy (median age 17 years) were each compared with 5 age- and sex-matched controls (Svensson *et al.*, 2018). The risk of PD was similar in patients who had undergone tonsillectomy and controls. However, the study population was relatively young, and PD cases may have been missed as a result.

A further analysis was carried out in the SNPR, and although there was a trend of prior tonsillectomy being associated with a lower risk for PD, associations did not reach statistical significance (Liu *et al.*, 2020).

8. Curcumin as a nutraceutical approach to PD treatment and prevention

Levodopa and other commonly used PD drugs may be associated with significant side effects with long-term use. In addition, none of these drugs halt or slow down disease progression by protecting against the degeneration of remaining neurons (Bharath, 2008). Therefore, developing alternative treatment strategies is important to reduce morbidity and mortality associated with PD. Treatments that target the gut have become an area of interest for therapeutic interventions to prevent or slow the progression of the disease.

Nutraceuticals, dietary supplements, and 'functional foods' have gained popularity over the past few decades due to the potential health benefits of these natural products which are believed to be less toxic than synthetic derivatives (Santini *et al.*, 2017). A popular nutraceutical with a wide variety of therapeutic properties is curcumin, a component of the

spice turmeric, which is derived from the *Curcuma longa* Linn. rhizome (Kochhar, 2008). The well-known issue of curcumin's low bioavailability has largely been overcome with the development of several formulations of curcumin such as nanoparticles, adjuvants, complexes with other molecules, and microemulsions (Tapal & Tiku, 2012; Xiao *et al.*, 2013; Panahi *et al.*, 2014; Govindaraju *et al.*, 2019). Curcumin is proposed here as a potentially effective approach to PD treatment and management. We speculate that curcumin may serve a protective role as it could act on α-synuclein in the gut and remove it from the body (illustrated in Figure 3).

The prevalence of neurological diseases in countries that consume more turmeric has been investigated (Ganguli *et al.*, 2000; Ng *et al.*, 2006). Turmeric and red chilies are the most commonly used spices in Indian households (Siruguri & Bhat, 2015; Bhathal *et al.*, 2020), where the average intake can be as high as 2000-2500mg/day (Basnet & Skalko-Basnet, 2011). Comparisons of the elderly in Eastern and Western populations have shown that frequent consumption of dietary curcumin in India may be linked to a lower risk of Alzheimer's disease and a delay in age-related cognitive impairments than North American populations (Ganguli *et al.*, 2000; Ng *et al.*, 2006). Although the prevalence and incidence of PD in India are reported to be low (Bharucha *et al.*, 1988; Razdan *et al.*, 1994; Das *et al.*, 2010; Surathi *et al.*, 2016), larger multi-center studies across India are required to produce more accurate epidemiological data on PD and to establish whether turmeric consumption is linked to lower PD prevalence and incidence rates.

A global paradigm shift is occurring away from monotherapy, in which compounds target one particular cellular pathway, to multi-therapy based on several targets, thereby increasing the likelihood of success (Bang *et al.*, 2019). Plant-based medicines such as curcumin align with this concept and thus, are being studied to develop better therapies for human diseases (Sparreboom *et al.*, 2004; Kumar, 2006). Curcumin has been shown to target

multiple pathways implicated in PD pathobiology (Mythri & Srinivas Bharath, 2012) and may prove useful for long-term PD treatment due to its effect on both α-synuclein as well as the GI tract which will be discussed below.

8.1. Effect on alpha-synuclein

Curcumin and its derivatives have been shown in multiple studies to inhibit the aggregation of α-synuclein *in vitro* (Figure 3) (Pandey *et al.*, 2008; Ahmad & Lapidus, 2012; Singh *et al.*, 2013; Jha *et al.*, 2016; Sharma & Nehru, 2018). In addition, curcumin has been reported to protect against mutant A53T α-synuclein-induced toxicity in cell models (Liu *et al.*, 2011). Furthermore, it acts to protect against α-synuclein-induced toxicity by downregulating the mammalian target of the rapamycin/p70 ribosomal protein S6 kinase (mTOR/p70S6k) signaling pathway and promoting the recovery of suppressed macroautophagy pathways (Jiang *et al.*, 2013). Curcumin has been shown to bind strongly to the NAC domain of α-synuclein thereby reducing α-synuclein aggregation (Figure 3) (Kamelabad *et al.*, 2020). Although using curcumin as an aggregation inhibitor is promising, the precise structures of monomeric and oligomeric α-synuclein are still poorly defined, thus limiting their use in rational drug design to target early protein aggregation (Tuttle *et al.*, 2016).

8.2. Effect on GI health

Dysbiosis in the gut can lead to intestinal hyperpermeability, or "leaky gut", a condition frequently found in PD patients (Maes, 2008; Thevaranjan *et al.*, 2017). The mucosal barrier of the intestines is a single layer of epithelium that allows for nutrient absorption while preventing the entry of exterior antigens from the intestinal lumen into the host. However, when this barrier is compromised, the individual develops a 'leaky gut' and foreign antigens enter host tissues and can initiate an immune response (Peterson & Artis, 2014). Curcumin has been found to relieve leaky gut in rats with intestinal ischemia-reperfusion injury, by reducing changes in intestinal Tumor Necrosis Factor alpha (TNF-α). This results in an improvement in

the histological abnormalities present in intestinal mucosa and restores tight junction protein Zonula Occludens-1 expression (Tian *et al.*, 2016). Rats have also been shown to have a reduction in methotrexate-induced damage to the intestinal mucosa barrier following treatment with curcumin (Song *et al.*, 2010). Constipation may also be treated by curcumin as it has been shown to have a dose-dependent mild laxative effect (Srinivasan, 1972; Bhowmik *et al.*, 2009). In addition, the lack of vitamin D found in many PD patients may be relieved by supplementation with curcumin which is reportedly taken up by intestinal epithelia and binds to the vitamin D receptor, thereby enhancing vitamin D signaling (Bartik *et al.*, 2010).

In 'diabetic' rats, in which GI complications were induced, the antioxidant properties of curcumin were found to successfully restore body weight, gastric emptying, and intestinal transit, all of which could also benefit PD patients (Kochar *et al.*, 2014). Therefore, curcumin has the potential to relieve GI complications in individuals living with PD but further studies, particularly in humans, are needed to show its efficacy and its possible adverse effects.

9. Concluding remarks

The gut is affected both early and extensively in PD and appears to play a role in disease pathogenesis and progression. There is ample evidence for the presence of pathogenic forms of α-synuclein, a hallmark of PD, in the gut, which may travel between the gut and the brain. There are, however, a number of theories to account for the development of PD, including the threshold theory (simultaneous degeneration in the CNS and PNS) and the brain-gut-microbiota axis theory, and further studies are therefore required to elucidate whether it is the gut, the brain, or a region in between that acts as a starting point for α-synuclein movement. It is plausible that the initiation site and the pattern of α-synuclein progression may vary between patients which may explain, in part, the clinical heterogeneity observed in the disease (Uversky & Eliezer, 2009). Notably, postmortem tissue gives a static view of this dynamic process and therefore, improved methods for detection of α-synuclein throughout the body and the ability

to distinguish between pathological and native forms of this protein, are needed to shed light on this topic (Schaeffer *et al.*, 2020).

Notably, gut dysfunction is known to contribute significantly to the morbidity and complications experienced by persons living with PD. Despite numerous studies, the possible protective effect of gut-associated surgeries against PD remains controversial. In India, gut dysfunction is traditionally treated with turmeric which is used to promote digestion, detoxify the liver and gallbladder, and improve intestinal flora (Bhowmik *et al.*, 2009) – benefits that may be attributable to its polyphenolic curcuminoids including curcumin. Turmeric-derived curcumin is one of many nutraceuticals which have become compelling therapeutic candidates in the treatment of several disorders including PD. Curcumin's low bioavailability may not limit its potential as a nutraceutical to treat disorders such as PD if the gut is the preferred site of action. In the gut, curcumin is able to bind α-synuclein over longer periods of time through life-long dietary intake and attenuate the initiation and spread of Lewy pathology. However, larger studies in humans need to be performed to investigate the long-term safety and efficacy of curcumin as a nutraceutical *in vivo*. If curcumin's beneficial properties are validated, it is proposed that life-long dietary supplementation with curcumin is an attractive therapeutic modality for PD. It is hypothesized that curcumin may bind to α-synuclein in the gut and be excreted from the body, thereby reducing the risk of PD or at least delaying disease onset. Consequently, this compound has the potential to slow disease progression as well as improve quality of life through the relief of gut dysfunction, thereby bridging PD prevention and management.

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Conflict of interest statement

The authors do not have any financial disclosures or conflicts of interest concerning the research related to this article.

Author contributions

DC wrote the first draft of the manuscript and created the figures. RVC and JC wrote sections of the manuscript. SA, CK, and SB conceptualized the study. All authors critically reviewed, edited, and approved the final version of the manuscript.

List of abbreviations

ANS	Autonomic nervous system
CJD	Creutzfeldt–Jakob disease
CNS	Central nervous system
DMNV	Dorsal motor nucleus of the vagus nerve
DNPR	Danish National Patient Registry
ENS	Enteric nervous system
GI	Gastrointestinal
LBs	Lewy bodies
mTOR/p70S6k	p70 ribosomal protein S6 kinase
NAC	Non-amyloid β-component
PD	Parkinson's disease
PNS	Peripheral nervous system
PPMI	Parkinson's Progression Markers Initiative
SNc	Substantia nigra pars compacta

SNPR   Swedish National Patient Registry

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