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THE BALANCE BETWEEN SCIENCE AND CULTURE OF USING THYMOQUINONE AS A POTENTIAL THERAPEUTIC AGENT FOR PARKINSON DISEASE

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ABSTRACT

Parkinson's disease is a progressive neurological condition affecting millions, with most patients taking daily symptomatic medications for the first decade after diagnosis. However, the most important unmet clinical need for Parkinson's patients is that currently, no treatment slows the progressive neurodegeneration that characterises this disease, which causes them to deteriorate relentlessly at an approximate rate of 5-7 % per year. This means their deteriorating symptoms may be 50%-70% worse ten years after their initial diagnosis. Biochemically, Thymoquinone (TQ) exhibits a range of neuroprotective actions, and several research teams have shown that it is highly effective in laboratory models of Parkinson's disease. Its otherwise promising use in the long-term management of neurodegenerative diseases has previously been hindered by its relatively rapid elimination half-life when administered orally (around 4-5 hours). However, a variety of excellent new technologies (microencapsulation, micro emulsification, nanocapsules, lipid carriers, and new derivatives of TQ) that each extend bioavailability to a more straightforward once-per-day oral dosing promises to be transformational in the context of using TQ for long-term neuroprotection. This review explores the possibility that TQ might represent an extremely promising new (and relatively inexpensive) therapeutic approach that may offer the potential for slowing or even stopping, the year-on-year trajectory of neurodegeneration that virtually all patients experience. It argues the case for testing this hypothesis, without delay, in a long-term clinical trial of TQ in patients with Parkinson's disease.

KEYWORDS: *Parkinson's disease; neurology; TQ; immunity*

1. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease that currently affects between 5 and 10 million patients worldwide. The number of new cases will sharply increase during the next two decades. At a population level, the unmet patient need and the substantial economic burden created by PD continues to increase, with global numbers now predicted to reach 13 million patients by 2040, a concern which has recently led experts to describe the situation as a Parkinson's "pandemic" (1–3). PD presents significant challenges in patient management and financial consequences for patients, families, and healthcare systems. Currently, patients have symptomatic treatments, leading to motor complications and neurodegeneration. With no regulatory-approved therapeutics, PD patients' disability increases, leading to increased healthcare costs.

Parkinson's disease (PD) is primarily associated with motor deficits due to the loss of dopaminergic neurons in the substantia nigra. Lewy bodies, cytoplasmic inclusions, are found in these neurons. Developing an imaging modality for α-syn could improve diagnosis, monitor disease progression, and evaluate therapeutic approaches.

For many years, the search for effective disease-modifying approaches was stalled by a consistent lack of efficacy in many clinical trials involving putative new therapeutic approaches initially thought promising (4). Recent advancements in molecular processes, biological targets, epidemiological findings, and genetic insights have led to a focus on disease-modifying PD therapeutics. While regulatory approval for these therapies has not yet been obtained, promising initial results are emerging in long-term patient studies. For example, Glucagon-like peptide (GLP-1) receptor agonists hold considerable promise for PD (5), with a placebo-controlled double-blind Phase II trial of Bydureon (Exenatide) successfully meeting its primary outcome of slowing disease progression (over a 1-year period) in PD patients (as measured by the UPDRS Part III: Motor Examination). It led to the start of Q2 of 2020 of a much longer-duration Phase III trial in 200 PD patients at various UK neurology centres (6-7).

Recent years have seen the emergence of new therapeutic prospects, including GLP-1 receptor agonists, with potential to slow or stop neurodegeneration in PD patients.These include poly ADP ribose polymerase (PARP) inhibition (8-9), modification of astrocyte subtypes (10–11), improving mitochondrial function (12), enhancing glycolysis (13), reducing α-syn burden (14), inhibition of c-Abl (15), iron chelation (16), β-adrenoreceptor agonism (17-18) and upregulating lysosomal function (19). An international PD clinical trial program unique to any therapeutic area has been responsible over the past eight years or launching a large number of PD patient studies, all with disease-modifying objectives, involving many of the therapeutic approaches outlined above. The notable ones include trials involving Exenatide, Liraglutide, Lixisenatide, Deferiprone, EPI-589, Simvastatin, UDCA, Nilotinib, K-0706, Ambroxol, NLY-01 and others (20). The largest global drug repurposing program, involving hundreds of hospitals and thousands of Parkinson's patients, is set to begin trials in 2021, involving complex and expensive decisions.

1.1. Research Gap

The absence of effective disease-modifying medicines presents a crucial gap in the research on Parkinson's disease (PD). Despite advancements, patients are still at risk for progressive neuro-degeneration because existing medications primarily address symptoms. This emphasizes the critical need which is unmet in the body of current literature for novel therapeutic strategies that can halt or delay the progression of disease.
PD research must be done in order to close this disparity and enhance patient outcomes. Research has the potential to lessen the burden of Parkinson's disease (PD) on individuals, families, and healthcare systems worldwide by discovering efficient disease-modifying medicines. Enhancing our knowledge of the mechanisms underlying Parkinson's disease (PD) may also result in tailored treatment plans that eventually raise the quality of life for those who have the disease.

1.2. Purpose of study

The purpose of this research is to look into thymoquinone (TQ) as a possible novel treatment for Parkinson's disease (PD). It is imperative to investigate novel avenues for delaying or halting neurodegeneration, as Parkinson's disease (PD) is a degenerative condition with no efficacious treatments available. Using the established antioxidant, anti-inflammatory, and neuroprotective benefits seen in preclinical investigations, this study attempts to assess TQ's neuroprotective qualities. The project aims to address a fundamental gap in patient care and management by determining if TQ can significantly decrease the progression of Parkinson's disease (PD) through a long-term clinical trial.

1.3. Thymoquinone

Nigella sativa, a traditional herb with anti-inflammatory, hypoglycemic, anti-hypertensive,

anti-fungal, and anti-histaminic properties, has been used for centuries to treat various health issues related to the cardiovascular, digestive, immune, and respiratory systems. Its black seeds contain around 25%-50% TQ and a large variety of biologically active components. Since its discovery in the 1960s, TQ has been studied for its antioxidant, anti-inflammatory, and anti-cancer potential. TQ has strong antioxidant properties. More recently, the additional hepatoprotective, anti-inflammatory and anti-cancer effects of TQ were also described (21), together with the range of other biochemical mechanisms of action and various potential molecular targets thought to be involved with its therapeutic effects. After this, several well-referenced reports have been published. In these reports, the properties of TQ have been comprehensively described in terms of each of its separate neuro-protective, anti-bacterial, anti-fungal, anti-oxidant, anti-inflammatory, anti-diabetic, anti-cancer, immunomodulatory, gastro-protective, hepato-protective, cardio-protective, and pulmonary-protective actions (22-24).

1.4. Pre-clinical studies of TQ in various neurological models

The neuroprotective properties of TQ in pre-clinical models of Parkinson's disease (PD) have led to a long-term clinical trial to evaluate its potential for slowing or stopping disease progression. The compound's benefits in other neurological contexts are also relevant to PD patients. Four informative reviews (25–28) examined evidence based on cellular and experimental models and supported the contention that TQ has protective effects against a wide range of neurodegenerative diseases, including cerebral ischemia, traumatic brain injury, encephalomyelitis, depression, epilepsy, Alzheimer's disease, and PD, apart from the considerable range of individual biological targets that are impacted by TQ. see Table 1).

Table 1: Aspects of TQ relevant to testing in clinical trials involving patients with Parkinson's disease

Drug Class	Quinone derivitive
Target Molecular Pathways	HDAC inhibitor CHEK1 PPAR-γ agonistMEK1/2 Nrf2/ARE activatorP13K signalling Heme-oxygenase 1 EGFR Anti-oxidant STAT3 Anti-inflammatory
Other examples within this drug class	Dithymoquinone
Efficacy in laboratory models of Parkinson's disease	Yes
Tested in humans	Yes
Mode of delivery	Oral
Safety record and toxicology studies	Excellent
Side effects	None reported
Major contraindications	None reported
Potentially protective or restorative	Protective
Specific monitoring requirements	None
Any potential to worsen PD?	Unlikely
Pharmacokinetics, pharmacodynamics, and ADME	Reported in results of multiple clinical trials
Dosages used in previous clinical studies in other therapeutic areas	Doses ranging from 75mg/day to 2600mg/day have previously been used in clinical trials of thymoquinine
Central nervous system (CNS) penetration	Yes Molecular Weight = 164.20108 g/mol
Any previous use in any other neurological disease?	Yes
Blinding possible within a clinical trial?	Yes
Current and previous clinical trials using TQ?	See Table 2

The neuroprotective effects of *Nigella sativa* were observed in a rat model of cerebral ischemia; these extracts significantly reduced brain infarct volume. The authors concluded that these neuroprotective effects were probably due to the antioxidant, free radical scavenging, and anti-inflammatory properties. Similar antioxidant and anti-inflammatory results were also found when testing TQ in a model of stroke (29), a model of status epilepticus (30), a model of cerebral small vessel disease (31), cerebral ischemia (32), experimental traumatic brain injury (33), and a model of temporal lobe epilepsy (34). TQ has also been reported to reduce the frequency of seizures in children with refractory seizures. It is worth noting that, in recent years, TQ has also been shown to possess antioxidant properties (35–41) and anti-inflammatory properties (42) in various therapeutic applications. As demonstrated in an animal model of depression, the effect of TQ on mitochondrial function is to increase levels of glutathione (43).

TQ significantly increased antioxidant enzyme activities in a rat model of hepatotoxicity, while significantly reducing TNF-α, iNOS, and IL-1β expression. It was recently demonstrated that TQ prevents learning and memory deficits in a model of

cerebral hypoperfusion (44). The authors also suggest that TQ may offer a beneficial role in cerebrovascular insufficiency and dementia. It was also recently shown that TQ protects brain tissue from radiation-induced oxidative stress (45).

The neuroprotective effects of TQ had previously been studied in cultured hippocampal and cortical neurons treated with amyloid-β peptide (Aβ1-42) and TQ simultaneously for 72 hours. It was shown efficiently to attenuate Aβ1-42-induced neurotoxicity by improving cell viability. Researchers found that TQ inhibits mitochondrial membrane potential depolarization, reactive oxygen species generation, restores synaptic vesicle recycling, and partially reverses spontaneous firing activity in neurons, protecting against α-syn-induced synaptic toxicity (46). TQ may be a promising therapeutic agent for PD patients and dementia with Lewy bodies, improving learning and protecting against Aβ neurotoxic effects in Alzheimer's disease patients (47-48). Researchers found that pre-treatment with TQ of human SH-SY5Y neuroblastoma cells 30 minutes before TNF-α challenge could prevent amyloid beta oxidation, resulting in decreased nitric oxide and increased glutathione levels, potentially reducing inflammation and oxidative stress.

TQ, a neuromodulator, has potential benefits in treating glial tumors due to its ability to successfully cross the blood-brain barrier (50). Some would disagree with that latter statement (about brain penetration), but effective steps are being made to address and, if necessary, overcome this question (see later). Others have also recommended that TQ should be evaluated in clinical trials to explore its potential benefits in various neurological diseases (51-52).

1.5. Pre-clinical studies of TQ in various models of Parkinson's disease

It was reported more than a decade ago that TQ was protective of primary dopaminergic neurons in MPP+ and rotenone models of PD. More recently, the results in that rotenone model of PD have been replicated. TQ significantly reduced the rotenone-induced motor defects and restored some key biochemical markers (53). While supporting previous findings in a pre-formed a-syn model of PD involving synapse damage (54), more recently, using an improved mouse model of PD, the neuroprotective effect of TQ against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced oxidative stress and neuroinflammation was recently demonstrated (55). Researchers found that TQ can rescue a-syn fibril dopaminergic loss, restore glutathione depletion, reduce oxidative stress, and attenuate pro-inflammatory cytokines and mediators. It also inhibits a-syn aggregation, a dysfunctional protein misfolding process leading to Lewy bodies in PD patients (56), The study suggests that TQ may offer clinical benefits in treating Parkinson's disease (PD) by protecting dopaminergic neurons through enhanced lysosomal degradation and inhibiting mitochondria-mediated apoptotic cell death, and decreasing lactate dehydrogenase release (57).

Experts believe PD can be caused by environmental toxins, genetic factors, or a combination of both, with some circumstantial evidence supporting this that TQ may protect against the development of PD due to exposure to toluene (a component of many glues and paint thinners) and contact with the pesticide/insecticide rotenone (58). It is also protective against hydrogen peroxide-induced neurotoxicity (59).

A drug screen of 84 antioxidants, including TQ, found that several inhibited kinase activities on LRRK2 substrates (60). The Gly2019Ser LRRK2 mutation, enriched in Ashkenazi Jewish and North African Berber Arab PD populations, is being researched for potential therapeutics like TQ, which could transform long-term neuroprotective management for these patients(61).TQ may also offer non-motor benefits for patients with PD, in particular some of the aspects of the gastrointestinal dysfunction that they widely and commonly experience (62), and this should be longitudinally studied in detail in a long-term disease-modifying trial while also exploring the range and extent of motor benefits it may also offer to patients (see below).

1.6. Relevance of TQ in the treatment of Parkinson's disease in the context of Diabetes type II

Many have proposed TQ as a possible therapeutic agent to treat diabetes via its ability to lower oxidative stress, cellular inflammation, and fasting blood glucose, and also to increase insulin levels, improve lipid profiles (63), and improve endothelial dysfunction (64). In addition, it has also been shown that both metformin and TQ are strong protective agents against ethanol-induced neuronal apoptosis in primary rat cortical neurons. Recently, Metformin and Nigella Sativa were tested (as individual monotherapies) in a 3-month clinical trial in patients with newly diagnosed type II diabetes (65). A study found Nigella Sativa, equivalent to metformin, effectively reduces body weight and BMI, but metformin is more effective for diabetes management, with therapeutic changes in serum glucose and insulin resistance (66). Nigella Sativa oil has shown benefits in clinical and glucose homeostasis, reduced inflammation, and decreased lipid profiles in nonalcoholic fatty liver disease patients, supporting previous studies (67).

Why are those findings on diabetes type II also

important for PD patients? Because there is a relationship between PD, insulin resistance and diabetes type II has already been widely reported (68). Diabetes type II is linked to PD severity, including rapid cognitive decline. Clinical trials have tested GLP-1 receptor agonists to slow neurodegeneration in PD patients, potentially relevant to TQ research. Exenatide, a 1-year clinical trial, successfully met its primary outcome in slowing down progressive motor decline in PD patients (69). A pharmacological intervention may slow Parkinson's disease progression, as demonstrated by a biomarker study involving brain-derived exosomes extracted from patients and demonstrating biological target engagement (70).

Clinical trials of GLP-1 receptor agonists, Exenatide, and Alogliptin are ongoing in Parkinson's disease patients, with a Phase II trial assessing Alogliptin's long-term neuroprotective efficacy.

Of direct relevance to these ongoing GLP-1 receptor agonist and Gliptin clinical trials in PD patients, last year, using a rat model of diabetes, it was reported (71) that TQ itself attenuated hyperglycemia and reduced hyperphagia and water intake in a dose-dependent manner. Researchers found that treatment with TQ increased plasma GLP-1 levels in rats, which were enhanced by sitagliptin and reduced by Ex 9-39. This suggests that TQ could be a more cost-effective therapy for addressing GLP-1 pathways in PD patients. Phase II neuroprotective clinical trials should evaluate TQ's effectiveness.

Mechanistically, the understanding of gut and pancreatic physiology of GLP-1 has been growing over the past couple of decades, culminating in a superb multi-centre review (72) published at the end of 2019 by those in the field responsible from laboratories around the world for making most of the major breakthroughs in recent years. Research at Johns Hopkins University reveals that GLP-1 attenuates dopaminergic neuron loss and protects against behavioral deficits in PD models by acting on M1 microglia (73). The finding that GLP-1 receptor agonists block microglial activation and the consequent generation of A1 neurotoxic astrocytes in the brain (rather than acting directly on neurons themselves) provides a further link to the likely multiple mechanisms of action of TQ, including its ability to reduce the inflammatory response and neurodegeneration via microglial activation (74), and to increase the plasma GLP-1 levels. Accordingly, this establishes an exceptionally strong rationale for testing it without delay in a long-term disease-modifying clinical trial in patients with PD.

Mechanistically related to this, other research has shown the effect of TQ on the AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPAR-γ), and on the PGC-1α pathway, thereby suggesting it is highly likely to exert some control over mitochondrial size and number (75), and microglia (74). The importance of reducing neuroinflammation in Parkinson's disease treatment has led to the launch of parallel clinical approaches, including Inzomelid and XPro1595, which are currently in early-stage clinical studies. Azathioprine, a repurposed drug used for treating Crohn's disease, ulcerative colitis, lupus, and rheumatoid arthritis, will also enter a clinical trial in PD patients to investigate its neuroprotective and disease-modifying properties.

2. PRACTICALITIES OF DESIGNING AND RUNNING A LONG-TERM CLINICAL TRIAL TO EXPLORE THE THERAPEUTIC POTENTIAL OF TQ AS A POTENTIALLY DISEASE-MODIFYING THERAPEUTIC FOR PATIENTS WITH PARKINSON'S DISEASE

The biochemical and pharmaceutical rationale for including TQ in a long-term neuroprotective clinical trial in PD patients is strong, with key clinical trials exploring its therapeutic benefits in other therapeutic areas.

Table 2: Clinical Trials already involving TQ or Nigella Sativa.

Indication	Number of Patients	Phase	Duration	Dose	Details on clinicaltrials.gov website
β-thalassemia	80	II	84 days	2000mg/day	https://clinicaltrials.gov/ct2/show/NCT02816957
Lipids in elderly	96	II	56 days	300mg BID	https://clinicaltrials.gov/ct2/show/NCT01531062
NASH	100	-	1 year	1000mg BID	https://clinicaltrials.gov/ct2/show/NCT02307344
BP in elderly	76	III	28 days	300mg BID	https://clinicaltrials.gov/ct2/show/NCT01393054
Keratosis	40	I/II	84 days	500mg BID	https://clinicaltrials.gov/ct2/show/NCT01735097
Dyslipidemia	123	I/II	42 days	n/a	https://clinicaltrials.gov/ct2/show/NCT00327054
Periodontitis	25	II	14 days	topical	https://clinicaltrials.gov/ct2/show/NCT03270280
Cholesterol	33	-	60 days	n/a	https://clinicaltrials.gov/ct2/show/NCT03175757
Asthma	80	II	28 days	1000mg	https://clinicaltrials.gov/ct2/show/NCT02407262
Gastritis	132	I/II	28 days	600mg TID	https://clinicaltrials.gov/ct2/show/NCT03428568
Oral Malignancies	81	II	28 days	200mg	https://clinicaltrials.gov/ct2/show/NCT03208790
Endothelial function in Diabetes Type II	50	II	84 days	900mg BID	https://clinicaltrials.gov/ct2/show/NCT03959306
Obesity	120	-	84 days	n/a	https://clinicaltrials.gov/ct2/show/NCT01833377
Blood Glucose levels	30	-	30 days	500mg QID	https://clinicaltrials.gov/ct2/show/NCT03776448

2.1. Considerations of dose, safety, toxicology, and tolerability

Patients with Parkinson's disease (PD) deteriorate at a rate of 5-7% per year, making clinical trials necessary for a change in disease progression. TQ, a drug used in PD trials, was well tolerated in dose-ranging trials in advanced-stage cancer patients, with no toxicities reported. This is supported by pre-clinical experience with no adverse events in mice at doses as high as 2.4 gm/kg.

In 2017 a 4-week clinical trial using Nigella Sativa oil (500 mg BID) to treat asthma patients reported similar tolerability in placebo and the treated patients (76). In addition, Nigella Sativa was well tolerated for 3 months, at a dose of 1,350 mg/day, in a recently published clinical trial in patients with newly diagnosed type II diabetes. In the pediatric seizure study mentioned earlier, TQ, at an administered dose of 1 mg/kg, was used as an adjunctive therapy. Its effects on the frequency of seizures were compared with those of a placebo. Twenty-two patients were assigned to two groups and received either TQ or placebo for four weeks: there was no evidence of toxicity and/or side effects. The consensus is that TQ is safe at various doses (77-78). The safety and tolerability of a substance used in long-term clinical trials for Parkinson's disease (PD) have not been specifically investigated in a specific subgroup, despite its widespread consumption in many countries.

2.2. Considerations of CNS bioavailability of TQ

Elmaci et al. (50) reported that treating glioma patients with TQ significantly crosses the blood-brain barrier and exerts neuromodulatory potential. TQ, a small molecule, has been used for clinical purposes but lacks sufficient blood-brain-barrier passage data in humans, despite its hydrophobic nature, indicating poor bioavailability and difficulty crossing the blood-brain barrier (51). Slow absorption and prompt elimination of TQ from the body, as shown in two species, add to this concern (79-80).

Two approaches are proposed to investigate the effectiveness of TQ in treating Parkinson's disease (PD). The first involves a preliminary dose-response study measuring TQ levels in cerebrospinal fluid (CSF) before moving into a Phase II trial. If TQ levels are detected, the trial can proceed. The second approach involves using newer formulations of TQ, particularly those containing nanoparticles, to enhance brain penetration and improve therapeutic response while limiting potential toxicity in peripheral tissues. These approaches aim to extend the bioavailability of oral TQ administration. These approaches include the application of nanotechnology, encapsulation, and designing new analogs of TQ to make them more soluble in the aqueous phase (81). It has also been reported that encapsulation of TQ into nanoparticles increased its anti-inflammatory properties. Another research team, also using a nanotechnology approach, achieved almost a 5-fold increase in the bioavailability of TQ (82). It has been demonstrated how an encapsulated nanocarrier formulation of TQ reduced toxicity and offered advantages for the long-term administration of this therapeutic (83). Based on that, it was reported that a fourfold increase in bioavailability of TQ could be achieved, together with an associated increase in efficacy when using what the authors described as a 'self-nano emulsifying drug delivery system' (84). Various other groups have reported a sixfold increase in bioavailability using another nanotechnology methodology (85). At the same time, micro emulsification also appears promising (86-87), as does a recent approach involving TQ-conjugated nanodroplets (88) and the application of chitosan grafted lipid nanocapsules (89). Also, some highly promising results have recently been achieved when applying a polyethylene glycol (PEG)-nanotechnology approach (90-91).

Last year, another microencapsulation approach was reported for its potential oral use in patients with inflammatory bowel disease (92), reinforcing earlier work involving the development of a nanostructured lipid carrier approach for TQ for potential use in treating gastric ulcers. Last year, a new TQ derivative called SkQ Thy was described for targeted mitochondria delivery due to its strong antioxidant properties. A self-nano-emulsifying drug delivery system for TQ and curcumin may improve delivery and oral bioavailability (93). A nanoparticle carrier approach involving chitosan may be the most promising for use in clinical situations like Parkinson's disease (PD). Another nanoparticle approach enhanced TQ provision to the midbrain, cortex, thalamus, and hypothalamus, while reducing TQ in the cerebellum (94). PD affects various parts of the body and brain, with striatum and midbrain dysfunction being a core feature. Cognitive loss in a significant proportion of PD patients is linked to anatomical changes in the cortex, possibly genetically controlled (94). However, whether (and how) the other brain regions that were studied by Fahmy et al. (in terms of brain perforation of TQ are affected in PD is not clear, although current evidence suggests that pharmaceutical improvement of the function of the cerebellum is likely to be clinically beneficial in Parkinson's (95), and this is also likely true for the function of the thalamus, hypothalamus (96), and medulla.

2.3. Considerations of the nature of Phase II disease-modifying trial of TQ in patients with Parkinson's disease

TQ slows neurodegenerative decline in Parkinson's

disease patients, benefiting early-stage and symptomatic dopaminergic patients. Trials should be suitable for neurological hospitals with hundreds of PD patients, with trials lasting at least one or two years.

The Movement Disorders Society's Unified Parkinson's disease rating scale (MDS-UPDRS) is the standard approach needed to evaluate the trial's primary outcome, specifically MDS-UPDRS Parts II and III. However, improvements (PDCORE) to these measures have recently been published (97). In addition, and given the specific and relevant biological targets that TQ is thought most to affect, the additional rating scales should also be utilized. These measure changes in sleep (SCOPA), depression (the Montgomery & Asberg Depression rating scale, MADRS), the Parkinson's 39-item Quality of life questionnaire (PDQ39), Levodopa equivalent doses (LED), and the Non-Motor Symptoms scale (NMSS). The majority of the many Parkinson's trials around the world that the present authors are centrally involved in (25–26) now also require patients in these disease-modifying trials to attach wearable devices that closely monitor and electronically record the subtleties of their movement disorders and their sleep patterns, as well as regular, highly detailed blood and CSF biochemical evaluations. The study suggests using DAT or PET imaging as a secondary outcome measure to monitor inflammation and microglial activation. Functional MRI could be used to track mitochondrial function and energy homeostasis. Brain imaging of α-syn should be incorporated once available for research and clinical use. Blood biomarkers should be collected at the beginning of the study, at regular intervals, and at the end of the study. The results could help expand the role of TQ in PD patients as an oral therapeutic, slowing neurodegeneration.

TQ is a promising therapeutic agent for primary prodromal prevention of Parkinson's disease (PD). It should be tested in pre-motor PD patients with olfactory or sleep disturbances. This study requires a different approach, recruiting pre-PD patients with high chances of developing PD. The primary outcome is a reduction in TQ preventative therapy-induced definitive disease symptoms.

3. SUMMARY

TQ, a safe, inexpensive, and well-tolerated drug, has the potential to be used as a neuroprotective agent in patients with Parkinson's disease (PD). The biochemical evidence for testing TQ is compelling, and a long-term clinical trial is needed to evaluate its potential in disease modulation. Further studies should be conducted as a preliminary to a definitive Phase II clinical trial, considering the formulation of TQ. Recent developments in new formulations increase its bioavailability, enabling effective daily oral dosing. TQ is ready for immediate clinical translation into a pilot disease-modifying Phase II study in PD patients.

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