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Flavonoids and related compounds targeting pathomechanisms of Parkinson's Disease – from bench to bedside: A focused review of current perspectives, clinical trial outcomes, and future directions

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ABSTRACT

Background: The pathomechanisms of Parkinson's Disease (PD) remain incompletely understood. Key mechanisms include oxidative stress, neuroinflammation, and mitochondrial dysfunction. Disease-modifying strategies are still being investigated. Flavonoids are suggested to be able to influence the neurodegenerative process, but clinical evidence is limited.
Purpose: This review explored current, key pre-clinical but mainly clinical evidence for the potential of flavonoids and related compounds in treating PD.
Study design and Methods: Retrospective analysis of ClinicalTrials.gov registry was performed with terms "Parkinson disease" and "parkinsonism". For trials marked as "completed", the results were searched in both the "ClinicalTrials" Database and PubMed. PubMed was also searched to identify original papers and meta-analyses of the effects of flavonoid intake in PD patients.
Results: 2810 interventional studies were identified in the ClinicalTrials registry (www.ClinicalTrials.gov). A total of 18 trials were registered, with only 5 of them published as a full text article. Data from preclinical studies showed the promising effects of flavonoids in PD models. Animal studies data and data on flavonoids' beneficial effects in population-based studies further confirmed their potential in reducing the risk of PD. However, a single, most efficacious flavonoid has yet to be identified.
Conclusion: Current evidence, including from epidemiological studies, suggests that diets rich in flavonoids can improve the course of PD. However, clinical trials data to date, which are quite limited, indicate no routine supplementation with flavonoids has proven useful so far in the specific context of eliciting neuroprotection as a primary outcome. More robust preclinical studies followed by more clinical trials are needed to generate sufficient and reliable data.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease. It is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) and decreases in striatal dopamine levels. These changes lead to characteristic clinical symptoms: rigidity, resting tremor, and bradykinesia. The discovery of Lewy bodies (abnormal deposits of alpha-synuclein) in the intestinal submucosal and myenteric plexuses of PD patients explicitly highlights the role of the intestine in PD etiology (Beach et al., 2010; Braak et al., 2006; Wakabayashi et al., 1988). The dual-hit theory, proposed by Hawkes, Tredici and Braak, implicates two

List of Abbreviations: 6-OHDA, 6-hydroxydopamine; BBB, blood-brain barrier; CNS, central nervous system; EGCG, Epigallocatechin gallate; GPx, glutathione peroxidase; HPFS, Health Professionals Follow-up Study; MAPK, mitogen-activated protein kinase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-kappaB, nuclear factor-kappaB; NHS, Registry of the Nurses' Health Study; Nrf2/ARE, Nuclear factor erythroid 2-related factor like-2-antioxidant response element; PD, Parkinson's disease; ROS, reactive oxygen species; SNc, substantia nigra pars compacta; SOD, superoxide dismutase; TNF-alpha, tumor necrosis factor-alpha; UPDRS, Unified Parkinson Disease Rating Scale.

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places in the body as sites of PD origin – the olfactory nerves and intestinal plexuses (Hawkes et al., 2007). Moreover, it suggests that the neuronal damage initiated in the gut spreads to the central nervous system (CNS) via the vagus nerve, and it is only after neurodegeneration reaches the substantia nigra that the motor phase of PD begins. Changes in gastroenteric microbiota composition of PD patients and increased permeability of the intestinal wall have also been described (Açar et al., 2023; Forsyth et al., 2011; Li et al., 2019; Sun and Shen, 2018). However, despite numerous efforts, no pharmacotherapy with established neuroprotective effect is available to date. This is partly due to the complex and not-fully-understood mechanisms of development of PD. The proposed pathomechanisms of PD, especially in relation to their crosstalk in engendering PD, are still largely unclear, but the prominent mechanisms include oxidative stress, neuroinflammatory process and mitochondrial dysfunction, among others (Hirsch and Hunot, 2009; Thomas et al., 2021). For example, excessive oxidative stress is an important hallmark from early stages of PD, for which the underlying cause may be uncontrolled production of reactive oxygen species (ROS) as a result of several factors, resulting in damage to proteins, lipids, and nucleic acids (DNA and RNA). The pathological processes can ultimately lead to cell (neuronal) death, numerous mechanisms of which have been postulated in PD pathogenesis, including regulated cell death paradigms: intrinsic and extrinsic apoptosis, necroptosis, parthanatos, ferroptosis, and mitochondrial permeability transition-driven necrosis (Dionísio et al., 2021). All these factors and the underlying intestinal dysfunction suggest dietary intervention may constitute an important neuroprotective strategy.

Interestingly, dopaminergic neurons in the SNc have some unique features not observed in other neurons (Trist et al., 2019). They maintain autonomic activity, regardless of synaptic input, to provide dopaminergic innervation to the striatum. This is obtained with the involvement of l-type calcium channels, which require constant buffering of Ca^{2+} concentrations in cells. This process consumes high amounts of energy and so features high mitochondrial activity. It leads to a high baseline level of oxidative stress in the SNc. Other mechanisms leading to increased oxidative stress in SNc neurons include high levels of free iron binding neuromelanin and excessive iron intake with increased ferritin, coupled with its reduced export marked by impaired ceruloplasmin ferroxidase activity (Dionísio et al., 2021). Meanwhile, reduction in mitochondrial complex I activity is a natural process involved in the aging of cells. This includes reduction in the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase, which has been observed in the SNc of healthy aging individuals post-mortem (Venkateshappa et al., 2012). This is in line with increase in the occurrence of PD with aging. Toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, paraquat etc., as well as some genetic mutations in genes such as *DJ-1, PARK-2 and PINK-1,* among others, also impair mitochondrial complex I activity. Accordingly, mitochondrial activity damage is a basis for *in vitro* and animal models of PD, using neurotoxic compounds such as 6-hydroxydopamine (6-OHDA) and MPTP. 6-OHDA is the most commonly used model of parkinsonism, but it does not cross the blood-brain barrier (BBB), so in animal models it has to be injected into the brain. The molecular mechanisms of action of 6-OHDA include anterograde degeneration of the nigrostriatal dopaminergic system due to generation of H_2O_2. It is not only highly cytotoxic per se but also triggers the production of oxygen radicals. 6-OHDA is also neurotoxic by impairing the activity of mitochondrial complex I (Blandini et al., 2008). MPTP (or its active metabolite, MPP^+), is also commonly used to mimic parkinsonism. It is, however, less potent to damage dopaminergic neurons in rodents than in primates. It works mainly by blocking mitochondrial complex I of the electron transport chain (Przedborski et al., 2000). While these models are often used to trigger dopaminergic neuron degeneration in cell lines, primary neurons and animal models, they have some limitations. Notably, they do not fully reflect the complex nature of the disease. For example, induction of Lewy body formation, a hallmark of PD, requires more elaborate methods, including seeding of pathological forms of alpha-synuclein (Mahul-Mellier et al., 2020). These models also do not adequately reflect the effects that aging, genetic predispositions or environmental factors may have on disease pathogenesis.

With regard to therapeutic opportunities in PD, the limited potential of increasing endogenous antioxidative activity makes investigating the potential intervention of exogenous compounds more attractive. Among such compounds are naturally derived molecules, especially those from plants, including flavonoids (Açar et al., 2023). Flavonoids are a wide group of plant derivatives (secondary metabolites), some of which have neuroprotective potential due to their proposed mechanisms of action. Sources of flavonoids include plant-based food and beverages (juice, tea, and wine, among others). They are divided into six major subclasses (flavones, flavonols, flavanones, flavanols, isoflavones, and anthocyanins), depending on which carbon of the C ring the B ring is attached to and the degree of oxidation and substitution of the C ring (Fig. 1) (Jung and Kim, 2018; Nishiumi et al., 2011). The proposed mechanisms of action of flavonoids in PD are numerous (Maher, 2019), including those summarised in Fig. 2.

In vitro, flavonoids mostly work by combating oxidative stress and scavenging free radicals. *In vivo*, flavonoids are absorbed in the small intestine and then further transformed in the liver and by gut microbiota in the colon (Spencer, 2008), processes that reduce their direct antioxidative potential. Also, only some of them are able to cross the BBB. Given these factors, as well as favorable availability of endogenous antioxidants, direct antioxidant scavenging of cellular oxidants by flavonoids is unlikely *in vivo*. However, even in lower concentrations they may act on cell signaling pathways that influence redox status indirectly via antioxidant and cytoprotective gene expression (Williams et al., 2004). Among the most investigated flavonoids, curcumin has been associated with lowering the levels of malondialdehyde, protein carbonyls, thiols and nitrotyrosines, and stimulation of the activities of SOD and GPx (Abrahams et al., 2019). Quercetin was described as acting indirectly on the cellular antioxidative system by the induction of the Nuclear factor erythroid 2-related factor like-2-antioxidant response element (Nrf2/ARE) pathway and the antioxidant/anti-inflammatory enzyme paraoxonase 2, in addition to its possible direct antioxidant effect (Costa et al., 2016). Resveratrol is another polyphenol that has

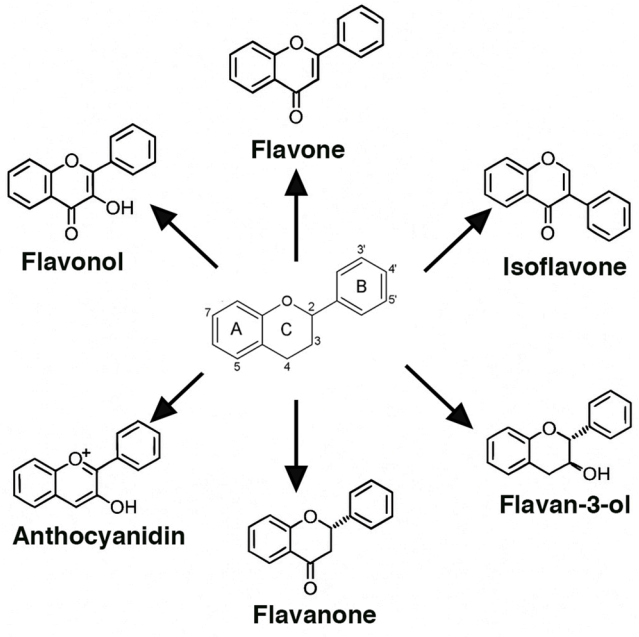

Fig. 1. Basic structure of a flavonoid (middle) and examples of the six subclasses.

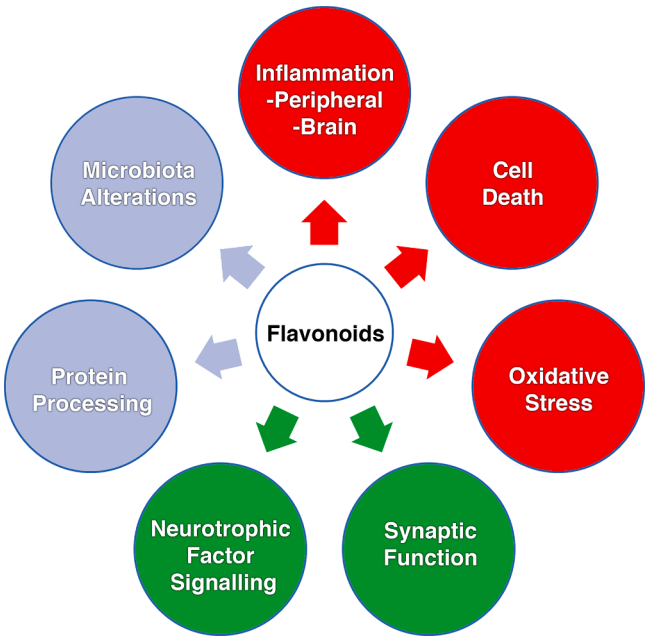

Fig. 2. Summary of postulated impact of flavonoids on different aspects of neuronal function. These pathways and processes are involved in Parkinson's disease pathogenesis. Green arrow - improved by flavonoids; red arrow - reduced by flavonoids; light blue - multimodal.

been identified to demonstrate neuroprotective properties. Studies in animals mention reduction by resveratrol of 6-OHDA-induced chromatin condensation, mitochondrial tumefaction and vacuolization of dopaminergic neurons, as well as decreases in the levels of COX-2 and tumor necrosis factor-alpha (TNF-alpha) mRNA in the SN (Jin et al., 2008). Its ability to decrease alpha-synuclein aggregation has also been described (Zhang et al., 2018), as well as its positive effect on activation of glutathione peroxidase and Nrf2 signaling pathway, resulting in restoration of redox balance (Gaballah et al., 2016). Epigallocatechin gallate (EGCG) is a flavonoid found in larger quantities in green tea and has been indicated as a particularly promising neuroprotective agent in different *in vitro* and animal models, as summarized by Sergi (Sergi, 2022). It has peripheral anti-inflammatory properties, including reduction of TNF-alpha and interleukin-6 in serum, and, in addition to some previously mentioned mechanisms such as antioxidative effect or halting protein misfolding, it has been implied to regulate iron homeostasis (Xu et al., 2017).

The postulated shared neuroprotective mechanisms of action of flavonoids, as summarized by Vafeiadou et al. (Vafeiadou et al., 2007), include (1) attenuation of the release of cytokines; (2) inhibitory action against nitrosative stress; (3) inhibition of the generation of ROS; (4) a capacity to down-regulate the activity of pro-inflammatory transcription factors such as nuclear factor-kappaB (NF-kappaB); and (5) the potential to modulate signalling pathways such as the mitogen-activated protein kinase (MAPK) cascade (Vafeiadou et al., 2007).

Despite the promise of therapeutic benefits of flavonoids in managing PD, studies assessing the effects of selected flavonoids have been conducted mostly in *in vitro* and animal models. Therefore, the aim of this paper was to assess progress beyond the *in vitro* and animal studies by reviewing some key studies highlighting the effects of human intake of flavonoids on clinical progression of PD as a neurodegenerative condition.

2. Methods

While numerous studies have reported potential neuroprotective effect of flavonoids in cell models and animal models, data on such effect in humans is scarce. We searched the ClinicalTrials Database (first on the 11th of November 2022 and then updated on the 4th of April 2024) using the term "Parkinson disease" and "Parkinsonism" to identify registered clinical trials on the efficacy of flavonoids intake and intake of other plant-based compounds in humans with PD. We also reviewed papers in which agents assessed in registered clinical trials were tested in *in vitro* and animal models, in order to provide some background on the flavonoid/plant agent used. Additionally, we reviewed papers assessing the general effects of flavonoid intake on the development of PD in humans.

3. Results

We identified 2810 interventional studies in the "ClinicalTrials" Database (www.ClinicalTrials.gov) with the term "Parkinson disease" or "parkinsonism" (4th of April 2024). We then performed a manual search of studies including intervention with plant products. We identified a total of 18 studies, with only 5 of them published as full text articles. For trials that were marked as "completed", the results of the studies were searched in both the "ClinicalTrials" Database and PubMed (some results were not published as a paper but as a summary in ClinicalTrials Database). Studies registered but with no results available are also mentioned to give a full scope of conducted clinical trials on flavonoids and other plant-based substances. We also searched PubMed to identify original papers and meta-analyses of the effects of flavonoid intake in PD patients. Table 1 summarises key clinical papers on effects of plant-based products and flavonoids in patients with parkinsonism.

Table 1
Summary of clinical trials and epidemiological studies on plant-based compounds and flavonoid intake in Parkinson's disease and multiple system atrophy.

Study	Compound	Study Design & Sample Size	Outcomes
Shin et al., 2018	DA-9701	Randomised study, comparator-domperidone. 38 patients completed	Not inferior to domperidone in 2-hour gastric emptying rate
Choi et al., 2020 (PASS-GI study)	DA-9701	Multicentre, randomised, placebo-controlled study, 144 patients	Improved GI symptom-related quality of life; reduced severity of GI symptoms after 12 weeks without affecting motor symptoms
Roy et al., 2021	STW5 (Iberogast)	Non-randomised open-label study; 44 patients	Increased stool frequency; significant decrease in stool consistency
Levin et al., 2019 (PROMESA trial)	EGCG	Multicentre, randomised, double-blind, placebo-controlled; 92 patients included	Assessed efficacy of EGCG on clinical outcomes of patients with multiple system atrophy - safe but no disease-modifying effect
Zhang et al., 2022	Flavonoids (Anthocyanins, Flavan-3-ols)	Population study from the Nurses' Health Study (NHS) & the Health Professionals Follow-Up Study (HPFS) cohorts	Higher flavonoid consumption linked to lower mortality in PD; berries and red wine (≥3x/week) most beneficial
Gao et al., 2012	Flavonoid-rich foods (tea, berries, apples, red wine, citrus)	20–22 year-long cohort follow-up; ~150,000 subjects; 805 developed PD	Highest flavonoid intake associated with 40 % lower PD risk in males only

GI- Gastrointestinal; EGCG- Epigallocatechin-3-gallate; PD- Parkinson's disease

3.1. Clinical studies on the efficacy of selected flavonoids in PD patients

Green tea flavonoids

Green tea flavonoids are considered an important neuroprotective player. A study on Green Tea Polyphenol extract in PD was registered in 2007 (ClinicalTrials.gov Identifier: NCT00461942). A total of 480 *de novo* PD patients were planned to be included, divided into three dosage groups of green tea polyphenol and one placebo control group. There was no information regarding the dose of treatment in study groups. The purpose of the study was to determine whether Green Tea Polyphenol (EGCG/EGC), an extract from Green Tea, was effective and safe in the treatment of *de novo* Parkinson's disease patients without taking any antiparkinsonian drug in one year of observation. The primary outcome measurement was change in Unified Parkinson Disease Rating Scale (UPDRS) using a delayed-start design. Recruitment status was registered as completed in 2011, but no results were reported.

A paper by Levin et al. summarized PROMESA – a randomized, double-blind, parallel group, placebo-controlled clinical trial assessing the efficacy of EGCG on progression of atypical parkinsonian syndrome - multiple systemic atrophy (Levin et al., 2019). Despite promising effects of preclinical trials, after 48-weeks of treatment no significant change in disease progression was observed in the treated group. Some hepatotoxicity was observed and doses higher than 1200 mg were not recommended for further use.

BIA 6–512 (Trans-resveratrol)

Seven clinical trials were registered regarding the efficacy of trans-resveratrol in the treatment of PD. The studies included assessment of the influence of BIA 6–512 (trans-resveratrol) on the pharmacokinetics of levodopa, as well as the effect of age and food on the pharmacokinetics of the flavonoid. While all registered studies were marked as completed, no results of the efficacy of treatment in PD patients were available in the ClinicalTrials Registry or the PubMed Database.

3.2. Clinical studies on the efficacy of plant-based recipes in PD

3.2.1. Products containing flavonoids in the mixture

WIN-1001X

A clinical trial examining the efficacy of an extract (WIN-1001X) from three plants: *Polygala tenuifolia, Angelica tenuissima*, and *Dimocarpus longan*, was identified (ClinicalTrials.gov Identifier: NCT04220762). The study was registered in January 2020, and it was still recruiting subjects. The purpose was to determine the optimal dose of WIN-1001X for its exploratory therapeutic study by evaluating and comparing the efficacy and safety of each of three dose groups of WIN-1001X (400 mg, 800 mg, and 1200 mg) and a placebo group in patients with early PD. Data from preclinical studies on MPTP-lesioned mice suggest that the extract may play a neuroprotective role by modulating autophagy (Li et al., 2021). The authors also reported attenuated loss of tyrosine hydroxylase in disease models. Onjisaponin B, derived from the root of *Polygala tenuifolia,* was identified as one of the major active components. Other active components are still to be established.

DA-9805

A study assessing the efficacy and safety of three doses of DA-9805 was conducted and registered as completed in Clinical Trials (ClinicalTrials.gov Identifier: NCT03189563). It assessed a mixed herbal ethanol extract containing the roots of Moutan Cortex (*Paeonia suffruticosa* Andrews), *Bupleurum falcatum*, and *Angelica dahurica*. Numerous active ingredients were indicated for each of the plants. These include imperatorin, isoimperatorin, oxypeucedanin, phellopterin, and byakangelicol in *A. dahurica* root. Saikosaponin A, C, D; triterpenoids; flavonoids; polyacetylenes; and polysaccharides were indicated as active components in *B. falcatum*. The study was based on a report summarizing the positive effect of the mixture in PD models – MPP-treated SH-SY5Y cell lines and chronic MPTP mouse model (Jeong et al., 2018). The postulated mechanisms of action include attenuated upregulation of glucose-regulated protein 78, C/EBP homologous protein and cleaved caspase-3 in SH-SY5Y cells. Jeong et al. concluded that DA-9805 may reduce mitochondrial dysfunction, have an anti-inflammatory effect, and reduce endoplasmic reticulum stress and oxidative stress (Jeong et al., 2018). The study included 61 subjects divided into 3 groups: placebo, 45 mg/day and 90 mg/day. The results were published only in ClinicalTrials Register. No significant differences were reported in the primary outcome (change in motor MDS-UPDRS score from baseline at Week 12) as well as the secondary outcomes (total UPDRS and its subscales, Schwab and England scale, Hoehn and Yahr scale, PDQ-39) (Jeong et al., 2018).

SWT5 (Iberogast)

Gastrointestinal disorders are among the most common non-motor symptoms of PD. A study examining the properties of STW5 in treatment of gastrointestinal problems of PD patients was registered with ClinicalTrials.gov (Identifier NCT02719496). STW5 (Iberogast) is a herbal agent composed of nine plant extracts (bitter candytuft (*Iberis amara*), angelica root (*Angelicae radix*), milk thistle fruit (*Silybi mariani fructus*), celandine herb (*Chelidonium majus*), caraway fruit (*Carvi fructus*), liquorice root (*Liquiritiae radix*), peppermint herb (*Menthae piperitae folium*), balm leaf (*Melissae folium*) and chamomile flower (*Matricariae flos*)) (Saller et al., 2002). The proposed mechanism of action in PD was to improve constipation due to its prokinetic effects on the prosecretory enteric neurons. It could also improve dyspepsia and abdominal pain by its antispasmodic properties. The results were not published in ClinicalTrials Registry. However, a paper by Roy et al. summarizes findings from 44 patients enrolled in the study (Roy et al., 2021). The patients were treated with 20 drops of STW5 t.i.d for 28 days, after a seven-day titration period. The primary outcome was to increase stool frequency during the last week of treatment, compared with the reference week. The only significant difference observed before and after treatment was a decrease in stool consistency ($p = 0.0272$).

DA-9701 (Motilitone)

Another plant-based medication assessed for the treatment of gastrointestinal symptoms of PD is DA-9701. DA-9701 (Motilitone) is a recently developed herbal medication consisting of *Corydalis* tuber and Pharbitidis Semen, which has both 5-HT4 receptor agonism and D2 receptor antagonism (Jung et al., 2015). Furthermore, it does not cross the BBB and can be safely used in PD patients. A study comparing DA-9701 and domperidone (a dopamine receptor antagonist that stimulates peristalsis) was registered in ClinicalTrials with the number NCT03022201. It was described as comparing the efficacy of DA-9701 and domperidone in the double-blind, controlled phase 1 (4 weeks) and the long-term safety of DA-9701 in the open-label phase 2 (8 weeks after phase 1). The study was registered as completed, but no results were published in ClinicalTrials. However, there were two papers published summarizing the findings of the study. In the initial report on 40 patients, Shin et al. concluded that DA-9701 could be used in patients with PD to enhance gastric motility without aggravating PD symptoms when compared to domperidone (Shin et al., 2018). This was supported by the results of another study on 144 patients by Choi et al. (Choi et al., 2020). Authors concluded that DA-9701 therapy improved gastrointestinal, symptom-related quality of life, and 12 weeks of daily administration could relieve the overall severity of gastrointestinal symptoms in patients with PD without affecting motor symptoms (Choi et al., 2020).

Ethnodyne Visio

The efficacy of Ethnodyne Visio in PD was assessed in a study named ETHNOPARK (ClinicalTrials.gov Identifier: NCT02815800). While more exact data on the composition of Ethnodyne Visio was lacking, the authors stated that it is a plant extract that includes *Withania somnifera, Emblica officinalis* and *Bacopa monnieri*, combined with vitamin B2. The primary outcomes included a change in part III of the UPDRS scale after 3 months. We can hypothesize that flavonoids are present in this extract, although it was not stated clearly by the producer. The study included an open-label treatment with Ethnodyne Visio BID. While the study was marked as completed in 2018, no results were available either in ClinicalTrials or in PubMed.

HERB-PARK

A randomized study assessing the effects of some Chinese herbal medicine treatments as adjunct therapy for PD (HERB-PARK, ClinicalTrials.gov Identifier: NCT05001217) was registered in ClinicalTrials but marked as "not yet recruiting" patients. The effects of four Chinese herbal treatments would be assessed: 1. Huanglian Wendan Decoction, 2. Jin Gui Shen Qi Pill 3. Qi Ju Dihuang Pill plus Zhen Gan Xi Feng Decoction, and 4. Bu Yang Huan Wu Decoction combined with Chang Yuan Wendan Decoction. Patients would be randomized to either conventional medical treatment of PD (levodopa, dopamine agonists, etc.) or conventional medical treatment plus one of the traditional Chinese treatments. It is an attempt to provide high-quality data on the efficacy of Chinese traditional treatments in PD.

Saffron and Chamomile

A study assessing the efficacy of saffron and chamomile as well as their active compounds – crocin and apigenin – was registered with ClinicalTrials ID NCT05696665 . Apigenin belongs to the flavone class and crocin is a carotenoid. The researchers hypothesized that their anti-inflammatory and antioxidative properties may modify progression of PD. They were planning to compare the efficacy of chamomile and saffron and their active compounds. The study was planned as a randomized trial with three groups: standard treatment group, standard treatment plus 1000 mg chamomile and 30 mg saffron group, and standard treatment plus 500 mg apigenin and 30 mg crocin group. No results were available.

3.3. *Effect of dietary flavonoids – results of cohort studies*

While very few studies were undertaken to measure anti-parkinsonian effects of selected flavonoids, some clinical data suggest a general beneficial effect of flavonoid-rich diets in PD. We identified two population studies, both based on the Registry of the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) cohorts. Zhang et al. reported that, among individuals with PD, higher consumption of flavonoids – anthocyanins and flavan-3-ols – was likely to be associated with a lower risk of mortality (Zhang et al., 2022). In this large study, participants were divided into quartiles, depending on the average consumption of flavonoids. Flavonoid content was calculated based on semi-quantitative food frequency questionnaires. Berries and red wine consumed more than 3 times per week were indicated as especially beneficial in reducing mortality risk post-diagnosis of PD. The authors hypothesized that the main mechanisms of neuroprotection of these substances are free radical scavenging and regulation of oxidative stress (Zhang et al., 2022). They also indicated that, in animal studies, the concentration of anthocyanins in the brain rises very shortly after introducing it to the stomach; therefore, it can directly affect the CNS (Passamonti et al., 2005).

In a paper by Gao et al., the authors assessed intake of five sources of flavonoid-rich foods (tea, berry fruits, apples, red wine, and orange/orange juice). The study included a 20–22 year-long follow up of almost 150 000 subjects from the NHS and HPFS cohorts. 805 of them developed PD during follow-up. Authors concluded that patients with the highest intake of food flavonoids had 40% lower chance of developing PD. This effect was, however, only described in male patients (Gao et al., 2012).

A meta-analysis of the effect of tea drinking on the risk of PD development showed effects consistent with those in previous studies. A paper by Li et al. summarized findings from eight (8) studies, including 1418 cases and 4250 controls. Authors concluded that consumption of tea lowered the risk of PD. There was, however, no relation between the dose and the response observed. The antioxidative properties of tea polyphenols might be of importance here. However, theanine and caffeine may also lower the risk of PD, and the synergistic effects of the different constituents cannot be excluded (Li et al., 2012).

A paper by Fan et al. investigated the effect of supplementation with blackcurrant anthocyanins on cerebrospinal fluids' cyclic glycine-proline (cGP) (Fan et al., 2018). cGP is a metabolite of insulin growth factor-1 (IGF-1), a neurotrophic factor essential for neuronal survival. IGF-1 resistance may contribute to disease progression, cognitive impairment, and pathology of idiopathic PD. The authors concluded that supplementation with anthocyanin leads to increase in CSF cGP and may potentially lead to the improvement of IGF-1 function in PD brains.

4. Discussion

The high number of promising pre-clinical studies indicating neuroprotective potential of flavonoids stands in contrast with the low number of clinical trials testing these compounds and other plant-based interventions in general. Studies assessing single flavonoids (*e.g.*, EGCG, resveratrol) have so far not confirmed their neuroprotective properties in humans (Levin et al., 2019). However, data from epidemiological studies on large populations do indicate that consumption of flavonoids may prevent development of PD (Gao et al., 2012; Jung and Kim, 2018; Li et al., 2012). This may be due to the fact that different mechanisms are involved in neuroprotection *in vitro* than in humans. The concentrations of flavonoid compounds tested in *in vitro* studies are hardly attainable in the human body. Manach et al. performed a review of 97 bioavailability studies on polyphenols in humans (Manach et al., 2005). The flavonoids with the highest absorption according to the authors are isoflavones, followed by catechins, flavanones, and quercetin glucosides, but with different kinetics. The least well-absorbed polyphenols include the galloylated tea catechins and the anthocyanins (Manach et al., 2005). For example, after oral administration of the anthocyanins, only 1–2% remain in their original structures, due to digestion and enzymatic and microbiota catabolism (Tena et al., 2020). Some flavonoids are also largely metabolized by gut microbiota and may therefore influence its composition, with possible clinical effects on PD progression. Several studies already mentioned the positive effects of quercetin and cocoa polyphenols on lipid metabolism through change in gut microbiota composition (Porras et al., 2017; Sorrenti et al., 2020). It should, however, be noted that some flavonoids have been reported to be toxic in humans in higher doses. For example, a 2018 review showed that excessive intake of EGCG may cause liver toxicity (Hu et al., 2018). In 2018, the European Food Safety Authority stated that a daily intake of 800 mg or more of EGCG could increase the risk of liver damage (Younes et al., 2018). Maximum recommended safe dose of EGCG is 338 mg per day in a capsule or tablet or 704 mg per day consumed as a tea beverage (Younes et al., 2018).

Additionally, flavonoids cross the BBB to different extents. A study by Shimazu et al. measured concentrations of different flavonoids in animal models after oral intake. They observed that EGCG, daidzein, genistein, equol, and nobiletin each had high BBB permeability. Apigenin, luteolin, quercetin, and kaempferol each showed medium permeability, and for epicatechin, rutin, fisetin, resveratrol, and curcumin, BBB permeability was negligible (Shimazu et al., 2021). Therefore, the potential neuroprotective mechanisms of resveratrol or curcumin (with low BBB permeability) are unlikely to be associated with its direct antioxidative effect in the neuronal and glial cells. As a result, the potential mechanisms of neuroprotection elicited by flavonoids are probably, to a large extent, specific to the selected compounds, rather than predominantly universal for the whole group.

This complexity of mechanisms of neuroprotection postulated to explain flavonoids' effects in humans is further compounded by lack of robust disease models for preclinical studies. Although neurotoxin-based models are efficient in modelling neuronal damage and mimicking certain symptoms of parkinsonism, they do not reflect the complexity and multiorgan involvement observed in PD patients. This may be the reason why numerous substances with promising effects in cell-based studies fail to demonstrate neuroprotection in humans. To increase reliability of *in vitro* studies, the use of more than one neurotoxicity induction method is recommended, and this can also be done in a range of cell types, (primary neuronal cells, glial cells, neuron-like cell

lines) (Maher, 2019). The use of co-cultures of glial and neuronal cells, and of stem cells and patient-derived cells, can also improve the predictive accuracy and translational relevance of cell-based models. Organoids representing human midbrain are an example of such advancement (Galet et al., 2020).

There are also challenges with conducting clinical studies. For example, studies in human subjects may be limited by the inability to accurately assess the process of neurodegeneration of dopaminergic cells with clinical tools such as change in UPDRS scale (which is most commonly used). Late involvement of patients in clinical trials is another issue, as motor symptoms only appear when degeneration of the SNc is advanced and there is a spread of Levy pathology in the enteric system, brainstem and olfactory bulb, at what point it might be rather late for a neuroprotective intervention (Dickson, 2018).

5. Conclusion

In this review, we identified several clinical trials of flavonoids in PD, including those for which no results have been published to date. There is evidence of publication bias for studies on flavonoids and PD, meaning that studies showing promising or positive results are more likely to be published, while those with negative or inconclusive findings often remain unpublished. This can create a misleading impression that flavonoids consistently benefit Parkinson's patients, even if the overall evidence is less certain. As a result, the true effectiveness of flavonoids in PD may be overestimated, and a more balanced assessment is needed, including unpublished or negative findings. While regulating agencies make efforts to introduce mandatory publishing of negative results, our work identified that this is yet an unmet need. Based on the high number of undisclosed results, we can only speculate that the initial data for such trials were not promising, leading to discontinuation of the studies. The real reasons for discontinuation may, however, vary, which is why clarifications are crucial to avoid misleading conclusions. Besides, while there can be positive effects of flavonoids in studies of herbal medicines, the main active components of the plant mixtures or recipes are often poorly identified, limiting the reproducibility and understanding of the mechanisms of action of those products. However, we are aware of the possibility that the overall beneficial effect of a complex, multi-component recipe could often be attributable to the synergistic interactions between its various components. It is, therefore, important to ensure these products are standardized, and emerging analytical and omics techniques are beginning to herald significant development in that regard.

While epidemiological studies provide evidence for positive and possibly disease-modifying effects of dietary flavonoids in general, data on specific substances with neuroprotective potential is scarce. More robust preclinical studies followed by more clinical trials of the substances are definitely needed in order to generate sufficient and reliable data on the effects of the different compounds. Clinical studies should include not only meticulous clinical assessments of the patients but also robust sampling of cerebrospinal fluid, serum, urine and stool to maximize future understanding of how flavonoids affect subjects with PD. According to current evidence, diets rich in flavonoids can improve the course of PD and could be recommended for PD patients, but, based on clinical trials data to date (which are limited), no routine supplementation with flavonoids has proven useful so far in the specific context of eliciting neuroprotection as a primary outcome.

Overall, our work clearly highlights the potential benefits that the incorporation of flavonoid-based interventions could bring to clinical management of PD, whether through effects on mechanistic mediators or pathways contributing to the pathology of the disease or significant alleviation of its symptoms to improve the quality of life for patients. The review, therefore, amongst other things, sensitizes the research community to the critical and urgent need for more programmes of research whose designs truly incorporate and integrate pre-clinical and clinical studies, including clinical trials.

Author agreement statement

All authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proof.

CRediT authorship contribution statement

Monika Figura: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Conceptualization. **Amos A. Fatokun:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors have no interests to declare.

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Data availability

Not Applicable, as this is a review article.

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