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Review

Dietary flavonoids may have a protective and therapeutic effect in Parkinson disease: A systematic review

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ABSTRACT

Parkinson disease (PD) is characterized by the loss of dopaminergic neurons because of oxidative stress and neuroinflammation. Polyphenols in vegetables, known for their high antioxidant capacity, may prevent the onset, or delay the progression of the disease; among these, flavonoids are the most abundant class of polyphenols in foods. Clinical and cohort studies have evaluated the effect of polyphenol consumption on the risk of developing PD or of attenuating the symptoms after diagnosis; therefore, it is necessary to integrate the scientific evidence into making dietary recommendations. The objective of this study was to perform a systematic review of randomized controlled trials and cohort studies that have investigated the use of polyphenols in PD. The studies were identified through the PubMed, Science Direct, Scielo, and Web of Science databases. A total of 1100 studies were found; these were analyzed and filtered by 2 independent reviewers. After completion, 5 studies were included (3 randomized controlled trials and 2 cohort studies). The consumption of flavonoids, anthocyanins, or 2–5 servings/week of specific foods (apples, red wine, blueberries, and strawberries) reduces the risk of PD and associated mortality. Treatment with licorice, curcumin, or cocoa, which are rich in flavonoids and other polyphenols, improves motor function in PD patients. No statistically significant differences were found in quality of life, disease progression or nonmotor symptoms such as cognitive ability and mood. Although cohort studies suggest a neuroprotective effect, further clinical studies are urgently needed to evaluate the effect of specific flavonoids and other polyphenols in PD.

Abbreviations: 6-MWT, 6 minute walk test; 6-OHDA, 6-hydroxydopamine; ARE, antioxidant response element; IL, interleukin; Nrf2, nuclear erythroid-related factor 2; OS, oxidative stress; PD, Parkinson disease; PGC, peroxisome proliferator-activated receptor γ/coactivator 1α; RCT, randomized controlled trial; SIRT, sirtuin; TNF, tumor necrosis factor; UPDRS, Unified Parkinson's Rating Scale.

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1. Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder primarily affecting dopaminergic neurons in the substantia nigra pars compacta, characterized by Lewy body presence in substantia nigra and locus coeruleus [1,2]. The cardinal motor symptoms of PD are tremor, rigidity, bradykinesia/akinesia, and postural instability, but the clinical picture includes other motor and nonmotor symptoms that are classified into psychiatric, genitourinary, gastrointestinal, and cardiovascular symptoms (Supplemental Table 1) [3].

In the United States and some European countries, the incidence of PD is estimated at 14 cases per 100,000 people annually and 160 cases per 100,000 people aged 65 years or older [4]. PD is influenced by both modifiable (environment, lifestyle, eating habits) and nonmodifiable (genetics, age, race, sex) risk factors [5].

Oxidative stress (OS) plays an important role in the physiopathology of PD because both intrinsic and extrinsic factors can contribute to stress in the central nervous system, compromising its functionality [2,6].

Neuroinflammation, initiated as a defense mechanism, can contribute to neurodegeneration when glial cells are persistently activated [7–9]. The resulting release of inflammatory mediators such as prostaglandins and cytokines tumor necrosis factor (TNF-α), interleukin (IL-)1β, IL-2, and interferon-gamma, as well as reactive oxygen and nitrogen species, exacerbates the brain damage [8,10]. OS and neuroinflammation can cause mutations in protein synthesis, leading to the formation of amyloid-like fibrils involved in PD's pathogenesis [2,10]. For instance, the SNCA (PARK1) gene mutation results in misfolded α-synuclein, forming Lewy bodies [10,11]. Dopaminergic neurons are particularly susceptible to OS because of brain characteristics, their interaction with glia, and dopamine metabolism involving iron and oxidative catabolism [12,13].

Given the importance of OS in PD, polyphenols have been suggested as potential antioxidants to prevent or slow disease progression. Polyphenols, abundant in plant-based foods, belong to 5 families or classes: phenolic acids, flavonoids, stilbenes, lignans, and others [14,15]. Flavonoids are the most abundant polyphenols in nature, comprising 10 subclasses and 400 different types; the subclasses are anthocyanins, chalcones, dihydrochalcones, dihydroflavonols, flavanols, flavanones, flavones, flavonols, and isoflavonoids [14]. Some food sources of flavonoids are described in Supplemental Table 2.

Flavonoids and other polyphenols exhibit low redox potentials and donate hydrogen atoms to reduce oxidized radicals, while also inducing antioxidant enzymes and inhibiting proinflammatory enzymes [13,16,17].

Studies on polyphenols and PD primarily consist of *in vivo* or *in vitro* research [18]. Among the *in vivo* studies, some flavonoids have demonstrated beneficial effects in various models of PD.

Quercetin, a flavonol, has shown antioxidant properties in the rat model of PD induced with 6-hydroxydopamine (6-OHDA), where the activity of GSH, SOD, and CAT enzymes were restored, decreasing peroxidation lipid in the hippocampus [19]. Oral naringenin, a flavanone, pretreatment for 5 days significantly counteracted lipid peroxidation in an MPTP-induced PD model and motor impairment; the mechanisms of action were the increase of GSH, SOD, and CAT, as well as the decrease in the mRNA concentrations of proinflammatory mediators TNF-α, IL-1β, and iNOS [20]. Epigallocatechin gallate, the most abundant flavonoid in green tea (*Camellia sinensis*), inhibited αSyn misfolding (a marker of PD), and reduced intracellular levels of reactive oxygen species by chelating Fe(III) in PC12 cells transduced with wild-type αSyn, considered as an *in vitro* model of PD [21,22].

However, in addition to flavonoids, other polyphenols have also demonstrated a beneficial effect on PD. This is the case of ellagic acid and resveratrol, a phenolic acid and a stilbene, respectively [23,24].

Considering PD's global prevalence and the need for therapeutic alternatives, the scientific community aims to base decisions on evidence [25,26]. To establish dietary recommendations regarding polyphenol intake for the prevention or delay of PD progression, it is crucial to integrate available data and investigate human clinical studies. Furthermore, given the diversity of polyphenols, it is essential to identify which classes, subclasses, or specific compounds have this potential. Therefore, the aim of this paper was to perform a systematic review of randomized controlled trials (RCTs) and cohort studies on polyphenols in PD.

2. Methods and materials

The present systematic review followed the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), as its methodological model and was guided by the PICOS search strategy (Population, Intervention, Comparisons, Outcomes, and Settings). The criteria within each of these categories were as follows:

- Population: Patients with PD
- Intervention: Polyphenol-rich foods or supplementation of isolated phenolic compounds
- Comparison: No supplementation/polyphenol-rich food (control group or placebo)
- Results: Mortality, incidence, and symptoms of PD
- Settings: Randomized clinical trials and cohort studies.

2.1. *Eligibility criteria*

Eligible studies met the following criteria: they used an RCT design or cohort design, involved adult participants, and used an intervention or exposure to dietary phenolics. Exclusion criteria were book chapters, case reports, review studies, original *in vivo*, *in vitro* or *in silico* studies, and clinical studies that administered phenol supplementation in combination with a different compound.

2.2. *Search strategy*

The studies were identified through an exhaustive search in electronic databases: PubMed/MEDLINE, Science Direct, Scielo, and Web of Science of articles published from 2010 to June

2022 and only in the English language. The search terms that were used in the databases are found in Supplemental Table 3. Additionally, the data search was updated manually up until July 2022, which resulted in 1 additional record.

2.3. *Data extraction and quality assessment*

The review of the articles and classification was carried out independently by 2 evaluators and, in the case of any discrepancy, that was resolved by a third evaluator.

The assessment of risk of bias was performed according to the Cochrane Manual or Newcastle-Ottawa criteria. In the randomized clinical trials, the Cochrane manual [27] was used to assess the risk of bias using 7 criteria: random generation of the sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting of outcomes, and other biases; each was classified as "low risk," "high risk," or "unclear risk" of bias.

In cohort studies, the Newcastle-Ottawa guide was used [28], which evaluates the selectivity of the study, the comparability of the study design or analysis, and the results through 8 items that go on a rating scale of 0 to 9 from low to high quality, respectively. The maximum score was 9, and a score ≥6 indicates high methodological quality.

Finally, the relevant information was extracted in 2 tables, 1 with the study design, date of publication, country, objective, population, and conclusion of the study, and another with the characteristics of the population, inclusion criteria, intervention and follow-up time, variables, main results, and statistics used.

3. Results

3.1. *Studies selection*

The search in the PubMed, Science Direct, Scielo, and Web of Science databases, plus the manually identified record yielded a total of 1100 articles; of these, 57 articles were removed because they were duplicate studies. The titles and abstracts were examined and 1005 were excluded for not meeting the inclusion criteria. Therefore, 38 articles were read in full text to examine their design and assess their eligibility. Finally, only 5 studies met all the criteria and were included in the review. The most frequent reasons for exclusion of records were that they were *in vivo*, *in vitro* studies, or review articles (Fig. 1).

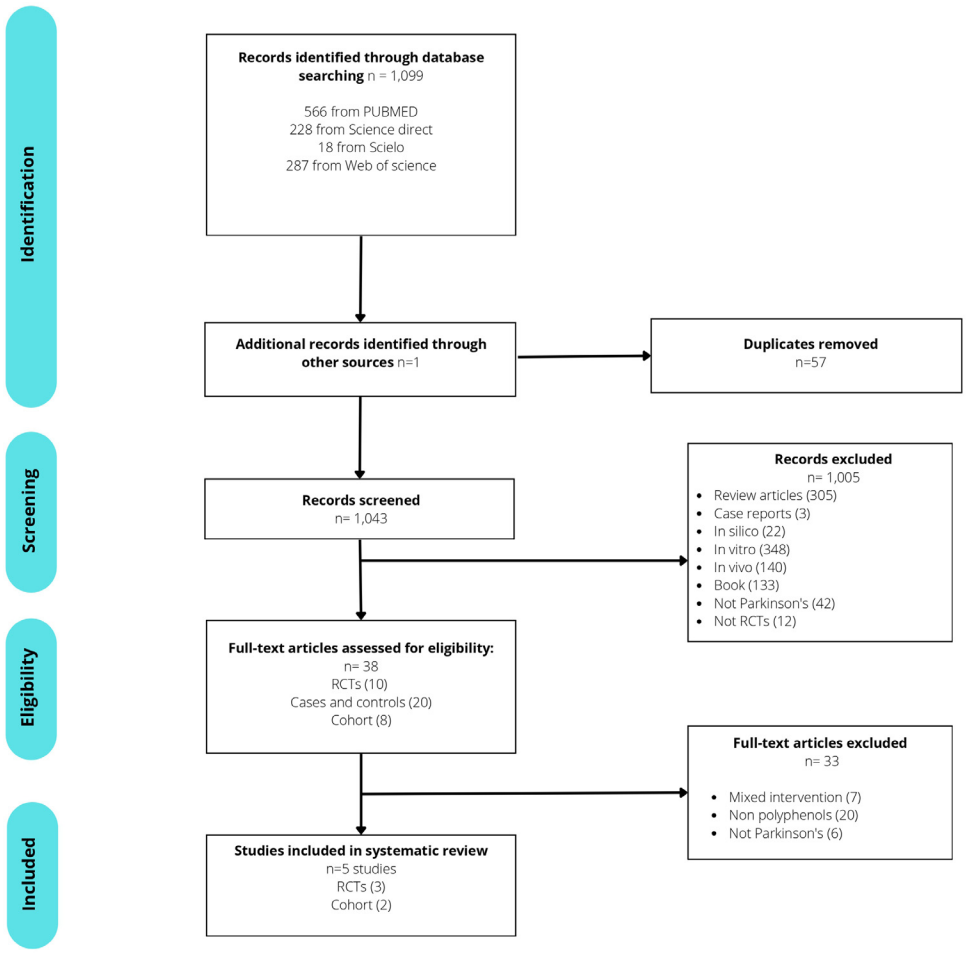

Fig. 1 – PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart summary of the review search process.

3.2. Risk of bias within studies

The risk of bias for both the RCTs (Supplemental Fig. 1) and the cohort studies was low (Supplemental Table 4). In clinical trials, 2 studies [29,30] had low risk of bias on all criteria, whereas only 1 study was classified as high risk of bias in the criteria "incomplete outcome data" because 1 person did not complete the study, and as unclear bias in "other biases" because 2 of the authors worked at the institution from which the participants were recruited [31].

In the cohort studies, both had high methodological quality with a score of seven points on the Newcastle-Ottawa scale [32,33]. In both cases, it was believed they did not meet the "representativeness of the exposed cohort" because the participants were a group of nurses and health professionals; nor was it believed that they met the "determination of the exposure" because it was carried out through self-registration, criteria that are not valid to be considered of high quality.

3.3. Studies characteristics

The total number of participants that were included in the selected studies was 130,997; 2 studies were prospective cohort studies and 3 studies were RCTs (Table 1). The 2 cohort studies were from a population made up of health personnel ($n = 130,868$) with an age range of 30 to 75 years [32,33].

Randomized clinical studies were conducted on subjects ($n = 129$) attending clinics, who were diagnosed with PD, and were under pharmacological treatment with levodopa and other medications, with a age range of 18 to 80 years [29–31]. Two of these studies included subjects with <3 on the Hoehn and Yahr scale [29,31].

3.4. Description of the measurements and instruments

Cohort studies evaluated the consumption of six flavonoid subclasses and their relationship with PD incidence and mortality, whereas RCTs evaluated exposure to an isolated polyphenol (curcumin) or foods rich in flavonoids (licorice or cocoa syrup).

The consumption of six flavonoid subclasses were quantified: flavonols (quercetin, kaempferol, myricetin, and isorhamnetin), flavanones (eriodictyol, hesperetin, and naringenin), anthocyanins (cyanidin, delphinidin, malvidin, pelargonidin, petunidin, and peonidin), flavan-3-ols (catechins, epicatechins, gallocatechins, epigallocatechin, epicatechin 3 gallate, epigallocatechin 3 gallate), polymers (proanthocyanidins, theaflavins, thearubigins), and flavones (luteolin, apigenin) [32,33].

Regarding the intervention studies, 1 used licorice syrup (5 mL containing 136 mg of total polyphenols and 2.6 mg of total flavonoids) compared with a placebo and was carried out over 6 months [29]. Another study compared the ingestion of 18 g of cocoa high in total flavanols, including catechins (10.79 mg/g and 8 mg/g, respectively), with the intake of cocoa low in total flavanols and catechins (1.02 mg/g and 0.99 mg/g) during 6 days [31]. The third study compared the ingestion of 80 mg/day of curcumin capsules, a source of other polyphenols, compared with a placebo for a period of 9 months [30].

Further information on the instruments used can be found in the Supplemental Material.

3.5. Main findings

3.5.1. Side effects

The most common side effects in the studies were nausea, diarrhea, and dizziness. In the licorice syrup intervention group, 3 patients discontinued treatment because of nausea, diarrhea, and urticaria [29], whereas 20% of the curcumin intervention group experienced vomiting and dizziness [30]; in the cocoa study, there were no adverse effects.

3.5.2. Life quality and disease stage

No significant changes were found in this section. As previously described, 3 studies used the Hoehn and Yahr scale, but only 2 measured it as a variable because in the third case the study was too short [31]. There were no significant changes in the PD stage [29,30]; regarding the quality of life of the participants, no significant changes were found in any of the 3 studies, evaluated by different instruments: Dizziness Handicap Inventory and Short Form-36 [29], Parkinson Disease Questionnaire-39 [30], and Barthel index [31].

3.5.3. Mortality and morbidity

Two of the 5 studies reported the effects of flavonoid ingestion on PD mortality and morbidity [32,33]. In the case of men, but not of women, the greater consumption of flavonoids or flavan-3-ols before the diagnosis of the PD reduced the mortality attributed to this disease; in both sexes, anthocyanin consumption also reduced PD mortality. For all-cause mortality, mortality decreased with higher anthocyanin consumption, 3 servings per week of red wine or blackberries, in both men and women [33].

Regarding the risk of developing PD, but only in men, the risk was lower when there was a higher consumption of flavonoids, flavonols, and polymers (epicatechin and proanthocyanidin dimers), or the ingestion of at least 5 portions of apples per week. In both men and women, the higher consumption of anthocyanins or 2 to 4 servings of strawberries or blueberries decreased the risk of PD [32].

3.5.4. Motor symptoms

Three studies evaluated the effect of flavonoid-rich foods on motor symptoms. A study used licorice syrup found that the intervention group had an improvement in the score of part II "daily activities" in all visits, as well as in part III "motor part" of the Unified Parkinson's Disease Rating Scale (UPDRS) in visits 3 and 4; on the tremor score at visits 2, 3, and 4; and in stiffness at visits 3 and 4 [29]. The study that evaluated curcumin supplementation also significantly improved part III, but not part II. On the other hand, the study that used a high-flavanol cocoa drink evaluated the motor symptoms through the Fatigue Numerical Scale (FNS), an accelerometer, and the 6-minute walk test (6-MWT), with only the latter being significantly different [31].

3.5.5. Nonmotor symptoms

The nonmotor symptoms measured were those related to cognitive thinking and mood. Three studies assessed these using

Table 1 – General characteristics of the randomized clinical trials or cohort studies investigating the effect of dietary polyphenols in Parkinson disease, included in this review.

Author (country)	Objective	Study design andopulation (*n*) characteristics	Duration and interventions	Main limitations
Zhang et al., 2022 (USA)	To study the association between pre- and post-Dx flavonoid intakes and risk of mortality among individuals with PD identified from 2 large cohorts of US men and women	Prospective cohort ($n = 1251$) Female registered nurses aged 30–55 years and male health professionals aged 40–75 years.	32 or 34 years Through an FFQ, it was determined intakes of the 6 main flavonoid subclasses in the US diet, (pre- and post-Dx of PD) every 2–4 years since 1984 (NHS) or 1986 (HPFS)	• Limited disease severity data, potentially confounding the association • Possible loss of cases and misclassified outcomes from data access limitations • No data on the quantity of flavonoid consumption • Self-administered FFQ • Predominantly white participants in NHS and HPFS
Gao X. et al., 2012 (USA)	To prospectively examine whether higher intakes of total flavonoids and their subclasses (flavanones, anthocyanins, flavan-3-ols, flavonols, flavones, and polymers) were associated with a lower risk of developing PD	Prospective cohort ($n = 129{,}617$) Female registered nurses aged 30–55 years and male health professionals aged 40–75 years.	20 or 22 years Through an FFQ, it was determined intakes of the 6 main flavonoid subclasses in the US diet, (pre- and post-Dx of PD) every 4 years since 1984 (NHS) or 1986 (HPFS)	• Limited disease severity data, potentially confounding the association • No data on the quantity of flavonoid consumption • Self-administered FFQ • Predominantly white participants in NHS and HPFS
Petramfar P., et al. 2019 (Iran)	To determine the licorice (root of *Glycyrrhiza glabra* L.) effectiveness as an adjunct Tx in PD management	Triple-blind randomized clinical trial ($n = 39$) Px (aged 30–80 years) with PD and onset of PD symptoms in the past 6 years	6 months Syr oral licorice ($n = 20$) or placebo ($n = 19$), 5 mL, 2 times per day Every 5 mL of syr licorice contained 136 μg of polyphenols, 2.6 μg of flavonoids, and 12.14 mg of glycyrrhizic acid *All had drug therapy	• The pharmacological treatment of the patients is diverse • Only 76.9% completed the study • The sample is from a single locality
Ghodsi H. et al., 2022 (Iran)	To evaluate the efficacy of adding nanomicelle curcumin on improving the motor and nonmotor symptoms of PD patients and their quality of life	Triple-blind randomized clinical trial ($n = 60$) Patients older than 30 years treated with DA drugs whose symptoms were under control	9 months 30 Px received curcumin nanomicelles in softgel capsules, 80 mg/day ($n = 30$) or placebo in identical softgel capsule ($n = 30$)	• Heterogeneity in PD patients' disease severity and duration might have masked the effect of curcumin • The sample is from a single locality • Only 70% of the population finished the study
Coe S. et al., 2022 (Italy)	To determine the feasibility and estimate the potential effect of flavonoid-rich cocoa on fatigue and fatigability in PD	Double-blind randomized clinical trial ($n = 30$) Px older than 18 years, with PD, sufficient mental capacity to consent	6 days A dose of 18 g of cocoa powder, with 200 mL of rice milk, every morning, at least 15–30 min before consuming any food or drink ($n = 15$) or placebo ($n = 15$)	• Only included subjects with a Hoehn Yahr scale between 1 and 3 • The duration of the intervention was short

Abbreviations: DA, dopaminergic; Dx, diagnosis; PD, Parkinson disease; FFQ, semiquantitative food frequency questionnaire; HPFS, Health Professionals Follow-up Study; syr, syrup; HNS, Health Nurses Study; Px, patients; Tx, treatment.

UPDRS part I intellectual activity, thinking, and behavior but none found significant changes [29–31]. One study assessed cognitive fatigue using the Adult Memory and Information Processing Battery but also found no significant differences [31].

The most important results are shown in Table 2 .

4. Discussion

The results of the studies included in this review indicate that higher consumption of total flavonoids and their subclasses (flavan-3-ols and flavonols), anthocyanins, or foods rich in them (apples, red wine, blueberries, and strawberries) reduce the risk of developing PD and its mortality. Treatment with licorice, curcumin, and cocoa, all of which are abundant in flavonoids and other polyphenols, improved motor skills as assessed by UPDRS section III or 6-MWT, but no significant differences were observed in cognitive symptoms, mood, or quality of life.

The reason that flavonoids and their subclasses or flavonoid-rich foods reduce PD risk and mortality is probably related to the reduction of OS induced by dopamine metabolism, mitochondrial dysfunction, and neuroinflammation [7,9,15].

It is well-established that flavonoids can act as antioxidants, and some can cross the blood–brain barrier [13–16,34]. Some subclasses of flavan-3-ols, such as catechin and epicatechin, have been shown to reach the brain, albeit at low concentrations, whereas anthocyanins contained in extracts of blueberry, blackberry, or strawberry can reach the brain in much higher concentrations compared with peripheral tissues [35–38].

In this regard, there is evidence that the consumption of foods rich in anthocyanins improves cognitive function. In a cohort study (n = 1572; adults 18–92 years old) conducted in Italy, a significant inverse association was found between higher intake of anthocyanin-rich fruits (strawberries, berries, cherries, prickly pears, grapes, blood oranges) and mental health issues, measured as poor sleep quality, perceived stress, and depressive symptoms [39].

Additionally, flavonoids could control redox imbalance by regulating phase II antioxidant enzyme gene expression via the nuclear erythroid-related factor 2/antioxidant response element (Nrf2/ARE) signaling pathway [17,40–43]. In this regard, the peroxisome proliferator-activated receptor γ/coactivator 1α (PGC-1α) signaling pathway regulates Nrf2 activation [44].

It has been reported that in patients with PD, the concentration of PGC-1α is decreased and that flavonoids such as the isoflavonoid genistein, the flavanol (-)-epigallocatechin-3-O-gallate, and the flavonol quercetin can regulate the activity of PGC-1α, which in turn would lead to Nrf2 activation [45].

On the other hand, hesperidin (flavanone subclass) has also been shown to protect against reactive oxygen species induced by 6-OHDA in a rat model by increasing the activity of the enzymes glutathione-reductase, catalase, and glutathione-peroxidase [46]. However, this has also been reported for ellagic acid, which is a polyphenol belonging to the class of phenolic acids.

Another mechanism proposed for flavonoids is through the activation of sirtuins (SIRT). Sirtuins are a family of class III NAD+-dependent proteinosacetylases that act on various cellular processes, including stress control, thus preventing DNA damage [47].

Resveratrol and quercetin (a stilbene and a flavonoid, respectively) confer neuroprotective effects in PD models, through the activation of SIRT1 [48,49].

SIRT1 activation leads to attenuation of neuroinflammation and mitochondrial damage, increased gene expression of neurotrophic factors, and autophagy in astrocytes [50].

Naringenin, a flavanone, has been shown to decrease the mRNA concentrations of proinflammatory cytokines TNF-α and IL-1β in the striatum and substantia nigra pars compacta [20]. Given that the activation of SIRT1 has an anti-inflammatory effect by suppressing the expression of proinflammatory cytokines such as IL-1 β, IL-6, and TNF-α, it is possible that the effect of naringenin could be due to the activation of SIRT1 [50].

All this suggests that flavonoids, as well as other polyphenols, can attenuate oxidative stress, inflammation, and mitochondrial damage in the brain, with an increase in the gene expression of neurotrophic factors, which could delay the onset and progression of PD.

Foods that were associated with lower mortality and morbidity in PD contain different types and amounts of polyphenols. For example, red wine and strawberries contain wide subclasses of flavonoids (anthocyanins, flavanols, flavonols), and phenolic acids (hydroxybenzoic acids and hydroxycinnamic acids) in high concentrations [51], whereas blackberries and apples contain anthocyanidins, flavan-3-ols, flavanones, flavones and flavonols, which are subclasses of flavonoids [52].

In general, the content of polyphenols in food depends on the secondary metabolism of plants that takes place through 2 important primary pathways: the shikimic acid pathway (light-dependent) and the poly-acetate pathway, both of which have plant physiological functions such as defense against stressful situations; they are also responsible for organoleptic characteristics such as fruit pigmentation, odor, and flavor [14]. Thus, environmental factors such as light, pH, soil nutrients, rainfall, and the degree of maturity or conservation of the fruit affect the total content of polyphenols [53].

Anthocyanins are present in red and purple fruits and vegetables, so there are other food sources besides blueberries and strawberries that could have the same biological effect, such as purple corn, raisins, strawberries, purple cabbage, grapes, radishes, among others, whose consumption might be higher in other populations [52,53].

The association between total flavonoid intake and PD was more pronounced in men than in women, using the same pooling cutoff values of consumption [32,33]. Although the authors, performed statistical adjustments and sensitivity analyses to control for potential confounding factors, it cannot be ruled out that the differences between men and women may be due to inherent differences between the cohorts, both in terms of sex and age (30–55 years in women vs. 40–75 years in men), given that the prevalence of PD is twice as common in men as in women, and although the incidence of PD increases with age in both sexes, the increase is more pronounced in men aged older than 60 years [54].

Table 2 – Main results of the randomized clinical trials or cohort studies investigating the effect of dietary polyphenols in Parkinson disease studies, included in the review.

Author	Exclusion criteria	Statistical test	Variable/outcomes/(*P*)	Conclusion
Zhang et al., 2022	None	Cox regression	**PD-associated mortality (↓)** • flavonoids intake pre-Dx / in M / ($P = .003$) • anthocyanins intake pre-Dx /in M and W / ($P = .002$) • anthocyanins intake post-Dx / in M and W / ($P < .001$) • flavan-3-ols intake pre-Dx/ in M / ($P = .009$) **All-cause mortality (↓)** • flavonoids intake pre-Dx / in M / ($P < .001$) • anthocyanins intake pre-Dx / in M and W / ($P < .001$) • flavones intake pre-Dx / in M and W / ($P = .03$) • ≥3 servings-wk RW intake post-Dx /in M and W/ ($P = .01$) • ≥3 servings-wk berries intake post-Dx / in M and W / ($P = .04$)	Among individuals with PD, higher consumption of flavonoids, especially anthocyanins and flavan-3-ols, and flavonoid-rich food such as berries and red wine was likely to be associated with a lower risk of mortality
Gao X. et al., 2012	Individuals with PD background, who did not report dietary information including DCI or missing information	Cox regression	**PD risk (↓)** • flavonoids intake / in M / ($P = .001$) • anthocyanins intake / in M and W / ($P = .02$) • flavonols intake / in M / ($P = .01$) • polymers intake / in M / ($P = .007$) • ≥5 servings-wk apples intake / in M / ($P < .0001$) • ≥2 to 4 servings-wk strawberries and blueberries intake / in M and W / ($P = .007$)	Intake of some flavonoids reduce PD risk, particularly in men, but a protective effect of other constituents of plant foods cannot be excluded
Petramfar P., et al 2019	Taking warfarin, SSRIs, MAOIs, or diuretics Background of DM, stroke, MI, HF, renal failure, cardiac arrhythmia, liver diseases, uncontrolled AHT, and hypokalemia Px who were suffered from a complication of Tx including urticarial, pruritus, nausea, vomiting, vertigo, etc Also, pregnant or lactating women	Independent samples *t*-test [a]	**UPDRS (total score)** • 1st and 2nd visit / (↓) / ($P = .01$) • 3rd and 4th visit / (↓) / ($P = .001$) **UPDRS-I** • 1-4th visit / (n.s.) / ($P > .05$) **UPDRS-II** • 1st and 2nd visit / (↓) / ($P = .01$) • 3rd and 4th visit / (↓) / ($P = .001$) **UPDRS-III** • 1st and 2nd visit / (n.s.) / ($P > .05$) • 3rd and 4th visit / (↓) / ($P < .005$) **Tremor** • 1st visit / (n.s.) / ($P = .16$) • 2nd–4th visit / (↓) / ($P < .05$) **Rigidity** • 1st and 2nd visit / (n.s.) / ($P > .05$) • 3rd and 4th visit / (↓) / ($P < .05$) **H&Y stage** • 1st – 4th visit / (n.s.) / ($P > .05$) **Others** • DHI, SF-36, glucose, sodium, potassium and blood pressure, side effects or tolerability / (n.s.)	The licorice intake could improve the symptoms in PD patients without serious adverse events

(*continued on next page*)

Table 2 (*continued*)

Author	Exclusion criteria	Statistical test	Variable/outcomes/(*P*)	Conclusion
Ghodsi H. et al., 2022	Severe systemic or psychologic disease, being qualified for DBS surgery, history of GI bleeding, aspirin use over 325 mg/day, any anticoagulant or antiplatelet use (other than low doses of aspirin), using antioxidant supplements, such as coenzyme Q10 and alpha-lipoic acid except for Vitamin E up to 2000 IU/day and Vitamin C up to 500 mg/day	Mixed linear models [a] Independent sample *t*-test [b] Mann-Whitney test [c] Fisher exact test [d]	**Global trend throughout the 9-month follow-up** • UPDRS total, I, II, and IV / (n.s) / ($P > .05$) [a] • UPDRS-III / (↓) / ($P = .04$) [a] • H&Y stage / (n.s.) / ($P = .27$) [a] • PDQ-39 / (n.s.) / ($P = .08$) [a] **UPDRS (total score, I, II, II,I and IV) between groups** • Baseline, 3, 6, or 9 months / (n.s.) / ($P > .05$) [b, c] **Hohen and Yahr stage** • Baseline, 3, 6, or 9 months / (n.s.) / ($P > .05$) [c] **PDQ-39** • Baseline, 3, 6, or 9 months / (n.s.) / ($P > .05$) [c] **Side effects** • Nausea, vomiting, gastroesophageal reflux, dyspepsia, or diarrhea / (n.s.) / ($P > .05$) [d]	Although there were not significantly different between the curcumin and placebo groups at any time points, UPDRS-III showed a significant difference in its overall trend. Curcumin is a well-tolerated natural compound, but this trial was unsuccessful in showing its efficacy in quality of life and clinical symptoms of PD patients
Coe S. et al., 2022	Contraindications tolerating the cocoa drink; other conditions that may be associated with fatigue, e.g. anemia; change in medication for the previous wk of the trial psychiatric disorder; not pregnant or lactating	Mann-Whitney *U* test [g] Effect size [h] Independent *t*-test [i]	• NFS / (n.s.) / ($P > .05$) [g] • AMIPB / (n.s.) / ($P > .05$) [h] • 6-MWT / (E.S. = 0.11) [h] • 24-h dietary recall / (n.s.) / ($P > .05$) [i] • Barthel index / (n.s.) / ($P > .05$) [g] • UDPRS-I / (n.s.) / ($P > .05$) [g]	The consumption of cocoa is feasible and well received in PD, and further investigation on the effect on fatigability is warranted, since there was a trend in decreasing the fatigue

Abbreviations: 6-MWT, 6-minute walk test; AHT, arterial hypertension; AMIPB, Adult Memory and Information Processing Battery; DCI, daily caloric intake; DHI, Dizziness Handicap Inventory; DM diabetes mellitus; Dx, diagnosis; ES, effect size; GI, gastrointestinal; HF, heart failure; H&YS, Hoehn and Yahr scale; M, men; MAOIs, monoamine oxidase inhibitors; MI, myocardial infarction; NFS, Numerical Fatigue Scale; PD, Parkinson disease; PDQ-39, Parkinson's Disease Questionnaire; Px, patients; RW, red wine; SF-36, questionnaire to assess health and quality of life; SSRIs, selective serotonin reuptake inhibitors; Tx, treatment; UPDRS, Unified Parkinson's Rating Scale; W, women; wk, week. The letters (a-i) indicate the statistical test used, within the same study.

Nevertheless, the interaction of genetic or hormonal factors and flavonoids cannot be excluded either because differences in the clinical manifestations of the disease between men and women have been described [54–57].

In healthy people, dopaminergic neurons projecting from the substantia nigra to the putamen perform important functions via dopamine D1 and D2 receptors, which inhibit and block the internal segment of the globus pallidus via GABAergic receptors, which regulate the normal motor function [58]. In PD, with the consequent loss of dopaminergic neurons, the signal to the putamen is lost, reducing the blockage and increasing excitation from the subthalamic nucleus to the internal segment of the globus pallidus [1,3]. This imbalance between inhibition and excitation results in an overall increase in inhibitory signals to the thalamus and brainstem and disorganizes movement, resulting in motor symptoms of PD [1,3].

Randomized clinical trials showed that treatment with licorice, curcumin, and cocoa improved motor skills as assessed by UPDRS section III or 6-MWT. These results suggest that flavonoids improve or delay dopaminergic denervation, attenuating motor impairment. In this sense, some important flavonoids in licorice such as isoliquiritigenin (chalcones subclass), liquiritigenin (flavanone subclass), liquiritin (flavone subclass), genistein, and glabridin (isoflavonoids subclass) have been shown to pass the blood–brain barrier [59–62], as is the case with cocoa catechins (flavanols subclass) that can reach the brain [36,38,63] and, in the case of curcumin (other polyphenols class, not a flavonoid), being a nano formulation, its pharmacokinetics favors its ability to cross the blood–brain barrier [64].

Among the mechanisms of action of licorice's flavonoids, it has been demonstrated that glabridin, liquiritin, and isoliquiritigenin can prevent apoptosis of dopaminergic neurons and neuroinflammation, through modulation of the PI3K/Akt pathway, inhibition of nuclear factor κB, increased production of neurotrophic factors, and increased antioxidant enzyme activity [65–69].

The neuroprotective effects of curcumin include antioxidant and antiapoptotic properties, mainly through the removal of reactive species, the upregulation of glutathione, restoration of mitochondrial membrane potential, and inhibition of α-synuclein aggregation [70–73]. In the case of cocoa, recent evidence indicates that it has antioxidant and antiapoptotic activity while inhibiting the accumulation of alpha-synuclein in the 6-OHDA–induced Parkinson model [74,75].

Reported side effects were assessed in 2 studies. The adverse effects of curcumin, including diarrhea, headache, nausea, vomiting, rash, and yellow stools have been previously reported in subjects receiving 0.45 to 12 g of curcumin, acutely or chronically [76]. In addition, consumption of licorice has been associated with diarrhea, among other more important side effects [77]. However, it is important to mention that in PD, there are also gastrointestinal symptoms that could favor the appearance of these side effects [78].

Regarding quality of life and cognitive functions, no significant differences were found. This could be attributed to the duration of the studies, the sensitivity of the instruments used, or that this variable is less related to OS.

The UPDRS instruments, the Intermediate Scale for the Assessment of Parkinson's Disease and the Hoehn and Yahr scale, are recognized as the gold standards for PD assessment. Although no study used the Intermediate Scale for the Assessment of Parkinson's Disease, it is considered to have a good correlation with the UPDRS [79]. However, to assess motor skills, there are other tests such as the "senior fitness test" that evaluates the physical capacity of older adults and that could be used in PD because it includes different physical tasks, such as sitting and rising from a chair, biceps curl, 6-MWT, the chair sit and reach test, the back-scratch test, and the 2.45 m Up-and-Go test [80].

To the best of our knowledge, this review is the only 1 that specifically evaluates the effect of polyphenols, specially flavonoids, on PD in human subjects, following a systematic methodology. Although there are 2 published systematic reviews, 1 focuses on *in vivo* (animal) studies [82], and the other includes a broader range of antioxidants, such as Vitamin C, E, β-carotene, and zinc, in addition to polyphenols [81].

Some limitations of the studies included in this review are the following: the number of studies found and the different methodological designs did not allow for a meta-analysis; the cohort studies correspond to the same population, being in both cases nurses and health care professionals, which makes the results difficult to extrapolate to the general population, and it is not possible to identify all dietary sources of flavonoids because a food frequency questionnaire was used. Also, in the RCTs, the selection criteria for the participants were different, with different stages on the Hoen and Yahr scale, and different pharmacological treatments. Finally, the average consumption of flavonoids was not reported in the cohort studies, which would make it possible to establish a dose with a beneficial effect on PD.

5. Conclusion

In this systematic review, we examined clinical studies focused on the relationship between flavonoids and PD published from 2010 to June 2022. Our search yielded a limited number of studies involving human subjects, including 2 cohort studies and 3 RCTs. The emphasis on studies involving human subjects, following the rigorous methodology of a systematic review, sets our work apart from the extensive body of *in vivo* and *in vitro* research in the field.

According to cohort studies, the consumption of flavonoids, anthocyanins, and specific anthocyanin-rich foods (apples, red wine, blueberries, and strawberries) reduces the risk of PD and the mortality associated with this disease. Our findings from RCTs reveals that treatment with licorice, curcumin, or cocoa (foods rich in flavonoids) improved motor skills, without significant differences in nonmotor symptoms.

This systematic review sheds light on the potential neuroprotective effects of specific flavonoids in the context of PD. However, more randomized controlled clinical trials are essential to evaluate the neuroprotective effect of specific flavonoids and other polyphenols in PD.

Author declarations

During preparation of this work, the authors used ChatGTP to check for grammar mistakes. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Christian Adrián González-May: Investigation, Writing – original draft. **María del Rosario Barradas-Castillo:** Methodology, Investigation. **Javier Humberto Perera-Rios:** Visualization, Writing – original draft. **Santiago Gallegos-Tintoré:** Methodology, Writing – review & editing. **Odette Pérez-Izquierdo:** Conceptualization, Writing – review & editing. **Irma Isela Aranda-González:** Conceptualization, Supervision, Writing – review & editing, Project administration.

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Supplementary materials

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