Cite as: Smalira J, Lęgas A, Przybysz B, Mormul A, Zawistowska J, Rogala W, Kawalec J, Rutkowska-Kawalec W, Pochodowicz K, Rogowska K:
Role of selected nutritional factors in the prevention and treatment of Parkinson's disease – a review.
Aktualn Neurol 2024; 24 (2): 51–58

Received: 05.05.2024
Accepted: 19.06.2024
Published: 28.08.2024

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Role of selected nutritional factors in the prevention and treatment of Parkinson's disease – a review

Rola wybranych składników diety w zapobieganiu chorobie Parkinsona i jej leczeniu – przegląd piśmiennictwa

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https://doi.org/10.15557/AN.2024.0008

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Abstract

Parkinson's disease is the second most common neurodegenerative disorder, characterised by progressive death of dopaminergic neurons in the substantia nigra. The prevalence of Parkinson's disease is increasing and becoming a major health problem nowadays due to the aging of society. The aim of this study was to conduct a comprehensive review of the literature exploring the association between Parkinson's disease and specific dietary components such as vitamin B_{12}, omega-3 fatty acids, vitamin D, vitamin E, and probiotics. A literature search was performed in the medical database PubMed. Articles in English were retrieved. The impact of various nutritional ingredients on the occurrence, symptom severity, and progression of Parkinson's disease was examined. An additional focus was on the underlying mechanisms, including oxidative stress and neuroinflammation, through which dietary components may exert their effects on the development of this disorder. Evidence suggests that early supplementation of vitamin B_{12} might mitigate cognitive dysfunction, omega-3 fatty acids may reduce disease progression, and probiotics may alleviate motor and non-motor symptoms, particularly constipation. In addition, vitamin D deficiency is common in patients with Parkinson's disease. Furthermore, researchers have reported neuroprotective effects of vitamin E in animal studies, though human studies are inconclusive. Current research provides evidence that diet may influence the onset and course of Parkinson's disease. A nutritional approach gives new possibilities regarding the prevention of the disorder. This review elucidates dietary interventions that may be considered as an adjunctive strategy in pharmacological therapies. However, further research on this topic is necessary.

Keywords: vitamins, probiotics, diet, Parkinson's disease

Streszczenie

Choroba Parkinsona jest drugą co do częstości występowania chorobą neurodegeneracyjną. Charakteryzuje się postępującą utratą neuronów dopaminergicznych w istocie czarnej śródmózgowia. Obecnie choroba Parkinsona występuje coraz częściej, stając się poważnym problemem zdrowotnym starzejącego się społeczeństwa. Celem niniejszej pracy jest przedstawienie najnowszych doniesień naukowych dotyczących związku pomiędzy chorobą Parkinsona a wybranymi składnikami diety, takimi jak witamina B_{12}, kwasy tłuszczowe omega-3, witamina D, witamina E i probiotyki. Przeszukano medyczną bazę danych PubMed. Przegląd zawiera analizę publikacji naukowych w języku angielskim. W przytoczonych badaniach wykazano wpływ wymienionych składników odżywczych na częstość występowania choroby Parkinsona oraz nasilenie i progresję objawów. Dodatkowo wskazano podstawowe mechanizmy, w tym stres oksydacyjny i procesy zapalne w układzie nerwowym, poprzez które składniki diety mogą odgrywać rolę w rozwoju choroby Parkinsona. Dowody sugerują, że wczesna suplementacja witaminy B_{12} może łagodzić dysfunkcje poznawcze, kwasy tłuszczowe omega-3 mogą spowalniać postęp choroby, a probiotyki mogą łagodzić objawy, zwłaszcza zaparcia. Niedobór witaminy D jest powszechny u pacjentów z chorobą Parkinsona. Pomimo badań na zwierzętach potwierdzających neuroprotekcyjne działanie witaminy E wyniki badań klinicznych pozostają niejednoznaczne. Aktualne badania udowadniają, że dieta może wpływać na wystąpienie i przebieg choroby Parkinsona. Interwencje żywieniowe wydają się obiecującą strategią w prewencji tej jednostki chorobowej. Odpowiednią suplementację składników diety można uznać za strategię wspomagającą w terapiach farmakologicznych. Konieczne są jednak dalsze badania na ten temat.

Słowa kluczowe: witaminy, probiotyki, dieta, choroba Parkinsona

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterised by progressive death of dopaminergic neurons in the substantia nigra (Poewe et al., 2017). Additionally, the accumulation of abnormal protein deposits underlies the development of the disease. These aggregates, known as Lewy bodies, consist of α-synuclein and are produced by nerve cells of the brain (Poewe et al., 2017). According to the World Health Organization, a total of 8.5 million individuals worldwide are predicted to be suffering from PD. The onset of PD usually occurs after the age of 65, and men are affected slightly more often than women (Tysnes and Storstein, 2017). The aging of society is expected to increase PD prevalence, with the number of cases predicted to double in the next two decades (Dorsey et al., 2018). The clinical diagnosis of PD is based primarily on motor impairment including an asymmetric resting tremor, muscle rigidity, and bradykinesia (Postuma et al., 2015). In addition, many patients experience constipation, depression, sleep disorder, and anosmia (Berganzo et al., 2016). Non-motor symptoms might develop a decade before motor deficits (Kurlawala et al., 2021). Progression of these symptoms and complications markedly contribute to disability, care requirements, and stress. The pathogenesis of PD remains complicated and multifactorial. Studies have suggested that mitochondrial dysfunction, neuroinflammation, and oxidative stress play a crucial role in the loss of dopaminergic neurons (Kouli et al., 2018). The specific elements that set off this immunological pathway are still unknown. PD is thought to result from a combination of genetic predisposition and environmental influences. It is believed the main risk factors include traumatic brain injury, pesticide exposure, beta-blocker usage, and agricultural occupation (Kalia and Lang, 2015). Although PD is incurable, several strategies are currently in use to slow down neurodegeneration, reduce symptoms, and improve quality of life. The first line of treatment typically begins with a pharmacologic dopamine replacement therapy (Armstrong and Okun, 2020). Other approaches include deep brain stimulation, rehabilitation therapy, and lifestyle modifications (Church, 2021). Since oxidative stress is considered one of the underlying factors contributing to PD, it may be beneficial to use dietary supplements with anti-inflammatory effects. Nutrition is a potential disease-modifying factor that can either reduce symptoms, when it is optimised – or worsen them, when it is inadequate. The established therapy is not combined with any specific nutritional recommendations. Despite this, studies suggest that diet may be considered as an adjunctive treatment to control progression of the disease.

OBJECTIVES

The aim of the study was to conduct a literature review focusing on the association between PD and diet, in order to establish the role of nutrition in PD development and determine its potential therapeutic properties. The authors selected several nutrients that are easily obtained from food and efficiently provided by dietary supplements. Thus, only oral administration was considered in this review.

MATERIALS AND METHODS

A literature search was performed in the medical database PubMed and was supplemented by manual searches of reference lists from the included studies. Articles in English were retrieved, based on the key words including "Parkinson's disease", "vitamin D", "vitamin B_{12}", "omega-3 fatty acid", "probiotic", and "vitamin E". A systematic evaluation was conducted on documents published from 1 January 2015 to 1 June 2024.

The selected articles investigated the relationship between selected dietary components and PD. Moreover, relevant articles reporting on studies conducted using animal models were included.

The exclusion criteria were studies that were not relevant to the topic of the review, such as other types of disorders, studies not analysing PD, and studies in languages other than English.

The researchers selected the studies based on their titles, excluding those that clearly did not meet the inclusion criteria. Then, they reviewed the abstracts, rejecting those that unequivocally did not meet the selection criteria. The final decision was made after a thorough assessment of the full texts. Studies considered relevant were included in the systematic literature review. Additionally, the references of these articles were examined to identify other relevant articles that were not discovered in the database search. A total of 23 studies were ultimately selected for the final analysis. The PRISMA flowchart was uq§qqsed to provide a clear overview of the study selection process (Fig. 1).

The characteristics of the included studies are shown in Tab. 1, where they are listed according to types of dietary components.

ANALYSIS OF THE LITERATURE

Vitamin B_{12}

Vitamin B_{12} has a fundamental role in both central and peripheral nervous system at all ages. It is primarily found in animal products, such as liver, beef, eggs and dairy foods (O'Leary and Samman, 2010). Some studies have reported lower levels of vitamin B_{12} in individuals with PD compared to healthy controls (Liu et al., 2023). It is important to highlight the link between this trend and dopaminergic medications. Levodopa treatment elevates plasma homocysteine levels (McCarter et al., 2019). It emerges due to the conversion of L-dopa by catechol-*O*-methyltransferase. The remethylation of homocysteine requires vitamin B_{12}. In the presence of hyperhomocysteinemia, there is a high demand for vitamin B_{12}. If the dietary intake of vitamin B_{12} is insufficient, it can lead to a relative deficiency of this vitamin (Paul et al., 2020). The correlation between vitamin B_{12} levels and the severity of PD is a subject of ongoing research. Christine et al. (2018) reported in their randomised clinical trial that low vitamin B_{12} level at baseline predicted greater worsening of mobility. A cohort study suggested the value of vitamin B_{12} as a predictor of dementia. It showed that higher serum levels of vitamin B_{12} at the time of PD diagnosis correlated with a decreased risk of the future development of dementia (McCarter et al., 2020). Authors of the meta-analysis had similar conclusions, observing an association between lower levels of vitamin B_{12} and cognitive impairment in PD patients (Xie et al., 2017). While the evidence regarding the relationship between vitamin B_{12} levels and PD severity is inconclusive, early administration of vitamin B_{12} through oral supplementation or dietary intake may slow the onset of cognitive dysfunction in PD. Additionally, monitoring vitamin B_{12} status in individuals with PD may be crucial, especially considering the potential impact of its deficiency on neurological function.

Omega-3 fatty acids

Omega-3 fatty acids (omega-3 FAs) are another group of antioxidant compounds with promising biological potential due to their anti-inflammatory and metabolic properties (de Bus et al., 2019). Currently, the most clinically relevant omega-3 FAs are α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Krupa et al., 2024). They must be o btained through the diet, since the human body is unable to synthesise them in sufficient quantities. The primary dietary sources of omega-3 FAs include oily fish, and some nuts and seeds (Krupa et al., 2024). In an animal study, Hernando et al. (2019) showed that a high omega-3 FAs dietary intake exerted neuroprotective actions in a rat model of parkinsonism induced by the neurotoxin 6-hydroxydopamine hydrochloride (6-OHDA). A substantial number of human studies have highlighted the anti-inflammatory role of omega-3 FAs. In a randomised double-blind, placebo-controlled trial, Pantzaris et al. (2021) studied the effects of a nutritional formula in PD. NEUROASPIS® plp10 is a dietary mixture of omega-3 and omega-6 fatty acids, vitamin A, vitamin E, and pure gamma (γ)-tocopherol derived from fish oil and plant sources. Forty patients were divided into two groups, with one group receiving 20 mL of this supplement of fatty acids and vitamins and the other group receiving placebo, once daily, for a total of 30 months. Patients were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) III. The cocktail mixture-based intervention was found to reduce disease progression (Pantzaris et al., 2021). Another double-blind placebo-controlled study provided evidence of an improvement related to the consumption of omega-3 FAs in clinical symptoms of PD, as indicated by a decrease in the average UPDRS score (Taghizadeh et al., 2017). Unfortunately, some randomised trials have provided conflicting results and failed to confirm a definitive protective effect. This inconsistency may result from a shorter study duration or poor patient adherence to therapy. Consequently, longer duration studies are needed to establish a strong correlation.

Vitamin D

In recent years, the effect of vitamin D on nervous system has been widely studied. Vitamin D plays a significant role in various functions, including the development of nerve cells, neurotransmitter synthesis, and immunomodulation. Additionally, the vitamin has been implicated in neuroprotection and reduction of oxidative stress (Garcion et al., 2002). The vitamin D receptor and the enzyme (1α-OHase),

 DOI: 10.15557/AN.2024.0008

		Author	Topic	Year of publication	Study design	Results
Vitamin B_{12}	1	Liu et al.	Features of plasma homocysteine, vitamin B12, and folate in Parkinson's disease: an updated meta-analysis	2023	Meta-analysis	PD patients had significantly increased homocysteine level and decreased vitamin B_{12} level compared to healthy controls
	2	McCarter et al.	Low vitamin B12 and Parkinson disease: potential link to reduced cholinergic transmission and severity of disease	2019	Systemic review	Levodopa-treated patients with PD had significantly higher homocysteine levels compared with both controls and levodopa-naive patients with PD
	3	Paul et al.	Peripheral neuropathy in Parkinson's disease	2020	Systemic review	Vitamin B_{12} and L-dopa have an inverse relationship
	4	Christine et al.	Vitamin B12 and homocysteine levels predict different outcomes in early Parkinson's disease	2018	Randomised clinical trial	Low vitamin B_{12} levels at baseline predicted greater worsening of mobility, while high levels of homocysteine were associated with cognitive impairment
	5	McCarter et al.	Higher vitamin B12 level at Parkinson's disease diagnosis is associated with lower risk of future dementia	2020	Cohort study	Vitamin B_{12} level below 587 ng/L at the time of PD diagnosis predicted development of dementia. Dementia risk is reduced with each 100 ng/L increase in serum vitamin B_{12}
	6	Xie et al.	Association of plasma homocysteine, vitamin B12 and folate levels with cognitive function in Parkinson's disease: a meta-analysis	2017	Meta-analysis	PD patients with cognitive dysfunction had lower vitamin B_{12} levels
Omega-3 fatty acids	7	Hernando et al.	Beneficial effects of n-3 polyunsaturated fatty acids administration in a partial lesion model of Parkinson's disease: the role of glia and NRf2 regulation	2019	*In vivo* animal experiment	Omega-3 fatty acids supplementation demonstrated a positive effect on dopaminergic system, neuroinflammation and oxidative stress. DHA administration decreased the astrogliosis and microgliosis in the substantia nigra
	8	Pantzaris et al.	Neuroaspis PLP10™, a nutritional formula rich in omega-3 and omega-6 fatty acids with antioxidant vitamins including gamma-tocopherol in early Parkinson's disease: a randomized, double-blind, placebo-controlled trial	2021	Randomised clinical trial	Supplementation of omega-3 and omega-6 fatty acids with antioxidant vitamins for 30 months in PD patients significantly delayed disease progression according to UPDRS compared to placebo
	9	Taghizadeh et al.	The effects of omega-3 fatty acids and vitamin E co-supplementation on clinical and metabolic status in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled trial	2017	Randomised clinical trial	Omega-3 FAs and vitamin E co-supplementation in PD patients significantly improved UPDRS compared to placebo
Vitamin D	10	Lima et al.	Vitamin D protects dopaminergic neurons against neuroinflammation and oxidative stress in hemiparkinsonian rats	2018	*In vivo* animal experiment	Vitamin D protected the dopaminergic neurons through its anti-inflammatory and antioxidant properties in a rat model of PD
	11	Zhou et al.	The association between vitamin D status, vitamin D supplementation, sunlight exposure, and Parkinson's disease: a systematic review and meta-analysis	2019	Systemic review and meta-analysis	Vitamin D levels below the normal range are associated with higher risk of PD. The risk increases as vitamin D levels drop further
	12	Wang et al.	Vitamin D from different sources is inversely associated with Parkinson disease	2015	Case-control study	An inverse association was reported between PD risk and serum levels of all forms of vitamin D, including dietary 25-OH-D_2, which is obtained from diet and supplements
	13	Sleeman et al.	The role of vitamin D in disease progression in early Parkinson's disease	2017	Prospective observational study	The worst PD progression in terms of motor impairment severity evaluated by UPDRS part III, was related to lower serum vitamin D level at baseline
	14	Fullard and Duda	A review of the relationship between vitamin D and Parkinson disease symptoms	2020	Systemic review	The relationship between vitamin D and non-motor symptoms is not clear. There is some evidence that vitamin D is associated with verbal fluency and verbal memory in PD
Vitamin E	15	Atiq et al.	Vitamin E analog Trolox attenuates MPTP-induced Parkinson's disease in mice, mitigating oxidative stress, neuroinflammation, and motor impairment	2023	*In vivo* animal experiment	Analogue of vitamin E can potentially protect the brain from MPTP-induced PD
	16	Hao et al.	Dietary vitamin E intake and risk of Parkinson's disease: a cross-sectional study	2024	Cross-sectional study	Higher dietary intake of vitamin E may reduce risk of developing PD
	17	Schirinzi et al.	Dietary vitamin E as a protective factor for Parkinson's disease: clinical and experimental evidence	2019	Case-control study	High vitamin E intake was inversely associated with the risk of PD
	18	Hughes et al.	Intake of antioxidant vitamins and risk of Parkinson's disease	2016	Cohort study	Dietary intake of vitamin E was not associated with PD risk

Tab. 1. Characteristics of studies included in the review

DOI: 10.15557/AN.2024.0008 AKTUALN NEUROL 2024, 24 (2), p. 51–58

		Author	Topic	Year of publication	Study design	Results
Probiotics	19	Klann et al.	The gut–brain axis and its relation to Parkinson's disease: a review	2022	Systemic review	The microbiome–gut–brain axis may contribute to the development of PD. There is a potential pathway via the formation of α-synuclein aggregates
	20	Jin et al.	Efficacy of probiotic supplements on Parkinson's disease: a systematic review and meta-analysis	2024	Systemic review and meta-analysis	Probiotics could alleviate the symptoms of PD-related constipation
	21	Xie et al.	Efficacy and safety of probiotics in Parkinson's constipation: a systematic review and meta-analysis	2023	Systemic review and meta-analysis	Constipation symptoms improved after probiotic treatment
	22	Tamtaji et al.	Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial	2019	Randomised clinical trial	Probiotic supplementation had useful impact on MDS-UPDRS scores. Moreover, it reduced high-sensitivity C-reactive protein
	23	Park et al.	Effect of probiotic supplementation on gastrointestinal motility, inflammation, motor, non-motor symptoms and mental health in Parkinson's disease: a meta-analysis of randomized controlled trials	2023	Meta-analysis	Probiotics significantly alleviate motor, non-motor and depressive symptoms in PD patients

Tab. 1. Characteristics of studies included in the review (cont.)

required for the production of the active form of vitamin D, were detected in the neurons of the substantia nigra (Eyles et al., 2005). This finding may suggest an involvement of vitamin D in the pathogenesis of PD. An experimental study conducted in an animal model of PD revealed that vitamin D supplementation protected dopaminergic neurons by reducing oxidative stress (Lima et al., 2018). Zhou et al. (2019) conducted a meta-analysis, concluding that low levels of vitamin D might increase the risk of developing PD. Wang et al. (2015) reported an inverse association between PD risk and serum levels of all forms of vitamin D, including $25(OH)D_2$, which is obtained from dietary and supplement sources. Since $25(OH)D_2$ levels are not dependent on sunlight exposure, this finding indicates that vitamin D deficiency in PD patients is not merely due to the lack of sunlight exposure caused by their reduced mobility (Wang et al., 2015). Sleeman et al. (2017) assessed the association between the serum vitamin D concentration in newly diagnosed PD patients and disease severity over a 36-month follow-up period. Lower vitamin D levels at baseline were linked to greater PD progression in terms of motor impairment severity evaluated by UPDRS part III (Sleeman et al., 2017). To date, it is not clear whether there is a correlation with non-motor symptoms (Fullard and Duda, 2020). Recent studies suggest that maintaining normal vitamin D levels may be helpful in the prevention of PD. However, the evidence in favour of vitamin D supplementation in the treatment of PD remains limited and insufficient. Further research is needed to elucidate its therapeutic potential.

Vitamin E

Vitamin E is a fat-soluble nutrient with a variety of functions in immunity, physical performance, and regulation of gene expression (Zhao et al., 2019). The primary sources of vitamin E are plant-based foods such as oils, nuts, and fruit and vegetables. Vitamin E has been at the centre of the researchers' attention. According to the current literature review, there are both studies that confirm and refute the beneficial effects of this vitamin. Animal studies have provided promising results. Atiq et al. (2023) investigated the neuroprotective effects of a water-soluble analogue of vitamin E (Trolox) in a mouse model of PD. The study found that Trolox improved motor function, decreased the α-synuclein expression, and prevented neuronal loss due to strong antioxidant properties (Atiq et al., 2023). The beneficial effects of vitamin E on human cognitive function have been demonstrated in a cross-sectional Chinese study. It was conducted among 13,340 participants aged over 40 and showed that a higher dietary intake of vitamin E might reduce risk of developing PD (Hao et al., 2024). The same tendency in terms of lower occurrence of PD due to vitamin E was suggested in a study by Schirinzi et al. (2019). Contrary results were observed in the study by Hughes et al. (2016). These findings did not indicate that vitamin E affected the risk of PD (Hughes et al., 2016). Further research is thus essential to determine whether vitamin E can be used as a potential treatment of PD.

Probiotics

Probiotics refer to food or nutritional supplements that comprise vital microbial species with regulatory effects on the immune system of the host organism (Rupa and Mine, 2012). The gut–brain axis, a bidirectional communication system between the gut and the brain, is thought to play a significant role in PD pathogenesis. Changes in the gut microbiota composition, known as dysbiosis, have been observed in individuals with PD, and it is believed that these changes could influence the progression of the disease

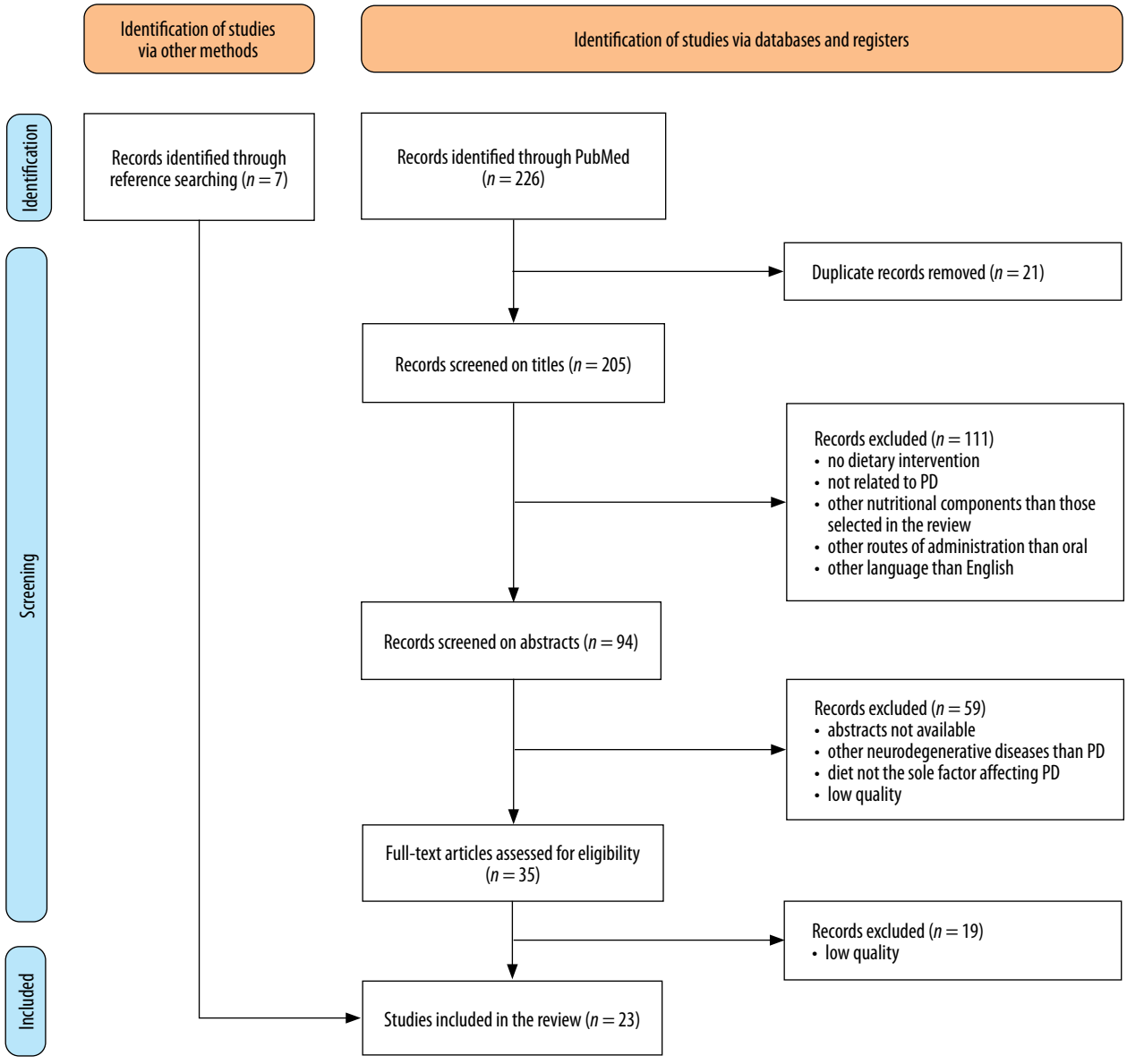

Fig. 1. PRISMA flowchart outlining the selection process of relevant studies

(Klann et al., 2022). Several studies have demonstrated the benefits of probiotic supplementation in PD patients who experience constipation. A meta-analysis pooling data from 11 randomised clinical trials showed that constipation symptoms were ameliorated after probiotic treatment (Jin et al., 2024). A similar outcome was reported in a meta-analysis by Xie et al. (2023). The authors highlighted the value of the administered probiotic for improvements in stool frequency, stool consistency, and frequency of laxative usage (Xie et al., 2023). In a randomised, double-blind, placebo-controlled clinical trial, the effect of probiotic supplementation was assessed in 60 individuals with PD. All patients were randomised into two treatment groups to take probiotic containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri* and *Lactobacillus fermentum* or placebo for 12 weeks. Probiotic consumption was related to decreased Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores (Tamtaji et al., 2019). MDS-UPDRS is the most commonly used scale in PD, designed to assess both motor and non-motor symptoms. A meta-analysis including 11 randomised trials found that probiotic therapy improved motor function and non-motor symptoms, and reduced depression in PD patients (Park et al., 2023). Probiotic supplementation may be an affordable and safe adjuvant therapeutic option for PD management, particularly as a treatment for constipation.

CONCLUSIONS

It is crucial to define suitable dietary interventions for patients with PD to ameliorate the disease course. So far, there are no precise recommendations regarding a specific diet. However, several studies have strongly suggested the effects of nutrition on both immunomodulatory and

DOI: 10.15557/AN.2024.0008

neurodegenerative processes in PD. A nutritional approach could be a promising strategy to achieve a more efficient prevention and management of the early stages of the disease, when the benefit is most noticeable. It may be appropriate for general practitioners and dieticians to raise awareness on the relevance of optimal nutrition in the prevention of PD. However, it is important to consider that, to date, there have been insufficient relevant trials comparing the efficacy of dietary interventions to medications. Thus, nutrients can only be considered as an adjunctive strategy at this point. It should be of interest for public health prevention that can lead to sizable gains in reducing the cost burden for the society. Further research on this topic should be directed toward determining best doses of nutrients and establishing clinical recommendations. Hopefully, in the near future the adoption of personalised treatment strategies, aimed to predict individual responses, will help to optimise the effectiveness of such interventions.

Conflict of interest

The authors report no conflict of interest. The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript; critical review of manuscript; final approval of manuscript: JS, AL, BP, AM, JZ, WR, JK, WRK, KP, KR.

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DOI: 10.15557/AN.2024.0008 AKTUALN NEUROL 2024, 24 (2), p. 51–58