

# Supplementary Material

## Natural Health Products for Symptomatic Relief of Parkinson's Disease: Prevalence, Interest, and Awareness

### Supplementary Material 1. Regulatory pathways of commercially available NHP

A number of NHP are commercially available. Their therapeutic indications often derive from ancestral knowledge documented in local pharmacopoeia, although regulations and classifications vary according to the country of commercialization. Indeed, the practice of traditional herbal medicine can be a primary source of healthcare for patients across Asia and Africa [1]. In the European Union (EU), three main regulatory pathways are offered to market herbal medicinal products, including Traditional Use Registration, Well-Established Use Marketing Authorization, and Stand-Alone or Mixed Applications [1]. These regulatory pathways impose varying requirements depending on the existence of established traditional uses within the EU, and/or scientific evidence of safety and efficacy.

## **Supplementary Material 2. The PRIME-NL study**

This cross-sectional survey was embedded in the Proactive and Integrated Management and Empowerment of Parkinson's Disease – Netherlands (PRIME-NL) study [2]. The PRIME-NL study is an ongoing observational cohort study that evaluates the utility of a new integrated care model (PRIME Parkinson care) using two data sources: pseudoanonymized medical claims data on the complete population and annual questionnaires. The current survey is embedded in the questionnaire subcohort. The questionnaires are administered annually, including a baseline assessment (in 2020) and five annual follow up- assessments (2021-2025). The PRIME-NL study has been approved by the Ethical Board of the Radboud University Medical Center. Participants in the PRIME-NL study were recruited through ParkinsonNEXT (an online platform to connect PwP and researchers in the Netherlands) [3], the Dutch Parkinson patient association [4], and neurologists in the PRIME Parkinson care region. All participants provided digital or written informed consent before inclusion in the study. The only inclusion criterion was having a clinical diagnosis of parkinsonism. Diagnosis of all participants was established by a neurologist. Exclusion criteria at the time of enrolment were: parkinsonism caused by medication, receiving treatment at a university medical center, or not having visited the neurology outpatient clinic in the year prior to inclusion. In the PRIME-NL cohort, 920 of 984 participants had PD, while 64 participants had a form of atypical parkinsonism. For this report, we only included PwP and excluded people with atypical parkinsonism. A previous study showed that the characteristics of the PRIME-NL cohort are largely representative of the full spectrum of PwP in the Netherlands, with the exception of a slightly lower age (69.6 years compared to 72.7 years) and a slightly longer disease duration (6.2 years compared to 5.3 years) [5].

The 566 participants who responded to the PRIME-NL questionnaires between July 2022 and May 2023, i.e., in the second and third follow-up years, were offered to answer the NHP survey. Questionnaires were self-administered by the participants, either electronically (n=307), on paper (n=58) or by a well-trained research employee over the phone (n=2).

### Supplementary Material 3. Questionnaire items

1. Have you ever used cannabis products or coffee with the purpose of alleviating symptoms related to Parkinson's Disease?
  - a. No
  - b. Yes, only cannabis
  - c. Yes, only coffee
  - d. Yes, both
2. Have you ever used any of the following herbal remedies with the purpose of alleviating symptoms related to Parkinson's Disease? You can select more than one option or indicate that you have not used herbal remedies:
  - a. Chamomile (e.g., *Matricaria recutita*, *Chamaemelum nobile*)
  - b. Curcumin
  - c. Guarana
  - d. Passion flower (*Passiflora incarnata*)
  - e. Resveratrol
  - f. Rhodiola (*Rhodiola rosea*)
  - g. St. John's Wort (*Hypericum perforatum*)
  - h. Turmeric (*Curcuma longa*)
  - i. Velvet bean (*Mucuna pruriens*)
  - j. Other:
  - k. I have not used herbal remedies
3. Have you ever discussed the possible use of herbal remedies with your neurologist or PD nurse specialist?
  - a. Yes
  - b. No
4. Would you be interested in learning more about possible herbal remedies to alleviate certain symptoms related to Parkinson's Disease?
  - a. Yes
  - b. No
5. Are you aware that some herbal remedies and prescribed Parkinson's Disease medications may work together (or against each other)?
  - a. Yes
  - b. No

#### **Supplementary Material 4. Statistical analyses**

We quantified the prevalence of ever use of NHP, interest and determinants of NHP use, awareness of potential herb-drug interactions, and the prevalence of discussing NHP use with PD healthcare professionals among PwP using descriptive statistics. Categorical data were analyzed using a Pearson exact Chi-square test with Monte Carlo estimation when appropriate. Continuous data were analyzed using a Student's t-test. Descriptive statistics were performed using the SPSS software (IBM SPSS Statistics for Windows version 27.0, IBM Corp., Armonk, NY, USA) with the significance level set at  $p \leq 0.05$ . We also performed several sensitivity analyses. First, we performed a sensitivity analysis to evaluate the proportion of NHP users and the percentage of participants interested in learning more about these products, in which we tested the most conservative scenario by assuming that none of the non-responders had ever used or had any interest in exploring NHP. Second, we determined the external validity of the sample of participants by comparing both demographical and clinical characteristics of responders versus non-responders. Third, we performed a sensitivity analysis to evaluate the proportion of participants who used NHP other than coffee and cannabis. Fourth, we determined how many participants used multiple products, as illustrated in Venn diagrams and a frequency histogram. Additional analyses were performed to identify determinants of NHP use, and consisted in a multivariate Logistic Regression model with consumption of herbal remedies as dependent variable and gender identity, age, education level, disease duration, and Hoehn and Yahr stage as independent variables. We determined odds ratios and p-values for the independent variables and considered  $p < 0.05$  as significant association. Regression analysis was performed in R Statistics.

**Supplementary Material 5. Participant characteristics stratified by gender.**

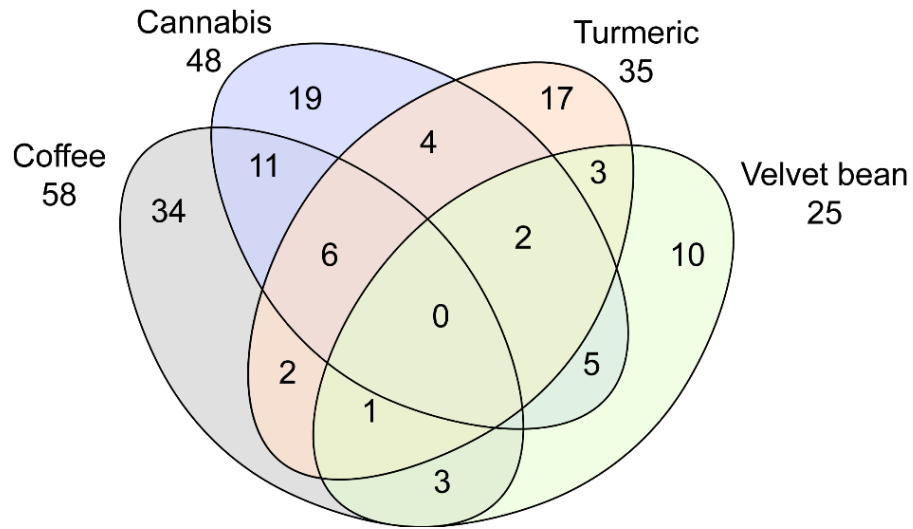
<b>Demographics</b>				
	Total (n=367)	Men (n=201)	Women (n=166)	p
Age, y, mean (SD)	70.3 (8.1)	71.1 (7.9)	69.4 (8.3)	0.046
Gender identity, % (n)		54.8 (201)	45.2 (166)	
<b>Education, % (n)</b>				
	Total (n=367)	Men (n=201)	Women (n=166)	p
Low	23.0 (83)	18.9 (38)	27.1 (45)	0.089
Medium	25.0 (91)	22.9 (46)	27.1 (45)	
Higher	51.5 (191)	57.7 (116)	45.2 (75)	
<b>Disease severity</b>				
	Total (n=367)	Men (n=201)	Women (n=166)	p
Disease duration, y, median (IQR)	6.2 (4.6)	5.6 (3.7)	6.9 (5.7)	<0.001
H&Y (1-5 scale), mean (SD)	2.5 (1.2)	2.3 (1.1)	2.6 (1.2)	0.039
H&Y=1, % (n)	22.6 (81)	26 (51)	18.5 (30)	0.020
H&Y=2, % (n)	34.1 (122)	32.1 (63)	36.4 (59)	
H&Y=3, % (n)	31.8 (78)	35.5 (50)	17.3 (28)	
H&Y=4, % (n)	18.4 (66)	14.8 (29)	22.8 (37)	
H&Y=5, % (n)	3.1 (11)	1.5 (3)	4.9 (8)	

The p-values were calculated to compare the responses by gender identity. Mean and standard deviation are reported, unless noted otherwise. H&Y, Hoehn and Yahr; IQR, interquartile range; SD, standard deviation; n, number.

**Supplementary Material 6. Comparison of characteristics between participants and non-participants to the survey.**

	Participants (n=367)	Non-participants (n=199)	p
<b>Demographics</b>			
Gender identity, men, % (n)	54.8 (201)	66.8 (133)	0.005
Age, y, mean (SD)	70.3 (8.1)	70.7 (7.9)	0.582
<b>Education, % (n)</b>			
Low	22.6 (83)	27.1 (54)	0.527
Medium	24.8 (91)	25.6 (51)	
Higher	52.0 (191)	46.2 (92)	
<b>Disease severity</b>			
Disease duration, y, median (IQR)	6.2 (4.6)	7.2 (5.5)	<0.001
H&Y (1-5 scale), mean (SD)	2.5 (1.1)	2.55 (1)	0.600
H&Y=1, % (n)	22.6 (81)	15.0 (29)	0.164
H&Y=2, % (n)	34.1 (122)	38.9 (75)	
H&Y=3, % (n)	21.8 (78)	23.3 (45)	
H&Y=4, % (n)	18.4 (66)	21.2 (41)	
H&Y=5, % (n)	3.1 (11)	1.6 (3)	

Comparison of the demographics and clinical characteristics of responders (PRIME-NL participants who completed the survey) and non-responders (PRIME-NL participants who did not agree to respond to the survey). Mean and standard deviation are reported, unless noted otherwise. H&Y, Hoehn and Yahr; IQR, interquartile range; SD, standard deviation; n, number.



**Supplementary Material 7. Usage distribution of the top 4 NHP reported by PwP.** Venn diagram illustrating the number of participants who acknowledged using the four most reported herbs listed in Table 1. Each oval represents the use of one product (coffee, cannabis, turmeric and velvet bean). The numbers in these ovals represent the number of participants using the corresponding NHP combination, while the total numbers of participants who use each NHP (either alone or in combination) is provided outside the ovals.

## **Supplementary Material 8. Discussion on the benefits of natural health products (NHP) to mitigate motor and non-motor symptoms experienced by people with Parkinson's disease (PwP)**

The results from the study presented herein can inform on how NHP may serve PwP improve their quality of life. We included the following 11 NHP based on their potential to mitigate PD-related motor and non-motor symptoms, and the survey did not distinguish between supplements and foods.

*Cannabis products.* One of the products of interest is medical cannabis, for which randomized and non-randomized clinical trials have been conducted. The results suggest a potential attenuation of the severity of motor (e.g., tremor) and non-motor (e.g., sleep, pain) symptoms over the course of several weeks of treatment [6].

*Chamomile.* Chamomile is traditionally used in the treatment of mild anxiety and sleep disorders [7-10], and could therefore attenuate non-motor symptoms experienced by PwP.

*Coffee.* We inquired about coffee consumption, which has been associated with a reduced risk of developing PD and symptom reduction [11, 12]. Studies suggest that caffeine is the bioactive molecule largely responsible for these effects, as drinking decaffeinated coffee abrogates the benefits, and other caffeine-containing products also attenuate motor and non-motor symptoms [12-14].

*Turmeric.* This Indian spice is enriched in curcumin, a polyphenolic compound largely studied for its beneficial effects on brain health [15], and under extensive investigation to translate promising *in vitro* and *in vivo* neuroprotective activities to the clinic [16, 17].

*Velvet bean.* Velvet bean has been explored as a natural source of L-DOPA, with studies estimating concentrations ranging from 4 to 7% of the dried seeds [18, 19]. Clinical use of velvet bean to replace L-DOPA therapy has been reported to induce beneficial effects on motor symptoms [20-22].

*Other NHP of interest.* An additional three NHP were included in this survey for their traditional uses as psychoactive (guarana, *Paullinia cupana*, an alternative source of caffeine), calming (passionflower, *Passiflora incarnata*), or antidepressant (St John's Wort, *Hypericum perforatum*; rhodiola, *Rhodiola rosea*) agents [23-27], and might therefore mitigate non-motor PD symptoms.



The study revealed that respondents more often reported crude herbal preparations (e.g., turmeric) than isolated natural products found in these plants (e.g., curcumin) (Table 1). Published reports suggest that isolated natural compounds, in particular curcumin, are less bioavailable compared to the crude preparation [28, 29]. It is unclear why turmeric was favored compared to curcumin, but a possibility is PwP's prior knowledge of these physiological differences or the preference for food products vs. commercial supplements. Overall, NHP are bioactive molecules that could alter patients' responses to a therapeutic treatment, and a significant concern is the concomitant use and potential interference between PD medication and herbal supplements, which could lead to decreased potency of the prescribed treatment and/or detrimental herb-drug interactions. Future studies could investigate the preferential use of food vs. supplements by PwP, and evaluate the prevalence of NHP-drug interactions in patient populations.

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