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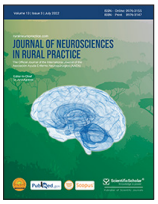

Original Article

Cannabidiol-enriched cannabis extraction product in Parkinson's disease: A randomized, double-blind, and placebo-controlled trial in Buriram Hospital

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ABSTRACT

Objectives: The objective of this study was to assess cannabidiol-enriched cannabis extraction product (CBDEP) efficacy in patients with Parkinson's disease (PD).

Materials and Methods: Forty patients with PD were randomly assigned to the sublingual CBDEP (n = 20) or placebo (n = 20) group. All patients were prescribed a low initial dose with gradual titration within 2 weeks based on individual response – including side effects – followed by 6 weeks of stable dosing. The primary outcome was the Unified Parkinson's Disease Rating Scale (UPDRS) score. The secondary outcomes were as follows: Quality of life (QOL) evaluated by the EQ-5D-5L, timed up and go (TUG) test, 5 times sit to stand (FTSTS) test, gait velocity, hospital anxiety and depression scale (HADS), renal and liver function indices, and adverse events. All outcomes were measured at baseline and at 8 weeks. The generalized estimating equation adjusted for baseline scores was used to compare the values at baseline and at 8 weeks, and between the groups.

Results: Four patients were lost to follow-up (CBDEP group, n = 1; placebo group, n = 3) and 36 were included in the analysis (CBDEP group, n = 19; placebo group, n = 17). The CBDEP group received mean cannabidiol and tetrahydrocannabinol dosages of 15.59 ± 5.04 mg/day and 0.61 ± 0.19 mg/day, respectively. No significant differences were found between the groups in terms of the UPDRS, TUG test, FTSTS test, gait velocity, HADS-anxiety, and HADS-depression. The placebo group had significantly improved EQ-5D-5L scores for QOL (P = 0.004). The CBDEP group showed significantly improved blood urea nitrogen (BUN), serum albumin, serum globulin levels, and albumin/globulin ratio (P = 0.037, P < 0.001, P = 0.011, and P = 0.002, respectively) compared with the placebo group. Neither group had serious side effects.

Conclusion: No evidence was found that CBDEP can reduce disease severity or improve functional performance, anxiety, or depression in PD. However, CBDEP is safe and can improve the levels of BUN, serum albumin, serum globulin, and albumin/globulin ratio in patients with PD.

Trial Registration: Thai Clinical Trials Registry (registration number: TCTR 20210303005).

Keywords: Cannabidiol-enriched cannabis extraction product, Blood urea nitrogen, Albumin, Globulin, Albumin/globulin ratio, Parkinson's disease, Cannabidiol

INTRODUCTION

The prevalence of Parkinson's disease (PD) ranges from 66 to 12,500/100,000 people and increases to 1/100 people in individuals aged 65–74 years.[1,2] PD is caused by the pathological degeneration of dopaminergic neurons in the substantia nigra, resulting in motor symptoms (resting tremor, bradykinesia, rigidity, and postural instability) and non-motor symptoms (dementia, depression, anxiety, sleep disorder, autonomic dysfunction, and psychosis).[3] Levodopa, the most commonly used medication for treating PD,[4] improves motor symptoms and is the most effective agent for treating PD. However, its long-term use is often associated with motor complications and fluctuations[5] that complicate treatment and affect patient quality of life (QOL).[6]

Cannabidiol is a non-psychoactive substance of cannabis and an endocannabinoid modulator. *In vitro,* cannabidiol can antagonize cannabinoid receptor 1 (CB1) and agonize cannabinoid receptor 2 (CB2).[7] Many researches have shown

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the potential of endocannabinoid systems in manipulating PD. The CB1 action leads to dopamine and glutamate modulation and excitotoxicity reduction. Through CB2, the endocannabinoid system can regulate immunomodulation, confer neuroprotection, and reduce neuroinflammation.[8-13] Cannabidiol also antagonizes G protein-coupled receptor 55, which may help improve PD symptoms.[14,15] These processes are all related to PD pathogenesis. Cannabidiol, the main modulator of the endocannabinoid system, may have beneficial effects in PD.

In 2009, Zuardi *et al*. reported that administrating 150 mg/day of cannabidiol reduced psychotic symptoms in PD.[16] In 2014, Chagas *et al*. reported that administrating 75–300 mg/day of cannabidiol improved sleep disorders and the QOL of patients with PD.[17,18] In 2020, de Faria *et al*. showed that a 300 mg/day dosage of cannabidiol significantly reduced anxiety and tremor in PD.[19] These studies did not report any serious side effects of cannabidiol. Another study showed that 50.3 mg/day of cannabidiol in the healthy population did not affect liver function.[20]

Studies on cannabidiol use for PD treatment are limited, and most studies have a small sample size. Hence, this trial was conducted to examine the efficacy of a cannabidiol-enriched cannabis extraction product (CBDEP) on disease severity, QOL, functional performance, anxiety, depression, and renal and liver functions in patients with PD.

MATERIALS AND METHODS

Ethics

The ethics committee of Buriram Hospital approved this study (approval number BR.0032.102.1/7). The study was conducted according to the principles of the Declaration of Helsinki. The protocol was registered in the Thai Clinical Trials Registry (thaiclinicaltrials.org; identifier: TCTR 20210303005). Written informed consent was obtained from all patients.

Study design and population

This was a prospective, double-blind, randomized, and placebo-controlled trial involving patients with PD who visited the Neurology Outpatient Clinic of Buriram Hospital between March 18, 2021, and May 31, 2021.

The sample size was calculated based on the primary outcome measure, the Unified Parkinson's Disease Rating Scale (UPDRS) score. The previous studies[17,21] reported that the mean changes in the UPDRS in the groups receiving cannabis and placebo were 9.9 and 3.8 points, respectively. A sample size of 20 patients for each group was calculated using a two-sample comparison of means with a one-sided α level of 0.05, 80% power, standard deviation (SD) of the mean change in both groups of 6.85, and a loss to follow-up rate of 20%.

The inclusion criteria were age >40 years, diagnosis of PD using the UK PD Society Brain Bank diagnostic criteria, Hoehn and Yahr Stages 1–3, stable dosage of PD medications for at least 3 months, and willingness of patients and caregivers to participate in the study. Patients were excluded if they had dementia, schizophrenia, or other psychotic disorders; kidney or liver disease; serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels >3 times the upper limit of the normal range; or a history of high-risk behavior related to substance abuse, including nicotine, cannabis, and alcohol.

Screening, initial instructions, and randomization

All patients with PD attending the Neurology Clinic of Buriram Hospital who fulfilled the inclusion criteria were informed of the study. Patients were educated about the possible advantages and disadvantages of using CBDEP and, if willing to participate, were sent to the Cannabis Clinic of Buriram Hospital. All 40 participants were assigned to groups using double-blind randomization, wherein multiple blocks with concealed consecutive numbers were created. The number was then randomly assigned to the product by a pharmacist who was not involved in the research. These randomly labeled products were prescribed such that neither the patient nor the researcher knew the specific treatment (CBDEP or placebo) provided.

CBDEP group

The CBDEP group received standard treatment for PD plus sublingual CBDEP manufactured from a cannabis factory certified by the World Health Organization Good Manufacturing Practice. CBDEP was extracted from the inflorescence of the Charlotte's Angel strain of cannabis using an ethanol extraction technique and dissolved in olive oil. It contained 100 mg/mL cannabidiol and 3.9 mg/mL tetrahydrocannabinol.

Placebo group

The placebo group received standard treatment for PD plus sublingual placebo. The placebo contained olive oil colored using a very tiny amount of green vegetable. The containers of placebo and CBDEP were identical.

Participants in both groups underwent telephonic dose adjustment and symptom monitoring. The CBDEP prescription started with a very low dose and was gradually up-titrated through telephonic instruction every 3–5 days for 2 weeks followed by 6 weeks of stable dosing. Both groups of patients were advised not to change their daily diet, physical activity, and PD medications.

Data collection and measurement

Data were recorded at baseline and at 8 weeks. All participants were on-period PD medications during data collection. The collected data were divided into six domains: Disease severity (total UPDRS and UPDRS parts I–IV); QOL using the EQ-5D-5L; functional performance tests using the timed up and go (TUG) test, gait velocity, and 5 times sit to stand (FTSTS) test; anxiety and depressive symptoms using the Hospital Anxiety and Depression Scale (HADS); renal and liver function indices; and adverse events.

The UPDRS[22] score was the primary outcome measure in this study. It measures disease severity in a range from 0 to 199 points: Higher scores indicate more disease severity. Scoring is classified into four parts: Part I, non-motor symptoms of daily living; part II, motor experiences of daily living; part III, physician-scored monitored motor evaluation; and part IV, complications of treatment.

The EQ-5D-5L[23] is a tool for measuring QOL. A score of 1 indicates the healthiest and 0 indicates the least healthy or dead.

The TUG[24] test is measured (in seconds) by having a participant stand from sitting in a chair with an armrest, walk forward 3 m, turn around, and return to the original sitting position.

Gait velocity,[25] reported in meters per second, was measured through a 10 m walk test.

The FTSTS[26] test (timed in seconds) measures a patient's lower extremity strength, balance, and fall risk. The test is performed by having participants sit and stand 5 times as quickly as possible.

The HADS[27] was used to assess anxiety and depression symptoms. The test consists of two parts: Anxiety (HADS-A) and depression (HADS-D). For each part, the score ranges from 0 to 21 points: A score ≥8 points indicates a diagnosis of anxiety and/or depression. The sensitivity and specificity of both HADS are approximately 0.80.

Data analyses

Statistical analyses were performed using STATA Ver.17. Continuous variables are presented as mean ± SD, whereas categorical variables are presented as counts and percentages. The generalized estimating equation adjusted for baseline scores was used to compare the values at baseline with those at 8 weeks and between the two groups.

RESULTS

Forty patients were included in the study: Four were lost to follow-up (CBDEP group, n=1; placebo group, n = 3) and 36 were included in the analysis (CBDEP group, n = 19; placebo group, n = 17) (Supplementary 1).

Supplementary 2 presents a summary of the patients' baseline demographic. In both groups, the patients were similar in sex, age, body mass index, comorbidity, equivalent dosage of levodopa, PD duration and onset, Hoehn and Yahr stage, and total UPDRS.

In the 2nd week, the CBDEP group received mean cannabidiol and tetrahydrocannabinol dosages of 15.59 ± 5.04 mg/day and 0.61 ± 0.19 mg/day, respectively. In the 8th week, there was no difference in the UPDRS, TUG, FTSTS, gait velocity, or HADS between the two groups. The placebo group had a significantly improved EQ-5D-5L score for QOL compared with the CBDEP group (P = 0.004; [Table 1]).

Laboratory parameters, such as serum creatinine, total protein, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, ALT, and AST levels, were not significantly different between the groups. However, the levels of blood urea nitrogen (BUN), serum albumin, serum globulin, and the albumin/globulin ratio were significantly improved in the CBDEP group (P = 0.037, P < 0.001, P = 0.011, and P = 0.002, respectively; [Table 2]).

The rates of adverse events in the CBDEP and placebo groups were 47.3% (nine participants) and 47.1% (eight participants), respectively. All adverse events were mild and well tolerated: Dry throat (eight participants) and mild gastrointestinal disturbance (one participant) in the CBDEP group, and dry throat (eight participants) in the placebo group. All patients continued to use the products until the end of the study. No serious adverse event was observed in either group.

DISCUSSION

To the best of our knowledge, this study is the first to demonstrate a significant link between a cannabidiol dosage of 15.59 mg/day and improvement in the levels of BUN, serum albumin, serum globulin, and in the albumin/globulin ratio in PD.

Patients in the CBDEP group received a cannabidiol dosage of 15.59 mg/day and a tetrahydrocannabinol dosage of 0.61 mg/day. However, due to the patients' satisfaction and concerns about the CBDEP side effects, the dosage of cannabidiol used in the present study was lower than that used in the previous studies (75–300 mg/day).[16-19] Under these circumstances, our study results may not reveal the CBDEP effect on disease severity, functional performance, anxiety, and depression. Thus, in future research, a higher dosage of cannabidiol should be considered to determine the CBDEP efficacy in PD.

BUN levels significantly decreased in the CBDEP group compared with those in the placebo group. Cannabidiol is likely to improve renal function by agonizing the CB2

Table 1: Comparison of the UPDRS, EQ-5D-5L, TUG, FTSTS, gait velocity, and HADS scores between baseline and eight weeks and between the two groups by using generalized estimating equation adjusted for baseline scores.

Variables	CBDEP group (*n*=19)		*P*-Value	Placebo group (*n*=17)		*P*-Value	Mean difference	95% CI	*P*-Value
	Baseline	8 weeks		Baseline	8 weeks				
Disease severity									
Total UPDRS	55.9±26.14	46.5±25.40	0.004*	68.1±32.4	53.1±33.0	<0.001*	4.32	−3.68 to 13.32	0.290
UPDRS part I	8.58±6.04	5.47±3.53	<0.001*	13.88±7.62	8.52±8.01	<0.001*	1.1	−1.16 to 3.36	0.340
UPDRS part II	10±6.11	8.53±6.48	0.109	13±6.52	10.12±7.58	0.013*	1.01	−1.34 to 3.36	0.400
UPDRS part III	34.78±16.19	29.68±16.28	0.020*	38.29±19.30	31.41±17.81	0.005*	1.28	−3.86 to 6.41	0.626
UPDRS part IV	2.57±3.77	2.8±2.69	0.478	2.88±4.38	3±3.75	0.673	0.092	−0.61 to 0.79	0.796
Quality of life									
EQ-5D-5L	0.77±0.27	0.87±0.30	0.006*	0.65±0.30	0.92±0.21	<0.001*	−0.14	−0.23 to−0.04	0.004*
Functional performance									
TUG (sec)	14.16±6.17	13.28±3.86	0.337	13.90±5.73	12.65±3.40	0.133	0.49	−1.08 to 2.06	0.537
FTSTS (sec)	13.95±4.29	13.66±3.54	0.490	15.10±7.41	13.91±5.38	0.096	0.63	−0.63 to 1.88	0.327
Gait velocity (m/sec)	1.08±0.23	1.13±0.21	0.107	1.07±0.25	1.18±0.23	0.043*	−0.06	−0.17 to 0.06	0.322
HADS score									
Anxiety score	3.73±2.66	2.94±2.12	0.067	5.05±2.86	4.76±3.41	0.822	−0.82	−1.97 to 0.33	0.160
Depression score	3.157±2.75	2.05±1.71	0.015*	5.11±3.14	3.23±3.13	0.066	−0.37	−1.73 to 0.98	0.590

Data are presented as mean±standard deviation, *P<0.05, CBDEP, cannabidiol-enriched cannabis extraction product; CI, confidence interval; UPDRS, Unified Parkinson's Disease Rating Scale; TUG, Timed Up and Go; FTSTS, Five Times Sit to Stand; HADS, Hospital Anxiety and Depression Scale.

Table 2: Comparison of the laboratory parameters between baseline and eight weeks and between the two groups by using generalized estimating equation adjusted for baseline scores.

Variables	CBDEP group (*n*=19)		*P*-Value	Placebo group (*n*=17)		*P*-Value	Mean difference	95% CI	*P*-Value
	Baseline	8 weeks		Baseline	8 weeks				
Renal function									
BUN (mg/dL)	14.29±4.09	13.34±3.72	0.193	12.82±3.56	13.67±5.14	0.274	−1.63	−3.16 to−0.95	0.037*
Cr (mg/dL)	0.86±0.19	0.87±0.17	0.616	0.87±0.19	0.87±0.20	0.858	0.006	−0.34 to 0.45	0.786
Liver function									
Total protein (g/dL)	7.83±0.31	7.70±0.30	0.012*	8.07±0.48	7.98±0.30	0.005*	0.02	−0.11 to 0.15	0.749
Albumin (g/dL)	4.09±0.19	4.11±0.17	0.943	4.23±0.21	4.09±0.23	<0.001*	0.13	0.06 to 0.19	<0.001*
Globulin (g/dL)	3.74±0.31	3.59±0.29	0.001*	3.84±0.46	3.81±0.47	0.695	−0.13	−0.24 to−0.03	0.011*
Total bilirubin (mg/dL)	0.59±0.13	0.65±0.18	0.060	0.59±0.14	0.71±0.19	0.001*	−0.05	−0.12 to 0.03	0.209
Direct bilirubin (mg/dL)	0.10±0.05	0.10±0.05	0.973	0.09±0.05	0.11±0.05	0.085	−0.02	−0.05 to 0.003	0.088
Indirect bilirubin (mg/dL)	0.49±0.11	0.56±0.15	0.018*	0.51±0.12	0.59±0.15	0.002*	−0.02	−0.85 to 0.04	0.492
ALP (U/L)	77.81±30.52	66.27±18.46	<0.001*	73.74±18.49	67.46±18.85	0.013*	−4.2	−9.57 to 1.17	0.126
AST (U/L)	27.73±6.94	26.26±7.47	0.110	27.7±6.91	24.74±5.28	0.002*	1.51	−0.53 to 3.54	0.147
ALT (U/L)	20.04±7.94	16.34±7.26	<0.001*	19.84±12.60	18.05±9.90	0.074	−1.88	−3.97 to 0.21	0.078
A/G ratio	1.10±0.12	1.15±0.11	0.026*	1.12±0.15	1.09±0.15	0.073	0.08	0.03 to 0.13	0.002*

Data are presented as mean±standard deviation, *P<0.05, CBDEP, cannabidiol-enriched cannabis extraction product; CI, confidence interval; BUN, blood urea nitrogen; Cr, creatinine; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; A/G ratio, albumin/globulin ratio.

receptor. This result is compatible with that of a previous study conducted in a mouse model,[28] which found that selective CB2 stimulation resulted in reduced tubular epithelial cell damage after renal ischemia-reperfusion injury. Yazar and Yazar.[29] reported that serum albumin levels had a negative correlation with age, UPDRS, disease duration, and Hoehn and Yahr stages in PD. The CBDEP group showed a significant increase in serum albumin levels. We postulated

that CBDEP may improve nutritional status by increasing appetite through the CB1 and CB2 receptors in the gastrointestinal tract.[30] The CBDEP group had lower serum globulin levels than the placebo group, possibly associated with decreased systemic inflammation through the anti-inflammatory actions of cannabidiol on CB2.[13] Therefore, reduction of neuroinflammatory markers might slow the degeneration of dopaminergic neurons in the substantia nigra. However, the levels of the inflammatory markers and other pro-inflammatory cytokines were not measured in this study. Thus, future research should investigate specific inflammatory markers, cytokines, and subtypes of globulin.

Changes in serum albumin and serum globulin levels resulted in a significant difference in the albumin/globulin ratios between the groups. The serum albumin/globulin ratio was found to positively correlate with cognitive function.[31,32] Therefore, CBDEP use resulting in a higher albumin/globulin ratio may improve cognitive function in PD. Further studies are needed to measure cognitive function and confirm these findings.

This study revealed an unexpected result: The placebo group had better QOL than the CBDEP group. Our result was different from that of a previous study that showed improvement in QOL after cannabidiol administration for PD using PD questionnaire-39.[17] There are two possible explanations for this observation. First, the CBDEP group may have experienced an adverse effect that was not defined or recorded. Second, several confounders may affect patient QOL, such as disease background or previous treatment complications. Therefore, future research questionnaires must include more details about the possible adverse effects of CBDEP. Moreover, increasing the sample size and balancing potential confounders would help improve data accuracy.

Strengths

This study was a randomized and placebo-controlled trial in which both clinicians and patients were blinded to group assignment.

Limitations

First, this study did not measure key factors, such as cognitive function, or levels of inflammatory markers, pro-inflammatory cytokines, or globulin subtypes. Second, the sample size was small. Third, the very low dosage of cannabidiol used may not represent an effective therapeutic dosage.

CONCLUSION

CBDEP, with mean cannabidiol and tetrahydrocannabinol dosages of 15.59 ± 5.04 and 0.61 ± 0.19 mg/day, respectively, is safe and can significantly improve the levels of BUN, serum albumin, serum globulin, and the albumin/globulin ratio in PD. Future research should consider a higher dosage of cannabidiol to determine the CBDEP efficacy in PD treatment.

Data sharing statement

We declare that the data supporting the findings of this study are available.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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CBDEP and placebo were obtained from Khu-Muang Hospital.

Conflicts of interest

There are no conflicts of interest.

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