

Original Article

Effects of butylphthalide plus donepezil on symptoms, cognitive function, and oxidative stress in patients with cognitive impairment in Parkinson's disease

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Abstract: Objective: To investigate the effects of butylphthalide combined with donepezil on clinical symptoms, cognitive function, and oxidative stress in patients with cognitive impairment associated with Parkinson's disease (PD). Methods: A total of 119 patients with PD-associated cognitive impairment who were admitted to Chengdu Sixth People's Hospital (Donghong Branch) were retrospectively included and divided into two groups. Both groups received levodopa and benserazide hydrochloride as basic treatment. In addition, patients in the control group (n = 55) received donepezil, and those in the research group (n = 64) received butylphthalide combined with donepezil. The two groups were compared in terms of therapeutic efficacy, clinical symptoms (assessed by the Unified Parkinson's Disease Rating Scale [UPDRS]), cognitive function (Montreal Cognitive Assessment [MoCA]), activities of daily living (ADLs; ADL scale), neurotransmitter levels (dopamine [DA], gamma-aminobutyric acid [GABA], 5-hydroxytryptamine [5-HT]), neurotrophic factors (neurotrophin-3 [NT-3], nerve growth factor [NGF]), oxidative stress (superoxide dismutase [SOD], malondialdehyde [MDA]), adverse events, and quality of life (QoL; the 36-Item Short Form Health Survey [SF-36]). Furthermore, exploratory subgroup analyses were performed according to Hoehn-Yahr staging (H-Y staging) and baseline MoCA scores. Results: Compared to the control group, patients in the research group exhibited much higher overall response rate, lower post-treatment UPDRSII, UPDRSIII, and MDA levels, and higher MoCA scores, ADL scores, DA, GABA, 5-HT, NT-3, NGF, SOD levels, and SF-36 scores. The overall incidence of adverse events was comparable between groups. Neither H-Y staging nor baseline MoCA scores significantly affected the efficacy of the combination therapy. Conclusion: Butylphthalide combined with donepezil may exert beneficial effects on symptom improvement, cognitive function enhancement, and oxidative stress regulation in patients with PD-associated cognitive impairment.

Keywords: Butylphthalide, donepezil, Parkinson's disease, cognitive impairment, symptoms, cognitive function, oxidative stress

Introduction

Parkinson's disease (PD) is a progressive and disabling neurodegenerative disorder, characterized by both motor and non-motor symptoms, with approximately 2% of cases initially showing non-motor symptoms [1]. Motor manifestations include resting tremor, rigidity, bradykinesia, and postural instability. Non-motor manifestations may include sensory disturbances and pain, sleep disorders, autonomic dysfunction, and mental disorders (e.g., cognitive impairment, psychotic symptoms, depression) [2, 3]. Among these symptoms, cognitive impairment is recognized as one of the most

common and severe non-motor symptoms of PD, with an incidence of up to 47% within 1-6 years after PD diagnosis [4]. In PD patients, cognitive impairment is closely associated with increased risks of surgical complications, dementia development, and difficulties in disease management [5]. It significantly impairs patients' daily functioning, imposes a substantial burden on family members and caregivers, and is associated with poorer survival outcome [6, 7]. Although the pathologic mechanisms underlying cognitive impairment in PD remain incompletely understood, they may involve multiple pathologic processes, including protein misfolding, neurodegeneration, inflammation, and

oxidative stress [8]. Current pharmacological treatments for cognitive impairment in PD provide limited benefits and fail to prevent disease progression; therefore, the development of novel, effective, and safe treatment strategies remains urgently needed.

Levodopa and benserazide hydrochloride is a compound preparation consisting of levodopa and benserazide, that is widely used in the clinical management of PD and may contribute to improving cognitive function and reducing neuronal damage [9]. Levodopa remains the preferred therapeutic agent for PD and can effectively alleviate clinical symptoms; however, its long-term efficacy may be compromised by progressive degeneration of dopamine-producing neurons in the substantia nigra [10]. Benserazide, a peripheral aromatic L-amino acid decarboxylase inhibitor, reduces the peripheral conversion of levodopa to dopamine, thereby increasing the availability of levodopa in the central nervous system and improving therapeutic efficacy [11]. As a selective acetylcholinesterase inhibitor, donepezil enhances cognitive function by inhibiting acetylcholine hydrolysis and increasing acetylcholine levels in the brain, although it may be associated with an increased risk of adverse reactions [12]. Butylphthalide is a pure component extracted from celery and has demonstrated protective effects against cerebral ischemia and vascular cognitive impairment. Its potential mechanisms involve inhibition of oxidative stress, inflammatory responses, and apoptosis, as well as its improvement of mitochondrial function [13]. In addition, butylphthalide can alleviate PD-related symptoms by promoting microglial polarization toward the M2 phenotype and suppressing neuroinflammation [14]. Pang et al. [15] reported that butylphthalide combined with donepezil effectively improved cognitive function and activities of daily living (ADLs) and alleviated neurologic deficits in patients with post-stroke cognitive impairment, without significantly increasing the incidence of adverse events.

Currently, the clinical efficacy of butylphthalide combined with donepezil in patients with PD-associated cognitive impairment remains unclear, and relevant studies are limited. The effects of this combination therapy on clinical symptoms, cognitive function, and oxidative stress require further exploration. Therefore, this study was conducted to provide novel

insight into the treatment strategies for cognitive impairment associated with PD.

Materials and methods

General data

This retrospective study included 119 patients with cognitive impairment associated with PD who were admitted to Chengdu Sixth People's Hospital (Donghong Branch) between February 2023 and February 2026. A non-randomized grouping method was used according to the specific treatment regimen received. Patients in both groups received levodopa and benserazide hydrochloride; additionally, patients in the control group ($n = 55$) received donepezil, whereas patients in the research group ($n = 64$) received butylphthalide combined with donepezil. This study was approved by the Ethics Committee of Chengdu Sixth People's Hospital (Donghong Branch).

Inclusion and exclusion criteria

Inclusion criteria: patients who met the diagnostic criteria for cognitive impairment associated with primary PD [16]; aged 50-80 years; normal communication ability; no known allergies to the investigated medications; and complete clinical data available.

Exclusion criteria: cognitive impairment due to other causes; concomitant cardiac, pulmonary, or renal dysfunction; malignant tumors; cerebral infarction, neuromuscular junction disorders, cerebrovascular disease, or other types of neurological diseases; infectious diseases; presence of psychiatric disorders such as depression or schizophrenia; a history of cognitive impairment or severe mental illness; receipt of relevant treatment within 1 month before treatment initiation; or PD superposition syndrome.

Treatment method

Patients in both groups received oral levodopa and benserazide hydrochloride capsules, with an initial dose of 0.125 g, three times daily. The total daily dose was subsequently increased by 0.125 g weekly, with a maximum daily dose not exceeding 1 g.

Patients in the control group received oral donepezil at an initial dose of 5 mg once per

day; after one week of treatment, the dose was increased to 10 mg once daily.

Based on the treatment regimen of the control group, patients in the research group additionally received butylphthalide soft capsules (0.1 g/capsule) orally, 2 capsules/dose, 3 times daily. The treatment continued for 3 months for both groups.

Outcome measures

Treatment efficacy. Therapeutic efficacy was evaluated 3 months after treatment according to the following criteria. Markedly effective: Clinical symptoms and neurological manifestations, including bradykinesia, resting tremor, parosmia, sleep disturbances, and cognitive impairment, basically recover after treatment, and patients were able to live independently and engage in social activities. Effective: Clinical symptoms were significantly improved after treatment, with no obvious impairment of social activities; however, slow response remained, and patients could only partially live independently. Ineffective: Patients did not meet the criteria for markedly effective or effective responses. The overall effective rate was calculated as follows: (number of markedly effective cases + number of effective cases)/total number of cases * 100%.

Symptoms. The Unified Parkinson's Disease Rating Scale (UPDRS) was employed to evaluate PD-related symptoms before treatment and 3 months after treatment [17]. The scale consists of UPDRS II (motor experiences of daily living; score range: 0-52) and UPDRS III (motor examination; score range: 0-108), with higher scores indicating more severe symptoms.

Cognitive function. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) scale [18] before treatment and at 3 months after treatment. The total score is 30 points, with lower scores indicating more severe cognitive impairment.

ADLs. The ADL scale was used to assess patients' activities of daily living before treatment and at 3 months after treatment [19]. The total score ranges from 0 to 100, with higher scores indicating better ADL performance.

Neurotransmitters. Fasting peripheral venous blood samples (3 mL) were collected from each

patient in the early morning before treatment and at 3 months after treatment. Serum samples were obtained by centrifugation, and serum levels of dopamine (DA), gamma-aminobutyric acid (GABA), and 5-hydroxytryptamine (5-HT) were measured using enzyme-linked immunosorbent assay (ELISA).

Neurotrophic factors. Serum levels of neurotrophin-3 (NT-3) and nerve growth factor (NGF) were measured using ELISA before treatment and at 3 months after treatment.

Oxidative stress. Serum levels of superoxide dismutase (SOD) and malondialdehyde (MDA) was measured using ELISA before treatment and at 3 months after treatment.

Adverse events. The incidence of treatment-related adverse events, including diarrhea, dizziness, nausea and vomiting, and dry mouth, was recorded.

QoL. The 36-Item Short Form Health Survey (SF-36) was used to assess QoL before treatment and at 3 months after treatment. The assessment included physical functioning (PF), role physical (RP), social functioning (SF), and role emotional (RE) [20]. Each dimension was scored from 0 to 100, with higher score indicating better QoL.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0. Normality was first assessed using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation (SD). Comparisons between two groups were performed using the independent-samples t test, whereas paired t-test were used for comparisons before and after treatment within groups. Non-normally distributed continuous variables were expressed as median (interquartile range), and inter-group comparisons were performed using the Mann-Whitney U test. Categorical variables were described as percentages (%) and compared using the chi-square test.

For outcomes measured repeatedly before and after treatment, analysis of covariance (ANCOVA) was performed, with post-treatment scores as the dependent variable, treatment group as the fixed factor, and baseline scores as covariates to adjust for baseline differences. Before

Table 1. Comparison of baseline characteristics between the two groups

Item	Control group (n = 55)	Research group (n = 64)	$\chi^2/t/Z$	P
Sex			0.341	0.559
Male	33 (60.00)	35 (54.69)		
Female	22 (40.00)	29 (45.31)		
Age (years)	66.22 ± 5.26	65.98 ± 5.73	0.237	0.813
Disease duration (years)	6.00 (5.00, 7.00)	6.00 (4.25, 8.00)	-1.677	0.093
H-Y staging			0.754	0.686
I	24 (43.64)	30 (46.88)		
II	19 (34.55)	24 (37.50)		
III	12 (21.82)	10 (15.63)		
Educational level			0.514	0.473
Junior high school or below	18 (32.73)	25 (39.06)		
High school or above	37 (67.27)	39 (60.94)		
Family history			0.225	0.635
Absent	40 (72.73)	44 (68.75)		
Present	15 (27.27)	20 (31.25)		

Note: H-Y, Hoehn-Yahr.

Table 2. Comparison of therapeutic efficacy between the two groups

Item	Control group (n = 55)	Research group (n = 64)	χ^2	P
Markedly effective	21 (38.18)	35 (54.69)		
Effective	22 (40.00)	24 (37.50)		
Ineffective	12 (21.82)	5 (7.81)		
Total effective rate	43 (78.18)	59 (92.19)	4.739	0.030

0.05 was considered significant.

Results

General data

No significant differences were observed in terms of sex, age, disease duration, Hoehn-Yahr staging (H-Y staging), educa-

tional level, or family history between the two groups ($P > 0.05$; **Table 1**), indicating good comparability between groups.

Therapeutic efficacy

The numbers of patients with markedly effective, effective, and ineffective outcomes were 21, 22, and 12, respectively, in the control group, and 35, 24, and 5, respectively, in the research group. The overall effective rate was notably higher in the research group than in the control group ($P = 0.030$). The absolute risk difference (ARD) between the two groups was 14.01%, corresponding to a number needed to treat (NNT) of 7.14, suggesting a clinical benefit of the combination therapy (**Table 2**).

Symptoms

No significant intergroup differences were observed in UPDRS II and UPDRS III scores before treatment ($P > 0.05$). After treatment, both

the analysis, the homogeneity of regression slopes was tested. When the interaction term between treatment group and covariate was not significant ($P > 0.05$), the main-effect model was adopted. Multiple comparisons were corrected using the Benjamini-Hochberg false discovery rate (FDR) method. Adjusted P values were calculated for inter-group comparisons of all outcome measures and significance was defined as adjusted $Q < 0.05$.

To explore whether the combination therapy offered greater benefit in specific subgroups, post-hoc exploratory subgroup analyses were conducted using a general linear model. Subgroup variables included baseline H-Y staging (early stage [I-II] vs. mid-to-late stage [III]) and baseline MoCA scores (as a continuous variable). Treatment efficacy (effective/ineffective) was taken as the dependent variable, and the interaction term "grouping $\times$ subgroup variable" was included to evaluate potential heterogeneity of treatment effects. A P value <

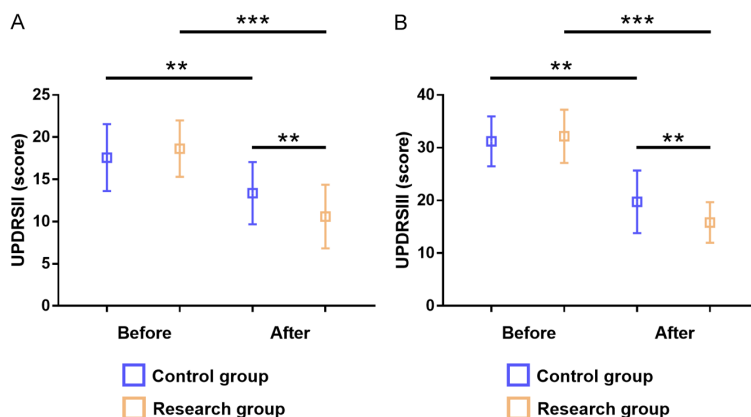


Figure 1. Comparison of UPDRS scores before and after treatment between the two groups. A. UPDRS II scores. B. UPDRS III scores. Note: ** $P < 0.01$, *** $P < 0.001$. UPDRS, Unified Parkinson's Disease Rating Scale.

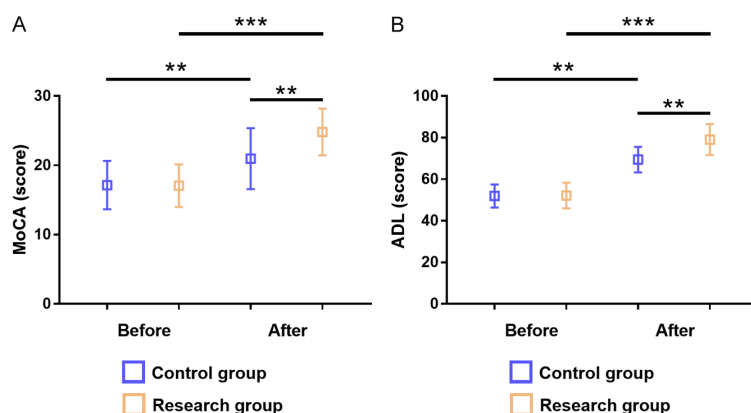


Figure 2. Comparison of MoCA scores (A) and ADL scores (B) before and after treatment between the two groups. Note: ** $P < 0.01$, *** $P < 0.001$. MoCA, Montreal Cognitive Assessment; ADL, activities of daily living.

scores significantly decreased in both groups and were lower in the research group (all $P < 0.01$) (**Figure 1**). After adjustment for baseline values using ANCOVA, the UPDRS II and UPDRS III scores in the research group were significantly lower than those of the control group (UPDRS II: $F = 15.348$, $P < 0.001$; UPDRS III: $F = 18.979$, $P < 0.001$). The test for homogeneity of regression slopes showed no significant interaction between treatment group and baseline scores ($P > 0.05$), confirming that the assumptions for ANCOVA were satisfied. After FDR correction, all adjusted q values for all the above indicators were < 0.05 .

Cognitive function and ADL

No significant intergroup differences were observed in MoCA and ADL scores before treat-

ment ($P > 0.05$). After treatment, both scores substantially increased in both groups and were higher in the research group (all $P < 0.01$; **Figure 2**). After adjustment for baseline values using ANCOVA, the MoCA and ADL scores in the research group were notably higher than those in the control group (MoCA: $F = 28.913$, $P < 0.001$; ADL: $F = 57.878$, $P < 0.001$). The test for homogeneity of regression slopes showed no significant interaction between treatment group and baseline scores ($P > 0.05$), indicating that the assumptions for ANCOVA were satisfied. After FDR correction, all adjusted q values were < 0.05 .

Neurotransmitters

There were no significant intergroup differences in DA, GABA, or 5-HT levels before treatment ($P > 0.05$). After treatment, all these neurotransmitter levels significantly increased in both groups, with higher levels observed in the research group ($P < 0.01$). After adjustment for baseline values using ANCOVA, the research group exhibited notably higher levels of DA, GABA, and 5-HT compared to the control group (DA: $F = 33.821$, $P < 0.001$; GABA: $F = 9.279$, $P = 0.003$; 5-HT: $F = 26.434$, $P < 0.001$). The test for homogeneity of regression slopes showed no significant interaction between treatment group and baseline values ($P > 0.05$), indicating that the assumptions for ANCOVA were satisfied. After FDR correction, all adjusted q values were < 0.05 (**Table 3**).

Neurotrophic factors

Intergroup comparison revealed no significant differences in baseline NT-3 or NGF levels ($P > 0.05$). After treatment, both markers significantly increased, with higher levels observed in the research group ($P < 0.001$). After adjustment for baseline values using ANCOVA, the research group exhibited notably higher NT-3

Table 3. Comparison of neurotransmitter levels before and after treatment between the two groups

Item	Control group (n = 55)	Research group (n = 64)	t	P
Pre-treatment DA (pg/mL)	5.26 ± 1.58	5.11 ± 1.83	0.475	0.636
Post-treatment DA (pg/mL)	6.70 ± 1.87	8.90 ± 2.20	5.825	< 0.001
Pre-treatment GABA (ng/L)	5.04 ± 1.10	5.30 ± 1.57	1.030	0.305
Post-treatment GABA (ng/L)	8.59 ± 2.41	9.96 ± 2.75	2.867	0.005
Pre-treatment 5-HT (μg/L)	216.95 ± 16.78	213.52 ± 20.83	0.978	0.330
Post-treatment 5-HT (μg/L)	243.29 ± 34.53	278.47 ± 38.04	35.080	< 0.001

Note: DA, dopamine; GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine.

Table 4. Comparison of neurotrophic factor levels before and after treatment between the two groups

Item	Control group (n = 55)	Research group (n = 64)	t	P
Pre-treatment NT-3 (μg/L)	17.36 ± 3.70	17.83 ± 3.38	0.724	0.471
Post-treatment NT-3 (μg/L)	23.76 ± 4.00	33.72 ± 5.96	10.521	< 0.001
Pre-treatment NGF (ng/mL)	5.60 ± 1.15	5.75 ± 1.64	0.569	0.571
Post-treatment NGF (ng/mL)	8.77 ± 2.68	12.39 ± 2.08	8.287	< 0.001

Note: NT-3, neurotrophin-3; NGF, nerve growth factor.

Table 5. Comparison of oxidative stress marker levels before and after treatment between the two groups

Item	Control group (n = 55)	Research group (n = 64)	t	P
Pre-treatment SOD (U/mL)	63.40 ± 6.75	63.00 ± 7.86	0.295	0.768
Post-treatment SOD (U/mL)	73.85 ± 6.70	82.89 ± 8.58	6.328	< 0.001
Pre-treatment MDA (nmol/L)	10.47 ± 2.62	10.14 ± 2.34	0.726	0.470
Post-treatment MDA (nmol/L)	7.70 ± 2.68	5.43 ± 1.93	5.352	< 0.001

Note: SOD, superoxide dismutase; MDA, malondialdehyde.

and NGF levels compared to the control group (NT-3: $F = 109.692$, $P < 0.001$; NGF: $F = 67.868$, $P < 0.001$). The test for homogeneity of regression slopes confirmed the validity of ANCOVA assumptions ($P > 0.05$). After FDR correction, all adjusted q values were < 0.05 (**Table 4**).

Oxidative stress

No significant intergroup differences were observed in SOD or MDA levels before treatment ($P > 0.05$). After treatment, SOD levels increased and MDA levels decreased significantly in both groups, with notably higher SOD levels and lower MDA levels observed in the research group ($P < 0.001$). After adjustment for baseline values using ANCOVA, the research group showed significantly higher SOD levels and lower MDA levels compared with the control group (SOD: $F = 40.211$, $P < 0.001$; MDA: $F = 28.455$, $P < 0.001$). The test for homogeneity of regression slopes showed no significant interaction between treatment group and base-

line values ($P > 0.05$). After FDR correction, all adjusted q values were < 0.05 (**Table 5**).

Adverse events

In the control group, diarrhea, dizziness, and nausea/vomiting occurred in 2 cases each, and dry mouth was observed in 3 cases. In the research group, dizziness and nausea/vomiting occurred in 1 case each, and dry mouth occurred in 3 cases. The overall incidence of adverse events was comparable between the two groups, with a risk difference of -8.55% ($P > 0.05$) (**Table 6**).

QoL

No significant intergroup differences were observed in SF-36 scores, including PF, RP, SF, and RE before treatment ($P > 0.05$). After treatment, SF-36 scores significantly increased in both groups, with higher scores observed in the research group across all dimensions ($P <$

Table 6. Comparison of the incidence of adverse events between the two groups

Item	Control group (n = 55)	Research group (n = 64)	χ^2	P
Diarrhea	2 (3.64)	0 (0.00)		
Dizziness	2 (3.64)	1 (1.56)		
Nausea and vomiting	2 (3.64)	1 (1.56)		
Dry mouth	3 (5.45)	3 (4.69)		
Total	9 (16.36)	5 (7.81)	2.084	0.149

0.001). After adjustment for baseline values using ANCOVA, the research group demonstrated significantly higher SF-36 scores in all dimensions (PF: $F = 42.155$, $P < 0.001$; SF: $F = 29.468$, $P < 0.001$; RP: $F = 30.249$, $P < 0.001$; RE: $F = 25.509$, $P < 0.001$). The test for homogeneity of regression slopes showed no significant interaction between treatment group and baseline scores ($P > 0.05$), supporting the validity of ANCOVA. After FDR correction, all adjusted q values were < 0.05 (Table 7).

Exploratory subgroup analysis based on baseline Hoehn-Yahr stage or MoCA scores

Exploratory subgroup analyses showed that neither H-Y staging (P for interaction = 0.472) nor baseline MoCA scores (P for interaction = 0.671) significantly affected the treatment efficacy of the combination therapy (Table 8). These findings suggest that the beneficial effects of the combination therapy were generally consistent across different disease stages and baseline cognitive function levels.

Discussion

The first finding of this study was that butylphthalide combined with donepezil achieved superior therapeutic efficacy in patients with cognitive impairment associated with PD compared to donepezil alone. Butylphthalide suppresses the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase-stimulator of interferon genes signaling pathway and inhibits rotenone-induced mitochondrial DNA (mtDNA) leakage, thereby alleviating neuroinflammation, exerting potential anti-PD effects, and improving cognitive function [21]. Donepezil improves cognitive function by inhibiting mitochondrial amyloid β accumulation and mitochondrial dysfunction and may positively regulate neurometabolism through

modulation of the adenosine monophosphate-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α) signaling pathway [22]. The enhanced efficacy observed with the combination therapy may be attributed to the distinct mechanisms of action of the two drugs, which may exert complementary effects

and produce synergistic therapeutic benefits. Liu P et al. [23] reported that butylphthalide combined with donepezil demonstrated a higher overall clinical response rate than donepezil alone in patients with vascular dementia, without significantly increasing the incidence of adverse events.

Second, this study showed that butylphthalide combined with donepezil notably alleviated clinical symptoms and reduced limitations in ADL and motor function for patients with cognitive impairment associated with PD. Furthermore, this combination therapy improved cognitive function and enhanced ADL performance. In a rat model of PD, butylphthalide intervention alleviated dyskinesia by inhibiting ferroptosis and oxidative stress, which may partially explain its beneficial effects on PD-related symptoms [24]. Another animal study indicated that butylphthalide improved cognitive dysfunction induced by chronic cerebral hypoperfusion through inhibition of hippocampal neuronal apoptosis and mitophagy, providing a possible explanation for its ameliorative effect on cognitive impairment in PD [25]. In the study by Fan et al. [26], butylphthalide intervention promoted improvements in cognitive function and ADLs in patients with post-stroke cognitive impairment, which was consistent with the findings of this study.

DA, GABA, and 5-HT are important neurotransmitters involved in PD pathophysiology, and are closely associated with cognitive function [27]. DA regulates reward processing, motivation, and memory by influencing tyrosine hydroxylase activity and DA transporter function [28]. GABA regulates synaptic transmission and plasticity through tonic inhibitory currents mediated by extrasynaptic receptors, thereby participating in cognitive processes such as learning and memory [29]. 5-HT contributes to learn-

Table 7. Comparison of SF-36 scores before and after treatment between the two groups

Item	Control group (n = 55)	Research group (n = 64)	t	P
Physical functioning (before treatment)	55.44 ± 5.21	54.45 ± 6.46	0.910	0.365
Physical functioning (after treatment)	70.64 ± 6.06	78.12 ± 6.56	6.423	< 0.001
Social functioning (before treatment)	58.73 ± 6.58	59.70 ± 6.27	0.822	0.413
Social functioning (after treatment)	68.04 ± 6.83	74.94 ± 6.90	5.464	< 0.001
Role physical (before treatment)	59.35 ± 6.77	59.05 ± 7.20	0.233	0.816
Role physical (after treatment)	71.67 ± 6.18	78.44 ± 7.06	5.522	< 0.001
Role emotional (before treatment)	54.49 ± 5.40	55.98 ± 6.21	1.311	0.193
Role emotional (after treatment)	72.20 ± 5.30	77.41 ± 5.60	5.186	< 0.001

Note: QoL, quality of life; SF-36, the 36-Item Short Form Health Survey.

Table 8. Exploratory subgroup analysis based on baseline Hoehn-Yahr staging or MoCA score

Subgroup variable	OR	95% CI	Interaction term (P for interaction)
H-Y staging (early stage vs. mid-to-late stage)	0.371	0.025-5.536	0.472
Baseline MoCA scores (continuous variable)	0.926	0.649-1.321	0.671

Note: H-Y staging, Hoehn-Yahr staging; MoCA, Montreal Cognitive Assessment.

ing and memory processes in brain regions such as the hippocampus through interactions with multiple receptor subtypes, including 5-HT_{1D}, 5-HT_{1F}, 5-HT₄, and 5-HT₇ receptors [30]. There is a certain correlation between alterations in neurotransmitter levels and cognitive changes. In this study, combined treatment with butylphthalide and donepezil significantly increased serum DA, GABA, and 5-HT levels in patients with PD-associated cognitive impairment.

PD is often accompanied by abnormalities in neurotrophic factors, which may contribute to cognitive decline. NT-3 and NGF are representative neurotrophic factors involved in neuronal maintenance and repair. NT-3 contributes to neuronal development and regeneration, and reduced NT-3 levels have been associated with neuronal injury and cognitive impairment caused by abnormal free radical metabolism [31]. NGF plays an important role in neuronal differentiation and survival, and its reduction following nerve injury may impede cognitive recovery [32]. In this study, combined treatment with butylphthalide and donepezil significantly increased the levels of NT-3 and NGF. In terms of oxidative stress, butylphthalide combined with donepezil more effectively improved oxidative stress in patients with cognitive impairment associated with PD. Wang et al. [33] reported that butylphthalide intervention achieved greater therapeutic benefits compared to

conventional treatment in patients with PD-related dementia, which actively upregulated the levels of neurotrophic factors and inhibited oxidative stress, consistent with the findings of this study.

Regarding safety, butylphthalide combined with donepezil did not significantly increase the overall incidence of adverse events. This may be related to the distinct pharmacologic mechanisms of the two drugs and the absence of significant pharmacologic interactions [34]. The combination therapy in this study demonstrated evident clinical benefits (NNT = 7.14) without increasing the risk of adverse events, suggesting favorable clinical applicability. Furthermore, butylphthalide combined with donepezil resulted in greater improvement in QoL across the PF, RP, SF, and RE dimensions of the SF-36 scale. This may be attributed to the enhanced symptom control, cognitive function, and ADL performance observed after combination therapy. Additionally, subgroup analysis revealed consistent benefits of the combination therapy regardless of disease stage and cognitive impairment severity, suggesting that its efficacy may not be restricted to specific patient subgroups.

Several limitations in this study should be acknowledged. First, a causal relationship among oxidative stress/neurotransmitter restoration/cognitive improvement was not statistically evaluated. Future studies incorporating cor-

relation analyses and mediation analyses are warranted to determine whether improvements in oxidative stress mediate the cognitive benefits of this treatment and to provide further mechanistic evidence. Second, this study adopted a non-random grouping design, which may have introduced selection bias. Future randomized controlled studies are needed to minimize potential selection bias.

Conclusion

Butylphthalide combined with donepezil may provide additional therapeutic benefits for patients with PD-associated cognitive impairment by improving clinical symptoms, cognitive function, ADLs, and QoL, elevating neurotransmitter and neurotrophic factor levels, and reducing oxidative stress, without significantly increasing the risk of overall adverse events. In addition, the efficacy of the combination therapy appears to be consistent regardless of baseline disease stage or cognitive impairment severity.

Disclosure of conflict of interest

None.

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