Original Article
Effect of Butylphthalide soft capsules on cognitive function and dementia-related factors in elderly patients with Parkinson's disease dementia during the COVID-19 pandemic

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Abstract: Objective: To observe the effect of Butylphthalide soft capsules on improving cognitive function, activity of daily living, and dementia-related factors of elderly patients with Parkinson's disease dementia (PDD) during the coronavirus disease 2019 (COVID-19) pandemic. Methods: The clinical data of 126 elderly patients with PDD admitted to the Second Affiliated Hospital of Zhengzhou University during the COVID-19 pandemic were analyzed retrospectively. Patients were assigned to a control group (conventional clinical treatment, n=50) and a research group (conventional clinical treatment combined with Butylphthalide soft capsules, n=76). The clinical response, clinical symptoms, cognitive function, activity of daily living (ADL), cerebral blood flow velocity, serum inflammatory factors, oxidative stress indices, neurotrophic factors, dementia-related factors, and drug safety were analyzed and compared between the two groups. Results: The overall response rate was significantly higher in the research group than in the control group (97.37% vs. 84.00%, P=0.017). After treatment, the clinical symptom-based scores and levels of serum inflammatory factors, malondialdehyde, and Parkinson disease protein 7 were significantly lower in the research group than in the control group (all P<0.001); the cognitive function and ADL scores, cerebral blood flow velocities, and levels of catalase, glutathione peroxidase, superoxide dismutase, neurotrophic factors, and neurotrophin-3 were significantly higher in the research group (all P<0.001). The incidence of adverse reactions was comparable between the two groups (4.00% vs. 6.58%, P=0.825). Conclusion: Butylphthalide soft capsules have a definite effect and good safety in elderly patients with PDD during the COVID-19 pandemic.

Keywords: Parkinson's disease dementia, COVID-19 pandemic, Butylphthalide soft capsules, cognitive function, dementia-related factor

Introduction

Parkinson's disease, characterized by non-motor symptoms and motor disturbance, is a clinically common neurodegenerative disease in the elderly population. If the condition is not controlled in time, it can develop into Parkinson's disease dementia (PDD), resulting in symptomatic deterioration, a further reduction in cognitive function, and even the loss of activity of daily living (ADL) [1, 2]. The coronavirus disease 2019 (COVID-19) is a highly contagious acute infectious disease that can be transmitted through close contact and respiratory droplets [3]. PDD is mostly diagnosed in the elderly people who are generally weak and complicated with underlying diseases. The elderly people are susceptible to the COVID-19. Once infected with novel coronavirus, they are likely to have a severe progressive disease [4]. Therefore, how to better treat elderly patients with PDD during the COVID-19 pandemic has become a topic of interest.

At present, no clinical specific treatment regimen is available for elderly patients with PDD, and disease progression is mainly controlled by medications [5, 6]. Donepezil, one of the common therapeutic drugs for elderly patients with PDD, can alleviate clinical symptoms by regulat-
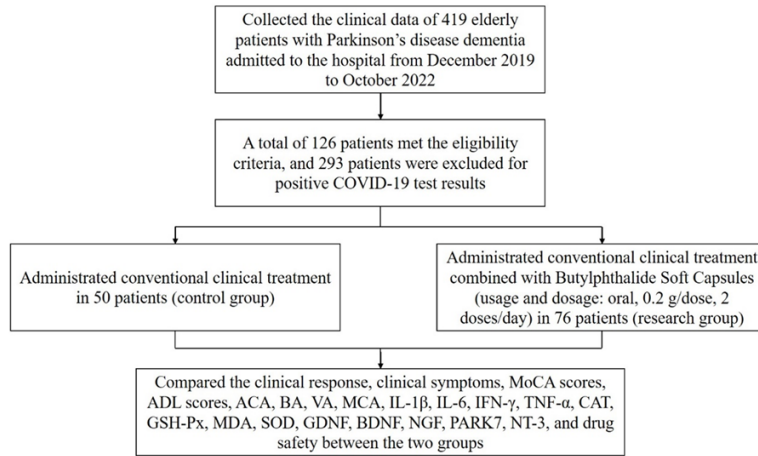
Figure 1. Study flow chart. MoCA: Montreal Cognitive Assessment; ADL: activity of daily living; ACA: anterior cerebral artery; BA: basilar artery; VA: vertebral artery; MCA: middle cerebral artery; IL: interleukin; IFN-γ: interferon-γ; TNF-α: tumor necrosis factor α; CAT: catalase; GSH-Px: glutathione peroxidase; MDA: malondialdehyde; SOD: superoxide dismutase; GDNF: glial cell line-derived neurotrophic factor; BDNF: brain-derived neurotrophic factor; NGF: nerve growth factor; PARK7: Parkinson disease protein 7; NT-3: neurotrophin-3.

ing neural signal transmission and increasing acetylcholine concentration, but it results in general overall response and unsatisfactory improvements in the cognitive function of some patients [7]. Butylphthalide soft capsules, common drugs for cerebrovascular diseases, can effectively improve the cognitive function of patients by reducing nerve cell injury, regulating cerebral nerve metabolism, and enhancing neurological function [8]. In recent years, Butylphthalide soft capsules have been applied in the clinical treatment of PDD in the elderly patients. Butylphthalide soft capsules can improve the neurological function of patients with PDD by inhibiting the neural signaling pathway, enhancing vascular endothelial function, and inhibiting oxygen free radical generation, but there are no systematic reports on their efficacy [9, 10]. In view of this, this study investigated the effect of Butylphthalide soft capsules on cognitive function and dementia-related factors in elderly patients with PDD during the COVID-19 pandemic.

Materials and methods

Clinical data

The clinical data of 126 elderly patients with PDD who had been treated in the Second Affiliated Hospital of Zhengzhou University during the COVID-19 pandemic from December

2019 to October 2022 were analyzed retrospectively. There were 68 males and 58 females, with an average age of 70.7±5.8 (61-87) years old. According to the Hoehn-Yahr scale, there were 50 patients with stage II condition, 35 patients with stage III condition, 25 patients with stage IV condition, and 16 patients with stage V condition. According to symptoms, there were 40 patients with tremor, 58 patients with muscle stiffness and slowness of movement, and 28 patients with mixed symptoms. The mean course of disease was 6.43± 2.05 (1-13) years. According to concomitant diseases, there were 38 patients with diabetes, 45 patients with hypertension, and 32 patients with coronary heart disease. According to the severity of dementia, there were 51 patients with mild dementia and 75 patients with moderate dementia. Patients were assigned to two groups by different treatment regimens: a control group (conventional clinical treatment, n=50) and a research group (conventional clinical treatment combined with Butylphthalide soft capsules, n=76). The study flow chart is shown in **Figure 1**. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhengzhou University.

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the diagnostic criteria for Parkinson's disease dementia [11]; Patients with complete clinical data; Patients with an age of 60-90 years old; Patients with mild or moderate dementia; and patients who received no drugs affecting response evaluation within 1 month before enrollment.

Exclusion criteria: Patients who were allergic to Butylphthalide or other drugs used in this study; Patients complicated with malignant tumors, severe organic diseases, cardiovascular/cerebrovascular diseases, autoimmune diseases, severe cognitive disorders or mental disorders; Patients with a past medical history of epilepsy

or neuropathy; or patients with other causes of dementia, or infected with novel coronavirus.

Methods

Treatment regimens for the two groups were developed by referring to the Chinese Guidelines for the Treatment of Parkinson's Disease (3rd Edition). All patients received conventional treatment including improving muscle tension, and donepezil (Jiangsu Haici Biological Pharmaceutical Co., Ltd., Yangtze River Pharmaceutical Group, GYZZ H20040102; usage and dosage: oral, initial dose of 5 mg/dose, once a day for 1 week, followed by a maintenance dose of 10 mg/day). The research group was treated with Butylphthalide soft capsules (CSPC-NBP Pharmaceutical Co., Ltd., GYZZ H20050299; usage and dosage: oral, 0.2 g/dose, twice a day) in addition to the above treatment. Both groups were treated for 12 weeks.

Outcome measures

Clinical response. Excellent response: symptoms basically disappeared or were significantly alleviated, patients were basically self-care in ADLs, and the Unified Parkinson's Disease Rating Scale (UPDRS) score was reduced by >60% relative to that before treatment [12]; response: symptoms were alleviated, patients were self-care in some ADLs, and the UPDRS score was reduced by 30%-60% relative to that before treatment; no response: symptoms were unrelieved or progressed, patients were unable to do self-care in ADLs, and the UPDRS score was reduced by <30% relative to that before treatment. The overall response rate was the sum of excellent response and response rates.

Clinical symptoms. Two experienced nurses were responsible for scale evaluation of patients. The nurses were trained first to master the evaluation methods of each scale and then evaluated motor activity using the UPDRS before treatment and after 12 weeks of treatment. The lower the score, the milder the symptoms.

Cognitive function. Visuospatial skills, attention and concentration were assessed using the Montreal Cognitive Assessment (MoCA) before treatment and after 12 weeks of treatment, with a total score of 30, and scores of <10,

10-17, and 18-26 indicated severe, moderate, and mild cognitive impairment, respectively [13].

ADLs. Activities of bathing and climbing up and down stairs were assessed using the ADL scale before treatment and after 12 weeks of treatment [14]. The lower the score, the worse the ADLs.

Cerebral blood flow velocity. Velocities of the anterior cerebral artery (ACA), basilar artery (BA), vertebral artery (VA), and middle cerebral artery (MCA) in the two groups were measured by transcranial doppler ultrasonography before treatment and after 12 weeks of treatment.

Inflammatory factors. Six mL of fasting venous blood were collected from the two groups of patients and centrifuged. The levels of interleukin (IL)-1β, IL-6, interferon-γ (IFN-γ), and tumor necrosis factor α (TNF-α) were measured by enzyme-linked immunosorbent assay (ELISA) before treatment and after 12 weeks of treatment. The IL-1β and IL-6 kits were provided by Shanghai Rayzbio Technology Co., Ltd. (catalog numbers: LZ-E031252 and LZ-E030739), and the IFN-γ and TNF-α kits were provided by Shanghai Jingfeng Biology Science and Technology Co., Ltd. (catalog numbers: TF0480R and TF33207M).

Oxidative stress. The levels of serum catalase (CAT), glutathione peroxidase (GSH-Px), malondialdehyde (MDA), and superoxide dismutase (SOD) in the patients of two groups were measured by ELISA before treatment and after 12 weeks of treatment using the kits provided by Beijing Kaishiyuan Biotechnology Co., Ltd. (catalog numbers: SH-1293, SH-1289, SH-1281, and SH-1550).

Neurotrophic factors. The levels of serum glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) in the patients of two groups were measured by ELISA before treatment and after 12 weeks of treatment using the kits provided by Shanghai Xuanke Biotechnology Co., Ltd. (catalog numbers: XK-E1168, XK-E1188, and XK-E1128).

Dementia-related factors. The levels of serum recombinant human Parkinson disease protein

Table 1. Comparison of baseline data between the two groups (n/($\bar{x}$±sd))

Group	Control (n=50)	Research (n=76)	χ^2/t	P
Sex			0.138	0.711
Male	28	40		
Female	22	36		
Age (years)	70.5±6.7	71.0±6.4	0.421	0.674
Hoehn-Yahr stage			1.141	0.767
II	20	30		
III	12	23		
IV	10	15		
V	8	8		
Symptom classification			0.950	0.622
Tremor	16	24		
Muscle stiffness and slowness of movement	25	33		
Mixed symptoms	9	19		
Course of disease (years)	6.21±2.06	6.59±2.11	0.998	0.320
Concomitant disease			0.047	0.977
Diabetes	16	22		
Hypertension	20	25		
Coronary heart disease	14	18		
Severity of dementia			0.080	0.777
Mild	21	30		
Moderate	29	46		

7 (PARK7) and neurotrophin-3 (NT-3) in the patients of two groups were measured by ELISA before treatment and after 12 weeks of treatment using the kits provided by Shenzhen HSA Biotech Co., Ltd. (catalog numbers: HAS-53183 and HAS-51674).

Drug safety. Adverse reactions were compared between the two groups.

Statistical analysis

SPSS 23.0 was used for data analysis. The measured data (clinical symptoms, cognitive function, ADLs, cerebral blood flow velocity, inflammatory factors, oxidative stress, neurotrophic factors, and dementia-related factors) were described by mean ± standard deviation ($\bar{x}$±sd), and intergroup and intragroup comparisons were conducted by independent samples *t* test and paired samples *t* test, respectively. The counted data (response and safety) were described by percentage and analyzed by the chi-square test. A *P* value less than 0.05 indicated a significant difference.

Results

Comparison of baseline data between the two groups

Baseline data such as age, Hoehn-Yahr stage, sex, symptom classification, course of disease, concomitant disease, and severity of dementia were comparable between the two groups (all *P*>0.05, **Table 1**).

Comparison of clinical response between the two groups

The overall response rate was significantly higher in the research group than in the control group (97.37% vs. 84.00%, *P*=0.017, **Table 2**).

Comparison of clinical symptoms, cognitive function, and activities of daily living between the two groups

Clinical symptoms, cognitive function, and ADL indices of the two groups were comparable before treatment (all P>0.05). After treatment,

Table 2. Comparison of clinical response between the two groups (n, %)

Group	Excellent response	Response	No response	Overall response rate
Control (n=50)	25 (50.00)	17 (34.00)	8 (16.00)	42 (84.00)
Research (n=76)	48 (63.16)	26 (34.21)	2 (2.63)	74 (97.37)
χ^2				5.660
P				0.017

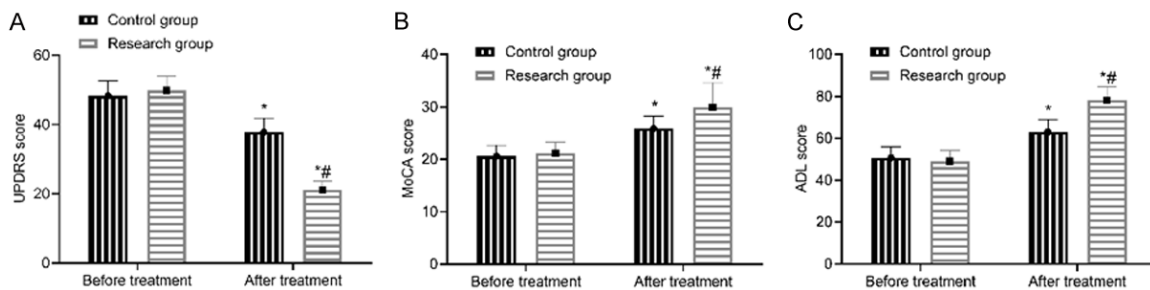Note: Rates were compared using the Chi-square test.

Figure 2. Comparison of clinical symptoms, cognitive function, and activities of daily living between the two groups. A: UPDRS score; B: MoCA score; C: ADL score. Compared to before treatment in the group, *$P<0.05$; compared to the control group, #$P<0.05$. UPDRS: Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; ADL: activity of daily living.

Table 3. Comparison of cerebral blood flow velocity between the two groups ($\bar{x}\pm$sd, m/s)

Group	Control (n=50)	Research (n=76)	t	P
ACA				
Before treatment	37.69±2.89	37.92±2.75	0.450	0.653
After treatment	45.88±3.67*	52.18±4.24*	8.597	<0.001
BA				
Before treatment	26.03±2.25	25.78±2.10	0.636	0.526
After treatment	33.45±2.56*	38.08±3.13*	8.713	<0.001
VA				
Before treatment	22.39±2.05	22.86±2.09	1.244	0.216
After treatment	29.77±2.43*	34.75±2.58*	10.845	<0.001
MCA				
Before treatment	40.85±3.62	41.25±3.71	0.598	0.551
After treatment	50.05±4.62*	60.18±5.24*	11.117	<0.001

Note: Compared to before treatment in the group, *$P<0.05$. ACA: anterior cerebral artery; BA: basilar artery; VA: vertebral artery; MCA: middle cerebral artery.

the UPDRS scores were significantly decreased in both groups and lower in the research group (P<0.05), while the MoCA and ADL scores were increased in both groups and higher in the research group (all P<0.05, **Figure 2**).

Comparison of cerebral blood flow velocity between the two groups

Cerebral blood flow velocities of the two groups were comparable before treatment (all *P*>0.05).

After treatment, the velocities of the ACA, BA, VA, and MCA were significantly increased in both groups and higher in the research group (all *P*<0.001, **Table 3**).

Comparison of inflammatory factors between the two groups

The levels of serum inflammatory factors were comparable between the two groups before treatment (all *P*>0.05). After treatment, the lev-

Table 4. Comparison of serum inflammatory factors between the two groups ($\bar{x}\pm sd$)

Group	Control (n=50)	Research (n=76)	t	P
IL-1β (ng/L)				
Before treatment	63.69±4.89	64.06±5.05	0.407	0.684
After treatment	44.06±3.82[*]	30.28±3.30[*,#]	21.531	<0.001
IL-6 (μg/L)				
Before treatment	218.65±22.15	217.46±21.39	0.301	0.764
After treatment	158.95±16.85[*]	115.15±13.05[*,#]	16.397	<0.001
IFN-γ (pg/mL)				
Before treatment	85.63±6.35	84.82±6.75	0.675	0.501
After treatment	60.58±5.09[*]	43.25±4.92[*,#]	19.081	<0.001
TNF-α (pg/L)				
Before treatment	61.29±5.15	61.74±5.24	0.475	0.636
After treatment	42.86±3.96[*]	31.08±3.14[*,#]	18.552	<0.001

Note: Compared to before treatment in the group, [*]$P<0.05$; compared to the control group, [#]$P<0.05$. IL: interleukin; IFN-γ: interferon-γ; TNF-α: tumor necrosis factor α.

Table 5. Comparison of oxidative stress indices between the two groups ($\bar{x}\pm sd$)

Group	Control (n=50)	Research (n=76)	t	P
CAT (U/mL)				
Before treatment	60.82±5.36	61.23±5.57	0.410	0.682
After treatment	70.84±6.22[*]	86.85±6.48[*]	13.268	<0.001
GSH-Px (U/mL)				
Before treatment	20.39±2.05	20.81±2.08	1.115	0.267
After treatment	25.96±2.12[*]	32.35±2.24[*]	15.999	<0.001
MDA (μmol/L)				
Before treatment	9.86±1.85	9.61±1.82	0.749	0.455
After treatment	6.58±1.66[*]	4.25±1.58[*]	7.937	<0.001
SOD (U/mL)				
Before treatment	75.89±6.16	76.47±6.31	0.510	0.611
After treatment	85.85±8.15[*]	97.85±8.68[*]	7.776	<0.001

Note: Compared to before treatment in the group, [*]$P<0.05$. CAT: catalase; GSH-Px: glutathione peroxidase; MDA: malondialdehyde; SOD: superoxide dismutase.

els of serum IL-1β, IL-6, IFN-γ, and TNF-α were significantly decreased in both groups and lower in the research group (all $P<0.001$, **Table 4**).

Comparison of oxidative stress indices between the two groups

The levels of oxidative stress indices were comparable between the two groups before treatment (all $P>0.05$). After treatment, the MDA level was significantly decreased in both groups and lower in the research group (all $P<0.001$), while the CAT, GSH-Px, and SOD levels were significantly increased in both groups and higher in the research group (all $P<0.001$, **Table 5**).

Comparison of neurotrophic factors between the two groups

The levels of neurotrophic factors were comparable between the two groups before treatment (all $P>0.05$). After treatment, the levels of serum GDNF, BDNF, and NGF were significantly increased in both groups and higher in the research group (all $P<0.05$, **Figure 3**).

Comparison of dementia-related factors between the two groups

The levels of dementia-related factors were comparable between the two groups before treatment (all $P>0.05$). After treatment, the
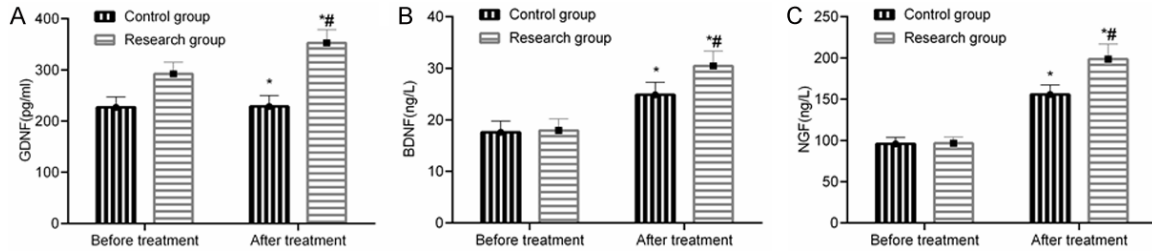
Figure 3. Comparison of neurotrophic factors between the two groups. A: GDNF; B: BDNF; C: NGF. Compared to before treatment in the group, $^*P<0.05$; compared to the control group, $^\#P<0.05$. GDNF: glial cell line-derived neurotrophic factor; BDNF: brain-derived neurotrophic factor; NGF: nerve growth factor.

Table 6. Comparison of dementia-related factors between the two groups ($\overline{x}\pm sd$)

Group	PARK7 (μg/L)		NT-3 (μg/L)	
	Before treatment	After treatment	Before treatment	After treatment
Control (n=50)	36.55±2.48	26.06±2.18*	18.69±2.65	25.69±2.86*
Research (n=76)	36.12±2.37	14.58±2.02*	19.12±2.77	33.75±3.05*
t	0.978	30.242	0.867	14.872
P	0.330	<0.001	0.388	<0.001

Note: Compared to before treatment in the group, $^*P<0.05$. PARK7: Parkinson disease protein 7; NT-3: neurotrophin-3.

Table 7. Comparison of drug safety between the two groups (n, %)

Group	Dizziness	Nausea	Diarrhea	Total
Control (n=50)	0	1 (2.00)	1 (2.00)	2 (4.00)
Research (n=76)	1 (1.32)	2 (2.63)	2 (2.63)	5 (6.58)
X^2	0.000	0.000	0.000	0.049
P	1.000	1.000	1.000	0.825

Note: Rates were compared using the Chi-square test.

PARK7 level was significantly decreased in both groups and lower in the research group ($P<0.001$), while the NT-3 level was significantly increased in both groups and higher in the research group ($P<0.001$, **Table 6**).

Comparison of drug safety between the two groups

The incidences of adverse reactions were comparable between the two groups (4.00% vs. 6.58%, $P=0.825$, **Table 7**).

Discussion

Elderly patients with Parkinson's disease dementia (PDD) are susceptible to COVID-19, so it is of great significance to strengthen treatment and management of these patients during the pandemic [15, 16].

In this study, elderly patients with PDD were treated with Butylphthalide soft capsules. The results showed that the overall response rate in the research group was higher than that in the control group. After treatment, the UPDRS scores were significantly decreased in both groups and lower in the research group, while the MoCA, ADL scores and velocities of the ACA, BA, VA, and MCA were significantly increased in both groups and higher in the research group. The incidence rates of adverse reactions were comparable between the two groups. The results suggested that Butylphthalide can effectively alleviate clinical symptoms, restore cognitive function and ADLs, and improve the cerebral blood flow velocity in elderly patients with PDD, with good safety. This may be attributable to the main component of Butylphthalide soft capsules, racemic 3-n-butylphthalide, being able toprotects neurological function by reducing the release of inflammatory cytokines, inhibiting inflammatory response, and avoiding neuroinflammatory necrosis through inhibiting the activity of glial cells and neural signaling pathways [17, 18]. Also, Butylphthalide soft capsules can act on the vascular endothelium to increase the expression of vascular endothelial growth factor and angiopoietin-1, improve

blood circulation in the brain tissue, maintain metabolic capacity, avoid neuronal apoptosis, and thus improve the cerebral blood flow velocity [19]. In addition, Butylphthalide soft capsules can effectively inhibit the generation of oxygen free radicals, improve mitochondrial function, inhibit dopamine release, and thus improve the neurological function of patients [20]. Animal experiments have found that Butylphthalide soft capsules can improve the chronic cerebral hypoperfusion state, reduce the content of amyloid beta-protein, and alleviate the degree of nerve cell damage induced by amyloid beta-protein in rats with Parkinson's disease dementia [21].

The inflammatory response has been clinically found to be involved in the pathologic process of Parkinson's disease dementia [22]. IL-1β, IL-6, and TNF-α, as proinflammatory factors, can activate microglial cells and macrophages and cause neuron damage by multiple pathways. IFN-γ can induce a series of neurologic symptoms such as motor function impairment and cognitive impairment by promoting tryptophan catabolism. Ramanzini et al. found that the levels of serum IL-6, TNF-α, and other inflammatory factors in patients with PDD were significantly higher than those in healthy population [23]. Relevant studies have found that oxygen free radical damage plays an important role in the occurrence and development of PDD [24]. Most patients with PDD have different degrees of free radical clearance disturbance in the brain tissue, mainly manifested as increased lipid peroxidation substances such as MDA, and decreased activity of antioxidant enzymes such as CAT, GSH-Px, and SOD. These further aggravate dopaminergic neuron damage and induce a series of dementia symptoms [25]. Neurotrophic factors such as GDNF, BDNF, and NGF have been confirmed to participate in the pathogenesis of various neurodegenerative diseases, and the mechanism of action is that neurotrophic factors promote the growth of neurons mainly by binding to tyrosine kinase receptors to activate downstream signaling pathways [26]. PARK7 and NT-3 are closely related to PDD, and PARK7 is a pathogenic gene for early onset and has anti-oxidative stress and proteolytic enzyme effects [27]. After the neurological function of patients with PDD is impaired, a large amount of PARK7 is released, which inhibits reactive oxygen spe-cies and damages neurons, and the PARK7 level is increased in patients. NT-3 is involved in the differentiation and growth of neurons and has the function of protecting nerve cells. NT-3 can reduce nerve injury induced by free radical excitation by promoting calcium ion balance and enhancing free radical metabolism. The study results showed that the levels of serum IL-1β, IL-6, IFN-γ, TNF-α, MDA, and PARK7 were significantly lower in the research group than in the control group, while the levels of CAT, GSH-Px, SOD, GDNF, BDNF, NGF, and NT-3 were significantly higher in the research group than in the control group. The results suggested that the mechanism of action of Butylphthalide soft capsules in the treatment of PDD in elderly patients may be related to the reduction in inflammatory response and oxidative stress and the regulation of levels of neurotrophic factors and dementia-related factors. This suggests that butylphthalide can inhibit the inflammatory response by suppressing the overactivation of microglia; at the same time, it can down-regulate the intracellular calcium concentration, reduce the release of glutamic acid, remove oxygen radicals, alleviate oxidative stress, and repair damaged nerve cells, thus promoting the recovery of neurons and improving the levels of serum neurotrophic factors such as GDNF, BDNF, and NGF [28, 29].

In conclusion, Butylphthalide soft capsules had efficacy and good safety in elderly patients with Parkinson's disease dementia during the COVID-19 pandemic, which can effectively alleviate symptoms, restore cognitive function and ADLs, improve cerebral blood flow velocity, reduce inflammatory response and oxidative stress, and regulate the levels of neurotrophic factors and dementia-related factors. However, this study has some limitations, such as a small sample size and a single center, and the results might be biased. The long-term response and recurrence of Parkinson's disease dementia in elderly patients using Butylphthalide soft capsules were not analyzed, which is also a future research direction.

Disclosure of conflict of interest

None.

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