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Effectiveness of DL-3-n-butylphthalide in the treatment of poststroke cognitive impairment and its associated predictive cytokines: a systematic review and meta-analysis

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Abstract

Background The efficacy of DL-3-n-butylphthalide (NBP) in the treatment of post-stroke cognitive impairment (PSCI) has been reported previously. However, the course of treatment that shows curative effect and cytokines predictive of the efficacy of NBP in the treatment of PSCI have not been systematically evaluated. This study aimed to assess the efficacy, course of treatment, and cytokines that can predict the effectiveness of NBP in treating poststroke cognitive impairment PSCI.

Methods This study has been registered with PROSPERO (registration number CRD42024518768). Randomized controlled trial (RCT) data dated by November 12, 2023 were retrieved from the PubMed, Embase, Cochrane Library, Web of Science, Wanfang, CNKI, CSTJ, and SinoMed databases using medical subject terms combined with free words. The updated Cochrane RoB-I Risk of Bias tool was utilized for literature quality evaluation. Statistical analysis were carried out using Review Manager 5.4.1 software.

Results Thirty-eight original studies involving 5417 PSCI patients were analyzed. The results showed that NBP had a beneficial impact on cognitive function in PSCI patients when used alone or in combination therapy, as assessed by the Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scale. The effect sizes were significant for both monotherapy and combination therapy. Subgroup analyses based on treatment cycle indicated that NBP enhanced cognitive function in PSCI patients from 1 week after intervention: MMSE (SMD = 0.43, 95% CI [0.28, 0.58], $P < 0.001$), MoCA (SMD = 0.44, 95% CI [0.27, 0.61], $P < 0.001$). There was a cumulative enhancement in cognitive function within 6 months after NBP treatment based on the MoCA scores (SMD = 0.61, 95% CI [0.30, 0.91], $P < 0.001$). Furthermore, decreased levels of the cytokines Hs-CRP, TNF-α, IL-6, IL-8, Hcy, NSE, MDA, MMP-9, and Cys-C

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(SMD = −2.28, 95% CI [−2.97, 1.58], $P < 0.001$) and increased levels of BDNF, VEGF, and TIMP-1 (SMD = 2.80, 95% CI [1.66, 3.94], $P < 0.001$) were also predictive of treatment efficacy.

Conclusion NBP plays a beneficial role in improving cognitive function in PSCI patients, and their prognoses could be predicted by serum cytokine levels. However, high-quality, multicenter, multisample, and RCTs are still needed to confirm the clinical validity of NBP due to its low methodological quality.

Keywords Cognitive function, MMSE, MoCA, Potential mechanisms, Randomized controlled trial

Introduction

Poststroke cognitive impairment (PSCI) is a common consequence following stroke, and is characterized by cognitive decline caused by stroke ranging from mild cognitive impairment to dementia [1, 2]. PSCI is most frequently observed in the first year after stroke, affecting up to 60% of survivors. Approximately 44% of patients experience cognitive issues 26 months after stroke [3, 4]. PSCI patients commonly exhibit cognitive deficits such as memory loss, attention issues, and linguistic function impairment. These challenges impact their daily performances, quality of life and capacity to resume work [5]. The expert consensus recommends the cholinesterase inhibitors donepezil, carboplatin, and galantamine; the N-methyl-D-aspartate (NMDA) receptor antagonist memantine; and the calcium antagonists nimodipine and olanzapine for the treatment of PSCI. However, there is inadequate evidence to support the efficacy of these medications in treatment [2, 6, 7]. Current clinical evidence for the use of medications to enhance cognitive function in PSCI patients is primarily derived from studies on Alzheimer's disease, whereas there is a lack of convincing basic or clinical evidence supporting the ability of pharmacological treatments for PSCI to promote cognitive recovery [8].

DL-3-n-butylphthalide (NBP) is a synthetic molecule derived from l-3-n-butylphthalide isolated from celery seeds. It is a compound independently developed in China that not only improves the acute ischemic stroke symptoms but also aids the long-term recovery of patients [9]. Multiple clinical studies have indicated that NBP has protective effects on animal models of ischemic stroke [10–12]. The protective mechanism of NBP against ischemic stroke may involve various pathophysiological processes, such as anti-inflammatory effects, oxidation reduction [13], reduction in cerebral edema and blood–brain barrier damage [14], decreased in neuronal apoptosis [15], prevention of thrombotic formation [16], and safeguarding of mitochondria [17]. A recent basic research indicated that, in addition to improving acute stroke symptoms, NBP might also promote cognitive recovery following stroke by reducing inflammation and oxidative stress [18]. The 2021 Expert Consensus on the Management of Cognitive Impairment after Stroke recommends the use of NBP as a pharmacologic treatment for PSCI with Class II, Level B evidence [2]. In 2022, Fan and colleagues conducted a meta-analysis to assess the therapeutic efficacy and safety of NBP against PSCI. The findings indicated that NBP effectively reduced neurological deficits symptoms and enhanced cognitive function and daily living abilities [19]. However, because most of the included original studies were randomized controlled trials (RCTs) with small sample sizes, and the simplistic search strategy might also cause incomplete data retrieval and publication bias. In addition, the meta-analysis did not specify the duration for which NBP affected patients with PSCI despite demonstrating the effectiveness of NBP in treating PSCI. Furthermore, there is a lack of objective indicators for predicting the efficacy of NBP in treating PSCI. The levels of serum cytokines such as IL-6, IL-8, CRP, MDA, BDNF, and Hcy [20–22] have been identified as biomarkers in studies, but there is inconsistency in whether changes of these cytokines are predictive of the therapeutic effect of NBP. Therefore, it is essential to systematically assess and analyze the clinical efficacy and time to act of NBP in treating PSCI, and to identify cytokines that can predict the effectiveness of NBP to provide a new evidence-based foundation for the clinical treatment of this disease.

Methods

Protocol and registration

This systematic review was conducted in accordance with the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions [23]. This systematic review has been registered on the PROSPERO International prospective register of systematic reviews (ID CRD42024518768).

Data retrieval strategy

Data retrieval was conducted across eight databases: China National Knowledge Infrastructure (CNKI, https://www.cnki.net), Wanfang Database (https://www.wanfangdata.com), China Science and Technology Journals Database (CSTJ, https://qikan.cqvip.com), Chinese Biomedical Literature Service System (SinoMed, https://www.sinomed.ac.cn), PubMed (www.ncbi.nlm.hih.gov), Embase (www.embase.com), Cochrane Library (https://www.cochrane.com), and Web of Science (WOS, https://

www.webofscience.com), using a combination of free words and the keywords "butylphthalide" and "poststroke cognitive impairment". The dates of retrieved data ranged from the establishment of the database to November 12, 2023.

Inclusion criteria

Type of studies

Eligible retrieved data were RCT studies on the improvement of cognitive function in PSCI patients using NBP.

Characteristics of the enrolled patients

Each study group in the publication contained between 30 and 90 patients diagnosed with PSCI. The average age of patients ranged between 35 and 73 years, with variable disease durations. All patients included in the analysis articles have signed written informed consent forms by themselves or their legal representatives when participating in relevant studies.

Interventions

All original studies included in the analysis administered NBP alone or in combination with other medications to the experiment group, whereas the control group received drugs such as donepezil, galantamine, memantine, olaxetan, and nimodipine as per expert consensus or only medications for the patients' pre-existing diseases. The only variable that differed between the experiment and control groups in the original studies was the administration of NBP. All other variables were controlled to ensure that the dosage, duration of treatment, and duration of continuous treatment were the same for both groups.

Outcome indicators for the included literature

The outcome indicators should include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) scales for the assessment of cognitive function.

Exclusion criteria

Literatures lacking raw data, reviews or systematic reviews, duplicate literatures, studies of undetermined type or not conforming to RCT standards, studies with inconsistent content or outcome indicators, and those involving animal experiments were excluded.

Literature review and quality assessment

We organized the literatures retrieved from databases using Endnote X9. Two researchers initially independently screened the literature by reviewing the title, abstract, and authors to eliminate duplicate studies. They then downloaded the full text of the remaining literature for thorough examination, and determined their relevance to this study following the above criteria. The common literatures agreed by both researchers were included in this study. In the case of differing opinions, a third researcher was consulted.

Two researchers independently assessed the literature quality using the RCT evaluation tool recommended by the Cochrane RoB-I Handbook of Systematic Evaluation 5.1, which included seven criteria: generation of randomized sequences, concealment of the allocation scheme, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting of findings, and other sources of bias. The literature was assessed and classified into three categories according to the evaluation indicators provided: "high risk of bias," "uncertain risk of bias," and "low risk of bias". A third researcher resolved any disagreements that occurred throughout the evaluation.

Data extraction

Data were extracted from qualified literature containing the following information: name of first author, publication year, research methods, sample size, age, sex, participant demographics, interventions, drug dosages, treatment duration, serum cytokines, and outcome indicators.

Statistical analysis

The gathered information was statistically analyzed using RevMan 5.4 software (Cochrane Collaboration). Relative risk (RR) was utilized for dichotomous variables, whereas mean difference (MD) or standardized mean difference (SMD) analysis was used for continuous variables. The 95% confidence intervals (CIs) were calculated for each effect size. Cochrane's I^2 and P values were utilized to assess the heterogeneity of the studies included. In case of $I^2<50\%$ and $P>0.1$, no statistical heterogeneity was found among the studies, and the fixed-effects model was employed for statistical analysis. $P<0.1$ or $I^2>50\%$ indicated statistical heterogeneity among studies, the source of which should be investigated. If heterogeneity persisted and clinical results were consistent, a random-effects model was applied for statistical analysis. We conducted subgroup analyses based on varied interventions on the control group of different literature sources to address potential heterogeneity. We utilized SMD analysis for continuous variable studies. In case of the existence of potential heterogeneity caused by missing information and different intervention strategies in the original studies, which could not be eliminated, a random effects model was utilized. Funnel plots were used to analyze publication bias.

Results

Literature screening

A total of 244 literatures were initially screened based on our methods, and 128 documents remained after removing duplicates using EndnoteX7. Next, 8 systematic reviews and 9 animal studies were excluded by reviewing the titles and abstracts, leaving 111 studies. After reviewing the full text, 55 studies were excluded for not conforming to the objective of this study, 6 for not meeting the outcome indicators, 8 for lacking data, and 4 for non-RCT. Ultimately, 38 remaining studies [24–61] were included in this study after thorough assessment. Figure 1 illustrates the detailed literature screening process.

Characteristics of the included literature

Our systematic evaluation comprised 38 RCTs published in Chinese-language between 2016 and 2023, involving 5417 individuals with PSCI. The average age of all patients varied between 35 and 73 years, and the duration of treatment ranged between 0.5 and 6 months. There were 30–90 patients in each treatment or control group in Each of 38 original trials. Twenty-seven studies utilized MMSE and 27 with MoCA to evaluate cognitive function as an outcome indicator. Fourteen studies compared the efficacy of NBP used alone with that of the standard treatment in the control group. Twenty-four studies compared the efficacy of NBP in combination with other drugs to that in the control group. Table 1 listed the features of all 38 investigations.

Methodological assessment of the included literature

Methodological assessment of the quality of the studies was performed (Supplementary Fig. 1). One study had a low risk of bias and was of relatively high quality. Twenty-seven studies had moderate risks of bias, and 10 studies had high risks of bias. Concerns were raised about the blinding process of these studies, as 36 out of 38 studies did not provide clear information regarding blinding. In addition, 10 studies provided insufficient information on randomization methods. Supplementary Fig. 2 illustrates the result of methodological assessments for each item.

Assessment of cognitive function

MMSE

Eleven studies (Fan et al. [25]; Fan et al. [34]; Fu and Ba [37]; Huang [42]; Mao et al. [47]; Meng et al. [48]; Ni et al. [61]; Su [52]; Zhang, 2021 [56]; Zhang and Ye [27]; Zhan et al. [55]) that enrolled a total of 1264 PSCI patients reported the clinical efficacy of NBP monotherapy, as shown in Fig. 2a. The control groups were all on baseline medication, and there was no significant heterogeneity in the results ($P=0.12$, $I^2=36\%$). After combining

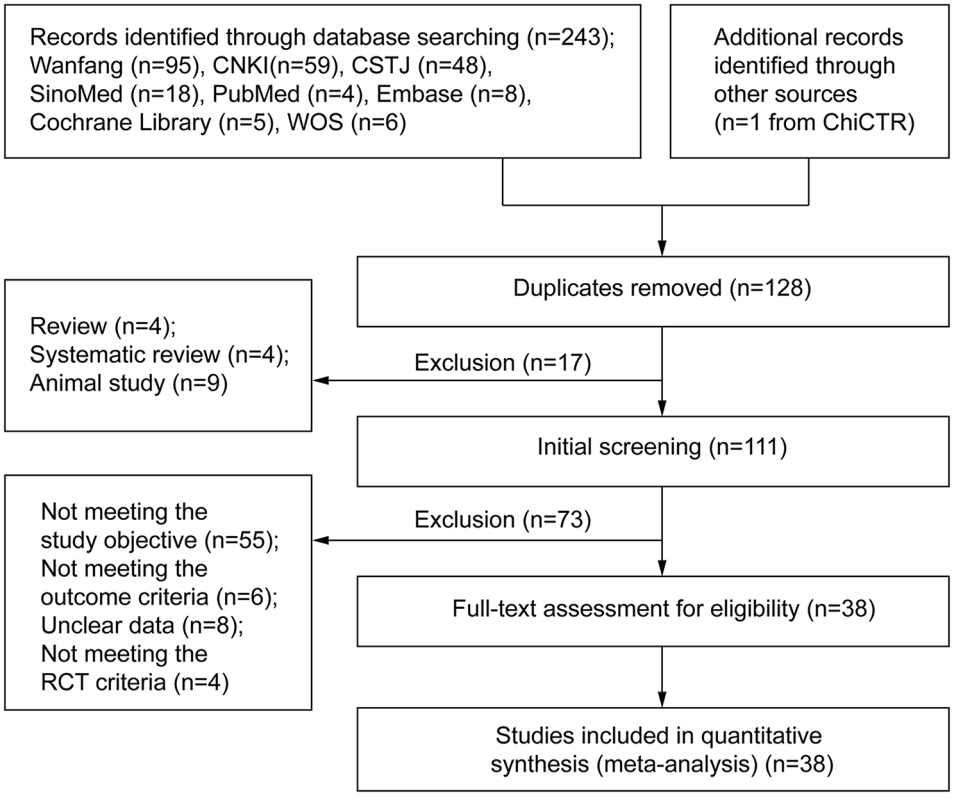

Fig. 1 Flowchart for data screen and filter

Table 1 Characteristics of included randomized controlled trials in literature

Ref no.	Sample size (*n*)	Age (year)	Male/Female (Male%)	Intervention	Drug dose	Course of treatment (month)	Cytokine	Outcome evaluation method
	Trial control	Trial control	Trial control	Trial control				
[24]	60 60	(62.52 ± 5.46); (62.39 ± 5.52)	(32/28) 53%; (33/27) 55%	NBP + Donepezil; Donepezil	NBP: 200 mg Tid; Donepezil: 20 mg qd	6	-	MoCA
[25]	32 30	(62.25 ± 5.10); (60.90 ± 5.77)	(18/14) 56%; (16/14) 53%	NBP; Basic treatment	NBP: 200 mg Tid; -	2	-	MMSE + MoCA
[26]	50 50	(45.0 ± 2.3); (45.0 ± 2.3)	(25/25) 50%; (30/20) 60%	NBP + Huperzine A; Huperzine A	NBP: 200 mg Qid; HuperzineA: 0.2 mg bid	2/3	-	MoCA
[27]	76 74	(58.12 ± 9.87); (56.98 ± 10.15)	(40/36) 53%; (39/35) 53%	NBP; Basic treatment	NBP: 100 ml/12 h; iv	0.5	-	MMSE + MoCA
[28]	73 73	(40–70); 	- 	NBP; Basic treatment	NBP: 200 mg Tid; -	3	-	MMSE
[29]	38 38	(63.6 ± 2.6); (63.5 ± 2.7)	(19/19) 50%; (20/18) 53%	NBP + Citicoline sodium; Citicoline sodium	NBP: 25 mg iv; Citicoline sodium: 500 mg qd	1/3	TNF-α, IL-6, NSE, BDNF	MMSE + MoCA
[30]	60 60	(63.8 ± 1.87); (64.0 ± 2.83)	(34/26) 57%; (33/27) 55%	NBP + Nimodipine; Nimodipine	NBP: 200 mg Tid; Nimodipine: 40mgTid	1	-	MMSE
[31]	79 79	(65.13 ± 7.24); (64.59 ± 6.38)	(40/39) 57%; (41/38) 55%	NBP + Donepezil; Donepezil	NBP: 200 mg Bid; Donepezil: 50 mg qd	-	Hs-CRP, NSE	MoCA
[32]	60 60	(62.52 ± 5.46); (62.39 ± 5.52)	(35/25) 58%; (38/22) 63%	NBP + Citicoline sodium; Citicoline sodium	NBP: 25 mg Bid; iv Citicoline sodium: 500 mg Bid	0.5	MMP-9, TIMP-1	MMSE
[33]	30 30	(67.0 ± 7.0); (62.0 ± 8.0)	(24/6) 80%; (16/14) 53%	NBP + Idebenone; Idebenone	NBP: 200 mg Tid; Idebenone: 30 mg Tid	2	-	MMSE
[34]	44 43	(51 ± 3.54); (53 ± 5.94)	(20/24) 45%; (22/21) 51%	NBP; Basic treatment	NBP: 200 mg Tid; -	3/4	-	MMSE + MoCA
[35]	60 60	(69.2 ± 4.5); (69.1 ± 4.6)	(35/25) 58%; (36/24) 60%	NBP + Citicoline sodium; Citicoline sodium	NBP: 200 mg Tid; Citicoline sodium: 500 mg Tid	0.5	-	MMSE
[36]	62 58	(66.80 ± 4.41); (65.56 ± 6.95)	(35/27) 56%; (33/25) 57%	NBP; Basic treatment	NBP: 200 mg Tid; -	6	-	MoCA
[37]	45 45	(65.89 ± 7.68); (62.64 ± 8.17)	(25/20) 56%; (22/23) 49%	NBP; Basic treatment	NBP: 200 mg Tid; -	6	-	MMSE + MoCA
[38]	42 42	(65.20 ± 4.01); (64.11 ± 3.54)	(27/15) 64%; (24/18) 57%	NBP + Galanthamine base; Galanthamine base	NBP: 200 mg Tid; Galanthamine base: 5 mg Tid	3	Hs-CRP, IL-6	MoCA
[39]	41 41	(62.74 ± 4.17); (63.26 ± 4.21)	(23/18) 56%; (24/17) 59%	NBP + Oxiracetam; Oxiracetam	NBP: 200 mg Tid; Oxiracetam: 800 mg Tid	2	Hs-CRP, TNF-α, IL-8, NSE	MMSE
[40]	50 50	(66.10 ± 2.89); (66.25 ± 2.41)	(30/20) 60%; (28/22) 56%	NBP + Edaravone; Edaravone	NBP: 100 mg Bid; Edaravone: 30 mg Qd	0.5	Hs-CRP	MMSE
[41]	40 40	(64.28 ± 0.30); (64.17 ± 0.29)	(22/18) 55%; (20/20) 50%	NBP + Urinary Kallindinogenase; Urinary Kallindinogenase	NBP: 200 mg Tid; Urinary Kallindinogenase: 0.15PNA Qd	1	MDA, BDNF, SOD	MMSE + MoCA
[42]	68 68	(62.8 ± 11.4); (63.5 ± 10.8)	(42/26) 61%; (47/21) 69%	NBP; Basic treatment	NBP: 200 mg Tid; -	3	-	MMSE
[43]	40 40	(63.94 ± 2.79); (64.19 ± 3.01)	(27/13) 68%; (26/14) 65%	NBP + Oxiracetam; Oxiracetam	NBP: 200 mg Tid; Oxiracetam: 4 g Qd	3	-	MoCA
[44]	35 35	(65.90 ± 6.02); (65.31 ± 5.95)	(22/13) 63%; (20/15) 57%	NBP + Urinary Kallindinogenase; Urinary Kallindinogenase	NBP: 200 mg Tid; Urinary Kallindinogenase: 0.15PNA Qd	1	-	MMSE + MoCA
[45]	52 52	(64.8 ± 10.8); (64.0 ± 10.9)	(28/24) 54%; (32/20) 62%	NBP + Oxiracetam; Oxiracetam	NBP: 200 mg Tid; Oxiracetam: 800 mg Tid	3	-	MoCA
[46]	54 54	(60.62 ± 19.35); (59.94 ± 20.13)	(29/25) 54%; (31/23) 57%	NBP + Oxiracetam; Oxiracetam	NBP: 200 mg Tid; Oxiracetam: 800 mg Tid	1	-	MoCA

Table 1 (continued)

Ref no.	Sample size (*n*)	Age (year)	Male/Female (Male%)	Intervention	Drug dose	Course of treatment (month)	Cytokine	Outcome evaluation method
	Trial control	Trial control	Trial control	Trial control				
[47]	58 58	(63.59 ± 2.77); (63.31 ± 2.57)	(29/29) 50%; (31/27) 53%	NBP; Basic treatment	NBP: 200 mg Tid; Basic treatment: -	3	-	MMSE
[48]	90 60	(36.3 ± 10.5); (35.2 ± 11.2)	(44/46) 49%; (32/28) 53%	NBP; Basic treatment	NBP: 200 mg Tid; Basic treatment: -	3	-	MMSE + MoCA
[49]	36 36	(73.12 ± 2.23); (72.08 ± 2.15)	(24/12) 67%; (21/15) 58%	NBP + Piracetam; Piracetam	NBP: 200 mg Tid; Piracetam: 400 mg Tid	1	Hs-CRP, Hcy	MMSE
[50]	43 43	(54.35 ± 7.88); (53.25 ± 7.25)	(28/15) 65%; (29/14) 67%	NBP + Citicoline sodium; Citicoline sodium	NBP: 200 mg Tid; Citicoline sodium: -	0.5	SOD	MoCA
[51]	60 60	(61.4 ± 7.8); (60.8 ± 7.5)	(35/25) 58%; (33/27) 55%	NBP; Basic treatment	NBP: 25 mg bid(iv) Basic treatment: -	0.5	-	MoCA
[52]	60 60	(57.19 ± 8.72); (58.13 ± 9.04)	(39/21) 65%; (37/23) 62%	NBP; Basic treatment	NBP: 200 mg Tid; Basic treatment: -	0.5	-	MMSE + MoCA
[53]	36 36	(68.5 ± 2.6); (68.4 ± 2.7)	(19/17) 53%; (18/18) 50%	NBP + urinary kallikrein; urinary kallikrein	NBP: 200 mg Tid; urinary kallikrein: 0.15PNA Qd	1	-	MMSE + MoCA
[54]	52 52	(66.52 ± 5.43); (64.42 ± 5.19)	(30/22) 58%; (32/20) 62%	NBP + Oxiracetam; Oxiracetam	NBP: 200 mg Tid; Oxiracetam: 4.0 g Qd	1	NSE, MMP-9	MMSE + MoCA
[55]	40 40	(48.67 ± 8.54); (48.92 ± 8.96)	(26/14) 65%; (29/11) 73%	NBP; Basic treatment	NBP: 200 mg Tid; Basic treatment: -	3	VEGF	MMSE
[56]	45 45	(63.16 ± 5.33); (63.87 ± 5.15)	(24/21) 53%; (23/22) 51%	NBP; Basic treatment	NBP: 200 mg Tid; Basic treatment: -	3	Hs-CRP, Hcy, Cys-C	MMSE + MoCA
[57]	37 36	(60.43 ± 8.64); (60.59 ± 8.05)	(17/20) 46%; (14/22) 39%	NBP + Piracetam; Piracetam	NBP: 200 mg Tid; Piracetam: 20 g Qd	3	-	MMSE + MoCA
[58]	42 42	(64.88 ± 3.94); (64.58 ± 3.84)	(18/24) 43%; (19/23) 45%	NBP + Oxiracetam; Oxiracetam	NBP: 200 mg Tid; Oxiracetam: 800 mg Tid	3	-	MoCA
[59]	40 40	(58.73 ± 9.26); (58.88 ± 9.32)	(21/19) 53%; (23/17) 58%	NBP + Piracetam; Piracetam	NBP: 900 mg Bid; Piracetam: 8 g Bid	0.5	-	MMSE + MoCA
[60]	35 35	(69.21 ± 11.34); (69.21 ± 11.34)	-	NBP + Citicoline sodium; Citicoline sodium	NBP: 200 mg Tid; Citicoline sodium: 250 Bid	0.5	-	MMSE + MoCA
[61]	84 84	(62.34 ± 2.08); (65.09 ± 2.85)	(43/41) 51%; (44/40) 52%	NBP; Basic treatment	NBP: 200 mg Tid; Basic treatment: -	6	IL-8	MMSE + MoCA

-: Not reported; NBP: DL-3-n-butylphthalide

the effect sizes using a fixed-effects model and performing a meta-analysis, we found that patients' cognitive function significantly improved after NBP monotherapy as suggested by MMSE scores (SMD = 0.70, 95% CI [0.58,0.82], $P<0.00001$). A funnel plot was drawn for the MMSE score of patients treated with NBP as monotherapy (Supplementary Fig. 3), where a slight asymmetry was found in the left and right region of scatter points, suggesting the possibility of publication bias. Sixteen studies, including 1446 patients with PSCI, reported the clinical effects of NBP combination therapy, as shown in Fig. 3a. Subgroup analyses were performed according to the combination drug. The control group was treated with urinary kallidinogenase ($P=0.50$, $I^2=0\%$) in three studies [41, 44, 53], with piracetam treatment ($P=0.0001$, $I^2=85\%$) in four studies [28, 47, 57, 59], with oxiracetam ($P=0.004$, $I^2=88\%$) in two studies [39, 54], with cyclozosin hydrochloride ($P=0.02$, $I^2=71\%$) in four studies [29, 32, 35, 60], and with edaravone [40], nimodipine [30], and idebenone [33] in one study each. Evaluation analyses were performed using a random-effects model, and the results showed a significant benefit of NBP as a combination therapy on MMSE scores ($SMD_U=0.73$, 95% CI [0.46, 1.00], $P<0.001$; $SMD_P=1.14$, 95% CI [0.54, 1.73], $P<0.0002$; $SMD_O=2.42$, 95% CI [1.29, 3.55], $P<0.0001$; $SMD_C=1.31$, 95% CI [0.89, 1.72], $P<0.00001$; $SMD_E=5.54$, 95% CI [4.67, 6.42], $P<0.00001$; $SMD_N=0.89$, 95% CI [0.51, 1.26], $P<0.00001$; $SMD_I=0.44$, 95% CI [−0.07, 0.95] $P=0.09$).

MoCA

Ten studies [25, 27, 34, 36, 37, 48, 51, 52, 56, 61], comprising 1157 patients, reported the clinical effects of treatment with NBP alone, as shown in Fig. 2b.

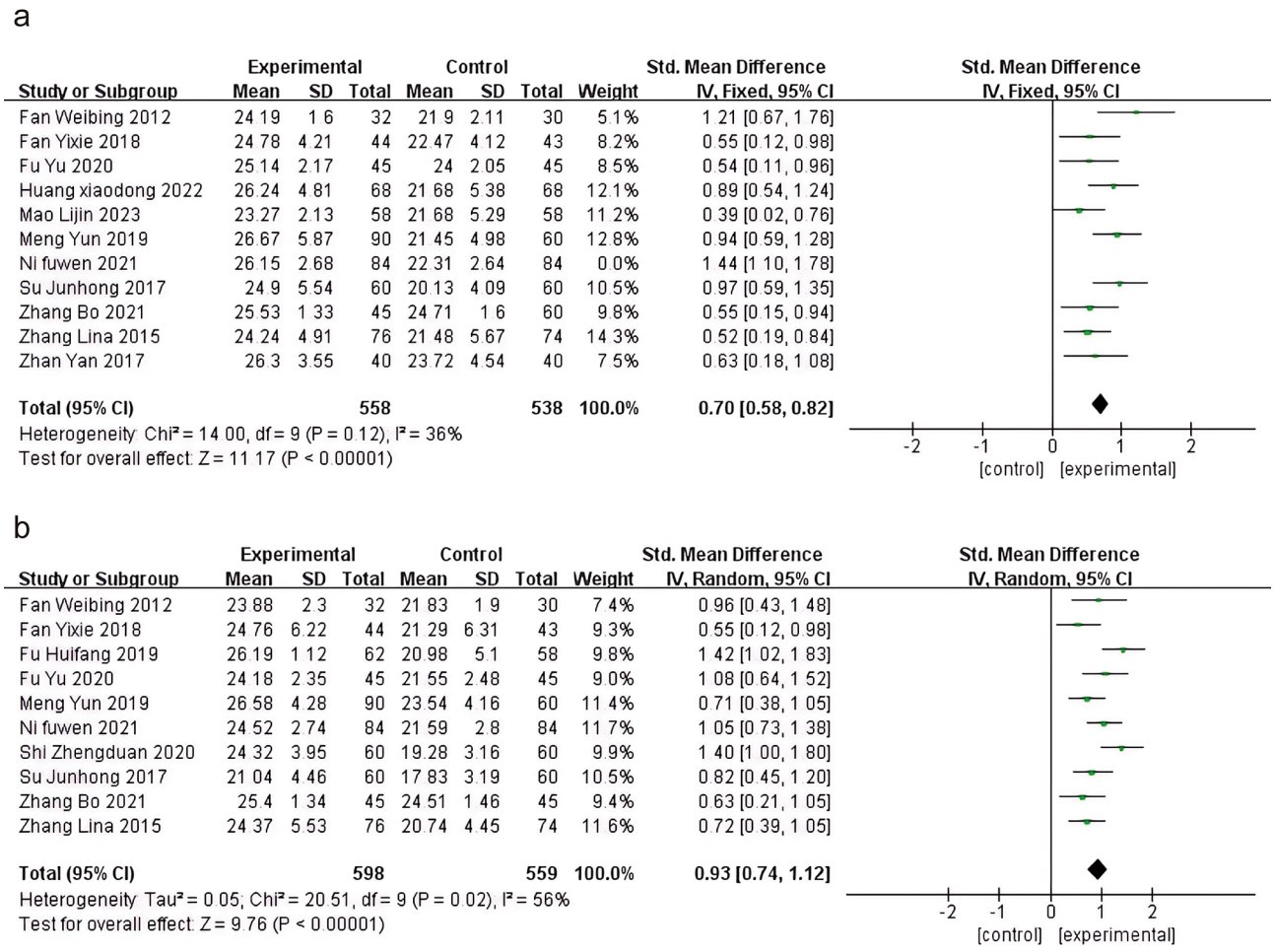

Fig. 2 Meta-analysis of cognitive assessment scale for NBP as monotherapy. **a** MMSE, **b** MoCA

Evaluation and analysis using a random-effects model with combined effect sizes demonstrated a significant benefit of NBP as a monotherapy in improving cognitive function in patients with PSCI in terms of MoCA scores (SMD=0.93, 95% CI [0.74, 1.12], $P<0.00001$). Seventeen studies, including 1550 patients, reported the clinical efficacy of NBP combination therapy for improving cognitive function in PSCI patients, as shown in Fig. 3b. Subgroup analyses were conducted according to the interventions. The control group was treated with Oxiracetam ($P<0.0001$, $I^2=85\%$) in five studies [43, 45, 46, 54, 58], with piracetam ($P=0.45$, $I^2=0\%$) in two studies [57, 59], with cyclazosin hydrochloride ($P<0.00001$, $I^2=97\%$) in three studies [29, 50, 60], with eurycoma ($P=0.50$, $I^2=0\%$) in three studies [41, 43, 53], with donepezil hydrochloride ($P=0.25$, $I^2=24\%$) in two studies [24, 31], and with Huperzine A [26] and Galanthamine [38] in one study each. We performed a meta-analysis using a random-effects model combining effect sizes, and the results demonstrated that NBP as a combination therapy had a statistically significant benefit in terms of the MoCA score ($SMD_O=0.90$, 95% CI [0.41,1.39], $P=0.0003$; $SMD_P=0.96$, 95% CI [0.63,1.30], $P<0.00001$; $SMD_C=2.07$, 95% CI [0.14,4.00], $P=0.04$; $SMD_U=0.82$, 95% CI [0.55,1.10], $P<0.00001$; $SMD_D=0.91$, 95% CI [0.62,1.19], $P<0.00001$; $SMD_H=2.03$, 95% CI [1.55,2.52], $P<0.00001$; $SMD_G=1.49$, 95% CI [1.00,1.97], $P<0.00001$).

Assessment of the treatment course

MMSE

Five studies [27, 33, 48, 55, 59], which included a total of 2340 C patients with PSCI, reported the clinical outcomes of the different courses of NBP treatment under the MMSE assessment, as shown in Fig. 4a. One of these studies [27] reported the clinical effects of NBP treatment by MMSE scores on 1 day ($SMD_{1d}=0.10$, 95% CI [−0.22, 0.42]), 2 days ($SMD_{2d}=0.03$, 95% CI [−0.29, 0.35]), 3 days ($SMD_{3d}=0.10$, 95% CI [−0.22, 0.42]), 7 days ($SMD_{7d}=0.51$, 95% CI [0.19, 0.84]), 14 days ($SMD_{14d}=0.49$, 95% CI [0.16, 0.81]), 30 days ($SMD_{30d}=0.73$, 95% CI [0.40, 1.06]), and 90 days ($SMD_{90d}=0.52$, 95% CI [0.19, 0.84]) from NBP treatment.

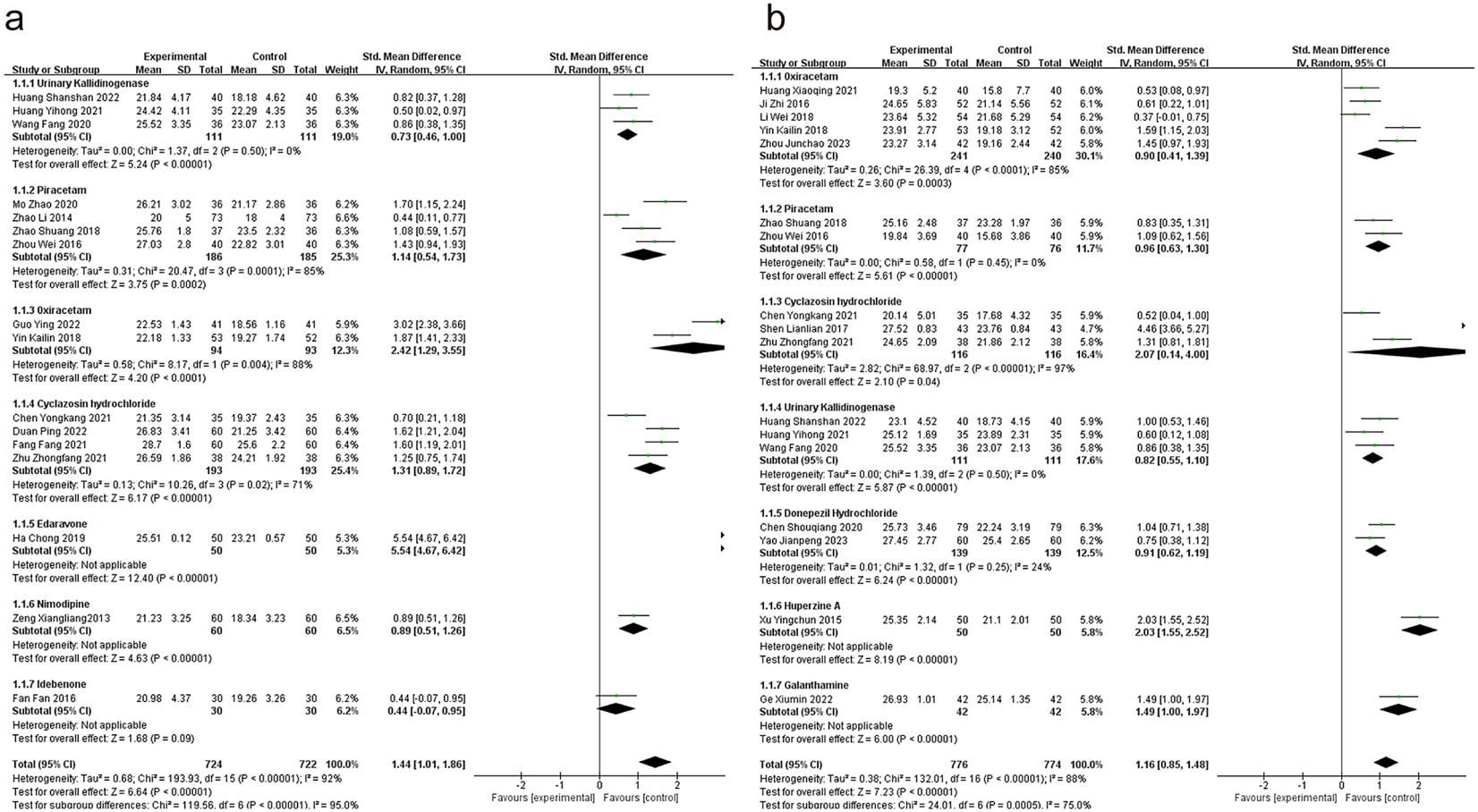

Fig. 3 Meta-analysis of cognitive assessment scale for NBP as combination therapy. **a** MMSE, **b** MoCA

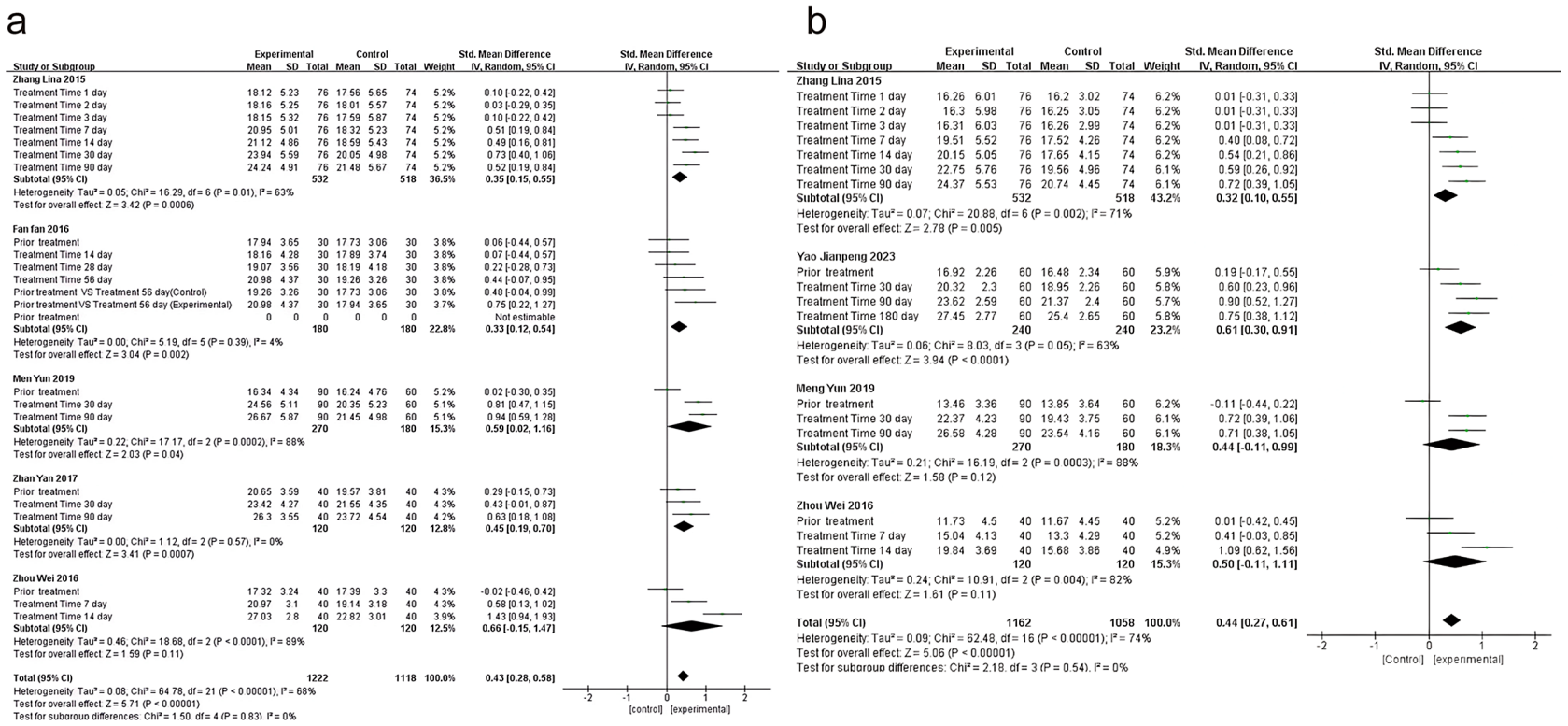

Fig. 4 Meta analysis of different treatment courses of NBP for cognitive assessment scale. **a** MMSE, **b** MoCA

In addition, the clinical effects of these different courses of treatment were summarized (SMD_{total}=0.35, 95% CI [0.15, 0.55], *P*=0.0006), which ultimately showed that the patients' cognitive function improved from day 7 of NBP treatment, and there was a cumulative improvement in cognitive function over the 3-month treatment course. Zhou et al. [59] reported clinical effects of NBP treatment by MMSE scores before treatment (SMD=–0.02, 95% CI [–0.46, 0.42]) and 7 days (SMD_{7d}=0.58, 95% CI [0.13, 1.02]) and 14 days (SMD_{14d}=1.43, 95% CI [0.94, 1.93]) from NBP treatment, which showed that patients started to show improvement in cognitive function from day 7, which was consistent with the results of Zhang's group [27]. Men et al. [48] assessed patient's cognitive function before treatment (SMD=0.02, 95% CI [–0.30, 0.35]) and 30 days (SMD_{30d}=0.81, 95% CI [0.47, 1.15]) and 90 days (SMD_{90d}=0.94, 95% CI [0.59, 1.28]) from treatment, and the clinical effects of different courses of treatment were combined (SMD_{total}=0.59, 95% CI [0.02, 1.16], *P*=0.04). The results demonstrated significant improvement in cognitive function on day 30 and day 90 of NBP treatment compared to pre-treatment, and the improvement was more pronounced on day 90 than that on day 30. Similar assessment was also performed in another study [55], which reported the cognitive function before treatment (SMD=0.29, 95% CI [–0.15, 0.73]C), on day 30 of treatment(SMD_{30d}=0.43, 95% CI [–0.01, 0.87]), and on day 90 of treatment (SMD_{90d}=0.6 3, 95% CI [0.18, 1.08]). Meta-analysis showed that patient's cognitive function improved on day 90 of treatment, but not on day 30 of treatment. In another study [33], it was found that patients' cognitive function started to improve from day 56 of NBP treatment compared to pre-treatment (SMD_{56d}=0.75, 95% CI [0.22, 1.27], *P*=0.002).

MoCA

Four studies [24, 27, 48, 59] including a total of 2220 PSCI patients reported the clinical outcomes of different courses of NBP treatment as reflected by MoCA scoring (Fig. 4b). One study [27] reported the clinical effects of NBP treatment at 1 day (SMD_{1d}=0.01, 95% CI [–0.31, 0.33]), 2 days (SMD_{2d}=0.01, 95% CI [–0.31, 0.33]), 3 days (SMD_{3d}=0.01, 95% CI [–0.31, 0.33]), 7 days (SMD_{7d}=0.4 0, 95% CI [0.08, 0.72]), 14 days (SMD_{14d}=0.54, 95% CI [0.21, 0.86]), 30 days (SMD_{30d}=0.59, 95% CI [0.26, 0.92]), and 90 days (SMD_{90d}=0.72, 95% CI [0.39, 1.05]) from NBP treatment. We combined the clinical effects of these different courses of treatment (SMD_{total}=0.32, 95% CI [0.10, 0.55], *P=0.*005), and found that patients showed improvement in cognitive function from day 7 of NBP treatment and there was cumulative improvement in cognitive function over the 3-month treatment course. Consistently, another study [59] also reported improvement of patients' cognitive functions from day 7 of NBP treatment (before treatment: SMD=0.01, 95% CI [–0.42, 0.45], day 7: SMD_{7d}=0.41, 95% CI [–0.03, 0.85], and day 14: SMD_{14d}=1.09, 95% CI [0.62, 1.56]). Yao et al. [24] observed improved cognitive function after 30 days of NBP treatment and cumulative improvement in cognitive function over the treatment course of 6 months (before treatment: SMD=0.19, 95% CI [–0.17, 0.55], 30 days: SMD_{30d}=0.60, 95% CI [0.23, 0.96], 90 days: SMD_{90d}=0.90, 95% CI [0.52, 1.27], 180 days: SMD_{180d}=0.75, 95% CI [0.38, 1.12], combined: SMD_{total}=0.61, 95% CI [0.30, 0.91], *P*<0.0001). Similarly, Meng et al. [48] reported improved cognitive function after day 30 of NBP treatment and cumulative improvement over a treatment course of 90 days (before treatment: SMD=–0.11, 95% CI [–0.44, 0.22], 30 days: SMD_{30d}=0.72, 95% CI [0.39, 1.06], 90 days: SMD_{90d}=0.71, 95% CI [0.38, 1.05]).

Serum cytokine assessment

Serum inflammatory factors

Eight studies [29, 31, 38–40, 49, 56, 61] comprising a total of 830 PSCI patients reported changes in serum levels of inflammatory factors HS-CRP [31, 38–40, 49, 56], TNF-α [29, 39], IL-6 [29, 38], IL-8 [39, 61] and Hcy [49, 56] in the experimental group compared with the control group after NBP treatment (Fig. 5a). Combined effect sizes revealed that patients' serum levels of HS-CRP (SMD_{HS-CRP}=–3.62, 95% CI [–5.16,–2.09], *P*<0.001), TNF-α($SMD_{TNF-\alpha}$=–3.09, 95% CI [–3.56,–2.61], *P*<0.001), IL-6 (SMD_{IL-6}=–2.00, 95% CI [–3.04, –0.96], *P*=0.0002), IL-8 (SMD_{IL-8}=–1.42, 95% CI [–2.82,–0.03], *P*=0.05) and Hcy (SMD_{Hcy}=–1.22, 95% CI [–1.73, –0.72], *P*<0.001) were all significantly lower in the experimental group compared with the control group, suggesting that NBP treatment significantly reduced serum HS-CRP, TNF-α, IL-6, IL-8 and Hcy levels in patients with PSCI.

Other serum cytokines

Nine studies [29, 31, 32, 39, 41, 50, 55, 56], which included a total of 876 PSCI patients, reported changes in serum levels of cytokines other than those mentioned above in the experimental group compared with the control group after treatment with NBP (Fig. 5b and c), including BDNF [29, 41], VEGF [55], SOD [41, 50], TIMP-1 [32], NSE [29, 31, 39, 54], MDA [41], and CyS-C [56]. After combining the effect sizes, we found significantly elevated levels of serum BDNF (SMD_{BDNF}=1.34, 95% CI [0.70, 1.98], *P*<0.001), VEGF (SMD_{VEGF}=1.12, 95% CI [0.64, 1.59], *P*<0.001), SOD (SMD_{SOD}=7.46, 95% CI [–3.77, 18.68], *P*=0.19) and TIMP-1 (SMD_{TIMP-1}=1.67, 95% CI [1.25, 2.09], *P*<0.001) and significantly reduced levels of serum NSE (SMD_{NSE}=–2.01, 95% CI [–2.44, –1.59], *P*<0.001), MDA (SMD_{MDA}=–1.84, 95% CI [–2.37, –1.31], *P*<0.001) and CyS-C (SMD_{CyS-C}=–0.74, 95% CI [–1.17, –0.31],

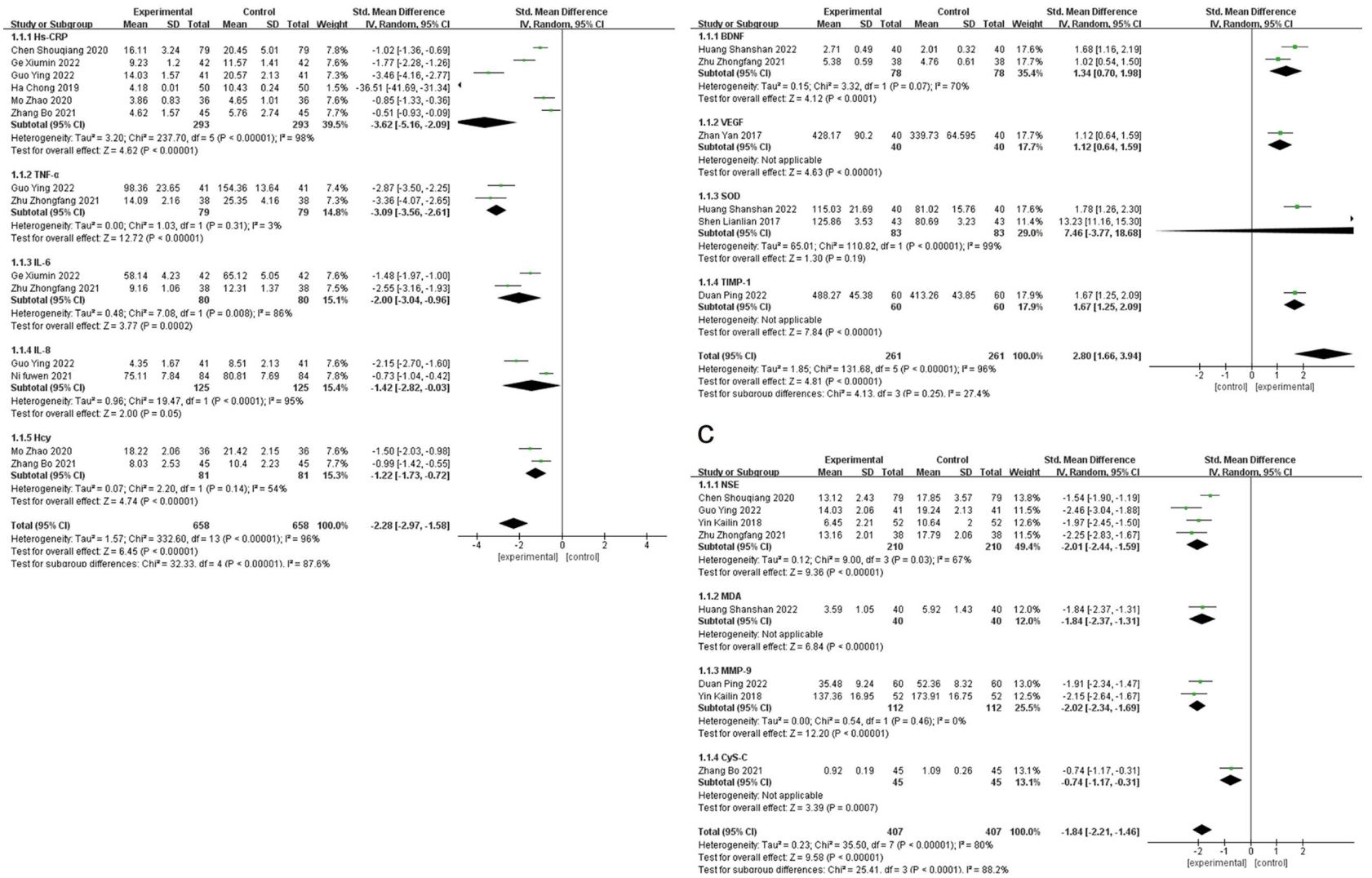

Fig. 5 Meta analysis of serum factors before and after treatment. **a** Inflammatory factors, **b** Nutrient factors and enzymes, **c** Other serum factors

$P=0.0007$) in the experimental group compared with the control group.

Discussion

Generalization of results

Our systematic evaluation included 38 randomized RCTs with a total of 5417 PSCI patients. Our investigation demonstrated that (1) NBP monotherapy or combination therapy enhanced cognitive function in individuals with PSCI, consistent with a previous study [19]; (2) NBP influenced the levels of certain cytokines in the blood while enhancing cognitive function in patients, which might be attributed to the antioxidant, anti-inflammatory, and antiapoptotic effects of NBP, the improvement of mitochondrial function, and the inhibition of neuronal apoptosis via pharmacological mechanisms [17, 20, 21]. (3) Previous studies have shown that NBP is useful in enhancing cognitive performance in individuals with PSCI, but there are no guidelines on the time to act of NBP treatment. Based on the individual differences in patients, our study suggested that the time to act of NBP is mostly 1 week for sensitive individuals, and can be longer for non-sensitive population. And once the response occurred, there is a cumulative improvement in cognitive function within 6 months of treatment. To our knowledge, these findings have not been reported previously.

Clinical implications

Currently, there is still a lack of standard guidelines on protocols for diagnosing and treating PSCI. Our study to some extent showed that NBP therapy, either used alone or in combination with other drugs, has a promising improvement effect on cognitive function in PSCI patients, although the time to act may vary depending on the sensibility of patients. Sensitive patients normally respond to NBP treatment within one week, which can be used to determine the sensibility of patients to NBP. In addition, cognition belongs to the high-energy functional areas of the brain, including memory, orientation, executive function, computation and attention. PSCI patients may have multiple cognitive impairments [22], for which MMSE and MoCA are often not sensitive enough to detect [62], or have a certain degree of delay in detection. Thus, these cognitive function assessment scales may not be sufficient enough for accurate early diagnosis of PSCI and timely response to therapeutic treatment. In addition, in our study, the serum levels of cytokines, including inflammatory factors (Hs-CRP, TNF-α, IL-6, and IL-8), growth factors (BDNF and VEGF), oxidative damage biomarkers (MDA and SOD), enzymes (NSE, MMP-9, Cys-C and TIMP-1), and metabolic biomarker (Hcy), significantly changed after NBP treatment. These changes might be related to the decline or improvement of cognitive function, which is consistent with the results of previous reports [1, 22]. On the one hand, these changes might be related to the mechanism of action of NBP, and on the other hand, these cytokines might play an auxiliary role in the early diagnosis of PSCI and in accurate indication of the effectiveness of NBP treatment. However, whether changes in the serum levels of these cytokines coincide with the time to act of NBP has not been studied, which may shed some light on future clinical studies. Future studies may consider the use of multiple serum cytokines in combination with cognitive assessment scales for the early diagnosis of PSCI and the evaluation of the efficacy of NBP, to improve the accuracy of the diagnosis and prognosis of PSCI and to provide new ideas for personalized diagnosis and treatment of PSCI.

Second, NBP was originally extracted from celery seeds, and one of its mechanisms of action has been shown to improve cognitive impairment by enhancing cerebral hemodynamics [15]. The effective treatment of PSCI is related to the timely restoration of blood supply to the brain tissue [63]. The standard use of NBP for stroke patients is within 72 h after onset, but the time from onset to NBP intervention had not been explicitly mentioned in the original study included in our meta-analysis. Therefore, it is necessary to pay attention to the significance of timely treatment for early cognitive function recovery in PSCI patients in future research.

Implications for basic research

We here propose an overview of the potential mechanism of action of NBP. Previous researches have indicated that NBP may act as an antioxidant by enhancing the expression of brain-derived neurotrophic factors in the hippocampus, increasing SOD activity, suppressing the TLR-4/MyD 88/NF-κB signaling pathway to decrease microglial cell proliferation and proinflammatory mediator production [13], activating the Akt/Nrf2 signaling pathway and inhibiting the apoptotic cascade to enhance cognitive function in patients with PSCI [64]. These finding were consistent with our finding that decrease in peripheral serum inflammatory factors Hs-CRP, TNF-α, IL-6, and IL-8 and oxidation-related factor MDA, or increase in neurotrophic factors BDNF and VEGF occurred simultaneously with the improvement in cognitive function after NBP treatment, suggesting that cytokines might play certain roles in the development of PSCI and in the therapeutic mechanism of NBP on PSCI. Meanwhile, it also suggested that changes in peripheral serum cytokines might reflect central nervous system diseases, but the key mechanisms involved are still not well elucidated. In the future, it will be valuable to study both peripheral and central changes together to thoroughly investigate the development of PSCI and the cellular-molecular mechanisms of NBP treatment.

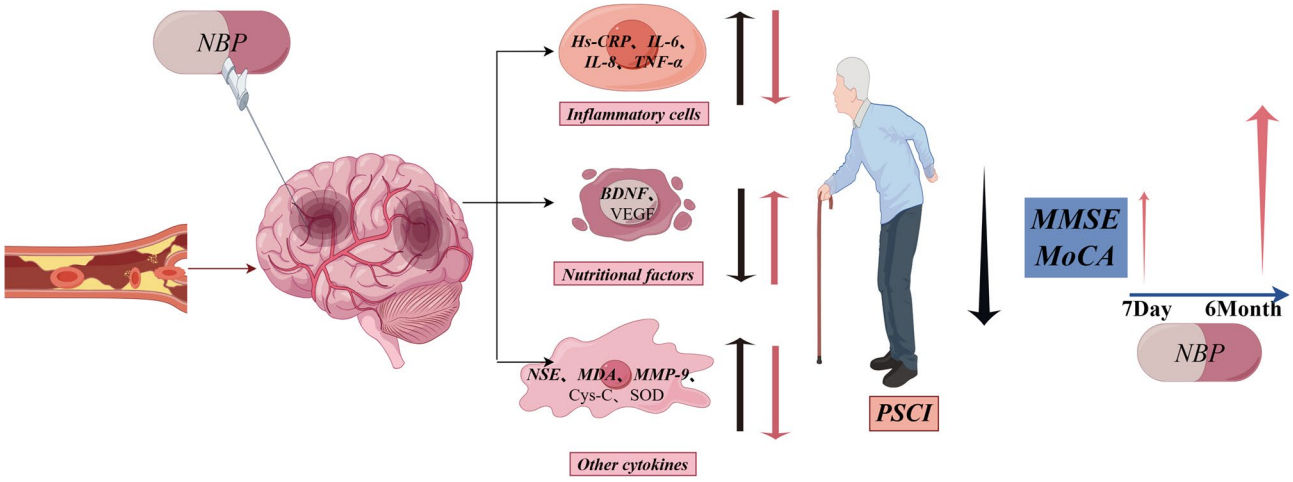

Fig. 6 Diagram of the mechanism of NBP treatment for PSCI

Strengths of the study

Previously, the majority of Meta-analysis studies explored the efficacy of butylphthalide in treating PSCI. In this study we have innovated on the following basis: (1) This study screened the blood indexes that changed before and after the treatment by NBP in PSCI patients from the studies included in the Meta-analysis, and mined biomarkers that can be used for both the diagnosis of PSCI and precise indication of the effect of NBP in the prevention and treatment of PSCI from multiple perspectives, which provides a new idea for personalized diagnosis and treatment of PSCI; (2) In the past, there has been no clear guideline on the time to act of NBP in treating PSCI. This issue was systematically summarized in this study, which will provide valuable guidance and reference in the clinical use of NBP in the future.

Limitations

In this study, we analyzed the clinical efficacy of NBP in the treatment of PSCI and found that several serum cytokines can be used as potential biomarkers for the prediction of its clinical effectiveness. However, our study has several limitations: (1) Despite rigorous searching and screening, the included literature in our study were all in Chinese, and the applicability of our findings to studies in non-Chinese regions needs to be further investigated. (2) In our meta-analysis, random-effects model was mostly used to combine the effect sizes, which made our final results inevitably affected by heterogeneity. (3) The underlying conditions of the patients in some of the studies that we included were unclear, and at the same time, there were variations in treatment courses in different studies, which had certain impacts on the outcome of drug treatment. (4) Due to the limited information provided by the original study, we only investigated the effect of NBP on cognitive function but not on patients' ability to perform activities of daily living and the effect of drug side effects, which deserves further study in the future.

Conclusion

NBP has a positive effect on improving cognitive function in PSCI patients. According to the subtype analysis of different treatment courses, we found that NBP showed improvement effect on cognitive function as quick as 1 week from treatment, and patients' cognitive function continuously improved within 6 months of treatment, which is important for guiding the clinical use of this drug. In addition, we also noticed altered serum cytokine levels of PSCI patients after NBP treatment. Reduced serum levels of Hs-CRP, TNF-α, IL-6, IL-8, Hcy, NSE, MDA, MMP-9, and Cys-C and elevated serum levels of BDNF and VEGF could reflect the effectiveness of NBP in the treatment of PSCI (Fig. 6). These cytokines might provide objective evidence for the early diagnosis of PSCI in clinical practice as well as a precise indication of the therapeutic effect of NBP. However, more high-quality RCTs are needed to further validate their effectiveness and feasibility.

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-024-00793-z .

Supplementary Material 1 Supplementary Fig. 1 Methodological quality of included studies

Supplementary Material 2 Supplementary Fig. 2 Distribution of the methodological quality of included studies

Supplementary Material 3 Supplementary Fig. 3 Funnel plot of MMSE score for NBP monotherapy

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Author contributions
ZW: Writing—review & editing, Writing—original draft, Visualization, Validation, Resources, Methodology, Investigation, Data curation. JW: Writing—review & editing, Writing—original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Data curation. JY: Writing—review & editing, Writing—original draft, Validation, Supervision, Resources, Methodology, Investigation, Data curation. JS: Validation, Methodology, Investigation, Data curation. QC: Writing—review & editing, Software, Resources, Methodology, Data curation, Funding acquisition. DW: Writing—review & editing, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization. CR: Writing—review & editing, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was evaluated and approved by the ethics committee of Yantai Yuhuangding Hospital, Yantai, China (ethics code: 2023-271).

Human ethics and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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