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Original Article

Unlocking The Efficacy of Tetrahydrobiopterin (BH4) Towards Metabolic Profile and Growth Status in Children with Phenylketonuria: A Meta Analysis

Rafi Alfian Razan[1,2], Nur Aisiyah Widjaja[1,2], Anggie Lorenza[3], Vianca Samara Andhary[4], Naoval Diza Ananda[5]

[1]Department of Child Health, Dr Soetomo General Academic Hospital, Surabaya, Indonesia
[2]Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[4]Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta
[5]Faculty of Medicine, Universitas Airlangga, Surabaya

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Corresponding author:
Rafi Alfian Razan
rafialfiann@gmail.com

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Abstract:

Background: Phenylketonuria (PKU) is one of the most common types of inborn error of metabolism. Low-phenylalanine diet has been the main treatment for children with PKU. However, recent therapeutic alternatives have emerged as a solution in children with PKU in the form of tetrahydrobiopterin (BH4). This meta analysis aims to assess the effectiveness of BH4 in terms of response rate, metabolic profile and growth status.

Methods: Meta analysis was conducted by searching databases such as PubMed, ScienceDirect, Cochrane Library, medRxiv, and Scopus based on the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) guidelines. Data synthesis and analyses were conducted using R version 4.5.1 (R Foundation for Statistical Computing).

Result: Fifteen studies were involved in this research, consisting of 1280 children (1063 given BH4). Eight studies reported BH4 reduced plasma phenylalanine concentration by around (686.83 mg/day [95% CI 394.85 to 978.82], p <0.001). Additionally, two studies reported a reduction in plasma phenylalanine concentration, measured in mg/kg/day, following BH4 administration. Children given BH4 and low phenylalanine diet combination showed a higher response rate compared to BH4 only (100% vs 76%). Two studies showed no difference in growth outcomes, which remained within the normal range.

Conclusion: BH4 shows promise as an adjunct therapy for children with PKU, but confirmation through larger, standardized, long-term studies assessing outcomes such as growth status and long-term neurocognitive outcome is needed.

Keyword: BH4, children, growth status, metabolic profile, phenylketonuria

Introduction

Phenylketonuria (PKU) is a rare autosomal recessive disorder resulting from a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH), which catalyzes the conversion of phenylalanine to tyrosine. The accumulation of phenylalanine in the blood and brain, if left untreated, can lead to severe intellectual disability, behavioral issues, and developmental delays.[1] Globally, the incidence of PKU varies significantly, with reported prevalence rates ranging from 1 in 10,000 to 1 in 15,000 live births in Europe and the United States.[2]

The primary treatment strategy for managing PKU has long centered on a lifelong, strictly controlled low-phenylalanine diet, typically initiated in infancy to prevent toxic accumulation of phenylalanine in the blood and central nervous system. This dietary intervention is effective in minimizing neurocognitive impairment and supporting normal development. However, maintaining strict dietary adherence becomes increasingly difficult with age, particularly during adolescence, often leading to poor compliance, reduced quality of life, and suboptimal long-term metabolic outcomes).[3]

In recent years, tetrahydrobiopterin (BH4), a natural cofactor of PAH has emerged as a pharmacological option for a subset of patients with residual PAH activity. By enhancing the enzyme's function, BH4 responsiveness allows more flexible diet and improved phenylalanine tolerance.[4] Sapropterin dihydrochloride, a synthetic formulation of BH4, has been approved for clinical use and shown to be effective in lowering phenylalanine levels, especially when used in combination with dietary management.[5]

Despite its increasing use, the broader impact of BH4 on growth status, safety profile, and metabolic tolerance remains an area of ongoing research, particularly in pediatric populations. Given the inconsistency in treatment responses and limited data, a comprehensive review is needed to elaborate BH4's role in PKU management. This meta analysis discussed current evidence on the efficacy of BH4 supplementation in children with PKU, focusing on response rates, metabolic profile, and growth outcomes.

Method

Conduct of Review

This review was planned and conducted following the Cochrane Handbook for Systematic Reviews of Interventions. The results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Given the anticipated substantial variability among studies, stemming from differences in study design and participant characteristics, we predetermined the use of a random effects model employing restricted maximum likelihood (REML) methodology for data pooling. The evaluation of statistical heterogeneity across the

studies was conducted using Cochran's Q and I^2 statistics. Values of 25%, 50%, and 75% for I2 are proposed to signify low, moderate, and high heterogeneity, respectively. The pooled mean change was used to estimate within-group differences (baseline and post-intervention) under the assumption that the correlation coefficient was 0.5. Data synthesis and analyses were conducted using R version 4.5.1 (R Foundation for Statistical Computing, https://www.r-project.org/).

Search Strategy

We conducted a comprehensive search in Pubmed, Sciencedirect, Cochrane Library, medRxiv, and Scopus for studies focusing on BH4 with outcomes of metabolic profile and growth status in children. Our search strategy included the following keywords: ("Tetrahydrobiopterin" OR "BH4" OR "Sapropterin" OR "Low Phenylalanine Diet") AND ("Phenylketonuria" OR "PKU"). We manually screened the bibliographic references of all selected studies in the Pubmed, ScienceDirect, Cochrane Library, medRxiv, and Scopus database. The final search was completed in August 2025.

Inclusion Criteria

We included randomized controlled trials, cohort, cross-sectional, and other observational studies involving children with phenylketonuria, especially studies focusing on BH4 with outcomes of metabolic profile and growth status.

Study Selection and Data Extraction

Titles and abstracts retrieved from the database were independently screened by four reviewers to identify relevant studies that met the selection criteria outlined above, who also independently assessed eligibility by further reviewing the full text. Disagreements were resolved through consultation with a fifth reviewer. Disagreements were determined when two or more reviewers assigned ratings that varied by more than 1 point on a 5-point scale. In these instances, a discussion was held among all reviewers, including a fifth independent reviewer who had not previously evaluated the manuscript. In this study, 12 of the 68 manuscripts (17.6%) necessitated the consensus process. The final score for each manuscript was established only after unanimous agreement was achieved among the review team.

Four reviewers extracted data independently and discrepancies were identified and resolved in consultation with a fifth reviewer. Standardized and pre-tested data collection tables were used to extract data from included studies using the Systematic Review Data Repository. The primary outcome of interest was phenylalanine intake per day before and after BH4 treatment.

Study Quality Assessment

We used the Cochrane Risk of Bias tool (RoB 2) for randomized controlled trials (RCTs), the Risk of Bias in Non-randomised Studies - of Interventions tool

(ROBINS-I) for non-randomized comparative studies (e.g., cohort, retrospective, or clinical trial without randomization), and the NIH Quality Assessment Tool for case series. Three reviewers independently assessed the RoB 2, ROBINS-I, and NIH Quality Assessment Tool quality of each study. Any disagreements between the reviewers were resolved by the fifth reviewer.

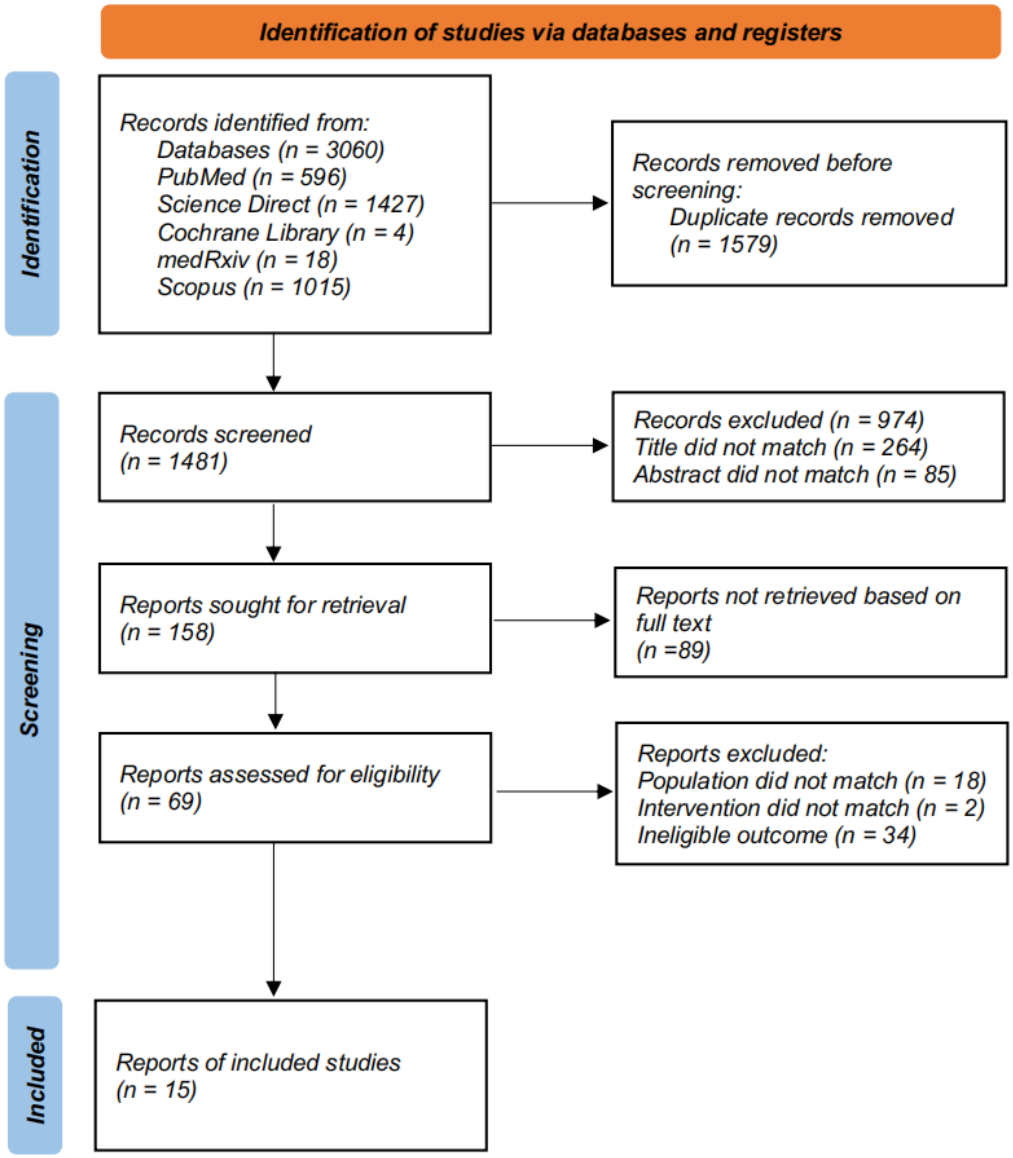

Figure 1. PRISMA flowchart on study screening and selection process

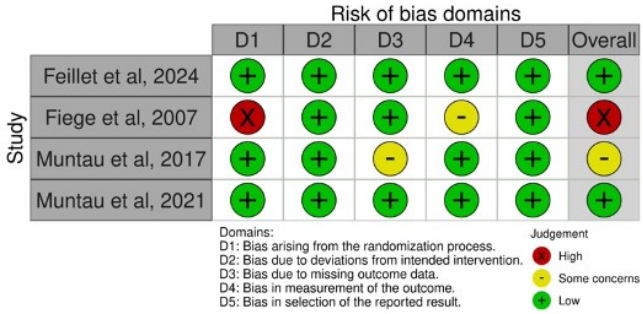

Figure 2. Quality assessment using Cochrane Risk of Bias tool for randomized controlled trials (RoB 2)

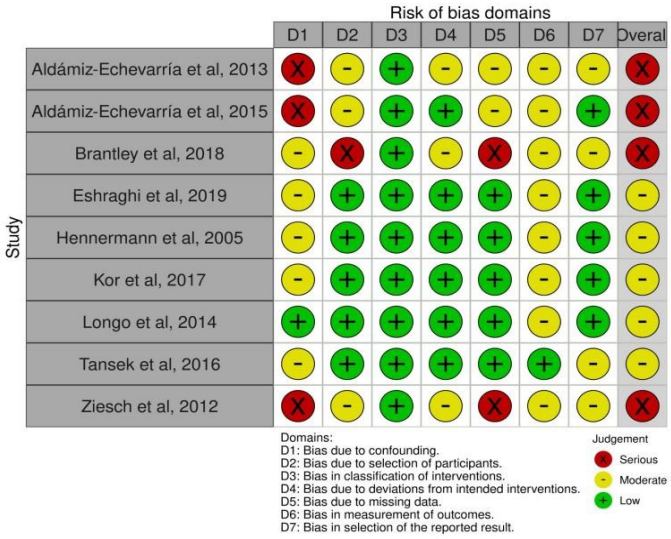

Figure 3. Quality assessment using Risk of Bias in Non-randomised Studies - of Interventions tool (ROBINS-I)

Table 1. Quality assessment using NIH Quality Assessment Tool for Case Series

	Tansek et al., 2012[6]	**Trefz et al., 2010[7]**
1. Clearly stated objective	Yes	Yes
2. Well-defined and representative population	Yes	Yes
3. Consecutive cases	Unclear	Yes
4. Comparable subjects	Yes	Yes
5. Intervention clearly described	Yes	Yes
6. Outcome measures clearly defined	Yes	Yes
7. Adequate follow-up	Yes	Yes
8. Results clearly reported	Yes	Yes
9. Appropriate statistical analysis	Yes	Partial
Overall RoB	Low	Moderate

Result

A total of 3060 articles were identified through the literature search, with 15 identified relevant to the topic and fulfilling the inclusion criteria as shown in **Figure 1**. The articles included were published between January 2005 - August 2025 involving 1280 pediatric patients who received BH4 administration in comparison to those on a low phenylalanine diet alone. **Table 2** presents the characteristics of the subjects.

We used the NIH case series tool for descriptive studies, ROBINS-I for non-randomized interventional and observational studies, and RoB 2 for randomised controlled trials to assess the risk of bias across the included studies in this review (**Figure 2, Figure 3, Table 1**), respectively. The overall risk of bias was deemed low for the randomised trials due to sufficient blinding, randomisation, and minimal missing data.[8-10] Despite being widely regarded as interventional, Fiege et al. in 2007 lacked randomisation and, as a result, were rated as having a high risk of bias when evaluated using RoB 2.[11] Confounding variables and the lack of blinding were the main causes of the non-randomized cohort and clinical studies' generally moderate risk of bias.[12-14] According to ROBINS-I, certain retrospective studies were deemed to be seriously at risk of bias due to limitations in outcome reporting and participant selection.[15-17] The NIH tool was used to evaluate case series.[6, 7] Although both were well-reported overall, assessments of low to moderate risk of bias were reached due to limitations like unclear consecutive recruitment and incomplete statistical analysis reporting. Overall, the highest certainty of evidence derives from the multicenter randomized trials[9, 10], while the observational and case series evidence should be interpreted with caution due to methodological limitations.

Table 2. The Characteristic of Subjects

Authors, year, country	Type of Study	Total Population		Characteristic Population		Age of BH4 treatment initiation, months		Response Definition
		I	C	I	C	I	C	
Kor et al., 2017[12] Turkey	Case Control	26	24	BH4 2x10 mg/kg/ day	BH4 SD (20 mg/kg /day)	55.9 ± 18.9 (53 [9–100])	48.3 ± 29.7 (40.5 [11–140])	Reduction of Phe levels at least 30% after 72 hours
Eshraghi et al., 2019[13]	Clinical Trial	24		BH4 SD (20 mg/kg/day) +		1-10 years		Reduction of Phe levels

Iran				Low Phe Diet 20–50 mg/kg				>30% after 48 hour BH4 administration
Aldámiz-Echevarría et al.,2015[16] Spain	Retrospective Study	22	44	BH4	Low Phe Diet	16.9 ± 10.4	-	Reduction of Phe ³50% after 24 hour BH4 administration
Trefz et al.,2010[7] Spain	Case Series	7	8	BH4	BH4 + Low Phe Diet	6.95 ± 12.02	77.87 ± 57.04	Reduction of blood phenylalanine >30%
Longo et al.,2014[18] USA, Canada	Cohort Prospective	55		BH4		3.14 ± 2.16		Reduction of blood Phe ≥30% after BH4 administration
Aldámiz-Echevarría et al.,2013[17] Spain	Retrospective Study	36	72	BH4 + Low Phe Diet	Low Phe Diet	5.0 ± 4.6 years	8.9 ± 5.0 years	Reduction of blood Phe ≥30% after BH4 administration
Ziesch et al.,2012[19] German	Prospective Clinical Study	8	6	BH4	Low Phe Diet	11.13 ± 4.4 years	9.23 ± 3.8 years	Reduction of blood phenylalanine >30% after BH4 administration
Brantley et al.,2018[15] USA	Cohort Prospective	11	8	BH4 + Low Phe Diet	Low Phe Diet	9.7 ± 3.4 years	10.4 ± 4.4 years	Reduction of Phe plasma at least 15%

Tansek et al.,2016[20] Slovenia	Retrospective Study	9	BH4 15.5 mg/kg, adjusted after	6.22 ± 3.0 years	Reduction of blood Phe at least 30% in 24 hours
Feillet et al.,2024[8] 9 European countries	Randomized control trials	481	BH4 20 mg/kg ± Low Phe Diet	<4 years (11) 4 - <12 years (329) 12 - <18 years (141)	≥30% reduction of blood Phe concnetration
Hennermann et al.,2005[14] Switzerland	Prospective Clinical Study	5	BH4-resplonsive PAH deficiency and a low phe tolerance of <20mg/kg	12.4 ± 18.1 months	≥30% reduction of blood Phe concentration in 8-24 hours
Tansek et al.,2012[6]	Case series	34	BH4 20 mg/kg	1 year - 18 years	≥30% reduction of blood Phe concentration in 24 hours
Fiege et al.,2007[11] Switzerland	Randomized control trials	293	BH4 20 mg/kg	1 year - 7 years	≥30% reduction of blood Phe concentration in 24 hours
Muntau et al.,2017[9] 9 countries	Randomized control trials	27 29	BH4 20 mg/kg + Low Phe Diet Low Phe Diet	27.2 ± 79.8 days 32.6 ± 72.2 days	≥30% reduction of blood Phe concentration in 24 hours

Muntau et al.,2021[10] 9 countries	Randomized control trials	25	26	BH4 20 mg/kg + Low Phe Diet	Low Phe Diet		≥30% reduction of blood Phe concentration in 24 hours

I: Intervention; C: Control

Eight comparisons, involving 619 participants, were aggregated to assess the primary outcome of blood phenylalanine levels after BH4 administration with low phenylalanine diet.[8, 12-15, 18-20] The use of BH4 shows significant benefits in reducing plasma phenylalanine concentration by around (686.83 mg/day [95% CI 394.85 to 978.82], p <0.001) (**Figure 4.)**. The statistical variability was substantial (I2 = 93.2%), with effect sizes of separate trials varying from 289.50 to 1502. The funnel plot (**Figure 5.**) shows some asymmetry, with fewer studies reporting smaller or no treatment effects on phenylalanine levels. This points to the possibility of publication bias or small-study effects. Additionally, the spread of points suggests variability among trials. This may reflect differences in genotype responsiveness, treatment protocols, and follow-up durations. Therefore, direct interpretation should be approached carefully. Additionally**,** two studies by Aldámiz-Echevarría et al. in 2013 and 2015 reported a reduction in plasma phenylalanine concentration, measured as mg/kg/day, after one and two years of BH4 administration in **Table 3**. [16, 17]

Table 3. Blood Phe Level Before and After BH4 (mg/kg day)

Author, year	Evaluation	Phe level before (mg/kg day)	Phe level after (mg/kg day)
Aldámiz-Echevarría et al, 2015[16]	1 year follow up	37.1 ± 19.1	53.0 ± 33.5
Aldámiz-Echevarría et al, 2013[17]	2 year follow up	29.9 ± 8.5	41.2 ± 6.5

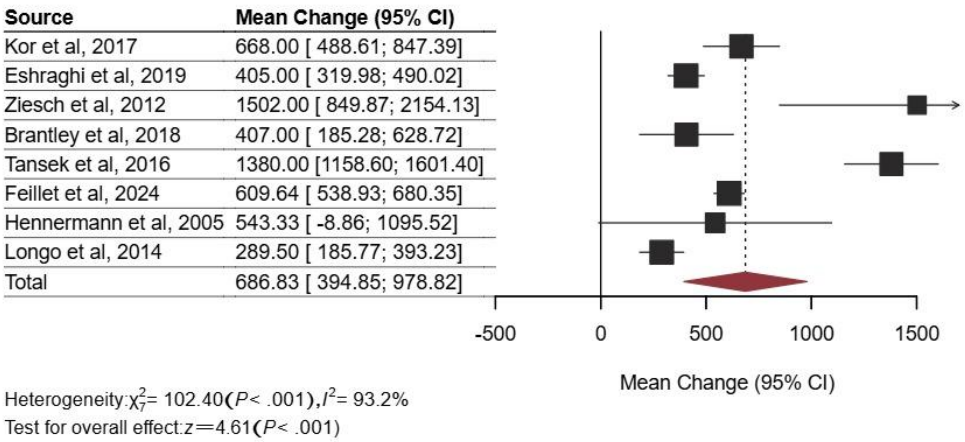

Figure 4. Forest plot about pooled standardized mean change of Blood Phe Level in children with PKU treated with BH4 administration + low Phe diet

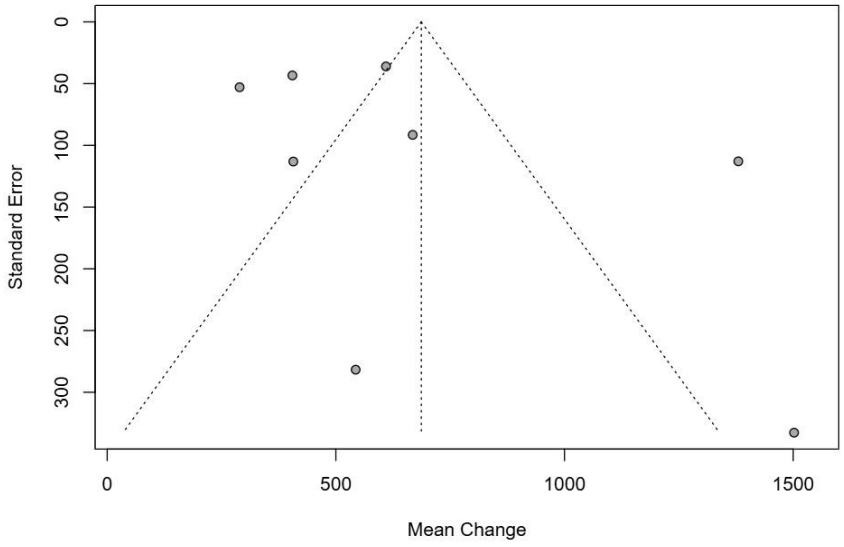

Figure 5. Funnel Plot about pooled standardized mean change of Blood Phe Level in children with PKU treated with BH4 administration + low Phe diet

Two studies evaluated the anthropometric status of children with PKU receiving a combination of BH4 and a low phenylalanine diet in comparison to those on a low phenylalanine diet alone in **Table 4**. Both studies showed that there was no significant difference in growth status between the two groups. [16, 17]

Table 4. Anthropometric Status

Author, year	Anthropometric Status							
	Weight Z-score		Height Z-score		Weight for Height Z-score		BMI Z-score	
	BH4 + Low Phe Diet	Low Phe Diet	BH4 + Low Phe Diet	Low Phe Diet	BH4 + Low Phe Diet	Low Phe Diet	BH4 + Low Phe Diet	Low Phe Diet
Aldámiz-Echevarría et al, 2015[16]	−0.19 ± 0.93	−0.48 ± 0.98	−0.52 ± 1.29	−0.78 ± 1.08	0.90 ± 1.42	1.26 ± 2.00	0.18 ± 1.00	−0.07 ± 1.03
Aldámiz-Echevarría et al, 2013[17]	− 0.75 ± 1.04	− 0.52 ± 0.85	− 0.73 ± 0.96	− 0.90 ± 1.00	NR	NR	0.37 ± 1.09	− 0.12 ± 0.89

In terms of response rate outcome, children given BH4 only showed a high response rate percentage of (76% [95% CI 49% to 92%]) in **Figure 6**.[6, 7, 11-14, 16-20] The statistical variability was substantial (I2 = 92.7%), with response rate of separate trials varying from 16% to 100%. The statistical variability was high (I2 = 92.7%), with response rates in separate trials ranging from 16% to 100%. The funnel plot for the pooled response rate to BH4 therapy (**Figure 7.**) shows mild asymmetry, with fewer studies reporting lower response rates. Smaller studies often report higher response rates, suggesting the possibility of small-study effects or publication bias. However, most studies are close to the pooled estimate, indicating a generally consistent treatment effect despite some potential bias toward positive results. Additionally, BH4 combined with low phenylalanine diet showed a higher response rate percentage of (100% [95% CI 0% to 100%]) in **Figure 8**.[7-10, 15] The statistical variability was not substantial (I2 = 0%), with response rate of separate trials varying from 58% to 100%. The funnel plot for the pooled response rate of BH4 combined with a low phenylalanine diet (**Figure 9.**) shows clear asymmetry, but the small number of available studies limits interpretation. The distribution indicates possible small-study effects, as smaller trials often report higher response rates. Furthermore, the wide range of effect estimates points to significant variability, which may come from differences in dietary compliance, genetic responses, and study design. Therefore, the results should be interpreted carefully.

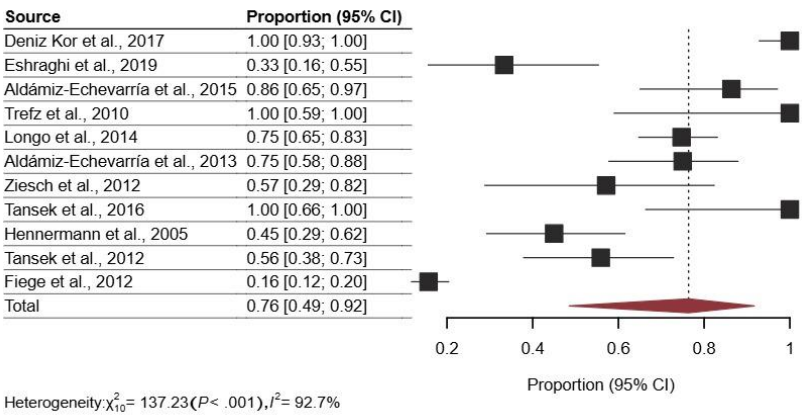

Figure 6. Meta-analysis and forest plot about pooled proportion of response rate in BH4 administration only.

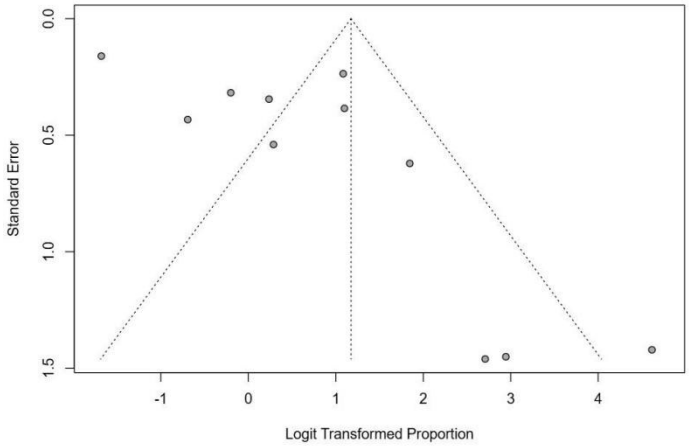

Figure 7. Funnel Plot about pooled proportion of response rate in BH4 administration only

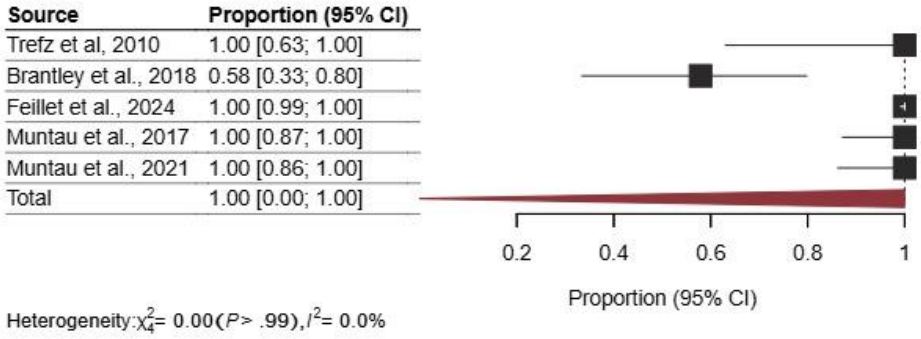

Figure 8. Meta-analysis and forest plot about pooled proportion of response rate in BH4 administration + low Phe diet

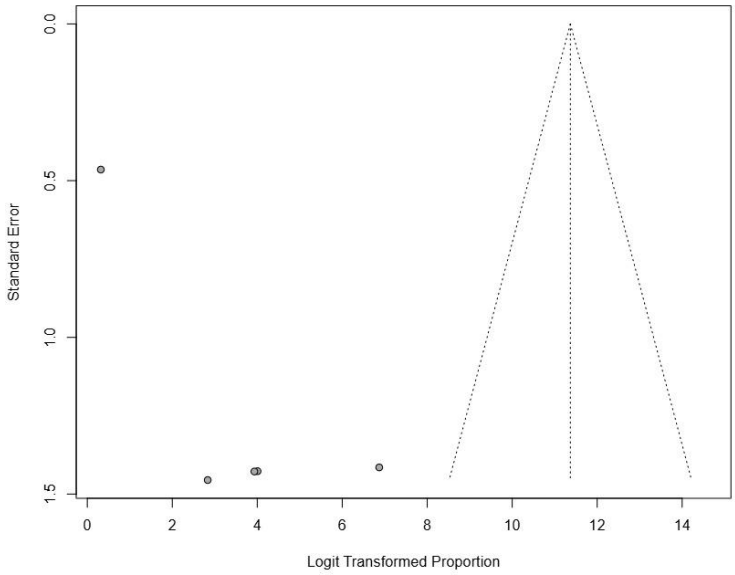

Figure 9. Funnel Plot about pooled proportion of response rate in BH4 administration + low Phe diet

Discussion

Dietary restriction of the amino acid phenylalanine is currently the main treatment for PKU. It preserves phenylalanine levels in the blood within the therapeutic range and prevent neurologic impairment. For PKU patients, BH4 was recommended as an adjuvant treatment, even though dietary restriction of the amino acid phenylalanine is still the primary treatment.[21] BH4 regulates by activating the PHA enzyme's residual activity.[22] In an attempt to lower the side effects of low-protein diets, typically seen in patients with PKU who are receiving early and ongoing treatment, BH4 treatment became an effective alternative along with PKU diet. This treatment enhances metabolic control and therapy compliance in BH4-responsive individuals by increasing their natural protein intake.[23] Treatment of PKU patients with BH4 has shown improvements in executive function, decreases in variability of blood phenylalanine levels, and enhancements in bone mineral accretion.[6, 8, 16] In this study, we conducted a meta analysis of studies focusing on BH4's effectiveness as it applies to growth status, metabolic profile, and response rate.

Research by Brantley et al. in 2018, with a prospective cohort, showed a decrease in phenylalanine levels in the blood of at least 15% with an administration of BH4 along with low phenylalanine diet.[15] However, compared to other research, BH4 only consistently reduced by at least 30% of phenylalanine levels. Phenylalanine levels in the blood may reduce by at least 30% in a day as BH4 is administered at a dose of 20 mg/kg/day, with or without a phenylalanine diet, based on several research in RCTs and prospective clinical studies.[8-11, 14, 19] This is similar to case series studies that shown at least 30% reduced blood Phe levels on BH4 treatment.[6, 7] The study conducted in

2013 by Aldámiz-Echevarría et al. showed that administering BH4 for 8 hours after a low-Phe diet led to a decrease in blood Phe levels of at least 30%.[17] Study in 2015 found that within 24 hours of administering BH4, Phe levels had decreased by at least 50%.[16] Within 24 hours after the administering of 15.5 mg/kg of BH4, blood phenylalanine levels were reduced by at least 30%, based to another retrospective study conducted in 2016.[20] According to a clinical trial investigation by Eshraghi et al. in 2019, phenylalanine levels decreased within 48 hours in 24 subjects that received 20 mg/kg/day of BH4 combined with a lower phenylalanine diet of 20–50 mg/kg/day.[13]

This meta analysis demonstrated a significant benefit of BH4 administration combined with a low phenylalanine diet in reducing plasma phenylalanine concentration (mean change 686.83 mg/day; 95% CI: 394.85–978.82, $p < 0.001$).[8, 12-15, 18, 20] However, substantial heterogeneity was present ($I^2 = 93.2\%$), with effect sizes of separate trials varying from 289.50 to 1502. Variability may be attributed to differences in sample size, baseline characteristics, and treatment protocols across studies. Additionally**,** two studies that reported plasma phenylalanine concentration with BH4 administration showed only a reduction (30.3 ± 4.2 vs 37.1 ± 5.0; 29.9 ± 8.5 vs 41.2 ± 6.5 mg/kg/day, respectively), highlighting that the effect may depend on concurrent dietary management.[16, 17] The funnel plot showed relative asymmetry, suggesting possible small-study effects or publication bias. These findings indicate that while BH4 appears beneficial, the magnitude of effect remains uncertain. Future investigation should be conducted in large-scale, multicenter settings with standardized treatment protocols and longer follow-up periods to reduce bias, improve comparability, and clarify the true therapeutic impact of BH4 administration.

In terms of response rate, children receiving BH4 administration only showed a high response rate percentage of 76% ([95% CI: 49–92%], p< 0.001), as shown in **Figure 6**.[6, 7, 11-14, 16-20] The statistical variability was substantial ($I^2 = 92.7\%$), with response rates ranging widely from 16% to 100%. The funnel plot **(Figure 7.)** revealed mild asymmetry, with smaller studies tending to report higher response rates, suggesting the possibility of small-study effects or publication bias. Nonetheless, most studies clustered near the pooled estimate, indicating a generally consistent treatment effect despite potential bias toward positive results. In contrast, BH4 combined with a low phenylalanine diet showed a higher response rate percentage of 100% ([95% CI: 0–100%], p>99) with no significant heterogeneity ($I^2 = 0.0\%$).[7-10, 15] Although the funnel plot showed asymmetry **(Figure 9.)**, interpretation was limited by the small number of available studies. Variability across trials may be influenced by dietary adherence, genetic differences, and study design, and thus the results should be interpreted with caution.

Z-scores on growth status in the HAZ, WAZ, WHZ, and BMI categories improved, indicating that patients being given BH4 in combination with low phenylalanine diet

had better nutritional status compared to low phenylalanine diet only.[16, 17] Regarding physical outcomes, previous studies showed that PKU patients mainly taking natural dietary sources for protein achieved normal growth with prolonged treatment of BH4.[17] However, a study conducted in 2015 found that after a year of BH4 treatment, there was no significant difference in Z-score for HAZ, WAZ or even BMI due to the lack of information on growth-related nutrients, the study stated that it was unable to rule out the potential of factors such as epigenetic variation, creatinine level and trace element that could result in insignificant anthropometric status for patients with PKU.[16]

Clinical study data suggests that preventing neurocognitive damage, particularly in the first few years of infancy, requires maintaining blood phenylalanine levels below predefined thresholds.[20] Although blood phenylalanine levels were closely monitored, outcomes were correlated with phenylalanine variability. However, studies showing neurocognitive outcomes are still limited.[18] The restricted type of food groups, in the low phenylalanine diets recommended for children with PKU causes problems for nutrition as well as food variety and satiety.[23] BH4 therapy may be able to prevent certain PKU diet adverse effects by enhancing the body's ability to metabolize hypostilation.[16] For many patients and their families, maintaining dietary adherence can result in significant time and financial costs, that may affect compliance. Patients are at risk of developing significant micronutrient deficiencies if they stop or reduce their protein intake without proportionally increasing their natural protein consumption.[24]

Patients with a free diet along with BH4 have been found to have a lower incidence of micronutrient deficiencies than those on a restricted protein diet.[25] Strict dietary intake may cause early growth retardation, which may affect developmental outcomes.[26] The growth period in "infancy" mainly nutrition-dependent and is gradually replaced by hormone-dependent during the "childhood" phase.[27] In certain patients with residual PAH enzyme activity, BH4 makes the enzyme more active by stabilizing it.[28, 29] According to a meta analysis at 2021, long-term BH4 treatment was associated to a significant increase in phenylalanine and natural protein intake, with most long-term patients achieving more than a twofold improvement in tolerance. The use of BH4 in long-term also showed a significant decrease in protein equivalent intake from protein subtitute with cofactor therapy. In the same studies, the long-term use of BH4 was also shown to significantly reduce the need for protein equivalent from protein subtitute, highlighting its beneficial effect in lowering dietary dependence through cofactor therapy. This finding suggest that BH4 not only improves metabolic control but also allows greater dietary flexibility, althought variability in individual response highlights the need for continued monitoring and patient-specific management.[29]

In summary, this study is the first meta analysis to evaluate the efficacy of BH4 only or as an adjunctive treatment along with low phenylalanine diet compared with low phenylalanine diets only, focusing on metabolic profile, growth status and response rate of BH4. However, the studies reviewed varied populations across different age groups and regions, potentially contributing to heterogeneity in the results. Additionally, the limited data on growth status and the absence of long-term neurocognitive outcomes further constrain the comprehensiveness of the findings. The small number of included studies also limits the broader applicability and long-term reliability of the conclusions. These limitations underscore the importance of conducting more extensive research with extended follow-up to strengthen the evidence base and clarify the sustained effects of BH4 treatment.

Conclusion

BH4 has shown to be effective as a treatment for children with PKU, with a high response rate and improvement of metabolic profile. BH4 can be considered as an alternative therapy instead of a low phenylalanine diet only. However, this study has considerable bias and significant heterogeneity. Therefore, further investigation should be conducted in large-scale, multicenter studies with standardized protocols and long-term studies assessing outcomes such as growth status and long-term neurocognitive are required to minimize bias and clarify the true therapeutic impact of BH4 administration.

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Conflict of Interest

None declared

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