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Folinic acid and autism spectrum disorder in children: A systematic review and meta-analysis of two double-blind randomized placebo-controlled trials

Asam folinat dan gejala autisme pada anak dengan autisme: Tinjauan sistematis dan meta-analisis dari dua uji coba terkontrol plasebo acak tersamar ganda

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Abstract

Folic acid is a synthetic vitamin B9 that plays an important role in folate metabolism, including the synthesis of DNA and RNA, and epigenetic methylation. These processes are essential for the development of the nervous system. Impaired folate metabolism contributes to the pathophysiology of ASD through the dysregulation of neurochemical and epigenetic processes. This meta-analysis aimed to evaluate the efficacy of folinic acid in alleviating ASD symptoms. Methods: Review Manager Software. Searches were conducted in PubMed, Science Direct, and Cochrane based on studies published in the last five years (2018-2023), with inclusion criteria of RCTs and exclusion of observational studies and non-English articles. Fixed-effects analysis was used because no heterogeneity was observed. Results: Two studies (n= 103) evaluated the effect of folinic acid on reducing ASD symptoms. Symptoms were assessed using the aberrant behavior checklist. The pooled mean difference was -0,66, with a 95% confidence interval ranging from -1,22 -0,10. The results showed statistical significance, with a p-value of 0,02. However, this analysis used only two studies with small sample sizes and modest mean differences. In conclusion, folinic acid administration has the potential to reduce ASD symptoms in children. Further research with a larger sample size is needed to generalize the clinically meaningful results.

Keywords: Autism spectrum disorder, folinic acid, meta-analysis,

Abstrak

Asam folinat merupakan sintetik vitamin B9 yang berperan penting dalam metabolisme folat, termasuk untuk sintesis DNA, RNA, dan metilasi epigenetik. Proses ini esensial bagi perkembangan sistem saraf. Gangguan metabolisme folat berkontribusi pada patofisiologi ASD melalui disregulasi proses neurokimia dan epigenetik. Meta-analisis ini bertujuan mengevaluasi efektivitas asam folinat dalam meringankan gejala ASD. Metode, perangkat lunak *Review Manager*. Pencarian dilakukan di PubMed, Science Direct, dan Cochrane berdasarkan dari studi yang telah diterbitkan lima tahun terakhir (2018 – 2023), dengan kriteria inklusi RCT dan mengecualikan studi observasional serta artikel non-Bahasa Inggris. Analisis menggunakan *fixed-effect*, karena tidak ditemukan heterogenitas. Hasil, terdapat dua penelitian (n= 103 peserta) yang mengevaluasi efek asam folinat dalam mengurangi gejala ASD. Penilaian terhadap gejala-gejala tersebut menggunakan *aberrant behavior checklist*. Perbedaan rata-rata gabungan yang didapat adalah -0,66, dengan interval kepercayaan 95% berkisar antara -1,22 hingga -0,10. Hasil yang diperoleh menunjukkan signifikansi statistik dengan nilai p 0,02. Namun, analisis ini hanya menggunakan dua studi dengan besar sampel yang kecil dan perbedaan rata-rata yang tidak terlalu besar. Kesimpulan, pemberian asam folinat berpotensi mengurangi gejala ASD pada anak-anak,

namun, diperlukan penelitian lebih lanjut dengan besar sampel yang lebih banyak sehingga dapat dilakukan generalisasi hasil yang bermakna secara klinis.

Kata Kunci: Asam folinat, gangguan spektrum autisme, meta-analisisfolat

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by persistent challenges in social communication and restricted repetitive behaviors (Sathe et al., 2017). The prevalence of ASD has been steadily increasing worldwide, with recent estimates indicating that approximately 1 in 100 children is affected globally (WHO, 2023). In Asia, studies suggest that the prevalence of ASD varies across countries, ranging from 0,11% to 1,89%, reflecting differences in the diagnostic criteria and awareness levels (Sun et al., 2019). A 2019 report by the Ministry of Health indicated that ASD affects approximately 2,4 million children in Indonesia, although this figure may be underestimated due to limited diagnostic resources and social stigma (Kemenkes, 2020).

The mental well-being of children diagnosed with autism spectrum disorder (ASD) is a significant subject of interest, particularly because of the growing global incidence of mental disorders (Fuld, 2018; Ivanović, 2021). The observed increase in the number could potentially be linked to the co-occurrence of psychiatric comorbidities in children diagnosed with ASD. Children with ASD frequently exhibit comorbid psychiatric conditions including anxiety disorders, mood disturbances, attention deficit hyperactivity disorder (ADHD), and other related conditions (Romero et al., 2016).

It has been suggested that the presence of comorbidities tends to result in heightened impairments, primarily due to the cumulative impact arising from the co-occurrence of multiple disorders (Gadow et al., 2012; Romero et al., 2016). Logan et al. (2015) demonstrated that early intervention strategies can optimize communicative, social, and behavioral development by minimizing deficits and maximizing abilities (Logan et al., 2015). Therefore, it is imperative to alleviate the symptoms associated with ASD to prevent the onset of the co-occurrence of mental illness.

The pathophysiology of ASD is complex, with genetic, epigenetic, and environmental factors playing interconnected roles (Hoxha et al., 2021). Among these, nutritional factors, particularly folate metabolism and oxidative damage, have attracted attention. These factors may contribute to ASD development by disrupting the neurodevelopmental pathways (Frye et al., 2017; Howsmon et al., 2017). Folate, known as vitamin B9 or folinic acid (in its reduced form), plays a vital role in DNA synthesis, methylation, and redox homeostasis, which are essential for neurodevelopment (Naninck et al., 2019). Disruptions in folate metabolism may impair methylation pathways, alter gene expression, and reduce antioxidant defenses, thereby contributing to oxidative damage and neuronal dysfunction (Frye et al., 2020; Naninck et al., 2019). Nutritional deficiencies in folate can exacerbate these effects, potentially worsening ASD symptoms.

Although folinic acid supplementation has been proposed as a therapeutic strategy for alleviating ASD symptoms, findings across studies remain inconsistent (Roufael et al., 2023). Evidence suggests that folinic acid supplementation could lead to improvements in language, social communication, and behavior, although the findings remain inconsistent across studies (Batebi et al., 2021; Frye et al., 2017; Renard et al., 2020; Thom et al., 2021; Zhou et al., 2021). These discrepancies highlight a critical gap in our understanding of the efficacy of folinic acid.

Given the growing recognition of nutrition's role in neurodevelopmental disorders as well as critical importance of early intervention in optimizing social, communication, and behavioral development the es in children diagnosed with ASD, acquiring up-to-date information about accessible and practical therapeutic options is essential. Folinic acid, an easily available and cost-effective intervention, has significant potential to address the challenges faced by children with ASD. This intervention was called folinic acid. Consequently, this meta-analysis aimed to systematically synthesize evidence from existing studies to evaluate the effectiveness of folinic acid supplementation in reducing ASD symptoms, and its potential integration into early intervention strategies. By consolidating and analyzing data across studies, this review

seeks to clarify the therapeutic potential of folinic acid and its potential integration into clinical practice. Furthermore, to the best of our knowledge, this is the first meta-analysis to assess the effectiveness of folinic acid supplementation in ameliorating symptoms associated with ASD in children.

Methods

A meta-analysis was performed to assess the effect of folinic acid on symptom relief in children with ASD. Two authors (JAFK and FDD) conducted a comprehensive literature review by searching various databases, such as PubMed, Science Direct, and Cochrane, from January 1, 2018, until October 10, 2023. Several articles were collected from these databases to analyze the mean difference (MD) and 95% confidence interval (95% CI) using random or fixed effect models. The present study adhered to the guidelines specified in the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) 2020 statement (Page et al., 2021).

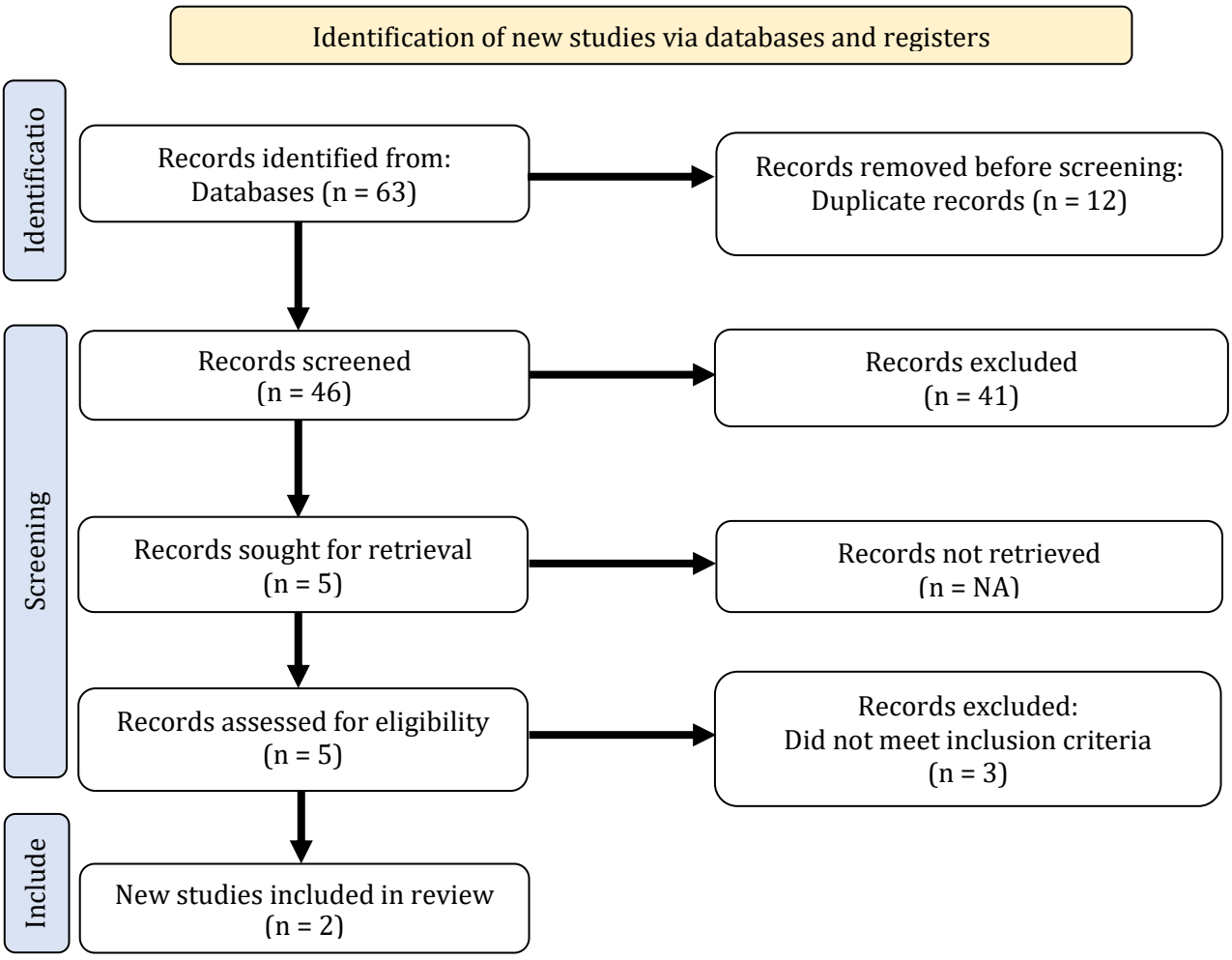

Figure 1. PRISMA 2020 flowchart.

To ensure the inclusion of only relevant studies in our analysis, we employed the following criteria: (1) the study aimed to assess the impact of folinic acid as a primary or adjuvant treatment in children diagnosed with ASD through the aberrant behavior checklist (ABC) questionnaire; (2) the study design was a randomized, double-blind, placebo-controlled trial; (3) in English; and (4) included sufficient information to calculate the MD and 95% CI. Moreover, we eliminated articles that met the following criteria: (1) review articles, (2) case-control or cohort studies, (3) unrelated titles and abstracts, (4) insufficient information for

MD and 95% CI calculation, and (5) duplications.

Table 1 presents a comprehensive compilation of keywords used in the literature search. Both authors (FAS and FDD) conducted independent literature searches and extracted the data from each study. The data extracted from each article included (1) first author name, (2) publication year, (3) study design, (4) duration, (5) age range, (6) country, (7) intervention, and (8) outcomes. The quality of the studies was assessed using the Cochrane risk of bias tool (Higgins et al., 2011). Two authors (FAS and JAFK) independently and critically assessed the quality of articles. The risk of bias assessment tool encompasses various types of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. If there was a discrepancy, consensus was reached by other authors.

Table 1. Keywords employed in the literature search.

Connected by OR	AND	Connected by OR	AND	Connected by OR
autism spectrum disorder[mh] OR asperger syndrome[mh] OR autistic disorder[mh] OR autism spectrum disorder[tiab] OR asperger syndrome[tiab] OR autistic disorder[tiab] OR autism[tiab]		leucovorin[mh] OR levoleucovorin[mh] OR leucovorin[tiab] OR levoleucovorin[tiab] OR folinic acid[tiab] OR nutritional[tiab]		randomized controlled trial[mh] OR clinical trial[mh] OR controlled clinical trial[mh] OR randomized controlled trial[tiab] OR clinical trial[tiab] OR controlled clinical trial[tiab] OR placebo-controlled randomized trial[tiab] OR placebo-controlled trial[tiab]

Data analysis was conducted using Review Manager, version 5.4.1. The effect size, measured as MD, was analyzed using the inverse variance statistical method (Seputra et al., 2021). To assess the significance of the pooled data, the Z-test was used, with a p-value threshold of less than 0.05, indicating statistical significance. The level of heterogeneity was evaluated using p-heterogeneity and I-square (I^2) analyses. When data heterogeneity was detected ($I^2 > 75\%$), a random effects model was employed (Purnomo et al., 2021).

Otherwise, if the data lacked heterogeneity, a fixed effects model was used. Furthermore, to mitigate the possibility of analytical errors, statistical analyses were performed independently by two authors (FAS and JAFK). Furthermore, because we used the ABC scale as the measured outcome, we analyzed it in a subgroup manner. The ABC scale comprises several subscales including irritability, lethargy, stereotyped behavior, hyperactivity, and inappropriate speech.

Result and Discussion

The initial search resulted in the identification of 63 publications, of which 12 were excluded from further analysis because of duplication. Forty-six papers were excluded from the screening process based on the criteria of having irrelevant titles and abstracts. Subsequently, five published papers were chosen for a comprehensive full-text investigation; nevertheless, only two were included in our meta-analysis because the remaining three papers failed to satisfy the predetermined inclusion criteria. The processes involved in conducting the literature searches are depicted in the PRISMA 2020 flowchart (Figure 1) (Haddaway et al., 2022). The characteristics of the articles analyzed are presented in Table 2.

Table 2. Characteristics of included studies.

First Author, Year	Study Design	Duration	Age Range	Country	Interventions	Primary outcome
Frye et al. (2018)	Double-bind, randomized placebo-	12 weeks	3 – 14 years of age	USA	Folinic acid 2 mg/kg (with a maximum daily limit of 50 mg) in two equally divided doses with half of the target	Verbal communication

	controlled trial				dose given during the first 2 weeks.	
Batebi et al., (2021)	Double-blind, randomized placebo-controlled trial	5 weeks and 10 weeks	4 – 12 years of age	Iran	Folinic acid 2 mg/kg (up to 50 mg per day) throughout the duration of the study in conjunction with risperidone at a dose of 0,5 mg with subsequent weekly increments of 0,5 mg for the first three weeks.	ABC

A hundred and three participants from two studies were included in this meta-analysis to assess the effectiveness of folinic acid therapy in ameliorating ASD symptoms (Batebi et al., 2021; Frye et al., 2018). In general, a notable decrease in the ABC score was observed, suggesting an amelioration of symptoms in children diagnosed with ASD compared to those who were administered either placebo or risperidone alone (MD [95% CI] = -0,66 [-1,22, -0,10]; p= 0,02) (Figure 2). Interestingly, the subgroup analysis demonstrated a statistically significant reduction in the stereotyped behavior subscale (MD [95% CI] = -1,60 [-3,03, -0,17]; p= 0,03). Nevertheless, the statistical analysis did not yield significant results for the other subscales.

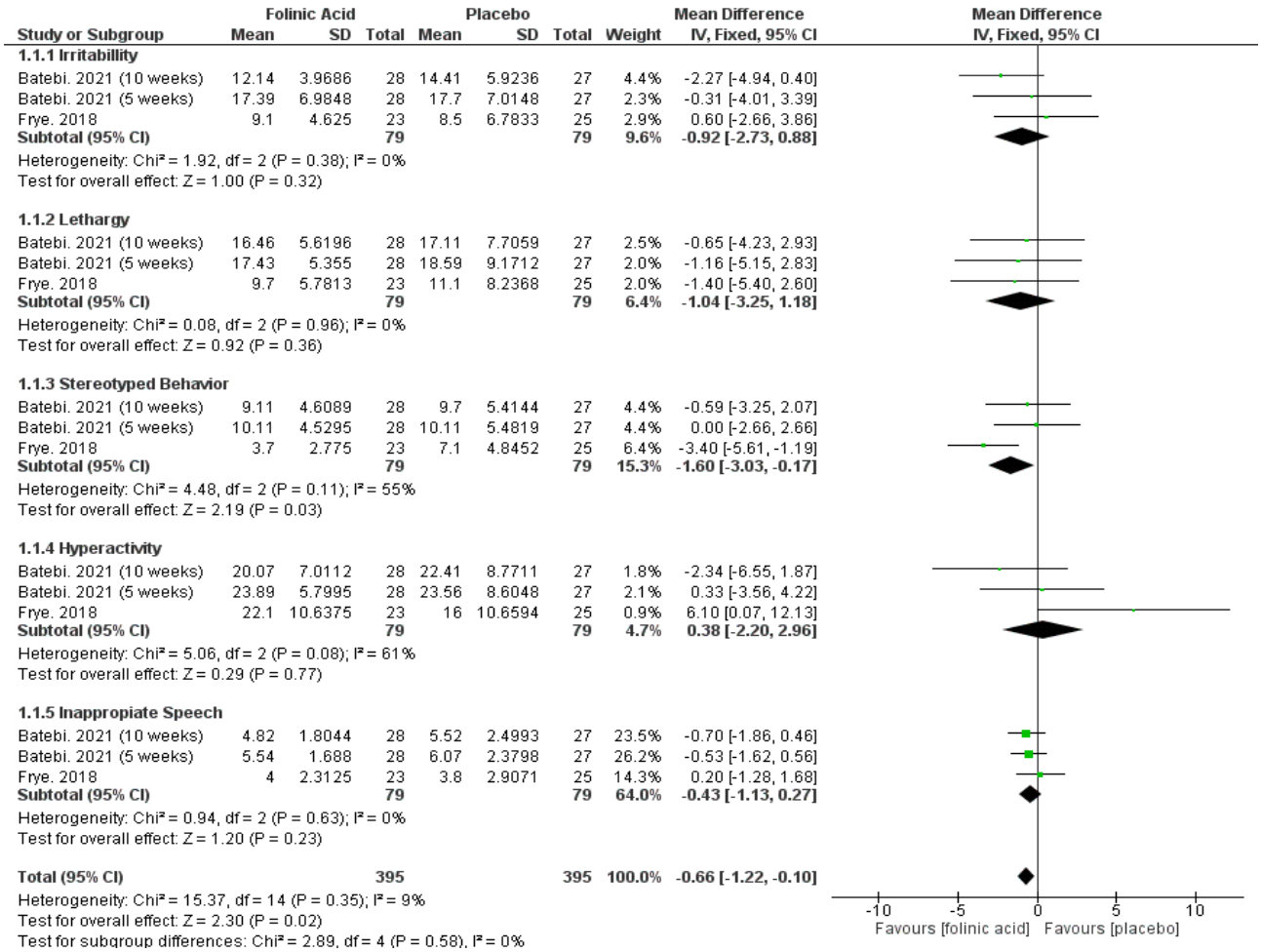

Figure 2. Forest plot comparing folinic acid, placebo, and risperidone.

Moreover, these two studies showed no evidence of heterogeneity (I^2 = 9%). Consequently, a fixed-effects model was employed to assess MD between the two groups. The Cochrane risk-of-bias tool was used to assess publication bias in the selected papers. Figures 3 provides a comprehensive overview of the biases reported in these studies.

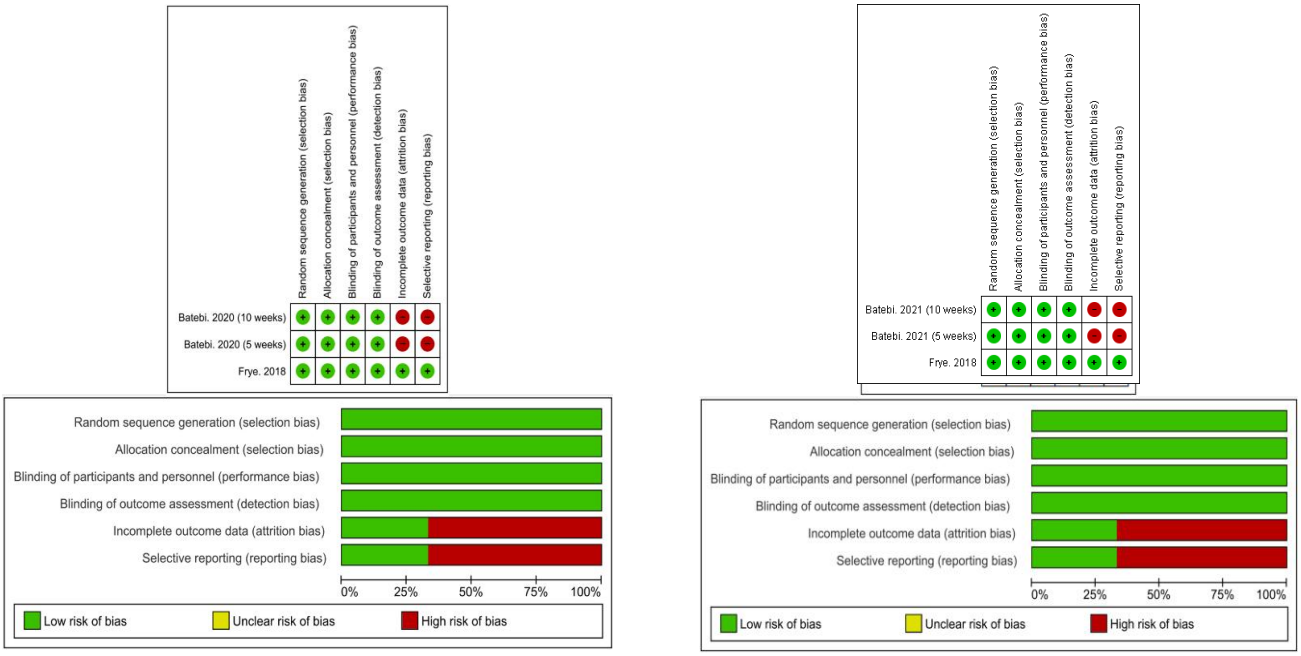

Figure 3. Risk of bias summary and graphs.

Mental health is an essential topic for the autism community (Roche et al. 2021). Current evidence indicates that there is a significantly higher proportion of mental health and behavioral problems in children with autism than in the general population (Lai et al. 2019; Wigham et al. 2017). The mental well-being of children with autism is of significant interest, as evidenced by longitudinal research indicating that, while behavioral issues and ADHD tend to diminish during childhood, anxiety levels persist at high levels or even escalate, and there is an observable increase in the prevalence of depression (McCauley et al., 2020; Rai et al., 2018). Hence, it is imperative to mitigate autism symptoms to enhance an individual's quality of life and mitigate the likelihood of comorbid mental health conditions.

This meta-analysis incorporated two studies based on the established inclusion criteria. Each of these studies assessed the effect of folinic acid in alleviating the symptoms of ASD using the ABC questionnaire and other relevant measures to evaluate outcomes. Frye et al. showed that a high dose of folinic acid for 12 weeks improved not only the ABC score but also verbal communication compared to placebo. No significant adverse events were noted. Another study conducted by Batebi et al. revealed that folinic acid as adjunct therapy with risperidone led to significant improvements in irritability, lethargy, stereotypical behavior, hyperactivity, and inappropriate speech (Batebi et al., 2021; Frye et al., 2018). The potential mechanism underlying the therapeutic effects of folinic acid in children with autism may be associated with alterations in folate metabolism (Frye et al., 2017). A growing body of evidence indicates a correlation between ASD and abnormalities in folate metabolism, such as purine, methylation, and redox metabolism (Dai et al., 2023; Howsmon et al., 2017; Stoccoro et al., 2023).

Deoxyribonucleic acid (DNA) synthesis and its cycle requires purines (Frye et al. 2020). Restrictions in purine synthesis can lead to mutations, chromosomal instability, and significant abnormalities in chromosomal structures, all of which are associated with ASD (Dai et al., 2023; Frye et al., 2020). Guanosine 5'-triphosphate, a purine derivative, serves as the precursor for tetrahydrobiopterin (BH_4), a crucial compound involved in the production of monoamine neurotransmitters and nitric oxide. These biochemical processes have been found to exhibit abnormalities in individuals with ASD (Frye et al., 2013). Moreover, ASD has been

linked to genetic variability in three key components of folate metabolism: dihydrofolate reductase (DHFR), reduced folate carrier (RFC), and methylenetetrahydrofolate reductase (MTHFR) (Frye et al., 2020; Roufael et al., 2023). DHFR plays a crucial role in the conversion of folate into its biologically active form, whereas RFC is responsible for transporting folate within the body. In contrast, MTHFR is essential for the efficient functioning of the folate cycle, particularly in children with ASD and behavioral issues (Roufael et al., 2023).

Deviant levels of crucial methylation metabolites, including S-adenosyl-L-homocysteine (SAH), methionine, and S-adenosyl-L-methionine (SAM) have been associated with ASD (Stoccoro et al., 2023). The significance of deficits in SAM cannot be overlooked given that SAM is the primary methyl donor necessary for DNA and histone methylation, a crucial epigenetic mechanism responsible for regulating gene expression (Tremblay & Jiang, 2019). Furthermore, redox abnormalities are commonly observed in ASD patients (Frye et al., 2020). Aberrations in the level of reduced glutathione (GSH), a significant intracellular redox buffer, can lead to oxidative stress, resulting in damage to cellular DNA, proteins, and lipids (Howsmon et al., 2017). There is ample evidence of this damage in ASD patients (Howsmon et al., 2017).

Although the results were statistically significant, several limitations should be addressed in future research. First, there was a limited number of participants and included studies; therefore, the results of this analysis should be considered preliminary. Second, the combination of folinic acid with risperidone in one study may have influenced the outcomes; thus, future studies should aim to evaluate folinic acid as a standalone intervention.

Conclusion

Based on our meta-analysis of two studies with 103 participants, folinic acid at a dose of 2 mg/kg showed promise in improving irritability, lethargy, stereotypical behavior, hyperactivity, and inappropriate speech in children with autism.

To build on these findings, further research, particularly larger, multicenter randomized controlled trials with standardized protocols, is necessary to confirm the efficacy of studies that did not use folinic acid and to clarify its clinical role in managing ASD symptoms. As monotherapy, but as a supplement to risperidone. Therefore, further analyses with larger sample sizes are warranted.

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