

Effect of Folic Acid Supplementation on Homocysteine Levels in Adults Receiving Antiepileptic Drugs: A Single-Blind Randomized Trial

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Citation this Article: Dr Shahu Ingole, Dr Uma Bhosale, “Effect of Folic Acid Supplementation on Homocysteine Levels in Adults Receiving Antiepileptic Drugs: A Single-Blind Randomized Trial”, IJMSIR - October – 2025, Vol – 10, Issue - 5, P. No. 43 – 51.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Antiepileptic drugs (AEDs) are known to interfere with folate metabolism and elevate plasma homocysteine levels, thereby increasing the risk of vascular complications and neurotoxicity. Folic acid supplementation may mitigate these adverse effects.

Objective: To evaluate the efficacy of folic acid supplementation in reducing serum homocysteine levels and modulating hyperhomocysteinemia-induced cardiovascular risk factors among adult epileptic patients on chronic AED therapy.

Methodology: In this single-blind, randomized controlled trial, 42 adult epileptic patients with elevated homocysteine levels ($>10.9 \mu\text{mol/L}$) were randomized in a 2:1 ratio to receive either folic acid (5 mg/day) or placebo for 1 month. Baseline and post-intervention assessments included serum homocysteine, lipid profile, blood pressure, and random blood sugar. Paired and independent t-tests were used for within- and between-group comparisons.

Results: The folic acid group ($n=28$) showed a significant reduction in mean homocysteine levels from 26.63 ± 8.52 to $20.23 \pm 7.37 \mu\text{mol/L}$ ($p = 0.0007$), whereas the placebo group ($n=14$) experienced a significant increase (from 23.96 ± 8.37 to $29.84 \pm 12.86 \mu\text{mol/L}$; $p = 0.0114$). The between-group difference in homocysteine change was highly significant ($p < 0.0001$). No significant changes were observed in blood pressure, LDL, or triglycerides. HDL levels significantly improved in the folic acid group compared to placebo ($p = 0.0006$).

Conclusion: Folic acid supplementation effectively reduces homocysteine levels in adult epileptic patients on AEDs. However, short-term supplementation may have limited impact on associated cardiovascular risk markers.

Keywords: Folic Acid Supplementation, Homocysteine, Hyperhomocysteinemia, Antiepileptic Drugs, Epilepsy, Cardiovascular Risk

Introduction

Epilepsy is a chronic neurological disorder affecting over 50 million individuals worldwide and is commonly managed with long-term antiepileptic drug (AED) therapy.¹ While AEDs are essential for seizure control, several commonly prescribed agents including phenytoin, carbamazepine, phenobarbital, and valproate are known to disrupt folate metabolism and contribute to elevated plasma homocysteine levels, a condition known as hyperhomocysteinemia.^{2,3}

Hyperhomocysteinemia has been recognized as an independent risk factor for cardiovascular diseases (CVD), including stroke, myocardial infarction, and atherosclerosis.⁴ In addition to vascular effects, elevated serum homocysteine levels in patients receiving chronic AED therapy have been implicated in worsened seizure control and neuronal excitability, with one study noting that increased homocysteine may be related to epileptogenesis or suboptimal seizure control.⁵ In experimental models, systemic administration of high homocysteine levels has been shown to induce convulsive seizures, highlighting its direct neurotoxic and excitatory potential.⁶ The exact prevalence of hyperhomocysteinemia in patients with epilepsy varies, but studies consistently report elevated levels in those on long-term AED therapy.^{7,8}

Folic acid, a water-soluble B-vitamin, plays a central role in the remethylation of homocysteine to methionine. Its deficiency or metabolic impairment due to enzyme-inducing AEDs can lead to an accumulation of homocysteine in plasma.⁹ Supplementation with folic acid has consistently been shown to effectively reduce plasma homocysteine levels across multiple populations, including individuals on chronic AED therapy as well as the general population. In an adult cohort, Wald et al. demonstrated that a daily intake of 0.8 mg of folic acid

achieved a maximum reduction in serum homocysteine levels across a wide concentration range.¹⁰ However, the clinical translation of homocysteine reduction into improved cardiovascular (CV) outcomes in such patients remains controversial. Some trials have shown modest benefits in lipid modulation and blood pressure regulation with folic acid supplementation, while others report no significant CV benefit, particularly in low-risk populations or with short treatment durations.^{11,12}

Given this background, the present randomized controlled trial was designed to evaluate the efficacy of folic acid supplementation in reducing serum homocysteine levels and modifying hyperhomocysteinemia-associated CV risk factors in adult epileptic patients on AEDs.

Materials and Methods

Study Design and Setting

This was a single-blind, two-arm, parallel-group, randomized controlled clinical trial conducted to evaluate the efficacy of folic acid supplementation on homocysteine levels and associated CV risk factors in adult patients with epilepsy receiving AEDs. The study was conducted at Smt. Kashibai Navale Medical College & General Hospital, Pune. The study was conducted in full accordance with the principles outlined in the Declaration of Helsinki (2013 revision) and the Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. Ethical approval was obtained from the Institutional Ethics Committee prior to initiation of the trial. All participants were provided with detailed information about the nature, purpose, and potential risks and benefits of the study, following which written informed consent was obtained from each participant before enrolment.

Eligibility Criteria

Adults of either sex aged more than 18 years, with a confirmed clinical diagnosis of epilepsy and on a stable dose of AEDs for a minimum duration of six months, were considered eligible for inclusion in the study. Only those patients who had elevated fasting serum homocysteine levels, defined as $>10.9 \mu\text{mol/L}$, were enrolled. All participants were required to provide written informed consent prior to enrolment. Patients were excluded if they had any comorbid conditions that could interfere with homocysteine metabolism or confound study outcomes. These included diabetes mellitus, ischemic heart disease, stroke, malignancy, psychiatric disorders, pregnancy or lactation, renal or thyroid dysfunction, and chronic inflammatory diseases. Individuals with known inborn errors of homocysteine, folate, or cobalamin metabolism, or those who had received vitamin supplementation within the preceding three months, were also excluded from the study.

Randomization, Allocation and Blinding

Eligible participants were randomized in a 2:1 ratio to the intervention group (folic acid supplementation) or the placebo group. The randomization sequence was generated using a table of random numbers from the OpenEpi software. Allocation was concealed in sealed opaque envelopes. This was a single-blind study in which the participants were unaware of their group allocation. Investigators and outcome assessors were not blinded.

Intervention

Participants randomized to the intervention group continued their ongoing AED therapy and received an additional oral folic acid supplement at a dose of 5 mg once daily for a one month. Those in the control group also continued their prescribed AED therapy and were administered an identical-looking placebo tablet once daily for the same duration. Both folic acid and placebo

tablets were similar in appearance, and participants were instructed to take the assigned tablet at a fixed time each day to ensure compliance.

Assessments and Follow-Up

At baseline, all participants underwent a comprehensive evaluation that included measurement of fasting serum homocysteine levels, systolic and diastolic blood pressure (SBP and DBP), and a fasting lipid profile comprising low-density lipoprotein (LDL), high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL), triglycerides (TG), and total cholesterol (TC). In addition, random blood sugar (RBS) levels were recorded. After one month of intervention or placebo administration, participants were reassessed for the same set of clinical and biochemical parameters. All laboratory investigations were conducted in the institutional central laboratory using standardized and validated methods to ensure consistency and accuracy.

Outcome Measures

The primary outcome of the study was the change in serum homocysteine levels observed after one month of intervention. Secondary outcomes included changes in SBP and DBP, as well as alterations in lipid profile parameters, specifically LDL, HDL, VLDL, and TG.

Statistical Analysis

Data were entered into Microsoft Excel and analysed using OpenEpi (version 2.3) software. Continuous variables were expressed as mean $\pm$ standard deviation (SD). Categorical data, such as sex distribution, were presented as counts and percentages. Baseline and post-intervention comparisons within each group (Folic Acid and Placebo) were analysed using the paired samples t-test. Between-group comparisons of mean change values were conducted using the independent samples t-test assuming unequal variances to determine the effect of

folic acid supplementation relative to placebo. A p-value of <0.05 was considered statistically significant.

Results

A total of 42 adult epileptic patients with elevated serum homocysteine levels (>10.9 mmol/L) were enrolled and randomized in a 2:1 ratio into two study arms. Of these, 28 participants were allocated to the folic acid intervention group and 14 participants were assigned to the placebo group. All participants completed the one-

Table 1: Baseline Demographic Characteristics of Study Participants

Characteristic	Folic Acid Group (n = 28)	Placebo Group (n = 14)
Age (years)	22.5 ± 1.8	22.6 ± 1.3
Male [n]	20	10
Height (cm)	165.0	166.0
Weight (kg)	54.4	56.3
BMI (kg/m^2)	19.9 ± 1.4	20.4 ± 1.2

Values are presented as mean $\pm$ standard deviation unless otherwise specified.

Baseline and Follow-up Homocysteine Levels

The mean baseline serum homocysteine level in the Folic Acid group was 26.63 ± 8.52 mmol/L, which significantly decreased to 20.23 ± 7.37 mmol/L after one month of folic acid supplementation (Table 2). The mean

Table 2: Effect of Folic Acid Supplementation on Homocysteine Levels in Epileptic Patients

Group	Baseline Homocysteine Level (mmol/L) (Mean $\pm$ SD)	1-Month Homocysteine Level (mmol/L) (Mean $\pm$ SD)	Change in Homocysteine Level (mmol/L) (Mean $\pm$ SD)
Folic Acid (n=28)	26.63 ± 8.52	20.23 ± 7.37	-6.40 ± 8.84
Placebo (n=14)	23.96 ± 8.37	29.84 ± 12.86	$+5.89 \pm 7.49$

The change in homocysteine levels from baseline to one month was compared between the Folic Acid and Placebo groups using an independent samples t-test. The analysis showed a highly significant difference in the change scores between the two groups ($t = -4.71$, $p <$

month follow-up period and were included in the final analysis. Baseline demographic and clinical characteristics were comparable between the two groups, ensuring the internal validity of the comparative assessments (Table 1). The mean age of participants was 22.5 ± 1.8 years in the folic acid group and 22.6 ± 1.3 years in the placebo group. The majority of participants in both groups were male.

reduction in homocysteine levels was statistically significant ($p = 0.0007$). In contrast, in the Placebo group, the mean baseline homocysteine level was 23.96 ± 8.37 mmol/L, which increased to 29.84 ± 12.86 mmol/L after one month. The mean increase in homocysteine was also statistically significant ($p = 0.0114$).

0.0001), favouring folic acid supplementation in reducing homocysteine levels. Figure 1 illustrates the statistically significant reduction in homocysteine in the Folic Acid group versus the increase in the Placebo group over one month.

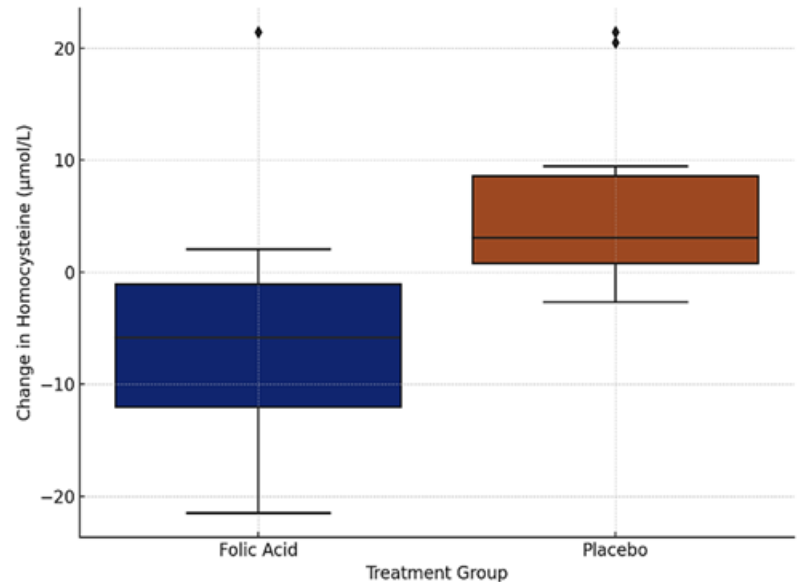


Figure 1: Comparison of Change in Serum Homocysteine Levels between Folic Acid and Placebo Groups after One Month of Intervention

Blood Pressure and Lipid Profile Changes

The effects of folic acid supplementation on blood pressure and lipid profile parameters were assessed over a one-month period and compared between the intervention and placebo groups (Table 3). In terms of blood pressure, the SBP showed a negligible mean change of -0.14 ± 1.80 mmHg in the folic acid group and an identical change of -0.14 ± 1.83 mmHg in the placebo group. These changes were not statistically significant within either group ($p = 0.678$ for folic acid, $p = 0.775$

for placebo), and there was no significant difference observed between the groups ($p = 1.000$). Similarly, DBP decreased by -0.50 ± 2.08 mmHg in the folic acid group and -1.00 ± 1.88 mmHg in the placebo group. Although the change within the placebo group approached significance ($p = 0.068$), the changes were not statistically significant within the folic acid group ($p = 0.215$), nor was the between-group difference statistically significant ($p = 0.440$).

Table 3: Effect of Folic Acid Supplementation on Lipid Parameters, Blood Pressure, and Random Blood Sugar

Parameter	Folic Acid (Baseline Mean $\pm$ SD)	Folic Acid (1-Month Mean $\pm$ SD)	Change (Mean $\pm$ SD)	Placebo (Baseline Mean $\pm$ SD)	Placebo (1- Month Mean $\pm$ SD)	Change (Mean $\pm$ SD)	p-value (Folic, within)	p-value (Placebo, within)	p-value (Between Groups)
LDL (mg/dL)	78.54 $\pm$ 4.07	78.64 $\pm$ 4.10	-0.14 $\pm$ 0.77	80.07 $\pm$ 5.27	79.93 $\pm$ 4.98	-0.14 $\pm$ 0.77	0.4153	0.5000	0.3145
HDL (mg/dL)	47.57 $\pm$ 1.40	48.21 $\pm$ 1.40	+0.64 $\pm$ 1.10	47.79 $\pm$ 1.31	42.43 $\pm$ 4.48	-5.36 $\pm$ 4.99	0.0044	0.0015	0.0006
Triglycerides (mg/dL)	119.86 $\pm$ 3.92	120.61 $\pm$ 3.81	+0.75 $\pm$ 2.32	19.14 $\pm$ 3.96	119.21 $\pm$ 3.70	-0.07 $\pm$ 2.81	0.0985	0.9258	0.4439
SBP (mmHg)	125.14 $\pm$ 2.85	125.00 $\pm$ 3.20	-0.14 $\pm$ 1.80	125.14 $\pm$ 2.44	125.00 $\pm$ 2.57	-0.14 $\pm$ 1.83	0.6777	0.7753	1.0000
DBP (mmHg)	82.50 $\pm$ 2.15	82.00 $\pm$ 1.63	-0.50 $\pm$ 2.08	83.29 $\pm$ 2.30	82.29 $\pm$ 1.54	-1.00 $\pm$ 1.88	0.2146	0.0682	0.4399

With regard to lipid parameters, the LDL levels exhibited a minor increase of 0.11 ± 0.69 mg/dL in the folic acid group and a small decrease of -0.14 ± 0.77 mg/dL in the placebo group. These changes were not statistically

significant either within the groups ($p = 0.415$ and $p = 0.500$, respectively) or between the groups ($p = 0.314$). Triglyceride levels increased slightly in both groups, with a change of 0.75 ± 2.32 mg/dL in the folic acid group and

0.07 ± 2.81 mg/dL in the placebo group; however, these changes were not statistically significant ($p = 0.099$ and $p = 0.926$, respectively), nor was the between-group comparison ($p = 0.444$).

In contrast, a statistically significant improvement was observed in HDL levels. The folic acid group demonstrated a significant increase in HDL by 0.64 ± 1.10 mg/dL ($p = 0.004$), whereas the placebo group experienced a significant decline of -5.36 ± 4.99 mg/dL ($p = 0.001$). The between-group comparison revealed a highly significant difference ($p = 0.0006$), favouring folic acid supplementation.

Discussion

The present randomized controlled trial evaluated the effect of folic acid supplementation on homocysteine levels and CV risk factors in adult epileptic patients receiving AEDs. A significant reduction in serum homocysteine levels was observed in the folic acid group compared to baseline and placebo, highlighting the beneficial role of folate supplementation in mitigating AED-induced hyperhomocysteinemia. Several commonly used AEDs such as phenytoin, carbamazepine, phenobarbital, and valproate have been implicated in causing elevated plasma homocysteine levels through various mechanisms. These drugs interfere with folate and vitamin B12 metabolism by inducing hepatic enzymes (notably cytochrome P450), thereby accelerating the degradation of folate and reducing its bioavailability.^{2,3} Additionally, AEDs like valproate may inhibit enzymes involved in homocysteine remethylation and trans-sulfuration, further contributing to elevated homocysteine levels.^{7,9} Hyperhomocysteinemia is a well-recognized independent risk factor for CVD and has been increasingly linked to neurological dysfunction, cognitive decline, and increased seizure frequency in epileptic patients.⁶ Thus, controlling homocysteine levels in

epileptic patients is of both CV and neurological relevance.

Our study demonstrated a statistically significant reduction in homocysteine levels following one month of folic acid supplementation. These findings are consistent with previous interventional studies. Apeland et al. (2001) reported that folic acid supplementation (0.4–5 mg/day) effectively decreased plasma homocysteine concentrations in patients taking phenytoin and carbamazepine.³ A similar reduction in serum homocysteine levels following folic acid supplementation was also reported in a randomized controlled trial conducted by Jeeja et al. (2014).¹³ In their study, daily supplementation with folic acid significantly decreased homocysteine concentrations over a 3-month period compared to the control group, without adverse effects.¹³ Further support for the efficacy of folic acid in normalizing elevated homocysteine levels among patients receiving antiepileptic drugs comes from a study by Huemer et al. (2005), which demonstrated that folic acid supplementation (5 mg/day for 6 weeks) effectively reversed hyperhomocysteinemia in children on chronic AED therapy.¹⁴

The mechanism underlying this effect lies in folate's role as a methyl donor in the remethylation of homocysteine to methionine, a reaction catalyzed by methionine synthase with vitamin B12 as a cofactor. Supplementation ensures an adequate substrate pool for homocysteine metabolism, thereby reducing its plasma levels.^{4,9}

Although a favourable increase in HDL levels was observed in the folic acid group in our study, there was no statistically significant improvement in other lipid parameters, blood pressure, or random blood sugar levels. These findings align with prior studies. A systematic review and meta-analysis by Tabrizi et al.

(2018) examined the impact of folate supplementation on lipid profiles and blood pressure among patients with metabolic diseases. The analysis of randomized controlled trials concluded that folate supplementation did not significantly affect systolic or diastolic blood pressure, nor did it alter triglycerides, total cholesterol, HDL, VLDL, or LDL levels, particularly when administered over short durations.¹²

While some studies suggest a modest antihypertensive effect with long-term folic acid supplementation in hypertensive populations, the duration and baseline risk status may play crucial roles in determining its efficacy.¹¹

A comprehensive 2023 meta-analysis by Asbaghi et al. consolidated data from 22 randomized controlled trials involving over 41,000 participants. It revealed that folic acid supplementation significantly reduced systolic blood pressure (SBP) by 1.10 mmHg (95% CI: -1.93 to -0.28 mmHg; $p = 0.008$) and diastolic blood pressure (DBP) by 0.24 mmHg (95% CI: -0.37 to -0.10 mmHg; $p < 0.001$). Notably, the antihypertensive effects were more evident in subgroups with higher baseline SBP (≥ 120 mmHg), short intervention durations (≤ 6 weeks), high folic acid doses (≥ 5 mg/day), and in participants already at cardiovascular risk.¹¹ The absence of significant CV risk modulation in our study could be attributed to the short duration of intervention (1 month), relatively young patient population, and the fact that hyperhomocysteinemia may contribute to CV risk over a longer time frame through endothelial dysfunction, pro-thrombotic effects, and vascular remodeling.¹⁵

Furthermore, our findings are consistent with those reported by Bhosale et al. (2019), who conducted a single-blind randomized controlled trial in adolescent epileptic patients receiving chronic antiepileptic therapy.¹⁶ In their study, folic acid supplementation (5 mg/day for 1 month) led to a statistically significant

reduction in plasma homocysteine levels among adolescents on enzyme-inducing AEDs, without significant alterations in blood pressure or lipid parameters. This similarity in outcomes across different age groups suggests a robust homocysteine-lowering effect of folic acid regardless of age. The lack of impact on CV parameters in both studies may further support the hypothesis that longer durations of supplementation or higher baseline CV risk are required to observe measurable changes in lipid metabolism or blood pressure. Thus, our study extends these findings to an adult population and reinforces the biochemical efficacy of folic acid in counteracting AED-induced hyperhomocysteinemia.

Study Limitations

Despite demonstrating a significant reduction in serum homocysteine levels with folic acid supplementation, the present study has certain limitations that warrant consideration. Firstly, the short duration of follow-up (one month) may have been insufficient to capture the long-term effects of folic acid on CV risk markers such as blood pressure and lipid profile, which may require prolonged intervention to manifest measurable changes. Moreover, dietary intake of folate or vitamin B12, which can influence homocysteine levels, was not controlled or assessed, potentially introducing confounding variables. Finally, the study population consisted predominantly of young adults, limiting the generalizability of the findings to older epileptic patients or those with established CV comorbidities who may derive different degrees of benefit from folic acid supplementation. These limitations highlight the need for larger, double-blind, placebo-controlled trials with longer follow-up durations and broader participant demographics to fully elucidate the clinical implications of folic acid therapy in patients

with epilepsy receiving chronic antiepileptic drug treatment.

Conclusion

Our findings support the short-term efficacy of folic acid supplementation in significantly reducing serum homocysteine levels in adult epileptic patients on AEDs. However, its impact on associated CV risk parameters appears limited over the one-month treatment period. Routine homocysteine monitoring and folate supplementation may be considered in chronic AED users to reduce long-term vascular and neurotoxic risks.

References

1. Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia*. 2011;52(Suppl 7):2–26. <https://doi.org/10.1111/j.1528-1167.2011.03121.x>
2. Schwaninger M, Ringleb P, Winter R, Hacke W. Elevated plasma homocysteine in antiepileptic drug treatment. *Epilepsia*. 1999;40(3):345–50. DOI: 10.1111/j.1528-1157.1999.tb00716.x
3. Apeland T, Mansoor MA, Strandjord RE. Antiepileptic drugs as independent predictors of plasma total homocysteine levels. *Epilepsy Research*. 2001;47(1–2):27–35. doi: 10.1016/S0920-1211(01)00288-1.
4. Paganelli F, Mottola G, Fromonot J, et al. Hyperhomocysteinemia and Cardiovascular Disease: Is the Adenosinergic System the Missing Link? *Int J Mol Sci*. 2021 Feb 8;22(4):1690. doi: 10.3390/ijms22041690.
5. Sener U, Zorlu Y, Karaguzel EO, Ozdamar O, Ozkayran T. Effects of antiepileptic drugs on plasma homocysteine levels in epilepsy patients. *Seizure*. 2006;15(1):79–83. doi: 10.1016/j.seizure. 2005.10.004
6. Diaz-Arrastia R. Homocysteine and neurologic disease. *Arch Neurol*. 2000;57(11):1422–8. doi: 10.1001/archneur.57.11.1422.
7. Belcastro V, Striano P, Gorgone G, et al. Hyperhomocysteinemia in epileptic patients on new antiepileptic drugs. *Epilepsia*. 2010;51(2):274–9. doi: 10.1111/j.1528-1167.2009.02303.x
8. Mintzer S, Skidmore CT, Abidin CJ, et al. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. *Ann Neurol*. 2009;65(4):448–56. doi: 10.1002/ana.21615
9. Townsend JH, Davis SR, Mackey AD, Gregory JF 3rd. Folate deprivation reduces homocysteine remethylation in a human intestinal epithelial cell culture model: role of serine in one-carbon donation. *Am J Physiol Gastrointest Liver Physiol*. 2004 Apr;286(4):G588-95. doi: 10.1152/ajpgi.00454.2003.
10. Wald DS, Law M, Morris JK, Wald NJ. Randomized trial of folic acid supplementation and serum homocysteine levels. *JAMA Intern Med*. 2001; 161(11):694–700. doi:10.1001/archinte.161.11.694.
11. Asbaghi O, Salehpour S, Rezaei et al. Folic acid supplementation and blood pressure: a GRADE-assessed systematic review and dose-response meta-analysis of 41,633 participants. *Crit Rev Food Sci Nutr*. 2023;63(13):1846-1861. doi: 10.1080/10408398.2021.1968787.
12. Tabrizi R, Lankarani KB, Akbari M, et al. The effects of folate supplementation on lipid profiles among patients with metabolic diseases: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab Syndr*. 2018 May;12(3):423-430. doi: 10.1016/j.dsx.2017.12.022
13. Jeeja MC, Jayakrishnan T, Narayanan PV, et al. Folic acid supplementation on homocysteine levels in children taking antiepileptic drugs: A randomized

- controlled trial. *J Pharmacol Pharmacother.* 2014;5(2):93-9. doi: 10.4103/0976-500X.130048.
14. Huemer M, Ausserer B, Graninger G, et al. Hyperhomocysteinemia in children treated with antiepileptic drugs is normalized by folic acid supplementation. *Epilepsia.* 2005;46(10):1677-83. doi: 10.1111/j.1528-1167.2005.00264.x
15. Lentz SR. Mechanisms of homocysteine-induced atherothrombosis. *J Thromb Haemost.* 2005; 3 (8): 1646–54. [https://doi.org/10.1111/ j.1538-7836. 2005. N01364.x](https://doi.org/10.1111/j.1538-7836.2005.N01364.x)
16. Bhosale UA, Yegnanarayan R, Agrawal A, et al. Efficacy study of folic acid supplementation on homocysteine levels in adolescent epileptics taking antiepileptic drugs: a single blind randomized controlled clinical trial. *Ann Neurosci.* 2019;26(3-4):50-54. doi: 10.1177/0972753120925560.