# Comparison of efficacy of folic acid and silymarin in the management of antiepileptic drug induced liver injury: a randomized clinical trial

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**BACKGROUND: Liver injury associated with antiepileptic drugs accounts for a large proportion of drug-induced liver injuries (DILI) in children. Although withdrawal of the causative agent is the only proved treatment for DILI, in some clinical situations it is not possible. Recent studies have reported promising results of using hepatoprotective drugs with antioxidant actions for the management of DILI. This study aimed to evaluate the efficacy of folic acid versus silymarin treatment in relation to decreasing liver enzymes in patients with DILI due to antiepileptic therapy.**

**METHODS: This randomized, open-label, clinical trial evaluated 55 children with epilepsy who were on antiepileptic treatment and experienced DILI. The children were randomized to receive either silymarin (5 mg/kg per day) or folic acid (1 mg per day) for one month and were followed up for three months.**

**RESULTS: Liver enzymes significantly decreased in both groups. The decrease trend in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were stronger in the folic acid group compared to silymarin group ($P$=0.04 and $P$=0.007, respectively). At the end of the study patients in the folic acid group had significantly lower ALT ($P$=0.04), AST ($P$=0.02), and gamma-glutamyl transferase (GGT) ($P$<0.001) levels and also higher percentage of normal ALT (30.7% vs 3.4%, $P$=0.009) and AST (42.3% vs 0%, $P$<0.001), and GGT (23.1% vs 0%, $P$=0.008) values compared to the patients in the silymarin group. No rebound elevations in ALT, AST and GGT levels or adverse reactions were noted in neither of the study groups.**

**CONCLUSION: Although both treatments were safe and effective in decreasing liver enzymes, folic acid seems to be superior to silymarin in the management of DILI.**

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**KEY WORDS:** anticonvulsant; antiepileptic; enzymes; hepatitis; hepatotoxicity

## Introduction

Drug-induced liver injury (DILI), is defined as biochemical abnormalities in liver tests or liver dysfunction due to medications or herbs and is usually diagnosed after exclusion of other etiologies.[1] DILI accounts for nearly 10% of cases of acute liver failure (ALF) in adults and 5%-10% of ALF in children,[1-4] and is the most common cause of ALF in the United States.[2, 5]

Many drugs cause DILI. However, antimicrobial and antiepileptic drugs are the most recognized.[1, 3] Liver injury associated with antiepileptic drugs accounts for as highly as 40% of DILI in children and can present through a wide range of hepatotoxic reactions from mild and transient elevations of liver enzymes to very serious liver failure leading to death or liver transplantation.[3, 6, 7] The management of DILI is largely supportive and withdrawal of the causative agent is the only proved treatment.[5] However, recent studies involving human and animal subjects reported promising results of using hepatoprotective drugs with antioxidant actions for the management of DILI.[5, 8-15] This is especially important in clinical setting when drug withdrawal is not possible or when the patient experiences continuous rising in liver enzymes even after substituting the offensive drug, and also in the milder forms of DILI that manifest only through a moderate increase in liver enzymes before seriously impairing liver function.

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Silybum marianum (milk thistle) is one of the oldest used plants in the treatment of hepatobiliary diseases and silymarin is the active constituent of this plant.[16] Silymarin treatment has been studied in patients with different liver injuries;[17] causing a significant improvement and decreased the liver enzymes in alcoholic liver disease,[18] non-alcoholic steatohepatitis (NASH),[19, 20] amanita mushroom poisoning,[5] and viral hepatitis.[21, 22] Different hepatoprotective activities of silymarin is recognized including antioxidant, cell membrane stabilizing, stimulating liver regeneration, and anti-inflammatory activities.[16]

Folic acid is the synthetic form of vitamin B9, which is an essential nutrient for the body with strong antioxidant activity. Folic acid supplementation has been studied in animal models with liver injury caused by alcohol, paracetanol and arsenic consumption,[14, 15, 23] and also in human subjects with methotrexate induced liver injury and also in patients with elevated aminotransferases with unknown liver diseases;[24, 25] in these studies folic acid supplementation decreased liver enzymes and attenuated the hepatotoxic effects of the drugs.[14, 15, 23-25] The hepatoprotective effects of folic acid is due to its strong antioxidant and reactive oxygen species (ROS) scavenging activities.[14, 15, 23-25]

Most of the published studies have evaluated the effects of silymarin and folic acid in animal models of DILI. By our extensive search we could not find enough studies assessing the efficacy of silymarin and folic acid in patients with DILI, especially those caused by antiepileptic drugs. Since liver injury due to antiepileptic drugs accounts for a large number of pediatric cases with DILI,[3] that can potentially progress to life threatening conditions,[6, 7] studies are required to evaluate the efficacy of hepatoprotective drug supplementation in children who are on antiepileptic treatment and who experience continuous rising in liver enzymes despite lowering the dose or substituting the offensive drug. Given the fact that antiepileptic treatment is associated with a significant decrease in folate levels and folic acid treatment is recommended in epileptic patients,[26] folic acid supplementation in these patients might be beneficial for both diseases control and hepatoprotection.

We conducted this study to evaluate the efficacy of silymarin and folic acid supplementation in relation to decreasing and normalization of liver enzymes in pediatric patients on antiepileptic treatment who experienced a continuous rise in liver enzymes despite lowering the dose or substituting the offensive drug.

## Methods

### Study population and study design

This prospective, randomized, open-label, clinical trial was conducted on 55 children with epilepsy who were on antiepileptic treatment and experienced DILI. The participants were recruited from the pediatric neurology clinic of our institute from February 2014 to February 2015. Participants were considered eligible when they were less than 18 years of age and were on antiepileptic treatment due to confirmed epilepsy and experienced DILI as a continuous rise in liver enzymes despite decreasing the dose of antiepileptic drugs or changing the antiepileptic drugs when possible. Exclusion criteria were: liver injury caused by viral, autoimmune or metabolic diseases, aminotransferase levels below three times the upper normal limit, spontaneous decrease in aminotransferase levels within two months preceding the beginning of treatment with silymarin or folic acid, having a functional liver failure presenting with icterus, coagulopathy or encephalopathy, anatomic abnormalities, and parents refusal to give an informed consent. After explaining the whole procedure, an informed written consent was obtained from the parents. This study was approved by the Ethics Committee of our institute. This study is registered at the Iranian Registry of Clinical Trials (www.irct.ir) which is a Primary Registry in the WHO Registry Network (Registration Number: IRCT2015010711392N2).

In this study, we used simple randomization with a 1:1 allocation ratio, and sequence generations was carried out using a computerized random number generator which was performed by Sheikh M. Consecutive opaque envelopes was used for the allocation concealment which was carried out by Shariat M. The envelopes were opened sequentially after the participant's name and other details were written on them. The implementation of assignments was carried out by Asgarshirazi M.

The primary outcome of our study was the decrease and normalization of liver enzymes during the study period. The secondary outcomes were the decreasing trend and the rebound elevation of enzymes after cessation of the treatment. Rebound elevation of liver enzymes was defined as an elevation of the liver enzymes of more than twice the upper limit of the normal range after cessation of the treatment for DILI.

### Data and specimen collection

All the participants were diagnosed with epilepsy and were on antiepileptic treatment at least for three months before recruitment. The participants were referred from the pediatric neurology clinic because of the continuous rise in liver enzymes despite the efforts to reduce the dose of antiepileptic drugs to minimal effective dose or if possible substituting the offensive drug with a safer