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Review Article

Early hepatoprotection with SAMe in patients with chronic liver disease

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ABSTRACT

S-adenosyl-L-methionine (SAMe) plays a crucial role in liver health by influencing various biochemical pathways involved in hepatic function. Early intervention with SAMe has been shown to reduce the progression rate of cirrhosis. A comprehensive literature search was performed to identify studies highlighting the benefits of early treatment with SAMe in conditions such as intrahepatic cholestasis (IHC), intrahepatic cholestasis of pregnancy (ICP), viral hepatitis, drug-induced liver injury (DILI), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC) and chemotherapy-induced liver injury (CILI). The mechanism of action of SAMe and its associated pathways were also detailed. Significant improvements in liver enzymes such as AST, ALT, GGT and ALP have been reported in the literature with treatment durations as short as 2 weeks. Reduction in symptoms such as pruritus, fatigue and jaundice has also been observed. The data suggest that SAMe has beneficial effects on liver biochemistry and clinical symptoms. It can act as an important clinical asset in the management of liver conditions alongside etiology-specific management. Further studies can be done to evaluate the benefits of SAMe as a hepatoprotective agent for the early treatment of liver dysfunction.

Keywords: Ademetionine, Chronic liver diseases, Hepatoprotective agent, Liver enzymes, Super nutrient, S-adenosyl-L-methionine

INTRODUCTION

The liver performs an essential and fundamental role in the regulation of diverse physiological processes. Metabolism, secretion, transformation and storage are some of the vital functions performed by the liver. The liver also plays a role in the biochemical and physiological processes of growth signalling pathways and in provision of nutrients, energy supply, endocrine control and reproduction.[1]

Damage to liver cells hampers the formation of bile and the removal of toxic substances. The overload of drugs or xenobiotics causes liver damage and/or hepatotoxicity.[2] Liver disease can be acute or chronic depending upon the temporal progression of the injurious process. Tissue damage and persistent liver injury trigger the process of fibrogenesis, which contributes further to decline in liver microenvironment unless proper healing is allowed. The process of repair and fibrogenesis in the case of persistent or recurrent damage progresses towards cirrhosis, liver failure and finally hepatocellular carcinoma. Hepatocyte death (apoptosis and necrosis) is a characteristic feature of alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), cholestasis, viral hepatitis, ischemia/reperfusion, liver preservation at transplantation and drug/toxin-induced liver injury (DILI).[3]

The best form of management of liver diseases is to correct the underlying etiology before it further progresses to cirrhosis or liver failure.[3] Hence, the need for early treatment of liver dysfunction is emphasized in light of appropriate risk evaluation, mitigation of disease progression and adequate disease management. Many over the counter medicinal and nutraceutical product are available and being prescribed (albeit in the absence of evidence) for the treatment of liver disorders. Some of these products are not only ineffective, but many herbal

formulations may even lead to drug induced liver injury.[2] Essential nutrients or super nutrients may, on the other hand, are considered harmless as they may not increase the load in liver disease for lack of requirement of getting metabolized by hepatic pathways.[4]

Ademetionine or S adenosyl L methionine (SAMe) is one such pleiotropic molecule which is used as a hepatoprotective agent. Some randomized trials have also explored their role in early treatment of liver diseases, but the data is limited.

This opinion review provides a thorough discussion about the data related to SAMe and its therapeutic use in liver diseases. It outlines the benefits of early initiation of treatment with SAMe in patients with chronic liver diseases. PubMed, Medline and Google Scholar were searched using terms s-adenosyl-L-methionine, AdoMetliver, hepatoprotectives, hepatoprotectors, ademetionine, intrahepatic cholestasis (IHC), liver cancer, chemoprevention, NAFLD, non-alcoholic steatohepatitis (NASH), ALD, DILI and pregnancy. Searches of studies in secondary (other) languages, studies cross-indexed by authors and reviews and hand searches of reference lists were also conducted. Abstracts of all citations and full-text articles were retrieved and reviewed.

MECHANISM OF ACTION OF SAMe

SAMe is a super nutrient produced by activation of methionine in the liver. This activation process undergoes deviations in various liver diseases which may alter the nutritional requirements during such times. After being activated in the liver, SAMe acts as an antioxidant and methyl group donor for multiple series of cellular methylation reactions. It has an essential role in diverse cellular processes including growth and death.[5,6] It is essential for the metabolism and regulation of nucleic acids and for the structure and function of membranes and many other cellular constituents.

The decrease in levels of SAMe, cysteine and glutathione can cause liver damage during the pathogenesis of alcoholic hepatitis and cirrhosis and also lead to abnormal hepatic gene expression in methionine and glutathione metabolism.[7] SAMe is particularly important for opposing the toxicity of free radicals generated by various toxins, including alcohol.[5] Because SAMe forms the basis of many cellular functions, its deficiency leads to pathological manifestations in liver diseases.

These can be corrected by supplying the missing supernutrient.[4] A meta-analysis by Guo et al concluded that SAMe replacement decreases total bilirubin and aspartate aminotransferase (AST) levels in patients with chronic liver diseases.[5] In vivo metabolism of SAMe occurs in three different ways, namely, transmethylation, transsulfuration and aminopropylation.[6] The manifestations of these three reactions form the basis for the use of SAMe to achieve clinical benefit.

Transmethylation

SAMe is an antioxidant and serves as a methyl group donor for multiple series of cellular methylation reactions, it has an essential role in diverse cellular processes including growth and death.[7] Methionine adenosyl transferase converts methionine to SAMe in the liver. It methylates the membrane phospholipids that promote fluidity of the liver cell membrane and enhances the activity of Na+-K+ ATPase, thereby improving the function of hepatocyte membrane-associated bile acid transport systems.[6]

Transsulfuration

SAMe is essential for the metabolism and regulation of nucleic acids and for the structure and function of membranes and many other cellular constituents.[9] Activation of the transsulfuration pathway by SAMe increases the production of reduced glutathione (GSH), an endogenous antioxidant that protects cells by scavenging free radicals.[8] In addition to increase in GSH levels, transsulfuration of SAMe causes change in DNA methylation, improvement in membrane fluidity, decrease in tumor necrosis factor-alpha expression and inhibition of collagen production by preventing transforming growth factor-beta induction of the collagen type I alpha 2 chain promoter.[10]

Aminopropylation

The transfer of the amino propyl group of SAMe to polyamines such as putrescine, spermine and spermidine plays an important role in the ribosomal structure and proliferation of hepatocytes. This specifically contributes to the regenerative/recovery action of SAMe.[6]

ROLE OF SAMe IN EARLY TREATMENT OF LIVER DISEASES

The relationship between depletion of intrahepatic SAMe and hepatic fibrosis has been confirmed by various animal models. Multiple studies have since been conducted to demonstrate the benefits of SAMe in the treatment of liver dysfunction of varying severity. The results of these studies in IHC, intrahepatic cholestasis of pregnancy (ICP), viral hepatitis, DILI, ALD, NAFLD/ NASH and in oncology are reported below and summarized in table 1.

Intrahepatic cholestasis and intrahepatic cholestasis of pregnancy

Cholestasis is an obstruction to or reduction in bile flow that leads to the build-up of bilirubin in the blood followed by its deposition in the skin and mucous membranes and Sclera or excretion into urine. The drift of bilirubin produced by the liver towards the blood may be due to obstruction of the layer bile ducts by stones or obstruction of smaller intrahepatic ducts and bile canaliculi or genetic mechanisms or hepatocellular secretory/functional

defects.Depletion of SAMe leads to an increase in cellular growth and proliferation, which has further deleterious effects resulting in the development of IHC.[7,25] Changes in the levels of liver enzymes such as AST, alanine aminotransferase (ALT), gamma-glutamyl transferase (γGT) and alkaline phosphatase (ALP) act as markers, which help in tracking the liver health.[11,25,26] Noureddin et al, carried out a systematic review describing the effect of early treatment with SAMe (within 2 weeks) in patients with IHC and reported decrease in plasma ALT, AST, ALP and/or γGT levels. Within a period of 6 weeks, an improvement in the symptoms of cholestasis such as fatigue, depression and pruritus were also observed. Studies evaluating fatigue recorded improvements in fatigue between 2 and 8 weeks of treatment with SAMe.[25] Virukalpattigopalratnam et al, conducted an observational study in patients with IHC due to various non-alcoholic liver disease (where 30% also had cirrhosis) wherein SAMe was prescribed as an adjunctive medical treatment. They reported significant improvement in symptoms of cholestasis, as well as parameters like the 'No. of days off work' and 'No. of visits to doctor'.[12] Ivashkin et al, conducted a multi-center, open-label study in patients of ALD with IHC (41 treated with Intravenous (IV) SAMe followed by oral and 31 with oral only) and demonstrated significant reduction in ALP and γGT ($p<0.0001$) after administration of oral or IV/oral SAMe step-therapy for 8 weeks.[13]

Table 1: Overview of studies of S-adenosylmethionine in various liver diseases.

Author	Condition	Study design	Treatment arms	Duration	Results
Frezza et al[11]	Cholestasis of pregnancy	RCT	30 women 800 mg/day SAMe IV vs placebo	Until delivery (mean18 d)	SAMe improved bile salts, bilirubin, ALT, ALP, pruritus,
Virukalpattigopalratnam et al[12]	IHC due to chronic NAFLD	Multicenter, observational, baseline-controlled study	SAMe 800-1200 mg daily (N = 244)	6 weeks	Significant reduction from baseline in ALT, AST, ALP, γGT, fatigue was observed by the end of the treatment duration
Ivashkin et al[13]	IHC due to ALD	Multicenter, baseline-controlled, open- label study	SAMe 1500 mg oral daily (N = 31) or 500/800 mg IV daily (N = 41) for 2 weeks followed by 1500 mg oral daily for 6 weeks	8 weeks	Significant decrease in ALP, γGT and improvement in fatigue, depressed mood was reported towards the end of study
Binder et al[14]	Obstetric cholestasis (ICP)	Randomized prospective comparative study	SAMe monotherapy (N=25) UDCA monotherapy (N=26) SAMe+UDCA (N=27)	4 weeks	SAMe along with UDCA improves the clinical outcomes in terms of ALT/AST/TBIL/ with no reported adverse events on fetuses or neonates
Feld et al[15]	Non-respondents to combination therapy with standard interferon or peginterferon and ribavirin	Observational study	Course A: Peginterferon alfa-2a (180 µg SC weekly) and weight-based ribavirin (1000 mg for <75kg and 1200 mg for ≥75 kg, by mouth daily) for 2 weeks.1-month washout period, with loading regimen of oral SAMe 800 mg twice daily for 2 weeks; followed by Course B: Peginterferon and ribavirin restarted with SAMe	2 weeks	Improved kinetics of the early anti-viral response; induction of ISGs in patients with HCV genotype 1 that do not respond to interferon therapy
Perlamutrov, et al[16]	DILI with IHC induced by immunosuppressive therapy	Multicentric, non-interventional, prospective observational study	Start up: SAMe (IV/IM) 400-800 mg/day, 2 weeks; Maintenance: 800-1600 mg/day, 4 weeks, orally; Follow up: At end of 4 weeks post- treatment	6 weeks	Significant clinical improvement in bilirubin, ALP, γ-glutamyl transpeptidase, ALT, AST, pruritus, fatigue. Jaundice and depressive symptoms decreased
Choudhuri, et al[17]	IHC with ALD cirrhosis was present in 42.8% cases	Observational study	Oral SAMe (up to 1600 mg/day)	42 days	There was significant decrease in STB, SCB, ALP, γGT, ALT and AST levels ($p<0.0001$) as well as significant ($p<0.0001$) reduction in health-

Continued.

Author	Condition	Study design	Treatment arms	Duration	Results
					economic burden, number of days in hospital. Statistically significant ($p<0.05$) shift towards improvement of fatigue, jaundice & pruritus
Boming et al[18]	NAFLD	-	Group 1: SAMe: (500 mg/ tablet) twice a day for 8 weeks of treatment course (N = 31), Group 2: Vitamin C (N = 31)	8 weeks	SAMe treatment resulted in decrease in TC, TG, ALT and AST levels and improvement in symptoms
MA et al[19]	NASH	-	Diammonium glycyrrhizinate -control group. Intravenous drip of 150 mg SAMe 1,4-butanedisulfonate for injection - once daily for 4 weeks of treatment course (N = 50)	4 weeks	Decrease levels of ALT, AST, TBIl, DBIl, yGT was significantly larger than that of control group ($P<0.05$). TC, TG levels decreased after treatment in SAMe group ($P<0.05$)
Antoniv et al[20]	NASH	-	Control group (1) (N=24): hypocaloric diet, metformin 500 mg twice daily, Essentiale has a hepatoprotective drug (1 capsule 3 times a day), canephron (50 mg 3 times a day). Second group (2) (N = 26): hypocaloric diet, metformin 500 mg twice daily, canephron (50 mg 3 times a day), SAMe as a hepato protective drug (200 mg 3 times on a sublingual day) Third group (3) (N = 25): hypocaloric diet, metformin 500 mg twice daily, canephron (50 mg 3 times daily), SAMe (200 mg 3 times daily sublingual) and Meldonium (vazonate) (V) (250 mg 2 times a day) as an energy, lipid and carbohydrate metabolism stabilizer	90 days	Improvement starts just within 3-4 days after the commencement of treatment with SAMe
Santini et al,[21]	HCC	Observational study	Supplemented SAMe with chemotherapy: Raltitrexed+weekly Oxaliplatin, Irinotecan+5-Fluorouracil+Folinic Acid (FOLFIRI regimen), Cyclophosphamide+Methotrexate+5-Fluorouracil (CMF regimen)	-	AST, ALT and LDH levels decreased since the first week of SAMe administration when given along with the chemotherapy and its beneficial effects
Ansorena et al,[22]	HCC	Pre-clinical studies	-	-	SAMe produces a proapoptotic effect on human hepatoma cells
Ramani et al,[23]	HCC	Pre-clinical studies	-	-	Reduction in the mitogenic effect of leptin in HepG2 liver cancer cells

ALD-alcoholic liver disease, ALP-alkaline phosphatase, ALT-aminotransferase, AST-alanine aspartate aminotransferase, DBIL-direct bilirubin, DILI-drug induced liver injury, γGT-gamma-glutamyl transferase, HCC-hepatocellular carcinoma, ICP-intrahepatic cholestasis of pregnancy, IHC-intrahepatic cholestasis, IM-intramuscular, ISGs-interferon-stimulated genes, IV-intravenous, LDH-lactate dehydrogenase, NAFLD-non-alcoholic fatty liver disease, RCT-randomized controlled trial, SAMe-S-adenosyl-L-methionine, SC-subcutaneous, SCB-serum conjugated bilirubin, STB-serum total bilirubin, TBIL-total bilirubin, TC-total cholesterol, TG-triglycerides, UDCA-ursodeoxycholic acid.

Similar results were obtained in studies where SAMe was used for ICP. ICP, also known as obstetric cholestasis, is a commonly occurring pregnancy-specific liver disease that manifests in the third trimester with pruritus when the hormonal levels are at their peak, thereby complicating 0.2% to 2% of pregnancies. ICP can lead to increased fetal risk in pregnancy.[27-29]

Binder et al, in an RCT, studied the effect of ursodeoxycholic acid (UDCA) monotherapy (n=26), SAMe monotherapy (n=25) or combination of UDCA and SAMe (n=27) in singleton pregnant women at <36 weeks with moderate or severe ICP for a period of 12 weeks and found that while UDCA was an effective intervention for ICP, when combined with SAMe, it exerted a synergistic effect on biochemical parameters thereby indicating effectiveness; however, a beneficial effect of the combination on the fetal outcomes remained to be elucidated.[14]

The combination therapy was also found to be superior to either drug alone for reducing AST levels and rate of preterm delivery in a metanalysis of 5 studies (n= 311).[30] A review by Anstee et al, discussed the results of a randomized controlled trial in 30 women receiving 800 mg/day IV SAMe versus placebo for a mean duration of 18 days and concluded that SAMe improved bile salts, bilirubin, ALT, ALP, pruritus and neonatal and maternal outcomes.[3]

Viral hepatitis and drug induced liver injury

SAMe has been shown to increase the induction of interferon stimulated genes by increasing STAT-1 methylation lending an antiviral effect on HCV along with peginterferon and ribavirin. Among non-responders with HCV genotype 1, Feld et al, conducted a study where peginterferon alfa-2a (180 μg subcutaneously weekly) and weight-based ribavirin (1000 mg for <75kg and 1200 mg for ≥75 kg, by mouth daily) treatment was given for 2 weeks (Course A). Post which a 1-month washout period was given. Thereafter, patients received a loading regimen of oral SAMe 800 mg twice daily for 2 weeks. This was then followed by Course B.

Treatment with peginterferon and ribavirin was resumed while SAMe was continued for a planned 48-week course. The results showed an improvement of the second phase slope of viral decline (p=0.009) following 2 weeks of treatment with SAMe in patients with hepatitis 53% of the patients achieved an early virological response and 48% had undetectable HCV ribonucleic acid (RNA) by week 24.[15] Now with the availability of directly acting antivirals (DAAs), HCV is treated by a short course of oral medications rather than PEG interferon, but the earlier study does show the adjuvant role played by SAMe. DILI due to prescription and non-prescription drugs are on the rise over last decades. Approximately 75% of idiosyncratic drug reactions that are associated with jaundice, lead to liver transplantation or death. Such progressions can easily be avoided by appropriate and timely interventions. Perlamutrov, et al, studied the use of SAMe in DILI with IHC induced by immunosuppressive therapy. Administration of SAMe for 6 weeks significantly decreased the levels of bilirubin, ALP, γ-glutamyl transpeptidase, ALT and AST (p<0.05). Symptoms like pruritus, fatigue and jaundice improved and the number of patients with depressive symptoms decreased.[16]

Alcoholic liver disease

Alcohol-related liver injury has a wide spectrum that ranges from simple steatosis to Alcoholic steatohepatitis, Alcoholic Hepatitis (AH) to Cirrhosis.[6] Alcohol metabolism leads to oxidative stress and the association between ALD and impaired activation of methionine to SAMe have been explored as potential targets for the treatment of ALD. Depletion of endogenous SAMe and associated liver pathology can be corrected by the administration of this therapeutically effective and safe nutrient.[4]

In an observational study conducted by Choudhuri et al, in patients with ALD cirrhosis, it was observed that there was a significant reduction in serum total bilirubin (STB), serum conjugated bilirubin (SCB), ALP, GGT, ALT and AST levels (p<0.0001) as well as a significant (p<0.0001) reduction in the economic burden (number of days off work (-4.28 days), number of visits to healthcare services as an outpatient (-0.72) and number of days in hospital (-1.42 days) compared to baseline values in just 3 weeks of treatment with SAMe. Statistically significant (p<0.05) shifts towards improvement of fatigue, jaundice and pruritus were also observed.[17] However, these findings need to be validated in randomized controlled trials.

Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

Insulin resistance causes the accumulation of triglycerides (TG) in the liver leading to NAFLD.[17] NAFLD encompasses a spectrum of hepatic damage that ranges from generally benign, simple fat accumulation in the liver (steatosis) to steatohepatitis, to fibrosis and cirrhosis and ultimately leading to hepatocellular carcinoma (HCC).[24] A meta-analysis by Younossi et al, reported NAFLD as a common cause of liver disease world-wide with estimated 25% of the adult population in the world having NAFLD with highest prevalence rates being reported from South America (31%) and the Middle East (32%) and the lowest prevalence being reported from Africa (14%).[31]

A meta-analysis by Shalimar, et al, found the overall pooled prevalence of NAFLD in India to be 38.6% among adults and 35.4% among children with similar prevalence in males and females.[32] NAFLD includes progressive NASH, which is linked to cellular injury and inflammation that can lead to cirrhosis and liver-related deaths.[33] Therefore, early intervention in NAFLD may provide clinical benefits in light of prevention of disease

progression and may contribute to reversal in some. It is hypothesized that a chronically altered SAMe level, by increasing the oxidative stress in the liver, may trigger a conversion from simple steatosis to NASH. In animal studies, SAMe administration has been shown to ameliorate hepatic oxidative injury.[34] SAMe has been evaluated in patients with NAFLD, with improvements observed in triglycerides (TG), total cholesterol (TC) and ultrasound features along with ALT and AST levels.[6] Boming et al, studied the effect of 8 weeks of treatment with SAMe (500 mg tablet twice a day) in patients with NAFLD and found a decrease in TC, TG, ALT and AST levels and improvement in symptoms.[18]

Similar results were obtained by Ma et al in patients with NASH who were treated with SAMe. These patients showed a decrease ALT AST, TG and TC levels; moreover, 60% of patients showed normalization of liver ultra-sonogram.[6,19] Antoniv, et al, studied the effect of SAMe and meld onium on the clinical course of NASH and chronic kidney disease stages I-II. The results showed an improvement of well-being, reduction of signs of astheno-vegetative, intoxication syndrome and dyspeptic manifestations in patients on SAMe within 3-4 days after treatment, whereas for patients without SAMe treatment improvement was observed only after 10 days. Four weeks after the start of therapy, the manifestation of astheno-vegetative syndrome in patients on SAMe was significantly less than those not treated with SAMe ($p<0.05$).[20]

Hepatocellular carcinoma and chemotherapy-induced liver injury

The use of SAMe within the oncology field is very diverse and not widely documented. Evidence suggests its application for the treatment of HCC to reduce the hepatotoxicity induced by chemotherapy and as a chemopreventive agent. Hepatocyte death response is regulated by SAMe. It ameliorates liver injury in which apoptosis has a contributory role.[35] The probable mechanism for this is the ability of SAMe to selectively induce the expression of the pro-apoptotic protein, Bcl-xS.[36] SAMe and its metabolite 5'-methylthioadenosine (MTA) also stimulate apoptosis and attenuate the pro-growth signals in colon and liver cancer cells thereby acting as a chemo preventive agent.[23,37,38]

Reports published by Ansorena, et al, suggest that SAMe could induce apoptosis in human HCC cells after treatment at varying concentrations for 24 hours.[22] Ramani et al, reported that SAMe and MTA can successfully reduce the mitogenic effect of leptin in HepG2 liver cancer cells by decreasing extracellular signal-regulated kinase and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling.[23,36] Therefore, understanding the reason for MAT1A silencing in HCC is crucial, because by increasing MAT1A expression in HCC cells, tumor growth and progression can be controlled.[7] Apart from this, SAMe has also demonstrated the ability to prevent oxidative stress and this effect was further explored for its potential in the prevention of chemotherapy-induced hepatotoxicity. An observational study by Santini et al, (2003) concluded that AST, ALT and lactate dehydrogenase (LDH) levels decreased from the first week of SAMe administration when given along with chemotherapy and its beneficial effect persisted in the following course of chemotherapy with minimal number of dose reductions or administration delays.[21]

Safety profile of SAMe

Surprisingly little research has been undertaken examining the effects of SAMe in liver in pediatric population. Although there has been some evidence for its use for neuropsychiatric disorders, evidence for hepatic disorders is lacking.[39-41]

Dose escalation in elderly population needs to be cautious and should be started at lower end of dosing range (400 mg per day). The use is contraindicated in patients with methionine cycle disorders such as those resulting in homocystinuria or hyperhomocysteinemia and with Vitamin B12 metabolism defects. As vitamin B12 and folate deficiencies may decrease SAMe levels, at risk patients (anemia, liver disease, pregnancy or potential for vitamin deficiencies due to other illnesses or eating habits such as vegans) should have routine blood tests to check the plasma levels of these vitamins. If a deficiency is found, treatment with B12 and folate is recommended prior to or concurrently with administration of SAMe. Ammonia levels should be monitored in patients with pre-cirrhotic and cirrhotic states of hyperammonemia.[42]

It has not been recommended to use SAMe in bipolar disorder. It also may potentially interact when co-administered with serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and over-the-counter and herbal supplements containing tryptophan.

CONCLUSION

The liver has the ability to repair and even regenerate itself. Early diagnosis and treatment may delay or halt the progression to advanced stages like liver fibrosis, cirrhosis and liver failure. Therefore, agents like SAMe, with a balanced safety and tolerability profile may provide means to slow down the progression of liver disease, early in the course. Chronic liver disorders like IHC, ALD, NAFLD and NASH are associated with depletion of SAMe, the main methylating agent of the liver. Hepatocellular SAMe concentration can influence diverse pathophysiological processes including tissue oxidative stress, mitochondrial function, hepatocellular apoptosis and malignant transformation. Clinical evidence from the studies above suggests that early intervention with SAMe has the potential to offer substantial benefits by effectively regulating the liver injury and other clinical parameters and associated symptoms. Its use as a prophylactic agent to reduce the progression of chronic liver disease may

improve the outcomes of patients with these diseases and potentially postpone liver failure. However, further prospective RCTs are warranted to assess the beneficial effects of SAMe as a hepatoprotective agent for early treatment of liver dysfunction and its impact on morbidity and mortality.

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