EFFECTIVENESS OF SILYMARIN IN ACUTE HEPATITIS

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ABSTRACT
To see the effectiveness of silymarin in patients of acute hepatitis. All ages, both sexes, inpatients and outpatients were included in the study. They were prescribed tablet silymarin at a dose of 400mg per day in two divided doses for six weeks. All patients were told to follow up with their liver function tests at three weeks. A total of 67 cases were enrolled in the study, 46 (68.65%) males and 21 (31.34%) females. Forty seven patients (70.14%) came for follow up and 20 (29.85%) lost follow up. It was found that out of 47 cases who returned for follow up 45 (67.16%) came with improved alanine aminotransferase (ALT) and only two patients (2.98%) had a raised ALT on follow up. Our study showed that 16.4% had hepatitis A virus (HAV), 10.44% had hepatitis E virus (HEV), 1.5% had hepatitis B virus (HBV), 1.5% had HAV and HEV, 1.5% had HAV and HBV, 1.5% had HBV and HCV and 34.32% had negative viral markers. It was concluded that silymarin is effective in patients with acute hepatitis and can be considered as a new hepatoprotective agent, though more data regarding chronic liver disease is yet required.

Keywords: Silymarin and Acute Hepatitis.

INTRODUCTION
Silymarin, derived from a milk thistle plant, *silybum marianum*. It is composed of four isomeric flavonolignans: *silibinin*, *isosilibinin*, *silydianin* and *silychristin*. This extract has been empirically used as a remedy for almost 2000 years and remains being used as a medicine for many types of acute and chronic liver diseases. Despite its routinely clinical use as hepatoprotectant, the mechanism underlying its beneficial effects remains largely unknown (Croce, 2006). Silymarin and its active constituent, silybin, act as antioxidants scavenging free radicals and inhibiting lipid peroxidation and also protect against genomic injury, increase hepatocyte protein synthesis, decrease the activity of tumour promoters, stabilize mast cells, chelate iron and slow calcium metabolism. Concentrations of silymarin are highest in the fruit of the milk thistle plant, as well as in the seeds and leaves (Hobbs, 1992), from which it is extracted with 95% ethyl alcohol, yielding a bright yellow fluid. A standard silymarin extract contains 70% silymarin (Williard, 1992). Pharmacokinetic studies have shown that there is rapid absorption of silybin into blood stream after an oral dose. Peak plasma concentrations are reached after two hours and eliminated in six hours (Lorenz et al., 1984; Barzaghi et al., 1990 and Orlando et al., 1990). From 3-8% of an oral dose is excreted in urine (Buelles et al., 1971). Buelles et al., Lorenz et al., and Schandalik et al have shown that 20-40% is recovered from the bile as glucoronide and sulfate conjugates (Buelles et al., 1971; Lorenz et al., 1982 and Schandalik et al., 1992). Silybin levels in the bile peaks within 2 to 9 hours (Rambaldi et al., 2005) and biliary excretion continues for 24 hours after the single dose (Flora et al., 1998). Aside from mild gastrointestinal distress and allergic reactions, side effects are rare and serious toxicity has rarely been reported. Milk thistle
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appears to be safe for up to 41 months of use. Significant drug reactions have not been reported (Rainone, 2005).

Alcoholic liver disease (ALD) is also a major cause of morbidity and mortality worldwide. The cornerstone of therapy for ALD is lifestyle modification, drinking cessation and treatment of decompensation, if appropriate. Nutritional intervention has been shown to play a positive role on in-patient and out-patient basis. Treatment with pentoxifylline appears to be a promising anti-inflammatory therapy. Recent studies have indicated anti-tumor necrosis factor (TNF) alpha therapy, at least for alcoholic hepatitis. Milk thistle and S-adenosylmethionine, may be effective in alcoholic cirrhosis (Bergheim et al., 2005).

Hepatocellular carcinoma (HCC) is one of the most common recurrent malignancies, for which currently there is no effective therapy. This study for the first time identified the biological efficacy of silybinin against the cells of HCC, suggesting the importance of conducting further investigations in pre-clinical HCC models (Varghese et al., 2005). Silymarin is used by many patients with chronic viral hepatitis, but its efficacy remains unknown. Silymarin compounds decrease serum aminotransferases in patients with chronic viral hepatitis, but do not effect the viral load or liver histology. Nevertheless it may be worthwhile to determine its effects in conjunction with standard anti-viral treatment (Mayer et al., 2005). Double blind studies on humans with acute viral hepatitis generally suggest that therapy with silymarin decreases complications (Plomteux et al., 1977), hastens recovery and shortens hospital stay (Flora et al., 1998).

The objective of the present study is to determine the effectiveness of silymarin in acute hepatitis in our part of the world.

**MATERIAL AND METHOD**

All patients with acute hepatitis, of all ages and both sexes in-patients and out-patients were enrolled in the study. All patients were registered in a pre-tested questionnaire, and liver function tests (LFT) were done. Viral markers which include HAV antibody (IgM), Hepatitis B surface antigen (HBsAg) and HCV antibody (Anti-HCV), HEV antibody (IgM) were determined. Rest of the investigations like typhidot, malarial parasite, dengue serology etc. was done according to clinical suspicion. All patients received tablet silymarin at a dose of 400mg per day in two divided doses for six weeks, were then followed after three weeks with a repeated LFT (single follow up).

<table>
<thead>
<tr>
<th>Age Ranges (years)</th>
<th>Number of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>1</td>
<td>1.49</td>
</tr>
<tr>
<td>11-30</td>
<td>43</td>
<td>64.17</td>
</tr>
<tr>
<td>31-50</td>
<td>19</td>
<td>28.35</td>
</tr>
<tr>
<td>51-70</td>
<td>2</td>
<td>2.98</td>
</tr>
<tr>
<td>Not specified</td>
<td>2</td>
<td>2.98</td>
</tr>
</tbody>
</table>

**Table-2**

Mean Alanine Aminotransferase levels before and after receiving Silymarin

<table>
<thead>
<tr>
<th>ALT levels (mean)</th>
<th>Before receiving silymarin</th>
<th>After Receiving silymarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1046.7</td>
<td>114.3</td>
</tr>
</tbody>
</table>
Inclusion Criteria:
All patients of both sexes coming with acute hepatitis with a raised ALT of more than 1.5 times the upper normal limit (normal range up to 40 IU) were included in the study.

Exclusion criteria:
Patients having clinical stigmata of chronic liver disease (compensated/decompensated) or had a history of clinical illness of more than six months were excluded.

RESULTS
A total of 67 cases of acute hepatitis were enrolled in the study, 46 (68.62%) were males and 21 (31.34%) were females (Figure 1). Forty three (64.17%) patients were between 11 to 30 years of age, 19 (28.35%) between an ages range of 31 to 50 years and the age range of 51 to 70 years included two (2.98%) patients. Only one (1.5%) patient was below ten years and ages of two patients remained unknown.
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unspecified (Table-1). Among 67 cases 47 (70.14%) came back for follow up and 20 (29.85%) patients did not come for follow up (Figure 3).

Among 67 patients, 11 (16.4%) were diagnosed HAV positive, 1 (1.45%) HBV, 7 (10.44%) HEV (which included three pregnant females), 3 (4.47%) had a positive dengue serology, 1 (1.49%) case each was of HCV and HBV, HAV and HBV, HAV and HEV enteric fever, malaria and cytomegalovirus as shown in Figure-2. Twenty three (34.32%) patients had negative viral markers (HAV, HBV, HCV, HEV) and 16 (23.88%) cases did not get their viral markers done (figure-2).

Only 47 (70.14) came back for follow up, 45 (67.16%) had an improved ALT while only two (2.98%) case came with raised ALT. The rest of 20 patients (29.85%) lost follow up (Figure-4).

DISCUSSION

A significant effect of silymarin in patients was shown with acute hepatitis, in reducing complications hastening recovery, normalization of transferases and shortens hospital stay. Similarly, a study of 57 patients with acute hepatitis A or B were randomize in a double blind fashion to receive silymarin 140mg thrice a day for three weeks. After five days mean levels of aspartate aminotransferase (AST), ALT and total bilirubin were significantly lower in the treated group. A second controlled trial showed a significantly shorter length of inpatient care in patients treated with silymarin when compared with patients who received supportive care only. Moreover, among the patients with hepatitis B, a shorter interval to the development of immunity was demonstrable in the silymarin group. Ninety seven patients with persistent liver function test abnormalities after abstinence from alcohol for over one month were randomized to four months of silymarin versus placebo. At the end of therapy mean serum AST levels has fallen by 30% and ALT levels fell by 41% with silymarin (Table-2). Another double blind, randomized placebo-controlled trial of patients who met biochemical and histological criteria for acute alcoholic hepatitis divided 66 patients into two groups, 31 who received silymarin and 35 who received placebo. Mean AST, ALT and gamma glutamyl transferase (GGT) levels normalized sooner and significantly more often in the treated over those in placebo group which is similarly seen in our study. Significant differences between the groups were noted by day seven (Flora et al., 1998). A total of 2637 patients with chronic liver disease were treated with high dose silymarin for 8 weeks. Resolution of subjective symptoms occurred in 63%. The mean AST fell by 36%, the mean ALT fell by 34% and the mean GGT by 46% (Flora et al., 1998).

In contrast Rambaldi et al. (2005) found no significant effect of silymarin on all-cause mortality. Though a potential beneficial effect of silymarin was observed on mortality, in patients with alcoholic liver disease. It was found that silymarin significantly improved two liver biochemical variables, serum bilirubin and GGT. For the remainder of our analyses on liver biochemical markers had no significant effects. They concluded that in all circumstances the effects of silymarin on liver biochemistry were not dramatic (Rambaldi et al., 2005).

Patients with acute hepatitis A or B receiving silymarin found that significantly more patients achieved normalization of AST and bilirubin after 21 days of treatment.

The impact of treatment with silymarin on patients with viral hepatitis in different studies is difficult to compare because of the disparity in the treatment populations and treatment regimens. However as a general trend there is improvement in the transaminases with treatment compared to baseline (Table-2 and Figure-4), but only equivocal effects on other liver enzymes (Rambaldi et al., 2005).
The use of silymarin in the clinical trials must be interpreted cautiously, as silymarin improves the clinical course and survival rates from acute hepatitis (Table-2 and Figure-4). With apparently minimal toxicity and lack of adverse drug interaction silymarin may be warranted as adjunctive therapy in patients with a variety of medically confirmed hepatic disorders (Saller et al., 2001).

CONCLUSION

This study concludes that silymarin is effective in lowering ALT levels in patients with acute hepatitis irrespective of the etiology and can be considered as a new hepatoprotective agent.

REFERENCES


