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EVALUATION OF HEPATOPROTECTIVE ACTIVITY OF ALOE VERA IN ACUTE VIRAL HEPATITIS

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ABSTRACT:
Background & objectives: Liver diseases are one of the major causes of disease burden all over world including our country so it is the need of hour to search for alternative drugs for the treatment of liver diseases. *Aloe Vera* is one of the most popular plants in the world, and is has been used frequently in history for its medicinal properties.

Material &Methods: A total of 110 male and female patients of age group between 15- 65 years, diagnosed clinically and biochemically as the case of acute viral hepatitis and ready to give consent were recruited in the study from SVBP Hospital, LLRM Medical College Meerut (U.P), 250004. Subjects who fulfilled selection criteria were randomized into two groups. Fifty patients belonging to control group received conventional treatment for acute viral hepatitis while 60 patients enrolled in treated group were given conventional treatment for acute viral hepatitis supplemented with *Aloe vera* juice (Patanjali Ayurved ltd, Haridwar) in dose of 20 ml BD orally. Every patient was followed up for 6 weeks. Serum bilirubin, serum Alanine transaminase (ALT), serum Aspartate transaminase (AST) and serum Alkaline phosphatase (ALP) levels were measured initially and at the end of 2, 4 and 6 weeks.

Results, Interpretation & Conclusions: Intragroup comparison using repeated measure ANOVA demonstrated a statistically significant (p<0.001) decrease in above mentioned parameters for both treated and control groups at all intervals of time. Intergroup comparison done by student-t-test, revealed statistically significant (p<0.001) difference in all the mentioned parameters between treated and control groups at all intervals of times.

INTRODUCTION: The liver is the largest glandular organ in the body and has more function than any other human organ. The liver has a pivotal role in human metabolism including production and secretion of bile and synthesis of prothrombin and fibrinogen. The liver also converts sugar into glycogen [19].

Acute and chronic liver diseases pose a global concern, and treatment for these diseases is difficult and has limited efficacy. Viral hepatitis is the most common cause of acute and chronic liver disease in the world with over half the world's population exposed to the different hepatotrophic viruses.

Conventional drugs used in treatment of liver disease are usually inadequate and can have serious side effects therefore it would appear worthwhile to search for alternative drugs for the treatment of liver diseases. Ayurvedic systems of medicine claim to have prescriptions of therapeutic value for hepatic diseases.

Various indigenous plants have been screened for hepatoprotective activity and many have been found to possess significant activity in this regard. To name a few *Silybum marianum*[13], *Boerhaavia diffusa* [4], *Solanum nigrum* [16], and *Phyllanthus niruri*[1] are some of the mentionable plants in this context.

Public interest in *Aloe vera* has grown quickly, and now there is a considerable amount of research to explore the therapeutic benefits of *Aloe vera.*

Therefore to reinforce the positive results obtained from various studies done for hepatoprotective activity of aloe Vera, like Hepatoprotective potential of Aloe Barbedensis against CCL4 induced hepatotoxicity[5].Hepatoprotective activity of Aloe vera gel against Paracetamol induced hepatotoxicity in Albino rats[15], Hepatotherapeutic effect of Aloe vera in alcohol induced hepatic damage[18].The present the study was conducted for evaluation of the hepatoprotective activity of Aloe vera in patients with acute liver diseases.

SUBJECTS AND METHODS: The current study was a prospective, randomized, open, parallel group, interventional study carried out in a tertiary care hospital which was designed to evaluate the hepatoprotective activity of *Aloe vera*. Approval was obtained from Institutional ethics committee (approval no. STP/2011/14) and registration was done under CTRI (no. CTRI/2011/12/003064) .Subject recruitment was done from out and in patient department of Medicine LLRM Medical College Meerut, U.P, India.

A total of 110 male and female patients ranging between the age group 15- 65 years diagnosed clinically and biochemically as a case of acute viral hepatitis and willing to give consent were recruited in the study while pregnant/lactating females and those of age group <15 years or >65 years or having congenital liver disease, decompensated liver disease/chronic debilitating illness other than liver disease were excluded from the study. Primary end point was set as normalisation of serum bilirubin levels while secondary end point was normalisation of other liver function tests serum alanine transaminase (S.ALT), serum aspartate transaminase (S.AST), serum alkaline phosphatase (S.ALP) or development of any

adverse effect. Routine blood investigations such as complete hemogram, blood glucose and serum creatinine were carried out at the time of recruitment for assessment of general health status of the patient. On randomization of subjects who fulfilled selection criteria using coin toss method, 50 patients were allocated to control group and were given conventional treatment for acute viral hepatitis while 60 patients were allocated to treated group and were given conventional treatment for acute viral hepatitis supplemented with *Aloe vera* juice (patanjali ayurved ltd) in dose of 20 ml twice daily orally. Every patient was followed up for 6 weeks.

Serum bilirubin, serum ALT, serum AST and serum ALP levels were measured at the time of recruitment and then at the end of 2, 4 and 6 weeks. Levels of these biochemical parameters were compared between control and treated group at all intervals of times. Safety monitoring was done throughout the study period for development of any adverse effect.

The results were expressed as Mean ± SE. Student's-*t*-test and multiple comparisons ANOVA were employed for comparison between the two means as a measure of significance. *P* value of <0.05 was regarded as a statistically significant.

RESULTS: Out of 150 subjects screened, 122 fullfilled the selection criteria and were randomized to control and treated groups, however 12 subjects were lost to follow up and did not attend the hospital after first visit. There was no statistically significant difference in baseline parameters of both the groups.

Effect on serum bilirubin: On Intragroup comparison Mean serum bilirubin level in control group was 7.16±0.25mg/dl initially and was seen to follow decreasing trend i.e. 4.768±0.18mg/dl, 3.16±0.10mg/dl and 2.24±0.06mg/dl at the end of 2, 4 and 6 weeks respectively.

Mean serum bilirubin level in treated group was 7.36±0.27 mg/dl initially and then, it was found to decrease progressively on repeated measurements and was 3.61±0.14mg/dl, 1.80±0.08mg/dl and 1.15±0.04mg/dl at the end of 2, 4 and 6 weeks of follow up respectively.

While on intergroup comparison mean serum bilirubin level initially was 7.16±0.25mg/dl in control group and 7.36±0.27mg/dl in treated group and at the end of 2 weeks was 4.76± 0.18mg/dl in control group and 3.61±0.14mg/dl in treated group, At the end of 4 weeks 3.16±0.10mg/dl in control group and 1.80±0.08mg/dl in treated group and at the end of 6 weeks 2.24±0.06 mg/dl in control group and 1.15±0.04mg/dl in treated group (table 1).

Effect on serum Alanine aminotransferases: On intragroup comparison of mean serum ALT levels, it was 213.14±6.87 IU/L initially for control group and was seen to be decreasing on successive measurements and was 156.04±5.46IU/L, 102.960 ±3.32 IU/L and 65.940±2.04 IU/L at the end of 2, 4 and 6 weeks respectively.

While mean serum ALT level in treated group was 204.51±6.70 IU/L initially and then it was found to be decreasing on repeated measurements and was 111.91±4.40 IU/L, 66.83±2.69 IU/L and 39.86±1.29 IU/L at the end of 2, 4 and 6 weeks of follow up respectively.

On intergroup comparison mean serum ALT level the value initially was 213.14±6.87IU/L in control group and 204.51±6.70IU/L in treated group. On further comparison, values of serum ALT levels were lesser in treated group than those of control group and were 156.04±5.46IU/L in control group and 111.92±4.4IU/L in treated group at the end of 2 weeks. 102.96±3.32IU/L in control group and 66.83±2.69 IU/L in treated group at the end of 4 weeks and 65.94±2.04 in control group and 39.86±1.29 at the end of 6 weeks (**table 2**)

Effect on serum Aspartate transaminase: On Intragroup comparison mean serum AST level, was 147.22±3.42 IU/L initially and was declining on repeated measurments and was 108.40±2.42 IU/L, 72.54±2.08 IU/L and 45.66±1.02 IU/L at the end of 2, 4 and 6 weeks respectively for control group.

Mean serum AST levels in treated group was 143.73±4.70 IU/L initially and then it was also found to be decreasing on repeated measurements

and was 84.28±3.47 IU/L, 49.48±2.00IU/L and 30.03±1.01 IU/L at the end of 2, 4 and 6 weeks of follow up.

On Intergroup comparison mean serum AST level initially was 147.22±3.42IU/L in control group and 143.73±4.70IU/L in treated group, at the end of 2 weeks was 108.40±2.42IU/L in control group and 84.28±3.47IU/L in treated group. At the end of 4 weeks 72.54±2.08 IU/L in control group and 49.48±2.00 IU/L in treated group and at the end of 6 weeks 45.66±1.02 IU/L in control group and 30.03±1.01 IU/L in treated group.

Effect on serum alkaline phosphatase: On intragroup comparison mean serum ALP levels it was observed that values were tending to follow decreasing trend and were 155.34±3.78 IU/L initially for control group and were 126.10±2.63 IU/L, 108.04±2.49 IU/L and 97.52±1.32IU/L at the end of 2, 4 and 6 weeks.

Mean serum ALP levels in treated group was 157.16±4.86 IU/L initially and then it was found to be decreasing on repeated measurements and was 112.31±3.70 IU/L, 84.73±2.48 IU/L and 63.78±1.34 IU/L at the end of 2, 4 and 6 weeks of follow up.

While on intergroup comparison mean serum ALP levels initially were 155.34±3.78IU/L in control group and 157.16±4.86IU/L in treated group, at the end of 2 weeks was 126.10±2.63IU/L in control group and 112.32±3.70IU/L in treated group, At the end of 4 weeks 108.04±2.49IU/L in control group and 84.73±2.48IU/L in treated group and at the end of 6 weeks 97.52±1.32IU/L in control group and 63.78±1.34IU/L in treated group.

On statistical evaluation of these values by applying student-t-test, and repeated measure ANOVA it was found that difference in mean serum bilirubin, serum ALT, serum AST and serum ALP levels of treated and control group is statistically significant (p<0.001) at all the intervals of time means at the end of 2 weeks, 4 weeks and 6 weeks with lowest levels being attained at the end of 6 weeks.

TABLE 1: Comparison between control (N_1=50) and *Aloe vera* treated group (N_2=60) on serum bilirubin levels initially (0weeks) and at the end of 2, 4 and 6 weeks

Duration (weeks)	Control group S. bilirubin (mg/dl) (Mean ± SE)	Treated group S. bilirubin (mg/dl) (Mean ± SE)
0	7.16±0.25	7.36±0.27
2	4.76±0.18	3.61±0.14[δ]
4	3.16±0.10	1.80±0.08[*]
6	2.24±0.06	1.15±0.04[#]

δ: $p < 0.001$ as compared to control group at the end of 2 weeks. *: $p < 0.001$ as compared to control group at the end of 4 weeks. #: $p < 0.001$ as compared to control group at the end of 6 weeks.

TABLE 2: Comparison between control (N_1=50) and *Aloe vera* treated group (N_2=60) on serum Alanine transaminase (ALT) levels initially (0weeks) and at the end of 2, 4 and 6 weeks

Duration (weeks)	Control group S. ALT (IU/L) (Mean ± SE)	Treated group S. ALT (IU/L) (Mean ± SE)
0	213.14±6.87	204.51±6.70
2	156.04±5.46	111.92±4.40[δ]
4	102.96±3.32	66.83±.2.69[*]
6	65.94±2.04	39.87±.1.29[#]

δ: $p < 0.001$ as compared to control group at the end of 2 weeks. *: $p < 0.001$ as compared to control group at the end of 4 weeks. #: $p < 0.001$ as compared to control group at the end of 6 weeks.

TABLE 3: Comparison between control (N_1=50) and *Aloe vera* treated group (N_2=60) on serum Aspartate transaminase (AST) levels initially (0weeks) and at the end of 2, 4 and 6 weeks.

Duration (weeks)	Control group S. AST (IU/L) (Mean ± SE)	Treated group S. AST (IU/L) (Mean ± SE)
0	147.22 ±3.42	143.73±4.70
2	108.40±2.42	84.28±3.47 [δ]
4	72.54±.2.08	49.48±2.00[*]
6	45.66±1.02	30.03±1.01[#]

δ: $p < 0.001$ as compared to control group at the end of 2 weeks. *: $p < 0.001$ as compared to control group at the end of 4 weeks. #: $p < 0.001$ as compared to control group at the end of 6 weeks.

TABLE 4: Comparison between control (N_1=50) and *Aloe vera* treated (N_2=60) group on serum alkaline phosphatase (ALP) levels initially (0 weeks) and at the end of 2, 4 and 6 weeks.

Duration (weeks)	Control group S. ALP (IU/L) (Mean ± SE)	Treated group S. ALP (IU/L) (Mean ± SE)
0	155.34 ±3.78	157.16±4.86
2	126.10±2.63	112.32±3.70[δ]
4	108.04±2.49	84.73±2.48[*]
6	97.52±1.32	63.78±.1.34[#]

δ: $p < 0.001$ as compared to control group at the end of 2 weeks. *: $p < 0.001$ as compared to control group at the end of 4 weeks. #: $p < 0.001$ as compared to control group at the end of 6 weeks.

DISCUSSION: Liver diseases are one of the crucial and prevalent health problems all over the world. Despite the need for agents to protect the liver from damage, it is hard to believe that modern medicines lack a reliable liver protective agent [16]. Therefore, there have been a plethora of efforts for a frantic search for clinically useful and effective therapy in alternative medicines for the treatment of liver diseases [7].

Popularity of herbal remedies is increasing globally and at least one quarter of patients with liver diseases use ethno botanicals. More efforts need to be directed towards methodological scientific evaluation of their safety and efficacy by subjecting them to vigorous preclinical studies followed by clinical trials to unravel the mysteries hidden in the plants.

A large number of plants and formulations have been claimed to have hepatoprotective activity. Nearly 160 phytoconstituents from 101 plants have been claimed to possess liver protecting activity. In India about 33 multi ingredient plant formulations are used for treatment of liver diseases [8].

Aloe vera is one of the important and popular plants which has long history of being used for various health problems. Various studies have been conducted for its hepatoprotective action. *Aloe vera* is claimed to have hepatoprotective activity against paracetamol induced hepatotoxicity in albino rats[15]. Another study for hepatoprotective activity of *Aloe vera* was conducted against alcohol induced hepatic damage, in albino rats, where it was again shown to cause significant reduction in ALT and AST levels [18]. Studies for hepatoprotective activity against CCl4 induced hepatotoxicity [5] and antioxidant activity of *Aloe vera* [20] have also been performed and results are corroborative of its hepatoprotective activity.

In a study conducted in department of pharmacology, LLRM Medical College for evaluation of hepatoprotective activity of *Aloe vera* and its comparison with Liv. 52 against hepatotoxicity induced by CCl4 in albino rats it was seen that hepatoprotective activity of *Aloe vera* was comparable to Liv. 52 and the aqueous extract of *Aloe vera* exhibited dose dependant hepato-protection, both biochemically and histologically (unpublished data).

However, most of the studies conducted for hepatoprotective activity of *Aloe vera* are experimental therefore there was a need to conduct a clinical study to evaluate and confirm the hepatoprotective activity of *Aloe vera*.

With this aim the present study was conducted in patients with acute liver diseases. The study comprised of two groups i.e. control and treated group and were given conventional treatment for acute liver disease only and conventional treatment for acute liver disease supplemented with aloe vera juice respectively. On repeated follow up at the end of 2, 4 and 6 weeks liver function tests including S.bilirubin, S. ALT, S.AST and S. ALP, were measured.

It was interesting to observe that the values of these parameters were at a lower level in treated group in comparison to control group at all the points of measurement and the difference was maximum at the end of 6 weeks. The difference of values of measured parameters were significant clinically in form of improvement in symptoms and statistically on statistical evaluation of the values ($p < .0001$).

The results obtained in present study were seen to be in consonance with the results given in other published studies

In a study conducted to evaluate Hepatoprotective activity of *Aloe vera* gel against Paracetamol induced hepatotoxicity in Albino rats, seven day treatment with *Aloe vera* significantly reduced the levels of AST, ALT and ALP significantly ($p < 0.01$) and restored the depleted liver thiol levels significantly ($p < 0.01$)[15].

In another study done for evaluation of hepatotherapeutic effect of *Aloe vera* in alcohol induced liver damage in albino rats the resultant hepatic dysfunction was abrogated by *Aloe vera* extract. Histopathological examination revealed that *Aloe vera* treatment maintained hepatic architecture similar to that seen in the control group. This study shows that aqueous extract of *Aloe vera* is hepatotherapeutic and thus lends credence to the use of the plant in folklore medicine in the management of alcohol-induced hepatic dysfunction [17].

Aloe vera extract has also been shown to confer significant hepatoprotection against CCl4 induced hepatotoxicity as evident by restoration of serum transaminases, alkaline phosphatase, bilirubin and triglycerides. Hepatoprotective potential was confirmed by the restoration of lipid peroxidation, glutathione, glucose-6-phosphatase and microsomal aniline hydroxylase and amidopyrine N-demethylase towards near normal.

Histopathology of the liver tissue further supports the biochemical findings confirming the hepatoprotective potential of *Aloe vera*. This study shows that the aqueous extract of *Aloe vera* is significantly capable of restoring integrity of hepatocytes indicated by improvement in physiological parameters [5].

The hepatoprotective effect of *Aloe vera* may be related to glutathione-mediated detoxification. Glutathione (g-glutamyl cysteinyl glycine, GSH) is a sulfhydryl (SH) antioxidant, antitoxin, and enzyme cofactor. Glutathione is found mainly in the cell cytosol and other aqueous phases of the living system [11, 12].

Aloe vera leaves contain a range of biologically active compounds, the best studied being acetylated mannans, polymannans, anthraquinone C-glycosides, anthrones and anthraquinones and various lectins [3, 6, 10].

Acemannan, and other polysaccharides present in Aloe vera increase reduced glutathione and thus reduce oxidative damage [9].

The increase in the hepatic glutathione level could result from either its effect on the de novo synthesis of glutathione and its regeneration, or both. The study suggests that the antioxidant properties may be one mechanism by which *Aloe vera* protects against liver damage. Previous findings are in agreement with the finding by Anilakumar[2] who showed that *Aloe vera* extract is able to reduce azoxymethane (AOM) induced-oxidative stress and toxicity in rat liver.

Intracellular GSH status is a sensitive indicator of the cell's overall health, and of its ability to resist toxic challenge. *Aloe vera* might have enhanced the GSH status in cells thereby protecting hepatic cells from toxic damages.

Liver damage induced by CCl_4 is a commonly used model for the screening of hepatoprotective drugs [20]. Since formation of free radicals by cytochrome P450 after metabolism of CCl_4 has been implicated in lipid peroxidation mediated hepatocyte injury, the hepatoprotective mechanisms of *Aloe vera* could be due to an inhibitory effect on the microsomal enzymes (cytochrome P450) so that generation of free radicals is limited [22].

Silymarin, a well-known hepatoprotective agent, shows its beneficial effects by antioxidant and free radical scavenging properties [13]. Like silymarin, *Aloe vera* may also act as a free radical scavenger and has antioxidant property as it may have an inhibitory effect on lipid peroxidation.

Hence, on the basis of results obtained in present study and other studies done for evaluation of hepatoprotective activity of *Aloe vera* and the suggestive mechanisms of hepatoprotection by *Aloe vera*, it can be construed that probably *Aloe vera* is a potent agent for treatment of liver ailments. However further extended clinical studies need to be undertaken on large number of patients for exploring hepatoprotective activity of *Aloe vera*.

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