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Original Article

Hepatocurative Effect of *Saussurea lappa* C.B Clarke and *Artemisia absinthium*, Linn in Chronic Hepatitis B

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ABSTRACT

Objective: Repeated immune attacks in chronic hepatitis B produce recurrent inflammation in the liver and render it to develop fibrous tissue and carcinoma. Hence, present study aims to evaluate the hepatocurative effect of qust (*Saussurea lappa*) and afsanteen (*Artemisia absinthium*) in the chronic hepatitis B patients. **Methods**: In a single arm pilot clinical study, 30 patients of chronic hepatitis B with ALT (alanine aminotransferase) >2 times of upper limit of normal were treated with decoction of qust (*Saussurea lappa*) and decoction of afsanteen (*Artemisia absinthium*) daily orally for 3 months. Patients were evaluated for liver function test at baseline, 6th week and 12th week of treatment. **Result**: Test drug reduced the mean serum bilirubin, ALT, AST highly significantly at 12th week of treatment. ($p<0.01$). **Conclusion**: We reviewed the literature related to the test drug, *Saussurea lappa* and *Artemisia absinthium* used for the treatment in these cases. The observed hepatocurative effect could be due anti-inflammatory, hepatoprtotective, antioxidant and immunomodulator properties of these drugs, substantiated in various animal studies. These findings indicate the hepatocurative effect of *Saussurea lappa* and *Artemisia absinthium* in chronic hepatitis B cases. Randomized controlled clinical studies should be conducted to explore the further efficacy.

Key words: *Saussurea lappa*, *Artemisia absinthium*, Hepatocurative, Unani medicine, Liver tonic, Hepatitis.

Key message: To establish hepatocurative nature of decoction of *Saussurea lappa* and *Artemisia absinthium* in chronic hepatitis B patients with deranged liver function test.

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INTRODUCTION

Chronic Hepatitis B (CHB) is a chronic necro-inflammatory condition in the liver characterized by the presence of detectable hepatitis B surface antigen (HBsAg) in the blood or body fluids for longer than 6 months.[1] Necro-inflammation of the liver cells occur as a result of immune attacks in response to hepatitis B virus. Persistent inflammation of the hepatic cells may lead to liver fibrosis and ultimately hepatocellular carcinoma. India has more than 40 million people infected with hepatitis B and every year 6 lakhs Indians die due to HBV-related end stage liver diseases.[2-3]

Unani system of medicine is one of the oldest traditional system of medicine which has been treating hepatitis efficiently with drugs of herbal origin since centuries. Water based decoctions of qust (*Saussurea lappa*) and afsanteen (*Artemisia absinthium*) has been documented to had highly beneficial therapeutic efficacy in resolution and normalization of abnormal liver conditions including hepatitis.[4-5] Thus, present study was done to evaluate the hepatocurative effect of decoction of *Saussurea lappa* and *Artemisia absinthium* in chronic hepatitis B.

MATERIAL AND METHODS

Ethical consideration

This study was registered in the clinical trial registry of India, Govt. of India with registration no. CTRI/2017/11/010386. The purpose, procedure and potential risks of this study have been explained to each participant. The protocol was approved by the Institutional Ethics Committee of Jamia Hamdard (Hamdard University) and was implemented in accordance with provisions of the Declaration of Helsinki, ICMR and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from the patients before beginning of the study. (JH IEC/ 1530 HOURS/ AUGUST 12/ 15)

Study subjects

This was an open single arm prospective study of 30 HBeAg positive and negative CHB patients who were recruited in inpatient and outpatient department of Majeedia Unani Hospital, Jamia Hamdard, New Delhi between August 2015 to June 2016. The inclusion criteria's were 1) clinically stable patients of both sexes in the age groups of 18 to 60 years 2) positive HBsAg for more than 6 months 5) HBV DNA quantitative greater than 2,000 IU/ mL, 6) ALT (alanine aminotransferase) >2 times of upper limit of normal and 7) both HBeAg positive and negative patients. The exclusion criteria's were 1) patient below 18 years 2) patient above 60 years 3) pregnant women and lactating mothers 4) mentally retarded person 5) patients who fail to give informed consent 6) patient with cirrhosis, portal hypertension/ ascites and obstructive jaundice, 7) patients of diabetes and hypertension, 8) patients with kidney and heart disease, and 9) patients with neurological disorder.

Study treatment

Identification: Roots of qust (*Saussurea lappa*) and plant of afsanteen (*Artemisia absinthium*) were purchased from the local market at Khari Baoli, Old Delhi, India. Voucher specimens were deposited in the Herbarium of Department of Botany, Faculty of Science, Jamia Hamdard, New Delhi, India and were identified and authenticated by Prof. (Dr.) M.P Sharma as qust (*Saussurea lappa*) and afsanteen (*Artemisia absinthium*) respectively. Physiochemical standardization of herbs was also done for quality control.

Dose: Decoction of crude root of qust (*Saussurea lappa*), 15 ml (containing approx. 1g of dried extract), advised in the morning empty stomach daily, for 12 weeks. Decoction of crude whole plant of afsanteen (*Artemisia absinthium*), 15 ml (containing approx. 1g of dried extract), advised in the evening empty stomach daily for 12 weeks.

Preparation of decoction

Decoction of each herb was prepared in the similar manner. *Saussurea lappa* and *Artemisia absinthium* were purchased in bulk to prevent batch to batch variation in quality of herbs.

Decoction of both the drugs was prepared in the similar manner. Drug (root of Saussurea or plant of Artemisia), 7g was dissolved in 16 times of w/v (approx. 115ml of water in 500ml round bottom flask) and soaked for overnight. Thereafter, drug solution was allowed to be heated at 40°C for 5 h till it reduced to 1/4th of the original volume. Strained and filtered solution thus obtained (approx. 30ml) was concentrated to its half (15ml) to give liquid extract containing 1g of dried extract. A single dose of 15 ml per day of decoction of each herb was established. Preservative was added. The decoction of both the drugs were stored at room temperature in the laboratory before use. High performance thin layer chromatography of decoction of both the drugs was also done for the purpose of quality control.

Measurements

Serum Bilirubin total, direct and indirect, serum glutamic oxaloacetic transaminase (SGOT/ AST), serum glutamic pyruvic transaminase (SGPT/ ALT), and alkaline phosphatase were measured at baseline, 45th day (mid-treatment) and 90th day (after treatment).

Statistical analysis

Normal-distributed continuous variables were given as mean ± standard deviation (SD). Continuous variables were compared by Tukey-Kramer multiple comparisons test through GraphPad Prism, version 7.00 for windows created on March 31, 2016. Differences were considered significant when the p value was less than 0.05. Test results were ranked as: ns - Non significant $p>0.05$, *$p < 0.05$ significant, **$p < 0.01$ very significant, ***$p < 0.001$ extremely significant.

RESULT

Effect of test drug on serum bilirubin

Mean serum bilirubin (total) in total patients (n=30) at baseline was 2.15±SD 2.33 mg/dL which reduced to 0.82±SD 0.47 mg/dL at 6th week (p<0.01) and furthermore significantly reduced to 0.74±SD 0.29 mg/dL at 12th week after treatment. (p<0.001) (Table 1, Figure 1)

Mean serum bilirubin (direct) in total patients (n=30) at baseline was 1.27±SD 1.66 mg/dL which reduced to 0.35±SD 0.23 mg/dL at 6th week (p<0.01) and furthermore significantly reduced to 0.31±SD 0.14 mg/dL at 12th week after treatment. (p<0.001) (Table 1, Figure 1)

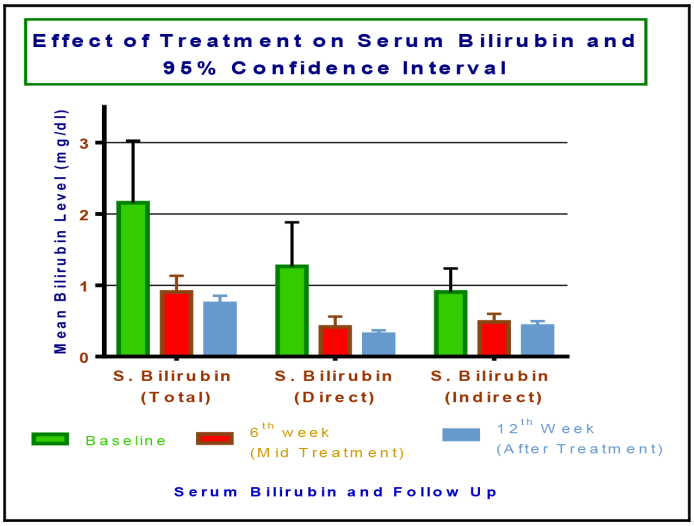

Figure 1: Effect of test drug on serum bilirubin.

Mean serum bilirubin (indirect) in total patients (n=30) at baseline was 0.90±SD 0.89 mg/dL which reduced to 0.46±SD 0.30 mg/dL at 6th week (p<0.01) and furthermore significantly reduced to 0.43±SD 0.19 mg/dL at 12th week after treatment. (p<0.001) Difference in mean values of serum bilirubin (total, direct and indirect) at mid vs. after treatment were non-significant . (p>0.05) (Table 1, Figure 1)

Percentage of patients achieved normal serum bilirubin (total) levels after treatment

Among 30 patients, 14 (46.66%) patients had deranged serum bilirubin (total) at baseline which was normalized in 12 (87.71%) patients after 12 weeks of treatment with test drug. (p<0.0001)

Effect of test drug on liver enzymes

Mean ALT in total patients (n=30) at baseline was 272±SD 463 IU/mL which significantly reduced to 69.28±SD 120 IU/mL at 6th week (p<0.05) and furthermore significantly reduced to 42.1±SD 48 IU/mL at 12th week after treatment. ($p<0.01$) (Table 2, Figure 2)

Mean AST in total patients (n=30) at baseline was 221.7±SD 377 IU/mL which significantly reduced to 48.9±SD 50 IU/mL at 6th week (p<0.01) and furthermore significantly reduced to 35± SD 26 IU/mL at 12th week after treatment. ($p<0.01$) (Table 2, Figure 2)

Difference in mean values of ALT and AST at mid vs. after treatment were non-significant. ($p>0.05$)

Mean alkaline phosphatase in total patients (n=30) at baseline was 182±SD 133 IU/mL which non-significantly reduced to 138±SD 51 IU/mL at 6th week ($p>0.05$) and further non-significantly reduced to

Table 1: Effect of test drug on serum bilirubin (mg/dL).

Mean Value		Baseline	Mid-Treatment	After Treatment	p Value (Tukey-Kramer multiple comparisons test)
S. Bilirubin (Total)	Mean	2.15	0.82	0.75	†p <0.01. #p<0.001.
	SD	2.33	0.47	0.29	$^{\gamma}$p>0.05
S. Bilirubin (Direct)	Mean	1.27	0.35	0.31	†p <0.01. #p<0.001
	SD	1.66	0.23	0.15	$^{\gamma}$p>0.05
S. Bilirubin (Indirect)	Mean	0.90	0.46	0.43	†p <0.01. #p<0.001
	SD	0.89	0.3	0.19	$^{\gamma}$p>0.05

†Baseline Vs. Mid Treatment; #Baseline Vs. After Treatment; γMid Treatment Vs. After Treatment.

Table 2: Effect of Test drug on Liver enzymes (IU/L).

Mean Value		Baseline	Mid-Treatment	After Treatment	Mean reduction#	p Value (Tukey-Kramer multiple comparisons test)
AST/ SGOT	Mean	221.7	48.9	34.9	186.8	†p<0.01
						#p<0.01
	SEM	68.8	9.13	4.84		ᵞp>0.05
ALT/ SGPT	Mean	272.13	69.28	42.1	230.03	†p<0.05
						#p<0.01
	SEM	84.59	22	8.7		ᵞp>0.05
Alkaline Phosphatase	Mean	182.5	138.3	137.3	45.2	†p>0.05
						#p>0.05
	SEM	24.4	9.3	8.1		ᵞp>0.05

†Baseline Vs. Mid Treatment; #Baseline Vs. After Treatment; γMid Treatment Vs. After Treatment.

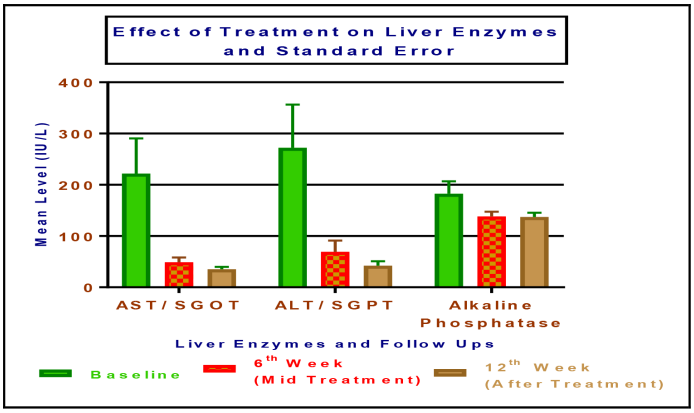

Figure 2: Effect of test drug on liver enzymes.

137±SD 44 IU/mL at 12th week after treatment. (p>0.05) Mean alkaline phosphatase was within normal limit at baseline. (Table 2, Figure 2)

DISCUSSION

Bae *et al.* (2010) have reported mean reduction of ALT from baseline at 12th week was −86.2±227.2, −73.2±118.6 and −128.1±170.4 IU/mL in lamivudine (n=68), clevudine (n=39) and entecavir (n=39) treated patients respectively which was non-significant at p>0.05.[6] In our study, mean reduction at 12th week was -230± SD 415 IU/mL (n=30) which was highly significant at p<0.01 which may substantiate potent efficacy of Unani test drug in resolution of liver inflammation. Significant reduction in abnormal liver profile in our study patients has validated hepatocurative potential of *Saussurea lappa* and *Artemisia absinthium* in chronic hepatitis B. The plausible mechanism of such effect could be attributed to the hepatoprotective, anti-inflammatory, immunomodulatory and anti-oxidant properties of *Saussurea lappa*[7-15] and *Artemisia absinthium*[16-22] have been reported in various studies. These drugs have either prevented the further rise of liver enzymes or resolved the inflammation of the liver through their mitigating effect by targeting inflammatory cascade or attenuating or scavenging effect on generation of ROS species. In chronic HBV infection, repeated immune attacks through T cells triggers production of inflammatory cytokines including IFN- γ, TNF- α, interleukin (IL) 2 etc. which produced inflammatory hepatic flares.[23] Amat *et al.* (2010), reported that aqueous extract of *Artemisia absinthium* modulated TNF and IL activity in LPS induced mice model.[16] Similarly, Pandey *et al.* (2012) have also reported the immunomodulatory action of *Saussurea lappa* through which inflammatory cascade could be modulated viz. inflammation of the liver.[24] In addition, *Saussurea lappa* and *Artemisia absinthium* are one of the important drugs in liver diseases. Both of them have been used as liver tonic (*muqawwiye jigar*) since long time in the treatment of hepatitis, jaundice and others diseases of the liver.[4-5]

CONCLUSION

These observations substantiate the hepatocurative effect of *Saussurea lappa* and *Artemisia absinthium* in the chronic hepatitis B. Hence, further studies should be conducted to provide the comparative efficacy with conventional medicine as well as elaborating the mechanism of action in hepatitis B virus induced cirrhosis of liver.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CHB: Chronic hepatitis B; **ALT:** Alanine aminotransferase; **AST:** Aspartate aminotransferase; **HBsAg:** Hepatitis B surface antigen; **HBeAg:** Hepatitis B e antigen; **SD:** Standard deviation; **SEM:** Standard error of mean; **IFN:** Interferon;**TNF:** Tumor necrosis factor; **IL:** Interleukin.

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