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ORIGINAL RESEARCH article

A human study on the effect of *Alhagi Maurorum* (camel thorn) on patients suffering from hepatitis B virus

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Abstract: Hepatitis B virus infection is a major health problem worldwide. More than 400 million people are suffering from this infectious disease. *Alhagi Maurorum* (camel thorn, CTE) is used in Libyan folk medicine for hepatitis. The aim of this study is to investigate the effect of the camel thorn on the hepatitis B virus. After a pharmacological and toxicological screening of camel thorns on experimental animals in our laboratories, in an open-label study, 15 patients of either gender were chosen at random with their consent (consent form signed). The patients had no liver cirrhosis and were not alcoholics. Following clinical testing, the patients were given a low, safe dose of camel thorn powder (2.6 g soaked in boiling water for 10 minutes) three times per day for six months. The viral load was measured before treatment and three and six months after the beginning of the experiment by polymerase chain reaction. The complete blood picture, the level of transaminases, bilirubin, creatinine, blood glucose, lipid profile, thyroid function, and prothrombin were assessed before and after three months after the beginning of the experiment. Our data showed no significant changes in the complete blood picture, creatinine, blood urea, glucose level, bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lipid profile, prothrombin, and thyroid function. The levels of viral load before, three months after, and six months after the beginning of our study were 1689±289, 558±160, and 271±026 IU per mL, respectively. From this study, we may conclude that the camel thorn is safe and showed activity against viral hepatitis B, however, further investigations are needed by increasing the number of patients and using higher doses of plant extract to explore its mechanism of action. Finally, the mechanism of camel thorn may be related either to its antiviral effect or to the stimulation of either endogenous interferon or the immune system.

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Introduction

Lately, it is estimated that there are between 750,000 and 1,000,000 plant species in the world. Each of the 500,000 has been identified and named. Every year, approximately 2,000 new flowering plant species are identified and named. The number of plants that have been used for treatment since ancient times shows a steady increase. According to a report released by the World Health Organization (WHO), the number of plants used for the treatment is estimated to be around 20,000. In recent years, studies on medicinal plants and active substances derived from them have increased interest in these plants [1]. The use of plants as a source of research in the search for active compounds for medicine has been proven to have a significant scientific output. An analysis of the scientific literature concerning medicinal plants clearly shows that in the last 20 years, progress has been rapid, with a peak in 2010. From this year onward, publications have stabilized at just over 5,000 per year ingredients that can be used in drug development and synthesis. Medicinal plants have a promising future because there are about half a million plants around the world, most of whose medical activities have not been investigated yet and whose medical activities could be decisive in the treatment of present or future studies [3]. Medicinal plants play a vital role in the development of new drugs. During 1950-1970, approximately 100 plant-based new drugs were introduced in the USA drug market, including deserpidine, reseinnamine, reserpine, vinblastine, and vincristine, which are derived from higher plants. From 1971-1990, new drugs such as ectoposide, e-guggulsterone, z-guggulsterone, teniposide, nabilone, plaunotol, lectinan, artemisinin, and ginkgolides appeared all over the world. 2.0% of drugs were introduced from 1991 to 1995, including paciltaxel, toptecan, gomishin, irinotecan, etc. [4]. Desert plants contain important phytochemicals, which are cheap sources of medicine for local communities. These phytochemicals are much better than synthetic medicine due to their harmless effects [5].

Alhagi Maurorum (Akool) is a spiny, deep-rooted perennial shrub, with roots that can reach six or seven feet into the ground. It has small pink to red pea flowers and brown legume pods [6]. Several studies indicated that Alhagi Mourorium has anti-ulcerogenic [7], anti-diarrheal [8], antibacterial [9, 10], anti-inflammatory [11], analgesic [12], and hepatoprotective activities [13-15]. Suliman et al. [16] discovered that camel thorn inhibits leukemic cell proliferation in a leukemia cell line (HL-60). Worldwide, it is estimated that more than 400 million people are currently living with chronic hepatitis B virus (HBV) infection, contributing to more than one million deaths annually as a result of liver cirrhosis and hepatocellular carcinoma [17, 18]. The approved treatment of chronic hepatitis B virus includes lamivudine (LMV), adefovir dipivoxil (ADV), telbivudine (TBV), entecavir (ETV), tenofovir disoproxil fumarate (TDF), and pegylated interferon alpha (Peg IFN 2a and 2b) [19-21]. Little is known about the role of herbal medicine or medicinal plants in the treatment of the hepatitis B virus. Thus, the aim of this study is to investigate the potential role of camel thorn extract as an alternative treatment for hepatitis B-suffering patients.

Materials and methods

After the pharmacological and toxicological screening of camel thorns in experimental animals in our laboratories [22]. The dose selected during this study was 2.6 g three times daily. This dose was extremely small compared with the LD_{50} in mice. In an open-label study, 13 patients were chosen at random and their agreements (consent forms signed) and ethical approval from the University of Benghazi, Benghazi, Libya, were obtained. Patients were of either gender (male=5, female=8), with an age range of 20-50 years. Patients had no previous history of liver cirrhosis or other co-morbid diseases (some patients had diabetes mellitus) and were not alcoholics. All patients underwent basic investigations, including checking their body weight and blood pressure before and

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during the study. After being clinically investigated, the patients were given a very low, safe dose of camel thorn powder (2.6 g soaked in boiling water for 10 minutes) three times per day for six months. The viral load was measured before treatment and three and six months after the beginning of the experiment by polymerase chain reaction using a COBAS analyzer (Roche Molecular Systems Inc., Branchburg, NJ). However, the other biochemical parameters were measured before and after the first three months of the experiment. The levels of hemoglobin (HB), white blood cells (WBC), and platelets were determined by a Colter counter, a hematology analyzer; prothrombin time (PT) was determined by a coagulation analyzer; and the international normalized ratio (INR) was all calculated. Thyroid function was determined using an immunoassay analyzer [23], creatinine [24], blood glucose levels [25], bilirubin [26], transaminases [27], alanine phosphatase (ALKP) [28], albumin by the bromocresol green method [29], and a lipid profile, which includes high-density lipoprotein, (HDL), low-density lipoprotein (LDL), and triglycerides (TG) cholesterol, was measured [30].

Statistical analysis: The experimental results were expressed as the mean±S.E.M. Results of the viral load at different time intervals were assessed by analysis of variance (one-way ANOVA). If this analysis indicated significant difference among the group means, then each group was compared by Post Hoc test: Fisher LSD or pairwise two-sample *t*-tests. The Student *t*-test was used to evaluate biochemical data. A value of $p<0.05$ was considered statistically significant.

Results

As presented in **Table 1**, no statistically significant decrease in patients' hepatitis B virus load was observed after three months of treatment. However, the level of virus load in the same patients was significantly decreased after six months of treatment with camel thorn extract ($p<0.05$). According to **Table 2**, the levels of HB virus pre-(before administration of Alhagi Maurorum) and post-treatment of daily administration of Alhagi Maurorum were 12.12±0.78 and 12.17±0.93 (g/l), respectively. The levels of WBC pre- and post-treatment were 7.83±0.35 and 7.68 ± 0.74 (10^9/l). The numbers of platelets in pre- and post-treatment patients were 268±24.71 and 257.8±18.96 (10^9/l), respectively. The pre- and post-treatment PTs (in seconds) were 12.17±3.95 and 9.67±3.0 6; the pre- and post-treatment INR readings were 1.18±0.40 and 0.8±0.25. Thus, by using the Student *t*-test, no significant statistical changes were observed on the previously mentioned parameters.

Table 1: Effect of camel thorn extract on the viral load of HBV of patients at different time intervals using real-time PCR

Treatment protocol	HBV Load (IU per ml)
Pre-treatment	1689±289
Three months after the beginning daily treatment	558±160
Six months after the beginning of daily treatment	271±026*

*Significantly different from pretreatment and three months after the beginning of treatment ($p<0.05$)

Table 2: Effect of *Alhagi Maurorum* on blood picture, PT and INR in HVB suffering patients

Treatment protocol	Hemoglobin (g / l)	White blood cells (10^9 / l)	Platelets (10^9 / l)	Prothrombin time (secs)	International normalized ratio
Pre-treatment	12.12±0.78	7.83±0.35	268±24.71	12.17±3.95	1.18±0.40
Post-treatment	12.17±0.93	7.68±0.74	257.8±18.96	9.67±3.06	0.80± 0.25
P value	0.88	0.86	0.66	0.076	0.08

Pre → Before administration of CTE, Post → After 3 months of daily administration of CTE

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Results in **Table 3** shows blood urea levels (mg/dl), pre- and post-treatment, were 19.5±4.10 and 24.5±2.67. The levels of creatinine (mg/dl) pre- and post-treatment were found to be 0.78±0.07 and 0.6±0.09 respectively. The pre- and post-treatment plasma glucose levels were 86.0±03.36 and 88.8±2.26, respectively. All these data indicate no significant statistical differences between the groups.

Table 3: Effect of *Alhagi Maurorum* on some renal parameters and on blood glucose levels in HBV-infected patients

Treatment protocol	Urea (mg/dl)	Creatinine (mg/dl)	Glucose (mg/dl)
Pre-treatment	19.5±4.10	0.78±0.07	86.0±3.36
Post-treatment with CTE	24.5±2.67	0.60±0.09	88.8±2.26
P value	0.06	0.21	0.53

Pre → before administration of CTE, Post → after 3 months of daily administration of CTE

Moreover, as indicated in **Table 4**, the levels of bilirubin in pre- and post-treatments were 0.56±0.091 and 0.45±0.022 mg/dl, respectively. The pre- and post-treatment ALT (U/l) levels were 22.67±4.69 and 20.83±2.94, respectively. Where the AST levels were 25.33±01.78 and 19.67±02.80. The activities of ALKP (U/dl) before three months and after three months of *Alhagi Maurorum* treatment were 84.17±6.67 and 91.67±5.96 (p=0.06). The albumin concentration (g/l) was 4.33±0.19 and 4.25±0.13 in the pre- and post-treatment patients, with no significant difference, respectively.

Table 4: Effect of treatment with CTE on some liver parameters and albumin in HBV-infected patients

	Bilirubin (mg/dl)	ALT (U/l)	AST (U/l)	ALKP (U/l)	Albumin (g/l)
Pre-treatment	0.56±0.091	22.67±4.69	25. 33±1.78	84.17±6.67	4.33±0.19
Post-treatment	0.45±0.022	20.83±2.94	19.67±2.80	91.67±5.96	4.25±0.13
P value	0.27	0.40	0.11	0.06	0.36

Data mean ± SEM, Pre → Before administration of CTE, Post → After 3 months of daily administration of CTE.

Concerning lipid profile (mg/dl), results in **Table 5**, indicated no significant difference between pre- and post-treatment with *Alhagi Maurorum* ($p<0.05$). The levels of cholesterol pre- and post-treatment were 138.6 ± 10 and 133.0±8.6 (P=0.64) and those of TG were 78.8±14.8 and 76.4±12.6 (p=0.88). The concentrations of blood HDL before and after treatment were 88.8±9.7 and 88.6±10.6 (p=0.9). Our data showed that pre- and post-treatment LDL levels were 42.8±7.3 and 42.4±6.3 respectively, with no significant difference (p=0.59). As seen in **Table 6**, no significant difference was observed in the thyroid function between pre- and post-treatment with *Alhagi Maurorum* ($p<0.05$). T3 levels (ng/dl) were 1.213±0.092 and 1.09±0.25 (P=0.66) before and after treatment, respectively. These figures in the case of T4 were 94.78±4.43 and 78.77±15.88 (p=0.39). TSH levels were 2.55±0.64 and 3.56±0.92 before and after treatment, with no statistical difference (p=0.16).

Table 6: Influence of *Alhagi Maurorum* on the thyroid function of HBV suffering patients

Treatment group	Triiodothyronine T3, (nmol/l)	Thyroxine T4, (nmol/l)	Thyroid Stimulation Hormone TSH, (m. IU/l)
Pretreatment	1.213±0.092	94.78±4.43	2.55±0.64
Post-treatment	1.09±0.25	78.77±15.88	3.56±0.92
P value	0.66	0.39	0.16

No significant changes were observed between pre-and post-treatment with CTE. Data are mean ± SEM.

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Discussion

Hepatitis B virus infection is a major global health problem, despite the availability of effective vaccine prophylaxis. According to the latest WHO reports, an estimated 240-280 million people are chronic hepatitis B (CHB) carriers, among whom the disease occurs with a very high burden, as approximately one million people die every year from CHB-related disease [31-34]. CHB causes almost 40.0% of cases of hepatocellular carcinoma, which is the second leading cause of cancer-related mortality worldwide [35]. Dramatic improvements in the efficacy of the treatment of CHB were made possible by the availability of highly potent direct antiviral agents, which created an expectation of similar results being achieved in chronic HBV. Despite the availability of highly effective direct antiviral agents for HBV for the last 20 years, a cure cannot be achieved in most cases because of the peculiar features of this virus. In fact, the viral life cycle of HBV involves formation of particularly stable episomal minichromosomes, covalently closed circular DNA (cccDNA) molecules, which serve as templates for transcription and a reservoir for future replication cycles [36, 37]. Further, the HBV genome is able to integrate into the host genome, reinforcing viral antigen production and favoring HBV oncogenesis [38]. The inability to arrest this complex replicative machinery leads to the persistence of viral antigen production, which in turn, progressively exacerbates the functional failure of the immune response; which represents the most effective tool for viral control [39].

There is no evidence that antiviral treatment is effective for acute hepatitis B. The hepatitis B vaccine, with 95.0% efficacy rate, is the cornerstone of preventing HBV infection and the consequences of chronic infection, such as cirrhosis, liver cancer, and death [40]. Chronic hepatitis B is defined as the persistence of the hepatitis B surface antigen for more than six months. Individuals with CHB are at risk of hepatocellular carcinoma and cirrhosis, but morbidity and mortality are reduced with adequate treatment [41]. Thus, in most cases, treatment must continue for life. However, even successfully virally suppressed patients may still develop liver cancer, especially if their livers are cirrhotic [42]. There is a continuing need for alternative options for treating viral HBV infections. Moreover, there is a need for treatment options that provide efficacy with minimal side effects. Recently, researchers have begun to investigate the potential role of herbs in the treatment of viral infections [43]. The effect of CTE extract on HBV was studied, and it was discovered that the extract reduced elevated liver enzymes and viral load (in HBV-infected patients). This could be due to the plant's ability to stimulate endogenous interferon production and the immune system, in addition to its antioxidant and detoxifying effects. Regarding the biochemical parameters obtained before and three months after treatment with CTE extract, our data showed that the blood count did not significantly change before or after treatment with CTE. The present findings also indicated that the PT and IR pre- and post-treatment did not show any statistical difference. CHB virus infection has been observed to be associated with nephropathy and reduced renal function [44]. Chronic HBV has been linked to renal disease for a decade, and approximately 02.0-15.0% of patients on hemodialysis have HBV [45]. The present study showed that the level of urea and creatinine did not statistically alter this, indicating that the tested herb did not interfere with the integrity of the kidney and that it may be having a protective effect. The liver plays an important role in thyroid hormone metabolism, specifically in its conjugation, excretion, and mono-deiodination. Liver disease can affect thyroid hormone metabolism. Altered thyroid hormone metabolism resulting in low serum triiodothyronine (T3), normal to low thyroxine (T4), a high reverse T3 (rT3), and an inappropriately normal thyroid stimulation hormone (TSH) in the absence of clinical hypothyroidism is well documented in chronic and cirrhotic liver diseases of various etiologies, such as hepatitis virus infection [46-49]. The most frequent change in plasma levels of thyroid hormones is decreased total T3 and free T3 concentration, which is reported to be associated with the severity of hepatic dysfunction [50, 51]. The current study indicated

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that the tested herb did not significantly change thyroid function. Patients with liver disorders are often found to have a deranged lipid profile. A clear decline is observed in the levels of cholesterol as well as TG among individuals with severe hepatitis and liver failure as the synthesis of lipoprotein is reduced [52]. The present results indicated that the lipid profile did not significantly change after three months of treatment with CTE. The CTE extract decreases the viral load in HBV-infected patients, in part because the plant may have the ability to stimulate endogenous interferon production, and the immune system in addition to its antioxidant and detoxifying effects. Data presented in this study showed that the tested plant did not interfere with the integrity of the kidney or the thyroid. Also, there was no change in the various hematological parameters, which indicate the herb may not be toxic and does not interfere with the circulating red cells, hematopoiesis and leucopoiesis. The present finding suggests the CTE is not toxic since no marked change in the biochemical, hematological, or thyroid parameters was observed. Consequently, CTE may be considered an alternative treatment option for subjects suffering from hepatitis B viral infections, providing an alternative treatment option that exhibits minimal side effects. Further studies are needed using a large number of populations, different doses, and a longer duration of treatment to explore the mechanism of action and efficacy of CTE as an alternative, safe treatment against HBV.

Conclusion: The camel thorn extract decreases the viral load in HBV-infected patients, in part because the plant may have the ability to stimulate endogenous interferon production and the immune system in addition to its antioxidant and detoxifying effects. These findings indicate no marked change in the biochemical and hematological as well as thyroid parameters, these suggesting that the safety of Alhagi Maurorum.

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Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

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