ORIGINAL ARTICLE

Hepatoprotective effect of hydroalcoholic extract of *Qurse Afsanteen*, apolyherbal Unani formulation, inchemically induced hepatotoxicity in rat

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Abstract

Aim: The liver plays a key role in the biotransformation of many chemicals and drugs. Thereby, it is a target organ for several toxicants. *Qurse Afsanteen*, an Unani formulation, is claimed to be effective as a hepatoprotective. **Materials and Methods:** To evaluate the hepatoprotective effect of hydroalcoholic extract of *Qurse Afsanteen* (HAEQA) against CCl_4 and Rifampicin induced hepatotoxicity, 36 rats were divided into six groups, each having six animals representing negative, positive, standard, and test Groups A, B, and C. CCl_4 was used in the dose of 0.7 ml/kg for 7 days whereas Rifampicin was given in the dose of 100 mg/kg for 15 days for inducing hepatotoxicity. In test and standard groups, CCl_4 and Rifampicin were administered after 30 min of receiving test and standard drug. Treatment Groups A, B, and C received HAEQA in three doses, that is, 40.32 mg, 67.2 mg, and 120.96 mg/kg to observe the dose-dependent effect. Silymarin (100mg/kg) was used as standard drug. Serum markers, namely, SGOT, SGPT, ALP, bilirubin, and cholesterol were estimated as parameter. Histopathology of the liver was also done. **Result and Discussion:** HAEQA showed significant hepatoprotection at therapeutic dose level (67.2 mg/kg) against CCl_4 and Rifampicin-induced hepatotoxicity which is evident by decreased enzyme markers in both methods. **Conclusion:** The findings were suggestive of the test drug possessing hepatoprotective activity.

Key words: CCl_4, hepatotoxicity, liver, *Qurse Afsanteen*, rifampicin

INTRODUCTION

The liver is avital organ intended regulating the homeostasis of the body.[1] It has an important place in the biotransformation of xenobiotics and plays a key role in the metabolism of many organic and inorganic chemicals and drugs. The liver is a target organ for several toxicants because of the large number of nutrients and xenobiotics pass through it.[2]

A liver injury produced by drugs and chemical may mimic any naturally occurring liver disease.[3] More than 1000 drugs have been reported to produce hepatic injury; half of them are produced only by biochemical changes and about one-third lead to acute hepatitis. Antibiotics including anti-tuberculosis drugs are the most common group of drugs that produce liver injury. In India, nearly 50% of cases of drug-induced liver injury may be due to anti-tuberculosis drugs.[4] Conventional medicine has not much to offer for easing of hepatic diseases.[5] It has been reported that medicinal plants have to offer effective and safe hepatoprotective drugs.[6] *Qurse Afsanteen* (QA) is an important Unani pharmacopeial preparation having four ingredients *viz.* Afsanteen (*Artemisia absinthium* Linn.), *Asarun* (*Valerianahardwickii*Wall.), *TukhmeKarafs* (*Apium graveolens* Linn.) and *MaghzBadam* (*Prunusamygdalus*Baill.)[7-11]

Unani medicine has described several single and compound formulations to treat hepatic diseases; of them, many are claimed to be hepatoprotective. Hepatoprotective drugs are those which improved ranged functions of the liver.[12] However, some single and compound drugs such as *Zarishk*

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(*Berberis vulgaris* Linn.),[13] *Kasni* (*Cichorium intybus* Linn.),[14] Afsanteen (*A. absinthium* Linn.),[7] *Badam* (*P. amygdalus* Baill.),[8] *Tukhmekarafs* (*A. graveolens* Linn.)[9] and compound formulation, like *MajoonDabeedul Ward*[10] have been investigated for the claimed action. However, most compound formulations have not been investigated scientifically. QA is one of them.

In Unani medicine, QA is reported to have pharmacological actions such as stomachic, deobstruent of liver, and spleen and is used in chronic fever, urinary retention,[7-15] and as a liver tonic.[16] Individual ingredients of QA are also mentioned as anti-inflammatory and liver tonic in Unani medicine.[17,18] Essential oil, glycosides, flavonoids, phenolics, and steroids are reported in these ingredients.[17,19,20] In various scientific studies, they have been investigated foranti-inflammatory,[18,21] antioxidant,[22,23] and hepatoprotective[7,24] activities.

MATERIALS AND METHODS

Test Drug

The ingredients of QA were procured from the local market of Bengaluru and authenticated by Institute of Trans-Disciplinary Health Sciences and Technology (FRLHT) vide Acc. No. 3481, 3482, 3480, 3479, respectively. A voucher specimen of the same has been deposited in the NIUM's drug museum vide No. 31/IA/Res/2015**.**

Preparation of Test Drug

The ingredients were taken in equal quantity as mentioned in the Unani literature.[11] They were powdered with the help of an electric grinder;100 g of which was used for extraction in 50% distilled water and 50% ethanol solvent about 6 h in Soxhlet apparatus at 80°C. The extract was cooled and filtered by filter paper and then evaporated on a water bath until it dried completely. The yield percentage of the extract was found as 13.44% w/w.

Doses of Drug

The dose of the extract of QA for a rat was calculated from the human therapeutic dose 4.5 g described as by Unani physicians.[11] The study was carried out at three dose levels. The therapeutic dose for a rat was calculated by the conversion factor of 7[25] and two more doses were calculated by Miller's formula to see dose-dependent effect.[26] Since the test drug was used in extract form, it was calculated based on yield % and was found to be 40.32 mg, 67.2 mg, and 120.96 mg/kg. The extract was suspended in 1 ml of 5%gum acacia and administered orally with the gastric cannula. Fresh suspension was prepared daily before each administration.

Chemical and Reagents

All the chemicals used in this study were of analytical grade. Silymarin was procured from Microlab Ltd., Rifampicin and CCl_4 were purchased from Lupin Ltd. and Central drug house Ltd. A standard kit of SGOT, SGPT, and cholesterol was obtained from Euro diagnostic system Pvt. Ltd. Alkaline phosphatase from Agape Diagnostic Ltd. and kit for Bilirubin estimation from Liner Chemicals were purchased.

Animals

A total of 36 rats were divided into six groups, each having six animals representing negative, positive, standard, and test Groups A, B, and C. CCl_4 was used in the dose of 0.7 ml/kg for 7 days whereas Rifampicin was given in the dose of 100 mg/kg for 15 days for inducing hepatotoxicity. In test and standard groups, CCl_4 and Rifampicin were administered after 30 minutes of receiving test and standard drug. Treatment Groups A, B, and C received HAEQAin three doses, that is, 40.32 mg, 67.2 mg, and 120.96 mg/kg to observe the dose-dependent effect. Silymarin (100 mg/kg) was used as standard drug.

Before starting the experiment, ethical clearance was obtained from the Institutional Animal Ethics Committee (IAEC) of NIUM vide no. IAEC11/03/IA. Wistar rats of either sex; weighing 150–200 g; 2–3 month of age were procured from Sri Venkateshwara Enterprises Bengaluru. The animal care procedures and experimental protocol were in accord with the guidelines of CPCSEA. The rats were housed individually in polypropylene cages for 7 days before the study to acclimatize and received standard pellets and water *ad libitum*. The animals were maintained on a normal light-dark schedule at temperature 25 ± 2°C, humidity at 45–55% throughout the experiment.

Experimental Design

Carbon tetrachloride-induced hepatotoxicity

The study was conducted by the method described by Dwiwedi *et al*., (1990)[27] with some modification in the treatment schedule. After 12 h of fasting, the animals were divided into six groups of six animals each. The animals in Group 1 received 5% of Gum Acacia suspension (1ml) orally once daily for 7 days and served as negative control. Animals in Group II were administered with carbon tetrachloride in the dose of 0.7 ml/kg (diluted in liquid paraffin 1:1) orally for 7 days that served as positive control. The animals in Group III treated with Silymarin (100 mg/kg) which served as Standard group. Groups IV, V, and VI treated with HAEQA in the dose of 40.32 mg/kg, 67.2 mg/kg, and 120.96 mg/kg, respectively orally for 7 days served as test Groups A, B and C. After 30 min of administration of Standard and test drug,

carbon tetrachloride in the dose of 0.7 ml/kg (diluted in liquid paraffin1:1) was given orally daily for 7 days.

Rifampicin Induced Hepatotoxicity

This study was conducted by the method described by Jadhav *et al*., (2010)[28] with some modification in the treatment schedule. After 12 h of fasting, the animals were divided into six groups of six animals each. The animals in Group 1 which received 5% of Gum Acacia suspension (1 ml) orally once daily for 15 days served as negative control. Animals in Group II administered Rifampicin 100 mg/kg orally for 15 days, served as positive control. The animals in Group III treated with Silymarin (100 mg/kg) served as Standard group, Group IV, V, and VI were treated with the test drug in the dose of 40.32 mg/kg, 67.2 mg/kg, and 120.96 mg/kg, respectively, orally for 15 days served as test Groups A, B, and C. After 30 min of administration of standard and test drug, Rifampicin 100 mg/kg was given orally daily for 15 days.

Assessment of Hepatoprotective Activity

After 24 h of the last dose of drug treatment, all the animals in both the tests were sacrificed using Thiopentone sodium (50 mg/kg/IP) as anesthetic. Blood samples were collected by retro-orbital sinus puncture, centrifuged at 3000 rpm for 10 min to obtain fresh serum for biochemical analysis. Liver of two rats from each group was dissected out, cleaned from extraneous tissues, washed with normal saline, and preserved in 10% formalin for histopathological examination.

Statistical Analysis

The observations in various groups were expressed as mean ± SEM. Findings were compared with negative and positive control groups. The intergroup comparison was made using one-way analysis of variance followed by Tukey-Pair comparisons test. The difference in means was regarded as significant at $P < 0.05$.

RESULTS

Effect of HAEQAon CCl_4 Induced Hepatotoxicity

When the mean SGOT, SGPT, and ALP of the positive control were compared with negative control, it was observed that the levels of these marker enzymes increased significantly ($P < 0.05$) in positive control. When the mean SGOT in the standard group, test Groups A, B, and C were compared with the positive control, SGOT reduced significantly ($P < 0.01$) in test Group B treated with the test drug at the dose of 67.2 mg/kg. When the mean SGPT in all the groups were compared with the positive control, no significant effect was observed in all the test groups while standard group showed a significant effect ($P < 0.01$). In case of ALP, standard group, test Group A, B, and C showed statistically significant ($P < 0.05$) response when compared to the positive control [Table 1 and Figure 1b]. The level of serum bilirubin and total cholesterol was found to be increased when compared with negative control but it was not statistically significant. Similarly, the test and standard drugs did not produce any significant response except test Group B when serum bilirubin was compared with positive control. The standard and test Group A showed a significant reduction ($P < 0.5$, < 0.1), respectively, in cholesterol level [Table 1 and Figure 1].

Effect of HAEQA on Rifampicin-induced Hepatotoxicity

When the mean SGOT, SGPT, ALP, serum bilirubin and cholesterol of positive control were compared with negative control, it was observed that in positive control, only SGOT and ALP were found to increase significantly ($P < 0.05$). When the mean SGOT of standard group, test Groups A, B, and C were compared with the positive control, it reduced in test Group B significantly ($P < 0.05$). The mean SGOT of standard group, test Groups A and C also reduced but not significantly. When the mean SGPT and ALP of standard group, test Groups A, B, and C were compared with the positive control, it reduced significantly only in test Groups B ($P < 0.05$) [Table 2]. While no significant effect was observed in serum bilirubin and cholesterol level in any of the test and standard groups when compared with positive control [Table 2 and Figure 2].

Histopathology of the Liver

Histopathological examination of the liver showed severe microvesicular steatosis and mild inflammatory infiltration in CCl_4 treated animals. In Rifampicin treated animals, liver showed moderate coagulative necrosis and moderate inflammatory infiltration. Standard and test drug-treated groups showed mild microvesicular steatosis and mild inflammatory infiltration [Figures 1 and 2].

DISCUSSION

The hepatotoxicity of CCl_4 is reported to be due to the formation of the reactive CC13 free radical, which react rapidly with oxygen to yield a highly reactive trichloromethyl radical.[5,29] It causes peroxidative degradation of the lipid membrane of the adipose tissue.[27-30] Rifampicin has been recognized to be hepatotoxic alone or in combination with other antituberculosis drugs.[10,28,31,32] It was evidenced that biotransformation of rifampicin into its active metabolite, 25-diacetyl rifampicin, reduces the drug-metabolizing enzymes and inhibits the nucleic acid and protein synthesis.[28]

Table 1: Effect of HAEQA on serum markers in CCl_4 induced hepatotoxicity

Group	SGOT (IU/dl)	SGPT (IU/dl)	ALP (IU/dl)	Total Bilirubin (mg/dl)	Total cholesterol (mg/dl)
Negative control (Gum Acacia 1 ml)	228.78±14.55	70.40±7.49	486.12±10.14	0.205±0.053	46.5±2.07
Positive control (CCl_4 0.7 ml/Kg)	330.95±32.20^{a*}	114.21±4.57^{a*}	644.41±20.99^{a*}	0.412±0.069	56.29±6.73
Standard group (Silymarin 100 mg/kg+CCl_4)	260.41±21.43	58.17±5.01^{b**c*}	496.28±55.08^{b*}	0.318±0.053	36.71±3.65^{b*}
Test group A (HAEQA 40.32 mg/kg+CCl_4)	311.00±18.82	96.59±13.32	491.13±14.28^{b*}	0.211±0.057	30.24±1.26^{b**}
Test group B (HAEQA 67.2 mg/kg+CCl_4)	193.08±18.99^{b**c**}	81.33±7.94	497.81±47.86^{b*}	0.170±0.024^{b*}	48.19±2.98
Test group C (HAEQA120.96 mg/kg+CCl_4)	250.83±20.68	82.96±10.51	535.53±25.71	0.238±0.068	44.91±7.06

HAEQA: Hydroalcoholic extract of *Qurse Afsanteen*. CCl_4 carbon tetrachloride. Values are mean±SEM (n=6 animals/group). Analyzed by ANOVA one way with Tukey pair comparison test, *P<0.05, **P<0.01, [a]With respect to the negative control, [b]With respect to the positive control, [c]With respect to test group HAEQA 40.32 mg/kg+CCl_4

Table 2: Effect of HAEQA on serum markers in Rifampicin induced hepatotoxicity

Group	SGOT (IU/dl)	SGPT (IU/dl)	ALP (IU/dl)	Total bilirubin (mg/dl)	Total cholesterol (mg/dl)
Negative control (Gum Acacia1ml)	202.76±17.42	70.14±6.24	436.33±55.95	0.312±0.09	45.47±5.26
Positive control (Rifampicin 100 mg/kg)	273.44±16.44^{a*}	81.92±6.74	671.86±62.85^{a*}	0.501±0.21	67.25±4.97
Standard Group (Silymarin 100 mg/kg+Rifampicin)	259.23±8.00	65.22±2.83^{a**}	543.35±34.91	0.227±0.04	52.85±8.85
Test Group A (HAEQA 40.32 mg/kg+Rifampicin)	237.26±11.47	69.13±3.58	551.43±35.19	0.280±0.10	59.15±2.61
Test Group B (HAEQA 67.2 mg/kg+Rifampicin)	203.25±18.97^{b*}	60.64±3.14^{b*c*}	461.70±31.35^{b*}	0.211±0.03	62.92±4.03
Test Group C (HAEQA 120.96mg/kg+Rifampicin)	261.65±12.16	82.04±4.74	501.65±34.48	0.277±0.07	66.48±2.60

HAEQA: Hydroalcoholic extract of *Qurse Afsanteen*. Values are mean±SEM (n=6 animals/group). Analyzed by ANOVA One Way with Tukey pair comparison test. *P<0.05, **P<0.01, [a]With respect to the Negative control, [b]With respect to the Positive control, [c]With respect to test Group C

In the present study, the elevated levels of SGOT, SGPT, and serum ALP in CCl_4 and Rifampicin treated animals may be due to the injury of hepatic cells, which liberate SGOT, SGPT, and ALP into serum. The injury may be a cytotoxic, cholestatic, or liver dysfunction.[30,33] Cytotoxic injury is degeneration or necrosis of hepatic parenchyma while cholestatic is due to bile, jaundice, and abnormal parenchymal cells.[30]

HAEQA minimized the elevated levels of SGOT, SGPT, ALP, bilirubin, and cholesterol, prominent effect was seen at therapeutic dose of test drug, that is, 67.2 mg/kg. These findings showed that the test drug has no dose-dependent effect. The finding is like a previous study conducted by Patil on hepatoprotective activity of *Mentha arvensis*.[29] It again validated the claims of Unani medicine. Histopathological examination also coincided the results as seen in liver parameters.

In Unani medicine, drugs used for hepatic diseases possess activities such as demulcent, deobstruent, resolvent, and astringent.[16] These activities are present in the test drugs. In the case of hepatitis, resolvent drugs play an important role. *A.absinthium* Linn.[34] *A. graveolens*[15] and *V. hardwickii*[34] are reported to have anti-inflammatory activity; therefore, the hepatoprotective property of the test drug may also be due to this property and antioxidant properties, which prevent inflammatory damage and the oxidative stress.[32] Hepatic functions may also get compromised due to obstruction in the

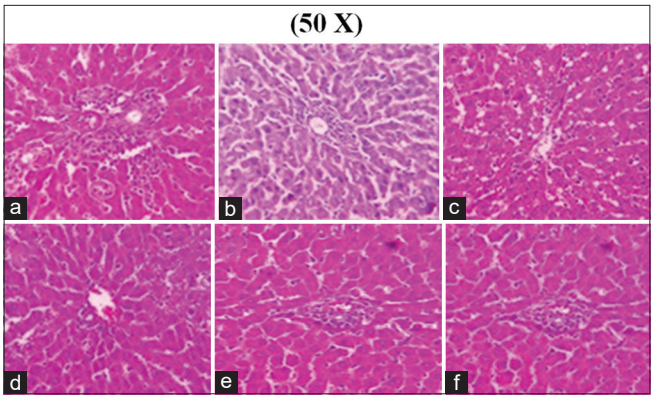

Figure 1: Histopathology of CCl_4-induced hepatotoxicity and effect of HAEQA. (a) Negative control showing normal architecture, (b) positive control showing severe microvesicular steatosis inflammatory infiltration, (c) standard Group showing mild microvesicular steatosis and mild inflammatory infiltration, (d) test Group A: showing mild microvesicular steatosis and mild inflammatory infiltration, (e) test Group B showing mild microvesicular steatosis and mild inflammatory infiltration, and (f) test Group C showing moderate microvesicular steatosis and mild inflammatory infiltration (50 X)

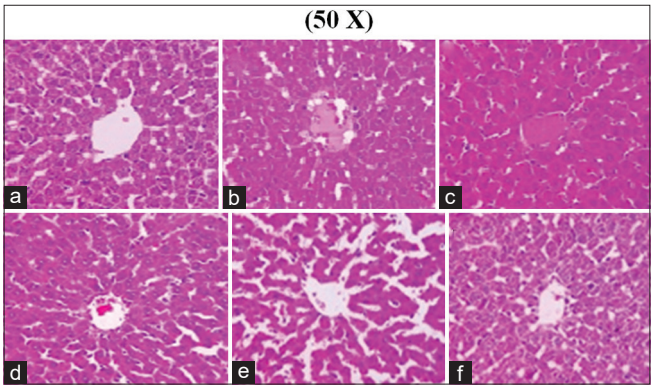

Figure 2: Histopathology of Rifampicin-induced hepatotoxicity and effect of HAEQA. (a) Negative control showing normal architecture. (b) Positive control showing moderate coagulative necrosis and moderate inflammatory infiltration. Standard group (c) showing mild inflammatory infiltration, (d) test Group A showing moderate inflammatory infiltration, (e) test Group B showing mild inflammatory infiltration, and (f) test Group C showing mild inflammatory infiltration. (50 X)

biliary tract, which results in weakness of excretory power of the liver and gall bladder.[35] Deobstruent drugs are useful in this condition.

Liver protective herbal drugs contain coumarins, lignans, essential oil, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids, and xanthone derivatives.[3] It is reported that flavonoids and steroids are hepatoprotective.[29] Ingredients of test drug have these constituents.[7,14]

Based on the above discussion, it can be concluded that *Qurse Afsanteen* has a significant hepatoprotective effect, which is evident by the reduction of marker enzymes in test groups. Further studies are needed to determine the exact mechanism of action and its chemical constituents responsible for hepatoprotective activity.

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