Abstract. Hepatitis C virus (HCV) infection represents a global health problem, particularly in developing countries such as Egypt, and is a principal cause of progressive liver disease (1). Currently, 130-180 million people are infected with HCV worldwide (2). Recently, a number of reports have suggested that HCV-related mortality rates will continue to rise for the next 20 years (3,4). Acute HCV infection differs from chronic infection in various aspects, including whether or not there is a previous history of increase in alanine aminotransferase (ALT), the duration of ALT elevation and the presence of symptoms, such as jaundice (5). In acute infections, HCV RNA may be detected in serum two weeks following exposure to HCV; however, anti-HCV antibodies cannot often be identified until 2-3 months after exposure to the virus (6).

Anti-HCV treatment regimens aim to prevent disease complications and decrease rates of HCV-associated mortality. Chronic HCV infection develops slowly, which makes it difficult to establish whether certain treatments prevent liver disease complications. Biochemical assays [normalization of ALT and aspartate aminotransferase (AST) levels in serum] and virological assays [absence of viral RNA from serum as measured by a sensitive polymerase chain reaction (PCR)-based assay] are employed to measure short-term outcomes of HCV infection (7,8).
Western countries (9) and Japan (10) have conducted major clinical trials concerning antiviral therapy for the treatment of chronic HCV infection. As the majority of published data addresses patients infected with HCV genotypes 1, 2 and 3, there is an established type of treatment and duration of anti-HCV therapy for these patients (11). Ray et al (12) demonstrated that an Egyptian HCV epidemic comprised multiple lineages of genotypes 1 and 4, with the predominance of genotype 4; however, no regional links in samples from 15 geographically diverse governorates in Egypt could be identified that suggested a pattern of spread. This was explained by the fact that multiple HCV strains were disseminated simultaneously to the entire population. Few studies have been published on the treatment of patients infected with HCV genotype 4, and results from clinical trials of combination therapy for these patients have not been encouraging (13-15). Randomized controlled clinical trials of several agents are required for the establishment of an appropriate treatment for HCV genotype 4. Vaccination is currently used against HCV; however, vaccines against some important pathogenic strains of HCV are not available. The high cost of vaccinations results in patients using traditional medicines as an alternative treatment for HCV infection. One example of a traditional medicine is camel milk; many traditional stories exist about camel milk utility as a therapy for patients infected with hepatitis diseases, particularly diseases caused by HCV.

The composition and physiology of camel milk is different from the milk of ruminants (16,17). Little fat (2%) is found in camel milk and lactose is present at a concentration of 4.8%, meaning that camel milk is easily metabolized by lactose-intolerant individuals (18). No β-lactoglobulin (19) and a different β-casein fragment derived from a non-tryptic type of parent protein cleavage (20) have been identified among camel milk proteins. Additionally, camel milk is rich in iron, calcium and vitamin C (16).

Two major families of proteins are identified in all types of milk, including camel and cow milk: Caseins and whey proteins (21). Whey proteins include immunoglobulins, lactalbumin, lactoperoxidase, lysozyme and lactoferrin (22). Camels produce a novel type of antibody devoid of light chains, referred to as a heavy chain antibody (23), in addition to conventional antibodies that are composed of two heavy and two light chains. Lactalbumin, when in a particular conformational state, possesses antimicrobial properties (24). Lactoferrin (alone or in combination with other milk proteins) exhibits antibacterial, antiviral, antifungal, antiparasitic, immunomodulatory, anti-inflammatory and even antineoplastic effects (25-29). It has been demonstrated that camel milk has therapeutic effects on cancer, jaundice, hepatitis B and C, diabetes, dropsy, tuberculosis, spleen problems, anemia, piles, food allergies, high cholesterol in the blood and asthma (30,31).

The present study aimed to examine how camels or products derived from camels may improve people’s lives or assist in protecting the health of animals and people. In vitro studies have delivered promising results supporting the use of camel milk against HCV infection (22,26,27,32-42), prompting the present in vivo investigation. The present study aimed to determine whether or not camel milk has therapeutic effects on HCV in infected Egyptian patients who did not take any medication in the 6 months prior to participation in the current study. In the present study, whole camel milk was examined as an alternative medicine. The ability of camel milk to reduce viral particle load, reduce the levels of antibodies against HCV in patient sera and improve patient liver functions (ALT and AST) was investigated.

**Materials and methods**

**Patients.** A total of 17 Egyptian patients (12 male and 5 female; aged 20-65 years) suffering from chronic hepatitis C infection caused by HCV genotype 4, participated in the present study. Clinical and laboratory evaluation of patients demonstrated that they were HCV RNA-positive, with mild to moderate fibrosis and raised levels of transaminases (ALT and AST). Patients were randomly recruited from the Tropical and Biochemistry Outpatient Clinic, Faculty of Medicine, Assiut University (Assiut, Egypt), which is in South Egypt where the HCV genotype 4 is more endemic than in North. Furthermore, the Assiut governorate is considered the poorest governorate in Egypt. All participating patients did not take medication against HCV within the 6 months prior to initiation of milk consumption. Three healthy adults (two male and one female) with normal hepatic serum parameters were recruited from the same Outpatient Clinic at Assiut University and included in the current study to serve as a control group. The patients consumed their routine daily meals in addition to camel milk during the experimental period. Patients were recommended to terminate their routine bovine milk consumption 6 months prior to and during the experiment. Patients consumed 250 ml camel milk every morning under physician supervision in the hospital for 4 months. The present study was conducted with approval from the Ethics Committee of the Genetic Engineering and Biotechnology Research Institute and Faculty of Medicine, Assiut University. Written informed consent was provided by all subjects prior to participation in this study and all patients will remain anonymous.

**Camel milk.** Fresh camel (Camelus dromedaries) milk was collected from a camel farm (ALKHIR, Alexandria, Egypt) containing a large herd of camels fed with natural herbs. Milk was collected in 250 ml bottles and frozen to be transferred to the laboratories of the Medical Biochemistry Department, Faculty of Medicine, Assiut University. Milk was kept frozen until consumption by patients in medical care rooms. Prior to milk collection, a sanitary inspection was conducted, supervised by the farm veterinarian staff. Camels and the obtained milk were inspected in this way twice a month at the farm. All camels used for milk production and their milk, were free from pathogenic and zoonotic microbes, and their mammary glands were free from infection and mastitis.

**Experimental design.** The present study was an open case control, randomized and parallel design investigation. Three types of assays were performed for HCV diagnosis and treatment: Liver function tests (ALT and AST); serologic tests that detected anti-HCV specific antibodies; and molecular assessments that determined the load of HCV RNA. Liver function tests were conducted twice for all patients and control adults, both prior and subsequent to consumption of camel milk. Levels of AST and ALT were evaluated by
conventional methods, using ALT/GPT and AST/GOT kits (catalogue nos. 11832 and 11830, respectively, BioSystems, Barcelona, Spain). Absorbance was measured at 340 nm using a Perkin-Elmer spectrophotometer (PerkinElmer GmbH, Überlingen, Germany) in the Medical Biochemistry Department, Faculty of Medicine, Assiut University. Quantitative assessment of HCV RNA was performed using Rotor-Gene Q (model no. R0708103; Corbett Life Science; Qiagen, Hilden, Germany). A positive response to camel milk treatment was determined by the patient being negative for qualitative HCV analysis or exhibiting a decreasing number of viral particles in quantitative HCV RNA analysis.

Reverse transcription-quantitative PCR (RT-qPCR) to evaluate antiviral activity of camel milk against HCV. HCV RNA was isolated and extracted from HCV patient and control sera using an INSTANT Virus RNA kit (AJ Roboscreen GmbH, Leipzig, Germany). DNA may potentially remain in the final eluted RNA following isolation, thus DNase treatment was performed in order to completely remove any trace DNA. One unit of RNase-free DNase I (New England Biolabs, Inc., Ipswich, MA, USA) was added to 1 µg RNA in an RNase-free tube containing 1 µl 10X reaction buffer with MgCl₂ and 10 µl DEPC-treated water, followed by incubation for 30 min at 37°C. Subsequently, 1 µl 50 mM EDTA was added and incubated for 10 min at 65°C in order to inactivate the DNase I. Amplification of HCV RNA in samples and standards was achieved and measured using a RoboGene HCV RNA Quantification kit (cat. no. 0207200141; AJ Roboscreen GmbH, Leipzig, Germany) and a Rotor-Gene real time PCR machine (model no. R0708103; Corbett Life Science; Qiagen). The RoboGene HCV RNA Quantification kit includes the following components: Extraction tubes coated with internal control (IC) RNA and carrier nucleic acid, sample tubes coated with amplification enhancer, quantification standard tubes of 8 different HCV RNA concentrations (ready-to-use reference curves), reagent mix with HCV/IC specific primers and probes, Mg-sulfate (50 mM), RT-PCR enzyme mix, 2X reaction mix, and PCR grade water. qPCR 1X master mix was prepared by mixing 3.5 µl PCR grade water, 12.5 µl 2X reaction mix, 2 µl 50 mM Mg-sulfate solution, 1 µl 25X reagent mix with HCV/IC specific primers and probes, and 1 µl RT-PCR enzyme mix. The mix was then vortexed at 1,000 rpm for 3 sec and centrifuged at 18,078 x g and 4°C for 5 sec. Twenty microliters of 1X master mix were added to sample tubes and quantification standard tubes. PCR grade water (5 µl) was added to sample tubes serving as a no template control (NTC), as well as all quantification standard tubes and 5 µl of isolated RNA were added to the respective sample tubes. The RoboGene HCV RNA Quantification kit detects all HCV genotypes using primers specific for a subsequence of the HCV 5’ untranslated region (5’ UTR). Each sample was tested in duplicate. Specific controls were included: i) IC to control RNA extraction and to indicate for inhibitory effects on detection; ii) two quantification standards in the kit to serve as HCV positive control; iii) sera samples from 3 healthy adults to serve as HCV negative control. qPCR cycling conditions were as follows: 1X of reverse transcription at 55°C for 30 min, 1X of Taq activation at 95°C for 2 min, 50X of melting at 95°C for 15 sec, stem formation at 45°C for 15 sec, annealing at 57°C for 40 sec. A quantification report was created by the Rotor-Gene Q Series Software 1.7, Build 94 (Corbett Life Science; QIAGEN GmbH). HCV RNA was evaluated based on the C_q values obtained for the sample HCV RNA and a standard curve resulted from quantification standard analysis and calibration coefficient specific for the assay (43). All methods were conducted according to the manufacturers’ protocols.

**Anti-HCV immunoglobulin (Ig) G profile.** ELISA plates (cat. no. 2592, Costar, Cambridge, USA) were coated with 50 µl of HCV peptide 1, 2, 3, 4 or 5 at a concentration of 5 µg/ml. Subsequent to an incubation period of 24 h at room temperature, the plates were washed 5 times with 0.12 M NaCl and phosphate-buffered saline (PBS; pH 7.2). Subsequently, 100 µl blocking buffer [2% bovine serum albumin (BSA) in PBS] was added to the ELISA plates, followed by incubation for 1 h at room temperature. Following this, 50 µl hepatitis C patient sera (prior and subsequent to camel milk drinking) diluted 1:100 in 2% BSA-PBS were added. After 1 h incubation at room temperature, the plates were washed five times, sequentially, with PBS and 50 µl biotin-labeled goat-anti-human IgG1 (1:1,000; cat. no. B6775), biotin-labeled goat-anti-human IgG2 (1:15,000; cat. no. B3398), biotin-labeled goat-anti-human IgG3 (1:4,000; cat. no. B3523), or biotin-labeled goat-anti-human IgG4 (1:15,000; cat. no. B3648; Sigma-Aldrich; Merck Millipore, Darmstadt, Germany) were added. The plates were incubated for 1 h at room temperature. The plates were washed five times to remove unbound antibodies and 50 µl streptavidin-alkaline phosphatase-conjugate (Sigma-Aldrich; Merck Millipore) diluted 1:4,000 with 2% BSA-PBS was subsequently added. Following this, the plates were incubated for 1 h at room temperature. Finally, para-Nitrophenyl phosphate (Sigma-Aldrich; Merck Millipore) was added for color development and absorbance was recorded immediately at a wavelength of 405 nm (44.45) using an ELISA microtiter plate reader (MicroPlate Reader; Bio-Rad Laboratories Inc., Hercules, CA, USA).

**HCV peptide design and synthesis.** ClustalW version 1.4 (46) was employed to analyze extracted sequences from the Los Alamos HCV sequence database (47). Five peptide (P) sequences were synthesized commercially (Anaspec Inc., San Jose, CA, USA) in the following design: P1 from the HCV core protein (DVKFPFGQGVVYLLPRR); P2 from the HCV core protein (IPRLGVATRKTGQSQPG); P3 from the HCV core protein (IPKARRPEGRTWAQPGY); P4 from the HCV core protein (IPKDRSTDGKSWGKPGY); and P5 from the HCV envelope 2 protein (NLQLINTNGS). The peptides were synthesized and purified commercially (AstraZeneca, Cambridge, UK).

**Statistical analysis.** Statistical analysis was performed on Microsoft Office Excel 2003 v11.0 (Microsoft Corporation, Redmond, WA, USA) using Student’s t-test and McNemar's
Results

Patients. A total of 17 patients were enrolled in the study: 12 males (70.59%) and five females (29.41%). Prior to initiation of the study, all patients suffered from generalized symptoms of malaise, anorexia, fever, abdominal distension and arthralgia. Additionally, 80% of patients suffered with jaundice, right hypochondrial pain, ankle swelling, hematemesis and melena and breast swelling (gynecomastia). Loss of libido, amenorrhea and changes in secondary sex characteristics affected 50% of patients. Within the 4 months of camel milk treatment, and after treatment, generalized symptoms, including malaise, anorexia, fever, arthralgia, indigestion and changes in secondary sex characteristics, were resolved in all patients. Jaundice, right hypochondrial pain, ankle swelling, hematemesis, melena and gynecomastia improved in 50% of patients who suffered from these conditions at the beginning of the study.

AST and ALT sera assays. Results of liver function tests revealed a marked decrease in ALT in 88.23% of patients and in AST in all patients (Table I). Subsequent to camel milk treatment, AST activity decreased in five patients to values within the international normal range of 10-34 international units (IU)/l. Camel milk treatment decreased AST activity in ten patients to mean ± standard deviation (SD) values between 37±3.94 and 52±1.81 IU/l, which are still promising when considering the high levels of AST activity exhibited prior to treatment, where mean ± SD values ranged between 70±3.19 and 132±0.99 IU/l. Furthermore, in two patients, AST activity decreased to 101±3.65 and 71±1.22 IU/l, compared to 199±1.54 and 121±1.84 IU/l, respectively, prior to treatment. However, this level of AST activity is high when compared to the international normal range. Additionally, ALT levels decreased in four patients subsequent to camel milk treatment to values within the normal range (up to 41 IU/l). Camel milk treatment decreased ALT levels in 11 patients to values between 43±1.24 and 58±2.36 IU/l, which are encouraging compared to the high levels of ALT observed prior to treatment (ranging from 80±1.65 to 161±2.11 IU/l). However, two patients did not respond to treatment and exhibited elevated ALT levels subsequent to treatment. The ratio of AST to ALT was <1 in 15 out of 17 patients (Table I).

HCV RNA RT-qPCR results. The results demonstrated that, following daily consumption of camel milk for four months, 13 patients (76.47%) experienced marked decreases in HCV RNA levels in their sera (Table II). One patient had undetectable viremia (viral load=0) following camel milk treatment. The remaining patients (23.53%) did not respond to the treatment.

Anti-HCV IgG isotyping. Results demonstrated that anti-HCV antibody isotype IgG1 exhibited significantly weaker (P<0.05)
colour signals (mean abs at 405 nm of IgG1 in 17 patients) subsequent to camel milk treatment against all HCV peptides used (Table III). By contrast, anti-HCV antibody isotypes IgG2, 3, and 4 exhibited significantly stronger (P<0.05) colour signals (mean abs at 405 nm of IgG2, 3, and 4 in 17 patients) following camel milk treatment against all tested HCV peptides. Fig. 1 presents the exact percentage of patients that experienced either an increase or decrease in color signals of anti-HCV antibody isotypes against all tested HCV peptides, following camel milk treatment. A marked reduction of IgG1 occurred in 70-76% of patients following camel milk treatment. By contrast, notable increases were demonstrated in levels of IgG2, 3 and 4 in 52-76, 41-76 and 58-82% of patients, respectively (Fig. 1).

Discussion

Studies suggest that Egypt has the highest HCV prevalence rate globally (51-53), possibly as a result of the use of unsterile injection tools during public anti-schistosomiasis injection campaigns. Egyptians are predominantly infected with HCV genotype 4 (subtype 4a), which has a reduced response rate to standard interferon (IFN)-based therapy compared with genotypes 1, 2, or 3 (54). The standard therapy for Egyptian HCV patients is the use of IFN as a monotherapy (IFN-α2a, -α2b and pegylated IFN) (55,56) or combined with ribavirin; however, patients often use various alternative medicines (57-59). Recent studies investigated the use of whey protein concentrate (57), pasteurized camel milk (58) and fresh camel milk (59) in the treatment of HCV genotype 4 infection; the results demonstrated significant decreases in viral load, markers of active inflammation and ALT and AST activity (57-59) following treatment. However, the study by Mohamed et al (59) did not clarify the camel milk source and how and where camel milk was consumed by participants. Furthermore, the camel milk was used as a treatment in combination with pegylated IFN/ribavirin in HCV-4 infected Egyptian patients.

One of the most popular alternative treatments for HCV infection, based on traditional beliefs, is camel milk, which is used among the main human dietary constituents in several parts of the world. In the present study, the potential role of camel milk components in viral inhibition and treatment of HCV infection was investigated. A total of 17 patients (12 male and 5 female) were treated by consumption of camel milk, without heating or the addition of chemical substances. This treatment continued for four months and each patient consumed 250 ml/day.

Following camel milk treatment, a marked improvement was observed in the general fatigue and health (personal observation) of the patients. Following 4 months treatment, serum samples were collected from patients to evaluate the antiviral activity of camel milk against HCV. Results demonstrated that 13 out of 17 patients responded to the treatment and exhibited reduced levels of HCV RNA in their sera, and one patient had no detectable HCV RNA in their serum following treatment. Four patients did not respond to the treatment at all, which may suggest that they required increased doses of camel milk. Results of liver function tests revealed a significant reduction in ALT and AST activity in 15 out of 17 patients and in all patients, respectively, subsequent to treatment. Results also demonstrated that the ratio of AST to ALT was <1 in 15 out of 17 patients, which is in agreement with the concept that in viral hepatitis the AST/ALT ratio is usually <1 (60). The AST/ALT ratio was >1 in two patients prior to treatment, which is an indication of cirrhosis (61,62).

In the present study, following treatment, IgG1 exhibited weaker color signals against different HCV peptides compared with other IgG subtypes in 70-76% of patients (Table III). Prior to treatment, chronic hepatitis C patients with high viremia exhibited detectable IgG1. The camel milk may, therefore, regulate the expression of Th1/Th2 immunity (63) towards the Th1-dependent immunity profile (IgG1). This resembles the immunity profile of chronic hepatitis B patients treated with camel milk (64). This supports the view that Th2 immunity in patients with chronic hepatitis C cannot regulate viral clearance (65). In keeping with previous findings concerning the use of camel milk to improve tuberculosis, problems with the spleen, dropsy, asthma, anemia, piles and jaundice (31), other lung ailments and treatment of diabetic patients (66), the present study demonstrated that, following treatment with camel milk, all generalized symptoms (including malaise, anorexia, fever, athralgia, indigestion and changes in the secondary sex characteristics) were resolved in all HCV patients in the present study.

Camel milk contains several proteins, including Ig and lactoferrin, and other components with anti-viral and immunomodulatory activities. In a previous study (34), it

| Patient no. | Prior to treatment (copies/ml) | Following treatment (copies/ml) |
|-------------|--------------------------------|--------------------------------|
| Control (n=3) | Undetected | Undetected |
| 1 | 5,400,000 | 1,095,000 |
| 2 | 4,460,000 | 277,000 |
| 3 | 1,004,600 | 1,540,600 |
| 4 | 3,035,800 | 23,690 |
| 5 | 1,173,020 | 1,525,500 |
| 6 | 3,328,680 | 69,372 |
| 7 | 4,859,500 | 354,650 |
| 8 | 4,617,070 | 332,567 |
| 9 | 5,407,000 | 63,880 |
| 10 | 1,130,130 | 41,860 |
| 11 | 2,329,000 | 171,200 |
| 12 | 1,379,000 | 0 |
| 13 | 1,148,000 | 29,490 |
| 14 | 5,070,000 | 31,740 |
| 15 | 7,905,600 | 9,806,000 |
| 16 | 4,596,000 | 222,800 |
| 17 | 6,800,367 | 7,870,000 |

Data are presented as mean ± standard deviation for 17 patients. *P<0.05, vs. the control group. IgG, immunoglobulin G.
was observed that purified camel polyclonal IgG exhibited in vitro inhibitory effects against HCV. This is in accordance with the results from a study by Martin et al. (67), which demonstrated similar inhibitory effects of recombinant camel heavy chain variable domain antibody against HCV nonstructural protease.

Previous studies (26,27,32-34) have demonstrated that natural and recombinant camel lactoferrin exerts strong antiviral activity against HCV in vitro. Camel lactoferrin is more potent over sheep, bovine and human lactoferrins against HCV cellular infectivity (36). The exact mechanisms by which lactoferrin regulates its immune modulating functions are incompletely understood; however, it has been demonstrated that lactoferrin enhances and improves immune response, both directly and/or indirectly, in response to a wide range of immune challenges (28).

There are some limitations to acknowledge for the present study. Firstly, the study included a small sample size due to the difficulty of obtaining volunteers and scheduling follow-up meetings. Future research should include a larger sample size. Secondly, there was no local epidemiological information that could be referred to or compared with throughout the study. Thirdly, the study was only concerned with Egyptian patients infected with HCV genotype 4; therefore, no knowledge was gained on genotypes 1, 2, or 3, or on the effect of camel milk in non-Egyptian populations infected with HCV.

In conclusion, the present study demonstrated that whole camel milk has marked in vivo efficacy against HCV, by reducing viral load in patient sera and converting the IgG isotype profile to Th1 immunity. Therefore, the use of camel milk is recommended for treating patients infected with HCV genotype 4; however, it is necessary for the benefits of camel milk to be investigated further.

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Table III. Response to camel milk treatment measured by determination of mean absorbance at 405 nm of 4 IgG isotypes against five hepatitis C virus peptides.

|        | IgG1 Prior to treatment | IgG2 Prior to treatment | IgG3 Prior to treatment | IgG4 Prior to treatment |
|--------|-------------------------|-------------------------|-------------------------|-------------------------|
|        | Following treatment     | Following treatment     | Following treatment     | Following treatment     |
|        | 0.53±0.06              | 0.29±0.09a              | 0.28±0.06               | 0.61±0.11              |
|        | 0.54±0.05              | 0.27±0.10a              | 0.22±0.11               | 0.63±0.10              |
|        | 0.63±0.12              | 0.34±0.09a              | 0.36±0.09               | 0.67±0.20              |
|        | 0.80±0.11              | 0.34±0.21a              | 0.33±0.10               | 0.57±0.10              |
|        | 0.53±0.06              | 0.21±0.05a              | 0.22±0.06               | 0.60±0.05              |
| Total  | 0.61±0.11              | 0.29±0.05a              | 0.28±0.06               | 0.63±0.10              |

Data are presented as mean ± standard deviation for 17 patients. *P<0.05, vs. the control group. IgG, immunoglobulin G.

Figure 1. Analysis of anti-HCV antibody isotypes following camel milk treatment. (A) The percentage of patients with elevated antibody response to each HCV antigen following treatment. (B) The percentage of patients with decreased antibody response to each HCV antigen prior to treatment. HCV, hepatitis C virus; Ig, immunoglobulin.
Camelus dromedarius

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